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Haemosiderosis, Liver and Renal Diseases among Thalassemia Patients in Sana'a City – Yemen

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Abstract:

Background: Thalassemia is a huge health problem that threatens the life of different population groups in the world particularly in developing countries, where the resources are limited. The management of thalassemia in Yemen is challenging due to insufficient treatments available. **Aims:** The objectives of the present study aimed to identify the haemosiderosis, liver, and renal diseases among thalassemia patients attending regularly to the Yemen Society for Thalassemia and Genetic Blood Disorders (YSTH) in Sana'a city, Yemen. **Methods:** This is a retrospective study conducted among data of 65 thalassemia patients aged between 2-43 years old attending YSTH during 2020. Data on haematological (blood transfusion), and biochemical [serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), total bilirubin, direct bilirubin, urea, and ferritin levels] were gathered from medical files of patients with thalassemia in YSTH. Also, demographic data such as age and gender were obtained. Data were analyzed by using the SPSS program version. **Result:** A total of 65 patients with thalassemia were included in this study (40; 61.54% males and 25; 38.46% females). About 29 patients (44.61%) suffered from severe anemia and required regular blood transfusions. The age group of 2-5 years had the highest rate of thalassemia prevalence (64.62%). The direct bilirubin and total bilirubin levels were 78.5% and 61% increased among participating subjects. Similar, serum SGOT and ferritin levels were 50.8% and 89.2%, respectively, recorded among thalassemia patients. In addition, a significant correlation between age groups and concentration levels of total bilirubin, SGOT, and SGPT ($P<0.05$). Also, a significant correlation between serum ferritin levels and SGPT and SGOT ($P<0.05$). **Conclusion:** The high levels of serum ferritin found in this study among thalassemia patients give an overall bleak view. Therefore, it is an urgent need for follow-up protocols for the management of thalassemia with importance on blood transfusion and iron chelation practices.

Keywords: Haemosiderosis; Liver function; Serum Ferritin; Thalassemia; Sana'a city, Yemen.

Article Info:

Received: 25 Sept 2022; **Revised:** 30 Sept 2022; **Accepted:** 7 Oct 2022; **Available online:** 8 Sept 2022

Cite this article:-

Banafa MA, Al-Awar MS, Edrees WH, Alyafrosi OA. Haemosiderosis, Liver and Renal Diseases among Thalassemia Patients in Sana'a City – Yemen. Al-Razi Univ J Med Sci. 2022; 6(2):1-10.

DOI: <https://doi.org/10.51610/rujms6.2.2022.142>

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Introduction

Thalassemia is globally the commonest single-gene disorder among humans. It is defined as a heterogeneous group of inherited disorders that impair the rate of the synthesis of hemoglobin resulting from a reduced rate of production of one or more of the globin chains of hemoglobin¹. Thalassemia disease leads to various complications including growth retardation, hypothyroidism, endocrine dysfunction, progressive liver failure, and abnormal kidney function².

Thalassemia is treated by regular blood transfusion and iron chelation therapy. Blood transfusion is used to reduce anemia complications, while chelation decreases iron overload due to multiple blood transfusions. Yet, it remains a huge health problem, particularly in low-resource countries, where the rate of thalassemia is the highest due to limited diagnostic and treatment facilities³.

Multiple blood transfusions can lead to iron overload and accumulate in the tissues like the liver and myocardium. The common complication of iron overload results in serious damage to various organs such as the heart, liver, and various other endocrine glands⁴.

Globally, about 5% of the population has a variation in the alpha or beta part of thalassemia. Approximately 1.5% of these cases (80–90 million people) are β -thalassemia carriers⁵. In addition, it was estimated that more than 50,000 individuals are globally born with a severe form of thalassemia each year. About 80% of these cases are distributed among people living in developing countries². This type of disease resulted in 16,800 deaths in 2015 down from 36,000 deaths in 1990⁶.

The previous reports documented that the frequency of β -thalassemia patients in India ranged between 65,000-67,000 cases and about 30 million (3.3%), carriers of β -thalassemia^{7,8}. Also, it was estimated that approximately 5000-9000 children are annually born in Pakistan with β thalassemia and between 5-7% of individuals are a carrier⁹. Similarly, the prevalence of thalassemia carriers was around 4% in Palestine¹⁰. In Yemen, about 700 new cases of thalassemia disease are diagnosed yearly, and 50,000 cases are on record so far according to the Yemen Society for Thalassemia and Genetic Blood Disorders (YSTH). In Yemen, a country ravaged by war since 2015 and so far, the treatment of thalassemia is a rare but much-needed miracle. This is why the support provided is

essential. With regular blood transfusions needed by these patients, safe blood saves lives and improves health².

Every day, the YSTH receives between 60–70 patients suffering from thalassemia and anemia. Once a case is examined, the patient is referred to the blood transfusion center to receive a blood transfusion².

There is a paucity of data on the haematological and biochemical among thalassemia patients in Sana'a capital of Yemen. Hence, the objectives of the present study aimed to identify the haemosiderosis, liver, and renal diseases among thalassemia patients attending YSTH in Sana'a city, Yemen. The finding of this study could be provided us with local statistics, used to modify the management protocols for thalassemia patients, and this will open a window for further research.

Materials and Methods

Study setting

This study was performed among thalassemia patients attending the Yemen Society for Thalassemia and Genetic Blood Disorders (YSTH) situated in Sana'a city, Yemen. YSTH is a non-profit humanitarian society that was founded on 15th April 2000 and its referral society receives all patients diagnosed with Thalassemia from all hospitals in Yemen. Also, it provides a unique charitable model in the treatment and care of thalassemia patients and prevents their health from deterioration and complications through awareness and early examination in partnership with the relevant authorities.

Study design and period

This is retrospective study was carried out at the laboratory department belonging to YSTH which situated in Sana'a city, Yemen. The current study used the recorded data to identify the haemosiderosis, liver, and renal diseases among thalassemia patients attending YSTH for one year, 2020.

Population study and sampling size

A total of 65 children and adolescents aged between 5-18 years old who were diagnosed with thalassemia disease and followed up at the YSTH during 2020 were enrolled in this study.

Inclusion and exclusion criteria

All thalassemia patients of children and adolescents aged between 2-43 years admitted and followed up at the YSTH during the study period were included in the study. The exclusion criteria were data patients with incorrect or not in routine follow-up or data that missing or not desirable information or death cases.

Data collection

Data on demographic (age and gender), haematological (gate of blood transfusion), and biochemical tests such as liver function test [Serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), total bilirubin, direct bilirubin], urea, and ferritin were collected from recorded data of laboratory department of thalassemia patients in YSTH.

Ethical considerations

Approval was obtained prior to carrying out this study from the ethical committee of the college of medical sciences of Al-Razi University. A cover letter was sent to the principle of the Yemen Society for Thalassemia and Genetic Blood Disorders to obtain approval to conduct this study. All procedures were in accordance with the ethical standards of the institutional and with the 1964 **Helsinki Declaration** and its later amendments or comparable ethical standards. The purpose and benefits of the study were explained to the participants. Parental consent and the child's assent were obtained upon agreeing to participate. All participants also have the right to refuse to participate or to withdraw from the study without any effect on their follow-up treatment.

Statistical analysis

Data coded, entered, and analyzed through SPSS version 21.0. A correlation was done to measure the relationship between factors and the outcome through Point-biserial correlation, Pearson's correlation, Spearman's Correlation, and Eta correlation as appropriate. Two-tailed, *P*-value <0.05 was considered statistically significant.

Results

Demographic characterizations

In this study, the thalassemia patient data of 40 males and 25 females (61.54% and 38.46% respectively) was collected from YSTH. It was found that half of the males (50%) and 9 females (36%) suffered from severe anemia and required regular blood transfusion (29 patients represent 44.61%), 4 males (10%) and 3 females (12%) don't require blood transfusion (totally 7 patients 10.77%), while in 40% of males (16) and 52% of females (13) the blood transfusion was as necessary (Table 1).

In this study, the age ranged from 2-43 years and were divided into three categories: first, 2-5 years, 26 males (65%) and 16 females (64%) (42 males and females 64.62%), second, 6-10 years, 10 males (25%) and 5 females (20%) totally 15 patients (23%), and third category, from 11 years and more, 8 patients (12.31%) [4 males (10%) and 4 females (16%)] (Table1).

Table 1. Demographic characterizations of thalassemia participants

Variable	Categories	Male	Female	Total No. (%)
		Frequency No. (%)	Frequency No. (%)	
Blood transfusion	Yes	20 (50)	9 (36)	29 (44.61)
	No	4 (10)	3 (12)	7 (10.77)
	As necessary	16 (40)	13 (52)	29 (44.61)
Total		40 (61.54)	25 (38.46)	65 (100)
Age (Years)	2-5	26 (65)	16 (64)	42 (64.62)
	6-10	10 (25)	5 (20)	15 (23.08)
	≥ 11	4 (10)	4 (16)	8 (12.31)
Total		40 (61.54)	25 (38.46)	65 (100)

Assessment of some biochemical tests among thalassemia patients

The present finding showed that 78.5% and 61% of cases had an increased level of direct bilirubin and total bilirubin, respectively. Also, the abnormal result of SGOT, SGPT, urea, and ferritin were significantly distributed among 33 (50.8%), 21 (32.3%), 8 (12.3%) and 58 (89.2%) patients, respectively (Table 2).

Table 2. Assessment of some biochemical tests among thalassemia patients

Parameters	Normality	Frequency	Rate (%)
Direct bilirubin	Normal	14	21.5
	Abnormal	51	78.5
Total bilirubin	Normal	25	38.5
	Abnormal	40	61.5
SGOT	Normal	32	49.2
	Abnormal	33	50.8
SGPT	Normal	44	67.7
	Abnormal	21	32.3
Urea	Normal	57	87.7
	Abnormal	8	12.3
Ferritin	Normal	7	10.8
	Abnormal	58	89.2

Biochemical assessment of patients according to gender

Table 3 shows that there was a non-statistically significant relationships between the gender and parameters study including direct bilirubin, total bilirubin, SGOT, SGPT, urea, and ferritin among thalassemia patients. The high rate of bilirubin, total bilirubin, SGOT, SGPT, and ferritin levels were 31(60.8%), 23(57.5%), 18(54.5), 12(57.1), and 36(62.1%), respectively, among males. Similar, the

high rate of direct bilirubin, total bilirubin, SGOT, SGPT, and urea levels in females were 20(39.2%), 17(42.5%), 15(45.5%), 9(42.9%), and 5(62.5%), respectively.

Biochemical assessment of patients according to blood transfusion

The current findings showed that there were non-statistically significant ($P > 0.05$) differences between blood transfusion and parameters study including direct bilirubin, total bilirubin, SGOT, SGPT, urea, and ferritin among participating patients listed in Table (4).

Biochemical assessment of patients according to age

The present results revealed that were statistical significant differences between the age of patients and concentration levels of total bilirubin, SGOT, and SGPT in serum ($P < 0.05$). In contrast, there were non-statistical significant differences between the age of patients and some biochemical tests including direct bilirubin, urea, and ferritin ($P > 0.05$) as summarized in Table (5).

Biochemical assessment of patients with serum ferritin levels

Table 6 shows that there were statistical significant differences between levels of ferritin concentration in serum and concentration levels of total bilirubin, SGOT, and SGPT in serum of thalassemia patients ($P < 0.05$), whereas there non-statistically significant were found between concentration levels of direct bilirubin and urea with ferritin level among thalassemia patients ($P > 0.05$).

Table 3. Biochemical assessment of patients according to gender

Parameters	Categories	Gender		Chai square	Phi	P value
		Male (%)	Female (%)			
Direct bilirubin	Normal	9(64.3)	5(35.7)	0.057	0.030	0.534
	Abnormal	31(60.8)	20(39.2)			
Total bilirubin	Normal	17(68)	8(32)	0.717	105.0	0.281
	Abnormal	23(57.5)	17(42.5)			
SGOT	Normal	22(68.7)	10(31.3)	1.385	0.146	0.178
	Abnormal	18(54.5)	15(45.5)			
SGPT	Normal	28(63.6)	16(36.4)	0.062	0.062	0.615
	Abnormal	12(57.1)	9(42.9)			
Urea	Normal	37(64.9)	20(35.1)	2.227	0.185	0.135
	Abnormal	3(37.5)	5(62.5)			
Ferritin	Normal	4(57.1)	3(42.9)	2.031	0.132	0.124
	Abnormal	36(62.1)	22(37.9)			

$P < 0.05$ is statistically significant

Table 4. Biochemical assessment of patients according to blood transfusion

Parameters	Categories	Blood transfusion			Chai square	Phi	P value
		Yes (%)	No (%)	As necessary (%)			
Direct bilirubin	Normal	7(50)	3(21.4)	4(29.6)	3.028 ^a	0.216	0.220
	Abnormal	22(43.1)	4(7.8)	25(49.1)			
Total bilirubin	Normal	11(44)	5(20)	9(36)	3.894 ^a	0.245	0.143
	Abnormal	18(45)	2(5)	20(50)			
SGOT	Normal	15(46.9)	5(15.6)	12(37.5)	2.167 ^a	0.183	0.338
	Abnormal	14(42.4)	2(6.1)	17(51.5)			
SGPT	Normal	18(40.9)	6(13.6)	20(45.5)	1.480 ^a	0.151	0.477
	Abnormal	11(52.4)	1(4.8)	9(42.8)			
Urea	Normal	23(40.4)	7(12.3)	27(47.3)	3.657 ^a	0.237	0.161
	Abnormal	6(75)	0(0)	2(25)			
Ferritin	Normal	3(42.8)	2(28.6)	2(28.6)	2.767 ^a	0.206	0.251
	Abnormal	26(44.8)	5(8.6)	27(46.6)			

P<0.05 is statistically significant

Table 5. Biochemical assessment of patients according to age

Parameters	Categories	Age (in years)			Chai square	Phi	P value
		2-5	6-10	≥ 11			
Direct bilirubin	Normal	9(64.3)	4(28.6)	1(7.1)	0.504 ^a	0.088	0.777
	Abnormal	32(62.8)	12(23.5)	7(13.7)			
Total bilirubin	Normal	19(76)	6(24)	0(0)	6.082 ^a	0.306	0.048
	Abnormal	22(55)	10(25)	8(20)			
SGOT	Normal	24(75)	4(12.5)	4(12.5)	5.181 ^a	0.282	0.075
	Abnormal	17(51.5)	12(36.4)	4(12.1)			
SGPT	Normal	35(79.5)	4(9.1)	5(11.4)	19.289 ^a	0.545	0.000
	Abnormal	6(28.6)	12(57.1)	3(14.3)			
Urea	Normal	35(61.4)	14(24.6)	8(14)	1.329 ^a	0.143	0.515
	Abnormal	6(75)	2(25)	0(0)			
Ferritin	Normal	6(85.7)	1(14.3)	0(0)	1.943 ^a	0.173	0.379
	Abnormal	35(60.3)	15(25.9)	8(13.8)			

P<0.05 is statistically significant

Table 6. Biochemical assessment of patients with serum ferritin levels

Parameters	Categories	Ferritin		Chai square	Phi	P value
		Yes No.(%)	No No.(%)			
Direct bilirubin	Normal	2 (14.3)	5 (9.8)	0.230 ^a	0.059	0.632
	Abnormal	12 (85.7)	46 (88.2)			
Total bilirubin	Normal	6 (24)	1 (2.5)	7.401 ^a	0.337	0.007
	Abnormal	19 (76)	39 (97.5)			
SGOT	Normal	7 (21.9)	0 (0)	8.090 ^a	0.353	0.004
	Abnormal	25 (78.1)	33 (100)			
SGPT	Normal	6 (13.6)	1 (4.8)	7.165 ^a	0.134	0.002
	Abnormal	38 (86.4)	20 (95.2)			
Urea	Normal	35 (85.4)	14 (87.5)	1.329 ^a	0.143	0.515
	Abnormal	6 (14.6)	2 (12.5)			

P<0.05 is statistically significant

Discussion

Thalassemia is a genetic disorder resulting from mutations on chromosome number 11 (α -thalassemia) or on chromosome number 16 (β -

thalassemia)^{11,12}. These mutations of an autosomal recessive gene result in the absence or decrease the production of one or two types globin chain^{12,13}. Abnormal or absent of globin chains cause abnormal production of hemoglobin which leads to

excessive destruction of red blood cells^{14,15}. Excessive destruction of RBC leads to high production of bilirubin more than liver capacity to metabolize or excrete¹⁶. In thalassemia patients, liver damage is increased when the age of the patients increase, due to increasing age with advancement of disease progression, repeated blood transfusion, less use/intolerance of iron chelating agent, decreased activity of hepatocyte to rescue them in such excess bilirubin and iron flood¹⁷.

In the current study, it was found that a higher rate of participating patients were males (61.54%) when compared to females (38.46%). Similar previous results were documented that the majority of the thalassemia patients were found to be male^{18,19,20}. In contrast, some studies revealed that the prevalence of a female of thalassemia disorder was higher than for male^{11,21,22}.

The present finding is that regular blood transfusion therapy among 44.61% of thalassemia patients which indicates that they are suffering from thalassemia major. Thalassemia patients with a hemoglobin level less than 7 g/dL suffer from chronic anemia and require regular transfusions^{23,24}. Patients with thalassemia intermedia (44.61%) need blood transfusions as necessary, such as when they have an illness or an infection^{22,25}. On the other hand, thalassemia patients with thalassemia minor (10.77%) usually do not need blood transfusions because they either have mild anemia or do not have anemia^{25,26}.

In the present study, the highest rate of thalassemia patients was among the age group of 2-5 years old (64.62%). Recently, an update of thalassemia data noticed that the total number of patients with thalassemia major decreased as age increased²⁷. Thalassemia major is usually discovered in an infant and children younger than five years of age with mild jaundice, hepatosplenomegaly, and severe microcytic anemia²⁷.

In the current study, the serum level of direct bilirubin and total bilirubin was 78.5% and 61% reported among participating subjects. The damage of the liver cells leads to leakage of the enzymes into the circulation causing raises in the liver enzymes such as direct and total bilirubin, SGOT, and SGPT in the blood^{16,29}.

The high level of SDB and STB, hyperbilirubinemia, can be attributed to the failure of the liver to

metabolize the high bilirubin production due to the destruction of RBC in thalassemia patients^{15,16,29,30}. The concentration of SGOT and GPT levels were 50.8% and 32.3%, respectively, recorded among thalassemia patients in this study. This result is thus concurrent with the results of other previous studies^{29,30,31,32}. The increased SGOT and SGPT enzymes in thalassemia patients are due to liver cirrhosis and hypertrophy^{32,33}.

Renal involvement in thalassemia patients is a terminal event, this explains the decrease in urea level in a few cases (12.3%) in the present study. Low urea concentration in the blood of thalassemia patients could be attributed either to the late stage of the disease or to the therapeutic effect of hydroxy urea or both^{34,35}.

In the current study, it was observed that the serum ferritin level increased in the majority of thalassemia patients (89.2%). Regular blood transfusion and suboptimal use of desferrioxamine are reasons for high serum ferritin leading to the loads body with excess iron. Also, thalassemia induces the gastrointestinal tract to increase absorption of dietary iron^{36,37}. Ultimately, high serum ferritin results in hemosiderosis and its complications, including multiple endocrinopathies which impaired growth and puberty^{37,38}.

Our results showed a non-significant relationship between the parameters studied (direct and total bilirubin, SGOT, SGPT, urea, and ferritin) among thalassemia patients according to gender. This result is consistency with the previous reports^{31,39}. Similarly, it was reported there serum bilirubin was significantly higher in males than females and in patients aged >10 years. Gender is the other factors that significantly influence serum bilirubin level in sickle cell anemia⁴⁰.

The liver is the earliest site of iron deposition in regularly transfused thalassemia patients and a common cause of morbidity⁴¹. Glomerular and tubular dysfunctions in β -thalassemia major (β -TM) patients (pts) have been attributed to iron overload⁴².

Our results showed a non-significant relationship between the parameters studied like direct bilirubin, total bilirubin, SGOT, SGPT, urea, and ferritin among thalassemia patients according to blood transfusion. This finding is in agreement with agree earliest reports conducted among thalassemia patients in different countries^{43,44}. In contrast, few

studies showed that serum levels of ferritin was significantly correlated with an increased number of blood transfusions^{45,46}. A study by Al-Moshary *et al.*³⁰ found elevated levels of AST, ALP, and serum bilirubin because of the hepatic damage caused by the iron overburden in thalassemia patients accepting a different blood transfusion.

The results of the present work found a significant correlation between the age of patients and concentration levels of total bilirubin, SGOT, and SGPT in serum ($P < 0.05$). Similar findings revealed that there was a significant correlation between age and some biochemical tests among thalassemia patient^{47,48}. Cystatin C and serum $\beta 2$ microglobulin show a strong correlation with creatinine clearance and age, while NAG positively correlates with proteinuria⁴⁹. Also, it has been indicated that renal dysfunction in thalassemia increases with age and duration of blood transfusions⁵⁰.

Within the upcoming years, around 60% of the thalassemia patients had abnormal urine protein to creatinine ratio (UPCR) of ≥ 200 mg/g, and 14% developed proteinuria with UPCR > 500 mg/g⁵¹. It seems that these markers may independently correlate with serum ferritin, transfusion rate, duration of chelation therapy, albumin/creatinine ratio, serum creatinine, LIC, and age, while also negatively correlating with eGFR, creatinine clearance, and hemoglobin^{52,53}.

The spleen is a major constituent of the total body iron load in TM patients and a rapid rise in serum ferritin level has been documented following the splenectomy in patients with hemoglobin H Constant Spring disease and TM patients. After splenectomy, the total body iron storage capacity decreased, whereas serum ferritin ($p = 0.0085$) and iron concentration in other organs appeared to increase despite the reduction in the rate of transfusions ($p = 0.0001$) and maintenance of hemoglobin levels. Normalization of the body iron stores at an early age could maintain the spleen at near normal capacity and avoid other complications (cardiac and hepatic)⁵⁴. An age difference in study groups and its implication for renal dysfunction might play a role in the different results, but the systemic analysis is needed to prove this⁴⁷.

This result showed a significant correlation between SGPT and SGOT levels with serum ferritin. These results are in agreement with Farida *et al.*⁵⁵ found a positive significant correlation between serum

ferritin with SGPT level. A previous study illustrated that ALT/GPT levels were significantly higher in patients with high ferritin levels as compared to those with normal ferritin levels⁵⁶.

The significant correlation between iron levels as indicated by serum ferritin levels and SGOT, and SGPT levels well documented. The mean serum ferritin level was significantly higher in thalassemia patients with elevated ALT or elevated AST compared to those patients with normal levels^{57,58,59}. Thalassemia patients suffer from a high bilirubin amount in the blood because of the increased destruction of the red blood cells. This is the major cause of hyperbilirubinemia resulting in the damage of other hepatic cells⁶⁰. A study by Wahidiyat *et al.*⁶¹ found Bilirubin level has no correlation with iron overload. Mohammad *et al.*²⁹ reported that there a significant increase in activity of AST, ALT, and bilirubin levels was found in patients with thalassemia.

Conclusion

The high levels of high bilirubin and serum ferritin among thalassemia patients in this study are at risk of developing severe anemia and biochemical abnormalities. The poverty, low education level, and inadequate facility of health care resulting from the bad circumstance due to war since 2015 and so far might be the main factors stumbling blocks to effective treatment of iron overload in thalassaemic patients. Therefore, it is an urgent necessity to follow-up protocols for the management of thalassemia with importance on blood transfusion and iron chelation practices. In addition, creating awareness is important about the consequences of iron overload in the patients to monitor the prevent complications. So, further detailed studies are recommended in order to find out the correlation between renal hemosiderosis and early markers of kidney dysfunction among thalassemia patients.

Conflict of interest

No conflict of interest is associated with this work.

Acknowledgment

The authors would like to thank the General Manager of the Yemen Society for Thalassemia and Genetic Blood Disorders and all staff working in it for their generosity help for permission and assistance with data collection.

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