Prevalence of Pulmonary Hypertension among Patients with β-thalassemia Major in Erbil Province -Iraq

Kawa Muhamedamin Hasan (MBChB, MD, FRCP, PhD)[1] **and Musaab Zubair Mohammad** (MBChB, MD)[2]

Abstract

Background: Cardiac manifestation including heart failure, arrhythmia, and pulmonary hypertension are well recognized among β-thalassemia major patients.Pulmonary hypertension is responsible for about half of their mortalities yearly.

Objective: To estimate the prevalence of pulmonary hypertension and identifying the risk factors among β-thalassemia major patients.

Patients and Methods: A cross sectional study was carried out in Thalassemia Center and Rizgary Teaching Hospital in Erbil-Iraq during the period from 1st of April to 31st of December, 2017 on a convenient sample of 100 patients with β-thalassemia major. The prevalence of pulmonary hypertension was determined and the diagnosis based on Echography findings.

Results: Pulmonary hypertension was observed among 31% of β-thalassemia major patients. The prevalence was significantly related to age, history of splenectomy, improper chelation therapy and obesity, as well (p value =0.04, 0.01, 0.03 and 0.01 respectively). Moreover; the severity of pulmonary hypertension was significantly associated with older age (p= 0.007) and mean lower ejection fraction (p <0.001).

Conclusion: The prevalence of pulmonary hypertension among our patients with β-thalassemia major is within acceptable range.

Keywords: Prevalence, β-thalassemia major, Pulmonary hypertension**.**

Corresponding Author: mah_kawa@yahoo.com

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[1]College of Medicine- Hawler Medical University -Erbil - Iraq.

[2] Diyala Health Governorate -Diyala- Iraq.

Introduction

β-thalassemia is characterized by decrease in the rate of production of β globin chains of hemoglobin, they are inherited disorders widely distributed throughout the world, with considerable frequencies in Iraq and other Eastern Mediterranean countries[1,2]. Both Beta thalassemia intermedia (BTI) and thalassemia major (BTM) are associated with pulmonary hypertension (PHT). Based upon echocardiography findings the evidence of PHT is 40–50% in BTI and 10–75% among BTM patients[3].

The mechanism of development of PHT in thalassemia syndromes is multifactorial, including firstly iron overload as a result of life-dependent blood transfusion.4-6 Second; splenectomy which consider to be an important risk factor in the development of PHT.7 Third the increased incidence of thromboembolic events among thalassemia patients due to the hypercoagulability are well known[8,9].

It is important to note because it is widely and easily available, relatively inexpensive and non-invasive echocardiography is frequently used to screen for PHT and monitoring its progression over time[10].

Echocardiography is often used as a screening tool to identify subjects at high risk for PHT. Tricuspid Regurgitant jet Velocity (TRV) is the flow of retrograde blood across the tricuspid valve during systole, is an echo finding which estimates right ventricular systolic pressure and correlates with mean pulmonary artery pressure (PAP)[11].

TRV in thalassemia is thought to be similar to that of other chronic hemolytic anemias in which echocardiographic findings may overestimate the risk of PHT.12 Most experts suggest that a "TRV greater than 2.5 m/s in thalassemia patients identifies a population at increased risk of PHT" who should undergo RHC[13]. The aim of the current study was to determine the prevalence of PHT among BTM patients, and identifying the main risk factors for PHT development.

Patients and Methods

A cross sectional study conducted in both Thalassemia Center and Rizgary Teaching Hospital in Erbil City-Kurdistan region of Iraq, from 1st of April to 31st of December 2017.

A convenient sample of 100 patients with ß-thalassemia major was selected after their approval to participate in the study, while those with thalassemia minor, thalassemia intermedia, severely ill patients, and those with multiple co-morbidities were excluded.

The patients enrolled were diagnosed cases of ß-thalassemia major since at least one year. A detail history concerning sociodemographic characteristics, cardiovascular symptoms, history of splenectomy, blood transfusion program, iron chelation therapy, type of iron chelation were considered. The body mass index (BMI), vital signs, and precordial examination were checked for all patients. A 5 ml venous blood sample was taken from each patient for complete blood count (CBC), liver function tests, serum ferritin, and viral screen (Hepatitis B and C). The Echocardiography (Echo) was done by (Echo Philips- CX50). Echocardiography used to estimate pulmonary artery systolic pressure (PASP) by measuring systolic pressure gradient from right ventricle to right atrium using modified Bernoulli equation, added to estimated right atrial pressure which determined by variation in size of inferior vena cava with respiration. Echocardiography was done in Erbil Cardiac Center, Rizgary Teaching Hospital and Raparin Pediatrics Hospital. The scientific and ethical committees of Arab Board for Health Specializations approved the study.

Statistical analysis

All patients' data were recorded then entered into the computer, and analyzed by using Statistical Package for Social Sciences (SPSS) version 21. Descriptive statistics presented as (mean ± standard deviation (SD)) and frequencies as percentages were achieved. Kolmogorov Smirnov analysis verified the normality of the data set. For comparison between categorical data Chi square test was used (Fishers exact test was used when expected variable were less than 2% of total number of variables). To compare between two means we used the t-test (Independent sample). The level of significance set as p value ≤ 0.05.

Results

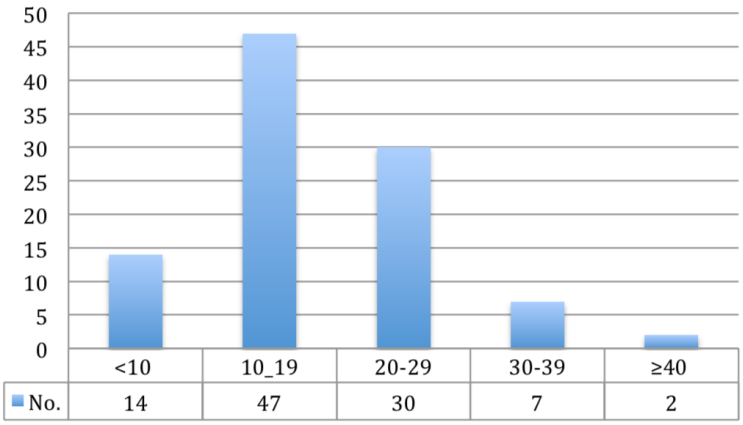
The mean age of enrolled patients was 18.5±8 years; the age of 47% of patients were between 10-19 years, male patients were 51% with male to female ratio was 1.04:1. The mean BMI was 20.5±2.1 Kg/m2 Table(1) & Figure(1). Approximately half of patients (54%) had splenectomy with mean duration since operation of 13.1±7.6 years.

The vast majority (99%) of patients had a proper blood transfusion program. Further; about two-third of patients received a proper iron chelation therapy, which includes; Deferoxamine (43%), Deferaserox (24%), Deferoxamine and Deferiprone (18%), Deferoxamine and Deferaserox (14%), Deferiprone (1%), as shown in Table 1 and Figure(2).The common cardiovascular symptoms were fatigue (54%), shortness of breath (24%), palpitation (23%), chest pain (1%), while the main physical findings were elevated jugular venous pressure (JVP) (12%), right parasternal heave (12%), accentuation of pulmonary component of 2nd heart sound (P2) (12%), audible 3rd heart sound (9%), splenomegaly (39%) with mean size (below costal margin) of 4.7±4.1 cm and hepatomegaly was detected among (24%) with mean size of 17±2.7 cm, as shown in Table (2).

The mean (±SD) heart rate of enrolled patients was 86.1±11.8, mean blood pressure was 119.6/75.4±12.2/7.4, and mean SpO2 was 96.1±1.0 Table (3).

Table (1): Baseline characteristics of 100 studied patients.

Variable	No. (%)
Age mean± SD (18.5±8 years)	
Gender	
Male	51 (51)
Female	49 (49)
BMI	
Normal	75 (75)
Over weight	8 (8)
Obese	17 (17)
History of blood transfusion	
Well transfused	99 (99)
Not Well transfused	1 (1)
Iron chelating therapy	
Well chelated	72 (72)
Not well chelated	28 (28)
History of splenectomy	54 (54)
Duration of splenectomy	
<10 years	22 (22)
≥10 years	32 (32)
History of chronic cardiac diseases	
Yes	20 (22)
No	80 (80)



Figure(1): Age group distribution.

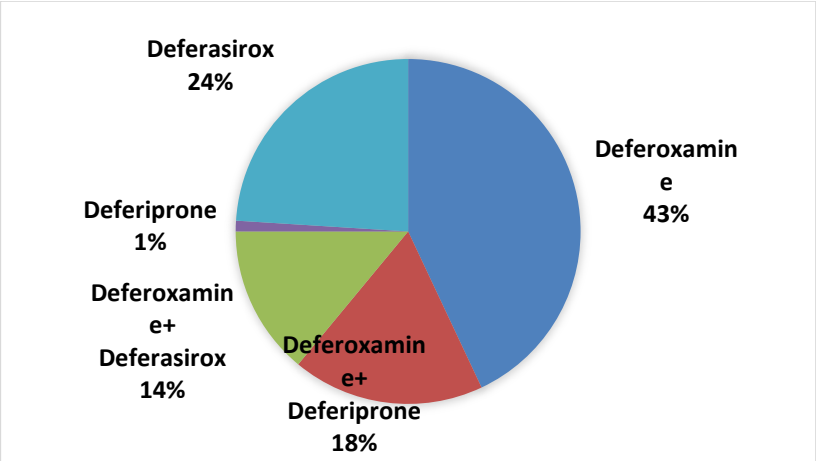


Figure (2): Types of iron chelation therapy.

Table (2): Cardiovascular symptoms with physical and echocardiography findings.

Variable	No. (%)
Shortness of breath	24 (24)
Chest pain	1 (1)
Palpitation	23 (23)
Fatigue	54 (54)
Syncope	0 (0)
Raised JVP	88 (88)
Palpable right parasternal heave	12 (12)
Accentuated P2*	12 (12)
Audible 3rd heart sound	9 (9)
Splenomegaly**	39 (39)
Hepatomegaly	24 (24)
Ejection fraction mean± SD (63.2±8.3 %)	
≥55%	91 (91)
<55%	9 (9)
Diastolic function	
Normal	67 (67)
Impaired	33 (33)
Mean pulmonary artery pressure	
Normal	69 (69)
Mild PHT	18 (18)
Moderate PHT	11 (11)
Severe PHT	2 (2)

*P2:pulmonary component of 2nd heart sound **54 (54%) patients had splenectomy

Table (3): Vital signs and laboratory findings.

Variable	Mean	SD
Heart rate (beat/min.)	86.1	11.8
Blood pressure (mmHg)	119.6/75.4	12.2/7.4
Respiratory rate (breath/min.)	15.8	1.7
SpO_2 (%)	96.1	1
Hb (g/dl)	9.2	1.2
WBC ($x10^9$/L)	15.0	10.8
Platelets ($x10^9$/L)	444.1	237.1
Serum ferritin (ng/ml)	3821.5	2920.7
TSB (mg/dl)	2.6	1.6
AST (IU/L)	85.7	43.5
ALT (IU/L)	62.6	58.6
ALP (IU/L)	205.6	138.0

The mean (± SD) of hemoglobin (Hb) was 9.2±1.2, white blood cell (WBC) 15.0±10.8, platelets count 444.1±237.1, serum ferritin was 3821.5±2920.7. Mean total serum bilirubin (TSB) was 2.6±1.6, aspartate aminotransferase (AST) 85.7±43.5, alanine aminotransferase (ALT) 62.6±58.6, and serum alkaline phosphatase (ALP) was 205.6±138.0. All these findings were shown in Table(3).All the studied patients had negative hepatitis B surface antigen (HBsAg) while 49% had positive hepatitis C virus (HCV) antibody. Regarding the echocardiographic findings; the mean (± SD) ejection fraction (EF) was 63.2±8.3%; only 9% had EF of less than 55%. There was diastolic dysfunction among 33% of patients. The mean pulmonary artery was normal in 69% of them, while PHT was observed among 31% of patients; it was mild for 18%, moderate in 11% and it was severe in only 2% of patients, these findings shown in Table(2) and Figure(3).

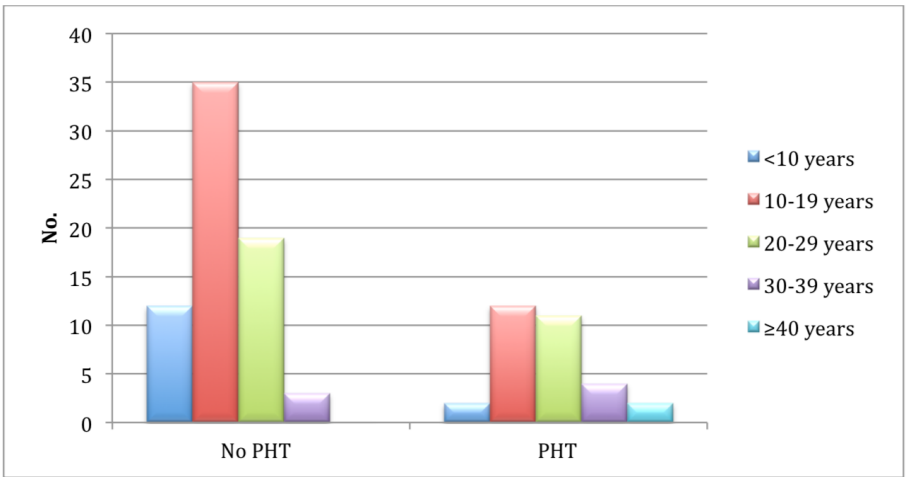


Figure (3): Age distribution according to prevalence of pulmonary hypertension.

PHT was significantly correlated with increasing age of patients, and BMI (p=0.04, p=0.01 respectively), but there was no significant difference regarding gender Table (4).Regarding therapeutic modalities there was a significant association between PHT and splenectomy (p=0.01), improper iron chelation (p=0.03), and type of chelation therapy (p=0.05); there was more PHT among patients whom used Desferoxamine alone, but there was no significant relation with adequate blood transfusion Table(4).

Table (4): Correlation of pulmonary hypertension with baseline patients' characteristics.

Variable	No PHT (No.)	PHT (No.)	Total	P value
Age mean± SD (18.5±8 years)				0.04
Gender				0.07
Male	31	20	51	
Female	38	11	49	
BMI				0.01
Normal	46	29	75	
Over weight	8	0	8	
Obese	15	2	17	
History of blood transfusion				0.05
Well transfused	68	31	99	
not well transfused	1	0	1	
Iron chelating therapy				0.03
Well chelated	54	18	72	
Not well chelated	15	13	28	
Type of chelation therapy				0.05
History of splenectomy	31	23	54	0.04
Duration of splenectomy				0.4
<10 years	14	8	22	
≥10 years	17	15	32	
History of chronic cardiac diseases (Dilated cardiomyopathy or HF)				<0.001
Yes	0	20	20	
No	69	11	80	

Concerning correlation of PHT with patients signs and symptoms; there was a highly significant association between each of shortness of breath, fatigue and palpitation with PHT (p<0.001), but conversely there was no significant correlation with chest pain, also there was a highly significant association of PHT with each of elevated JVP, palpable right parasternal heave, accentuated P2, and audible 3rd heart sound (p<0.001) Table (5). There was a significant association between splenomegaly and patients with no PHT (p=0.007), however, mean size of splenomegaly was increased significantly among patients with PHT (p=0.004). There

was a highly significant association between hepatomegaly and PHT (p<0.001), size of hepatomegaly was significantly increased among patients with PHT (<0.001), as shown in Table(5).

Means of heart rate, blood pressure and respiratory rate were significantly higher among patients with PHT while SpO2 mean was significantly lower among patients with PHT (p<0.001).

No significant association were observed between PHT and patients laboratory findings such as Hb%, WBC, platelets, serum ferritin, TSB and ALP, while means of AST and ALT were significantly higher among patients with PHT, Table (6).

Table (5): Distribution of symptoms, physical and Echo findings according to prevalence of pulmonary hypertension.

Variable	No PHT (No.)	PHT (No.)	Total	P value
Shortness of breath	2	22	24	<0.001
Chest pain	0	1	1	0.1
Palpitation	7	16	23	<0.001
Fatigue	29	25	54	<0.001
Raised JVP	0	12	12	<0.001
Palpable right parasternal heave	0	12	12	<0.001
Accentuated P2	0	12	12	<0.001
Audible 3rd heart sound	0	9	9	<0.001
Splenomegaly	33	6	39	0.007
Hepatomegaly	7	17	24	<0.001
Ejection fraction %				<0.001
≥55%	69	22	91	
<55%	0	9	9	
Diastolic function				<0.001
Normal	60	7	67	
Impaired	9	24	33	

Table(6): Distribution of vital signs and investigation findings according to prevalence of pulmonary hypertension.

Variable	No PHT	PHT	P value
	Mean ±SD	Mean ±SD	
Heart rate	84.5±12.8	89.5±8.1	0.04
Blood pressure	118.2/74±12/7.7	122.5/78.4±11/5	0.005
Respiratory rate	15.3±1.8	16.6±1.8	0.01
SpO2	96.3±0.8	95.4±1.1	<0.001
Hb	9.2±1.2	8.9±1.1	0.3
WBC ($x10^9$)	14.7±11.2	15.5±9.9	0.7
Platelets ($x10^9$)	434.8±240.7	264.8±231.1	0.5
Serum ferritin	3440.1±2583.5	4645.7±3445.4	0.06
TSB	2.4±1.1	3±2.3	0.1
AST	50.3±41.3	77.4±42.8	0.003
ALT	51.9±46.3	86.4±75	0.006
ALP	197±41.3	224.7±130.6	0.3

There was also a significant association between PHT with each one of "lower mean EF" (p<0.001) (29% of patients with PHT had low EF), and impaired diastolic function as well (p<0.001), Table (5). The severity of PHT was significantly associated with increased age of patients (p=0.007), and with lower BMI of patients (p<0.001). Similarly, increased size of both splenomegaly and hepatomegaly were significantly associated with increased severity of PHT. Means of heart rate, blood pressure and respiratory rate were significantly higher among patients with moderate PHT while SpO2 mean was lower significantly among patients with moderate PHT (p<0.001). Increased means of (TSB, AST and ALT) were correlated significantly with increased severity of PHT (p<0.001).

We found also that lower mean ejection fraction was significantly associated with increased severity of PHT (p<0.001), all these findings were shown in Table (7).

Table (7): Distribution of patients' characteristics means according to severity of pulmonary hypertension.

Variable	Mild	Moderate	Severe	P value
	Mean ±SD	Mean ±SD	Mean ±SD	
Age	16.7±7.1	21.8±10.4	23.9±5.3	0.007
BMI	21.1±1.9	19.5±1.6	18.3±0.6	<0.001
Splenomegaly	3.9±2.2	3.5±0.5	20±1.5	<0.001
Hepatomegaly	14±2.6	17.2±1.2	18.5±1.7	0.001
Heart rate	84.5±12.8	85.6±6.8	94.4±7.3	0.03
Blood pressure	118/74±12/7	124/78±12/5	125/79±12/5	0.04
Respiratory rate	15.3±1.8	15.8±1.5	17.5±1.3	<0.001
SpO_2	96.3±0.8	96.1±0.9	94.4±0.6	<0.001
TSB	2.4±1.1	1.9±0.8	4.5±2.9	<0.001
AST	50.3±41.3	55±27.7	105.9±44.7	<0.001
ALT	51.8±46.3	60.1±30.4	125.7±110.9	0.001
Ejection fraction	65.7±5.2	59.2±9	54.2±13.4	<0.001

Discussion

Many authors studied the prevalence of PHT among BTM patients and found that it is ranging between 10-79% [14,15]. The current study showed that prevalence of pulmonary hypertension among ß-thalassemia major patients was 31%. Our finding is higher than previously recorded data on prevalence of PHT among thalassemia intermedia in Northern Iraq (20.4%) and higher than prevalence of PHT among homozygous ß-thalassemia patients in Mosul city as (3.7%)[16,17]. However our study prevalence is lower than results of Elbedewy et al. in Egypt and Azami et al. study in Iran (40%, 47.2% respectively)[18,19].

In Saudi Arabia, Alama et al. study showed that 12.4% of BTM patients had tricuspid regurgitation with PHT.20 Dedeoglu et al. study in Turkey measured the PHT prevalence by tricuspid regurgitation jet velocity (TRV) and found that TRV more than 2.9 mls in 36% of patients with BTM.21 A previous Chinese study showed that 84.8% of patients with BTM had PHT that was detected by Doppler Echocardiography, whereas a previous Italian study found that only 10% of BTM patients had PHT.22,23 The discrepancies in PHT prevalence is attributed to variation in diagnostic techniques used to measure the pulmonary arterial pressure, differences in sample size and differences in characteristics if studied population[23].

Current study showed a significant association between increased age of BTM patients and PHT (p=0.04), our finding was similar to De Castro et al. results in USA which found that mean age of BTM patients with PHT was 43.3 years that is significantly higher than age of patients without PHT of 34.4 years.24 Borgna-Pignatti study in Italy documented that increased age of patients

with thalassemia major is always associated with increased rate of life threatening complications specifically cardiac disorders.25 Additionally, Berra et al. study in Switzerland reported that PHT tends to be more prevalent and severe among older age population than younger age population[26].

We found as well a significant association between the patients' BMI and PHT, this finding is consistent with results of Vlychou et al. study in Greece which documented that increased BMI of thalassemic patients represent a significant risk factor for cardiac diseases[27]. The main significant symptoms in present study were shortness of breath, fatigue and palpitation. These findings are similar to results of Fraidenburg et al. study in USA[3].

Our study showed that history of splenectomy was significantly related to PHT (p=0.01). This finding coincides with results of Fekri et al.28 study in Iran which found that the splenectomy increased the risk of higher pulmonary artery pressure among BTM patients leading to higher risk of PHT, Phrommintikul study in Taiwan revealed that splenectomy was an independent risk factor for pulmonary hypertension among patients with BTM[29].

In the current study, there was a significant association between unwell chelated BTM patients and PHT, especially Desferrioxamine intake. This is similar to results of Aessopos et al. study in Greece. Saliba et al. in Lebanon stated that Desferrioxamine had higher rates of low compliance by thalassemic patients that lead to iron overload[30,31]. The present study found that elevated JVP, positive right parasternal heave, positive accentuation of pulmonary component of 2nd heart sound were significantly associated with PHT ($p<0.001$), the similar to findings were concluded by Tam et al. study in USA[32].

The size of splenomegaly and hepatomegaly were significantly increased with PHT, the same finding was detected by Fathi et al. in Iran which stated that PHT in thalassemic patients increased the severity of thalassemia complications[33]. Our study found that low EF (heart failure) was significantly related to PHT ($p<0.001$) which was agreed with Alpendurada et al. findings in UK whom concluded that iron overload in BTM patients leads to PH then right ventricular dysfunction and consequently heart failure,34 also we found that impaired diastolic function was significantly associated with PHT ($p<0.001$). The same results were seen in another study in Iraq that was done by Abbas [35].

The severity of PHT in current study is significantly related to increased age, low BMI, increased size of both splenomegaly and hepatomegaly, and increased TSB, AST and ALT means. These findings are consistent with other literatures[30,3].

Conclusions

The prevalence of pulmonary hypertension among patients with BTM is within normal range. The common symptoms were shortness of breath, fatigue and palpitation. The common risk factors for development of PHT among BTM patients were older age,

obesity, history of splenectomy and failure of chelation therapy. The factors related to severity of PHT were increasing age, low BMI and increasing size of splenomegaly and hepatomegaly.

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