



2023

Section: Internal Medicine

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How to Cite This Article

Abbas, Ramadan Gamal Riyad; Eissa, Youssef Khalil; Mohamed, Yasser El-Sayed; and Nassar, Youssef Abd Allah (2023) "Prevalence Of Iron Overload Cardiomyopathy (IOC) In Transfusion-dependant Anaemic Patients," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 7, Article 33.

DOI: <https://doi.org/10.58675/2682-339X.1886>

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Prevalence of Iron Overload Cardiomyopathy (IOC) In Transfusion-dependant Anemic Patients

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Abstract

Introduction: The accumulation of iron in the myocardium causes iron overload cardiomyopathy (IOC), which is the primary cause of fatalities in individuals receiving long blood transfusion treatment.

Aim: The study's goal is to determine the prevalence of IOC in patients with blood transfusion-dependent chronic anemia.

Patients & methods: The current prospective study included 50 patients with chronic anemia with a history of repeated blood transfusion, attending to hematology unit, internal medicine department of the faculty of medicine, Al-Azhar University in Cairo, those patients had more than 2 years of diagnosis of anemia, repeated blood transfusion in last 2 years and age ranged between 18 and 35 years old, with the exclusion of the presence of a history of congenital heart disease, intrinsic cardiac abnormalities (as ischemia heart disease, hereditary cardiomyopathy), systemic hypertension, diabetes mellitus, autoimmune disease and liver cirrhosis, history of hereditary hemochromatosis or other disease affecting serum iron level as porphyrias.

Results: Of 6/32 patients who have had thalassemia developed cardiomyopathy by symptoms and (EF), while 2/3 patients who have had autoimmune hemolytic anemia (AIHA) developed cardiomyopathy by symptoms and (EF). We did not find a statistically significant correlation between cardiomyopathy (diagnosed by cardiac Magnetic resonance imaging (MRI)) and serum ferritin, as the number of patients who developed cardiomyopathy with the normal serum ferritin, was equal to those who developed cardiomyopathy with high serum ferritin 'above 1000 ng/ml', (P -value = 0.27).

Conclusion: Symptomatic patients with chronic blood transfusion are in need to exclude cardiomyopathy whatever the serum ferritin level is.

Keywords: Iron overload, cardiomyopathy, Anemia, Serum ferritin

1. Introduction

In patients with genetic anemias including thalassemia and sickle cell anemia, as well as acquired anemias such as myelodysplastic syndrome (MDS), myelofibrosis, and aplastic anemia. Blood transfusion is the backbone of treatment for sideroblastic anemia and bleckfan diamond anemia.¹

A unit of packed red blood cells (RBCs) typically contains 200–250 mg of essential iron, which develops excess in the body due to a lack of a

functioning iron excretion mechanism. Patients with transfusion reliance get around 20 times the typical iron intake.²

Serum iron overload is caused by excessive exogenous iron consumption by blood transfusion, which saturates the reticuloendothelial system with iron, which can then disseminate to other parenchymal cells.³

Iron overload cardiomyopathy (IOC) is caused by an excess of serum iron, which causes transferrin saturation and the release of non-transferrin bound iron into the circulation.

Pathological iron deposition begins in the pericardium, progresses to the myocardium, and lastly to the endocardium.⁴

IOC is a significant and initially treatable cause of heart failure characterized by diastolic dysfunction, increased vulnerability to arrhythmia, and end stage dilated cardiomyopathy.⁵

The study's goal is to determine the prevalence of IOC in patients with blood transfusion-dependent chronic anemia.

2. Patient and method

The current prospective study will include 50 patients with chronic anemia with history of repeated blood transfusion, attending hematology unit, internal medicine Department.

2.1. Inclusion criteria

More than 2 years diagnosis of anemia, repeated blood transfusion in last 2 years and age between 18 and 35 years old.

2.2. Exclusion criteria

History of congenital heart disease, intrinsic cardiac abnormalities (as ischemia heart disease, hereditary cardiomyopathy), systemic hypertension, diabetes mellitus, autoimmune disease and liver cirrhosis, and history of hereditary hemochromatosis or other disease affecting serum iron levels as porphyrias.

Eligible patient will be divided into two groups according to their cardiac evaluation: group 1: patients without cardiomyopathy, group 2: patients with cardiomyopathy.

All patients will be subjected to:

Detailed history taking including duration of anemia, blood transfusion, cardiac symptoms, bleeding tendency, arthritis, skin changes, hepatic symptoms, weight loss, drug history.

(1) Physical examination for demonstration of important signs of heart failure, endocrinal affection, liver affection, arthritis, pallor, lymphadenopathy, and/or splenomegaly.

(2) Local cardiac examination of the heart to assess (heart sounds, additional heart sounds and murmurs).

(3) Investigation:

(a) Lab: complete blood count (CBC), peripheral blood smear, hemoglobin (HB) electrophoresis, serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation, Liver function marker (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and indirect bilirubin, alkaline phosphatase, HBA1C, serum creatinine, uric acid, lipid profile, erythrocyte sedimentation rate (ESR), anti-nuclear antibodies (ANA), Transferrin saturation (serum iron/total iron binding capacity <45%) and serum ferritin (elevated <200 µg in males or < 150 µg in female, is considered as iron-overload.

(b) Electrocardiogram (ECG): Resting 12 lead ECG. Resting 12 leads ECG was done to all patients.

(c) Transthoracic Echocardiographic (ECHO) imaging:

It was done to all patients 48–72 h after admission. The ECHO was performed with the patient breathing quietly and lying in the left lateral position. Four acoustic views (parasternal long axis, parasternal short axis, apical four chamber, and apical two chamber) were obtained.

Assessment of systolic left ventricular (LV) function: LV systolic function detected by measuring the end diastolic and end systolic diameters of left ventricle using M-mode recording under guidance of two-dimensional ECHO according to the recommendation of the American Society of ECHO. The end diastole at the onset of QRS complex and the end systole at the point of maximum upward motion of LV posterior wall endocardium. These measurements should be made from leading edge to leading edge. The M-mode LV dimensions used to estimate ventricular volume and ejection fraction (EF) if desired most simply by merely cubing the value (D)³ or using Teicholz Technique and calculating the EF.

$$EF\% = \frac{L.V.\text{end diastolic volume } (D^3) - LV\text{ end systolic volume } (D^3)}{LV\text{ end diastolic volume } (D^3)}$$

EF or patient with cardiomyopathy only: T2* cardiac Magnetic resonance imaging (MRI) (value of 20 ms is considered the threshold for myocardial siderosis).

2.3. Statistical analysis

The numerical variables will be expressed as the mean \pm standard deviation (SD). The continuous data will be analyzed by the *t*-test and the Anova test. *P*-value of 0.05 or less will be considered as statistically significant.

3. Results

The mean age of studied patients was 24.9 (SD = 5.1), ranging from (18–35 years). 17 (34%) patients were females, while 33/50 (66%) patients were males and male to female ratio was = 1.9 : 1.

Category of patients who were less than 20 years old formed 26% of patients, while patients who were more than 20 years old formed 74% of patients, [Table 1](#).

Causes of repeated blood transfusion were variable, but the most common cause was thalassemia, as 32/50 patients (64%) have had thalassemia, 11/50 (22%) patients have had sickle cell anemia, 4/50 (8%) patients have had Myelodysplastic syndrome, while 3/50 (6%) patients have had Autoimmune hemolytic anemia, as shown in [Table 2](#).

As regard to cardiac affection in form of symptoms like shortness of breath, bilateral lower limb edema, or signs like audible heart sounds, or ECG changes, or ECHO changes regarding EF, in studied patients regarding their cause of repeated blood transfusion.

We realized that symptoms and EF were dependable factors for detecting cardiomyopathy, as shown in [Table 3](#).

On the other hand, autoimmune hemolytic anemia (AIHA) and Thalassemia were the most common diseases associated with cardiomyopathy. As 6/

Table 1. Showed Patient demographic data analysis which revealed median age of 25 y and prevalence of male over females in the studied patients.

Demographics and co-morbidities	Incidence
Age	
Mean (SD)	24.96 (5.1)
Median (range)	25 (18,35)
Age Categories	
Less than 20 years	13 (26%)
More than 20 years	37 (74%)
Sex	
Female	17 (34%)
Male	33 (66%)

Table 2. Showed causes of repeated blood transfusion data analysis, which revealed higher incidence of sickle cell anemia patients among those who underwent chronic blood transfusion.

Variable	Incidence
Autoimmune hemolytic anemia	
Yes	3 (6%)
No	47 (94%)
Myelodysplastic syndrome	
No	46 (92%)
Yes	4 (8%)
Sickle cell anemia	
No	39 (78%)
Yes	11 (22%)
Thalassemia	
No	8 (36%)
Yes	32 (64%)

32 (18.8%) patients who have had thalassemia developed cardiomyopathy by symptoms and EF, while 2/3 (66.7%) patients who have had AIHA developed cardiomyopathy by symptoms and EF.

Cardiac MRI was done for patients who developed cardiomyopathy to assess cardiac siderosis, we realized that all patients who developed cardiomyopathy have had T2 cardiac signal MRI of iron deposition, [Table 4](#).

Using χ^2 test, we realized that not all patients who have had T2 signal iron deposition in cardiac MRI, had elevated serum ferritin. Since there were 3/8 patients who have had cardiomyopathy, with positive cardiac MRI examination had no elevated serum ferritin, (*P* value = 0.27), [Table 5](#).

4. Discussion

In 1994, Liu and Oliveira described IOC, explaining that it is caused by a buildup of iron in the myocardium and is the major cause of mortality in patients receiving prolonged blood transfusion treatment.⁴

IOC is becoming more common over the world, and it is typically handled by cardiologists de Witte.⁶

Furthermore, as sickle cell and thalassemia patients live longer lives, the frequency of IOC climbs. It has been demonstrated that when IOC is detected early, appropriate medical care can reverse it, emphasizing the need for early identification of IOC Gujja and colleagues.⁷

IOC is defined as the presence of systolic or diastolic cardiac dysfunction caused by excessive iron deposition in the heart, regardless of any concurrent processes Liu and Olivieri.⁴

The purpose of this study was to determine the prevalence of IOC in chronic blood transfusion patients utilizing ECHO and cardiac MRI.

It is difficult to identify people at risk of heart failure early because global left ventricular

Table 3. Showed the relation between cause of repeated blood transfusion and cardiac affection. We realized that all patients who were symptomatic, developed cardiomyopathy by ECHO, *P*-value 0.03.

Cardiac variable	Cardiac affection				<i>P</i> -value	Significant
	AIHA Number = 3	MDS Number = 4	SCA Number = 11	Thalassemia Number = 32		
Symptoms						
Yes	2 (66.7%)	0	0	6 (18.8%)	0.03	S
No	1 (33.3%)	4 (100%)	11 (100%)	26 (81.3%)		
Signs						
Yes	0	0	0	3 (9.4%)	0.6	NS
No	3 (100.0%)	4 (100%)	11 (100%)	29 (90.6%)		
ECG changes						
Yes	0	0	2 (18.2%)	4 (12.5%)	0.71	NS
No	3 (100%)	4 (100%)	9 (81.8%)	28 (87.5%)		
EF						
Less than 50%	2 (66.7%)	0	0	6 (18.8%)	0.03	S
More than 50%	1 (33.3%)	4 (100%)	11 (100%)	26 (81.3%)		

AIHA, autoimmune hemolytic anemia.

Table 4. Showed the positive MRI examination for cardiomyopathic patients.

Cardiac MRI in cardiomyopathic patients	EF in ECHO		Total
	less than 50%	more than 50%	
T2 cardiac MRI not done			
Count	0	42	42
% Within EF in ECHO	0.0%	100.0%	84.0%
T2 signal Iron deposition			
Count	8	0	8
% Within EF in ECHO	100.0%	0.0%	16.0%

dysfunction and exercise capacity in persistently transfused patients with iron overload may be normal until late in the disease phase. MRI has only lately made it feasible to quantify myocardial iron content Anderson and colleagues.⁸

Although cardiac MRI is regarded the gold standard in myocardial iron overload, its frequent

Table 5. Showed the positive MRI examination according to serum ferritin.

T2 cardiac MRI	Titer of serum ferritin in ng/ml			Total	<i>P</i> value
	normal	400 : 1000	above 1000		
not done					
Count	13	22	7	42	0.27
% Within titer of serum ferritin in ng/ml	81.3%	91.7%	70.0%	84.0%	
T2 signal Iron deposition					
Count	3	2	3	8	16.0%
% Within titer of serum ferritin in ng/ml	18.8%	8.3%	30.0%	16.0%	

usage is hampered by its high price, restricted availability, relative acquisition difficulty, and time-consuming image interpretation Cappellini and colleagues.⁹

We discovered that all patients who developed cardiomyopathy showed T2 cardiac signal MRI of iron deposition in our research.

Reduced systolic and diastolic ventricular function is related with decreasing myocardial T2* levels. To present, the majority of known occurrences of heart failure in thalassemia have occurred in individuals with extremely low T2* levels (in the severe range) Pennell and Maceira.¹⁰

Anderson and colleagues demonstrated a gradual reduction in LVEF when T2* went below 20 ms, while Tanner and colleagues 2008 claimed that decreasing myocardial T2* is associated with left ventricular dilatation and hypertrophy Anderson and colleagues.⁸

Similarly, Liguori and Pitocco and Patton et al. (2010) discovered a substantial positive relationship between ejection percent and T2*.¹¹

We also discovered that not all individuals with T2 signal iron deposition in cardiac MRI had high blood ferritin. There were no raised blood ferritin levels in 3/8 of the individuals who had cardiomyopathy and had a positive cardiac MRI (*P* value = 0.27).

A 2014 study published in Iran revealed no significant link between serum ferritin and liver or cardiac MRI (*P* = 0.361, *r* = -0.120). However, there was a significant association between serum ferritin and liver T2*MRI (*P* = 0.021, *r* = -0.297) Eghbali and colleagues.¹²

L.J.Anderson and colleagues discovered that blood ferritin or liver iron cannot predict myocardial iron content, and standard measures of cardiac function can only detect people with severe illness.⁸

This wasn't in concordance with Shamsian and Esfahani, as they found that Cardiac T2 was in the range of 2.9–56.6 ms. Myocardial siderosis was detected in 44% of patients; 25 patients had moderate and severe siderosis with serum ferritin level (SFL) of 576–10,284 ng/ml. There was a significant correlation between SFL and cardiac T2 low asterisk ($P < 0.001$) Shamsian and Esfahani.¹³

Anderson and colleagues⁸ observed a weak connection between MR T2* and blood ferritin or liver iron determined by biopsy.

Despite the fact that individuals with mean serum ferritin levels greater than 2500 ng/ml had lower cardiac MRI T2* ($P = 0.201$) and higher liver iron concentrations ($P = 0.156$), the results were not statistically significant. Furthermore, there was no significant relationship between cardiac MRI T2* and mean serum ferritin ($P = 0.232$) Anderson and colleagues.⁸

Pennell and Maceira¹⁰ and Tanner et al., 2007 both concurred that cardiovascular MRI T2* consistently represented just the degree of myocardial iron load, and that total body iron reserves have limited immediate predictive value for the presence or absence of cardiac iron.

Elbeshlawy et al., 2014 also showed a low incidence of cardiac siderosis in Egyptian thalassemia major patients despite extremely high blood ferritin and high LIC, as well as the lack of a significant link between serum ferritin and MRIT2* of the patients Musallam and colleagues.¹⁴

Patients with IOC frequently complain of exertional shortness of breath due to LV diastolic dysfunction caused by a restricted etiology. This syndrome may lead to dilated cardiomyopathy with LV systolic failure later in life Hahalis and Manolis.¹⁵ Our results showed that variable degrees of cardiac affection in the form of symptoms like shortness of breath, bilateral lower limb edema, or signs like abnormalities in audible heart sounds, or ECG changes, or ECHO changes regarding EF, were found in studied patients irrespective of their cause of repeated blood transfusion.

These symptoms were accompanied with diminished EF, since all patients who developed symptoms and signs of cardiac affection, developed cardiomyopathy with ECHO, P value = 0.03.

We realized that symptoms and EF were dependable factors for detecting cardiomyopathy, on the other hand, AIHA and Thalassemia were the most common diseases associated with cardiomyopathy. As 6/32 patients who have had thalassemia developed cardiomyopathy by symptoms and EF, while 2/3 patients who have had AIHA developed cardiomyopathy by symptoms and EF.

We did not find statistically significant correlation between cardiomyopathy (diagnosed by cardiac MRI) and serum ferritin, as number of patients who developed cardiomyopathy with normal serum ferritin, was equal to those who developed cardiomyopathy with high serum ferritin 'above 1000 ng/ml', (P value = 0.27).

Similarly, Pennel et al. (2009) found no change in left ventricular ejection fraction (LVEF) between individuals with serum ferritin levels above and below 2500 g/L, with no significant link between serum ferritin and LVEF 10.

Aessopos and colleagues 2007, as well as Abbas and colleagues 2012, discovered no link between LV characteristics and serum ferritin in thalassemia patients.¹⁶

Similarly, neither (Abd Elmoktader et al., 2013) nor (Garadah et al., 2006) found a significant relationship between systolic cardiac dysfunction and serum ferritin Mishra and Tiwari.¹⁷

In contrast, Silvilairat et al. (2008) found that individuals with blood ferritin less than 2500 ng/ml had retained systolic and diastolic LV function compared with those with serum ferritin greater than 2500 ng/ml Silvilairat and colleagues.¹⁸ While (Hamdy and colleagues 2007) showed that the presence of RV systolic dysfunction in patients with beta-thalassemia major is related to the higher level of serum ferritin Hamdy and colleagues.¹⁹

However, Chirnomas and colleagues (2008) shown that systolic function has little sensitivity for identifying increased myocardial iron, with 18% of their patients having elevated myocardial iron while having a normal EF Murray and colleagues.²⁰

Serum ferritin or liver iron cannot predict myocardial iron level, and standard evaluations of cardiac function can only detect patients with severe illness Brittenham.²¹

In the Dubai Thalassemia Center, they discovered that only 1.8% of the studied B-thalassemia patients developed iron overload cardiomyopathy, with the most common sites of iron deposition being in the gonads and thyroid, which they assumed was due to different genomic characters other than those published internationally Belhouli and colleagues.²²

Splenectomy is a significant event in the lives of beta thalassemia sufferers. However, by improving the effectiveness of transfusion treatment, efficient clinical care may lessen the need for splenectomy.²³

There was no significant change in cardiac MRIT2* between splenectomized and non-splenectomized patients (Sherif et al., 2001). found that MRIT2* was considerably higher in the non-splenectomized group than in the splenectomized group. However, there was no significant difference

between the two groups in terms of EF and shortening fraction Paul and colleagues.²⁴

Regarding ECHO evaluation, we discovered that patients who had a splenectomy and acquired Iron overload Cardiomyopathy (IOC) were equivalent to those who had not had a splenectomy and developed IOC, *P* Value = 0.02. Our findings agreed with those of Azza et al. (2013) and Abd Elmoneim and associates (2012), who reported no change in shortening fraction and EF between splenectomized and nonsplenectomized individuals Tantawy and colleagues.²⁵

Our findings also revealed that there was no statistically significant difference in high serum ferritin levels between splenectomized and non-splenectomized individuals.

4.1. Conclusion

Symptomatic individuals receiving continuous blood transfusions must be evaluated for cardiomyopathy regardless of serum ferritin level.

Ethics committee

Approval for this study will be obtained from Al-Azhar University Ethical Committee.

Patient consent

Informed consent will be obtained from all included patient.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declared that there were no conflicts of interest.

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