ORIGINAL ARTICLE

Survival rate and mortality causes in patients with β-thalassemia major in Nineveh Governorate, Iraq

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ABSTRACT

Background: B-thalassemia a common hematological disorder in Nineveh Governorate; however, survival status was not formerly assessed.
Aim: To determine the survival rate and causes of death in patients with β- thalassemia major in Nineveh Governorate. Iraq.
Methods: This is a retrospective study involving 718 registered patients with β -thalassemia major in Ibn- Al Atheer center of thalassemia in Mosul city, northern of Iraq, during 17-year period from 1997 to 2014. Each patient was studied from the date of birth to the date of terminal follow-up of this study at 31/12/2014. Documented demographic, clinical and laboratory data were extracted from patients' medical records. Statistical analysis performed using Kaplan-Meier method to analyze survivals.
Results: There were 160(22.3%) deaths among locally registered patients with β -thalassemia major, 130 (81.4%) of them were due to cardiac causes. The median survival time was 16.15 year. Kaplan-Meier survival curves of enrolled patients showed that 5-, 10-, 15-, 20-,25-,30-,35, 40-,45-year survival rate was 98.7%, 95.1%, 81.6%, 61.6% ,49.8% 44.4%, 42.2% .42.1% and 36.9% respectively.
Conclusions: At age of 25 years, 49.8% of local thalassemia patients survived. Heart disease was the most common cause of death among studied patients with β- thalassemia major.
Keywords*:* Thalassemia, survival, mortality, Mosul. Iraq

INTRODUCTION

Thalassemia is regarded among the most important public health challenges worldwide1, 2. β-thalassemia is a common hematological condition in Iraq, with carriers prevalence of 4% and an approximate 15,000 registered thalassemia major/ intermediate patients in Iraq[3], with an average 13 deaths /year of thalassemia patients in Nineveh governorate-Iraq[4]. An evident awareness about epidemiological status of a disease such as survival rate can support policymaker in many viewpoints and it is crucial for the formation of control plans[5].There is a lack of knowledge regarding survival rate of patients with β-thalassemia major in Nineveh governorate. The present study designed to define survival rate of β-thalassemia major patients in our locality along with its mortality causes.

PATIENTS AND METHODS

This retrospective study was performed in 2014 in this retrospective study was performed in 2014 in Nineveh governorate/ Northern of Iraq. The study involved registered patients in Ibn Al Atheer center of thalassemia in Nineveh governorate, which is the only center in the governorate that provide medical management of patients with thalassemia since its establishment in 8/1/1997. Out of 1143 thalassemia patients who had been registered in the governorate till the end of the study at 31/12/2014, 226 patients were excluded as they were absent in the follow up record. Of the remaining 917 patients, 66 patients had been emigrated to other governorate, 112 patients were not on chelator therapy and another 21 patients were also excluded as they underwent bone marrow transplantation, which is considered to be a curative therapy, making only 718 patients appropriate for enrollment in this study. The sample included 280 patients born before 1997, managed in different Mosul hospitals, and registered after that in the thalassemia center to carry on treatment, along with other 459 patients born and registered after 1997. The follow-up of each patient was evaluated from the year of birth to the year of death or year of terminal follow up for the survivors.

Patients were studied by means of analysis of documented data in Ibn Al Atheer Thalassemia Center aiming to assess survival in relation to available documented variables including: age, date of birth, date of death (all were recorded in years), sex, cause of death, type of iron chelation therapy, time of appearance of complications related to patient's cause of death. With the exception of a period prior to 1997 when patient's management data were not documented, all 718 selected patients were treated afterward by regular blood transfusion in order to maintain hemoglobin level above 10 g/dl. Deferoxamine injection was used for patient at 3 years of age in a dose of 30-40mg/kg as a nightly 6-8 hours subcutaneous infusion via a pump. Since 2/11/2012 upon availability of Deferasirox (Exjade, Novartis) an oral chelator drug, 112 patients on Deferoxamine therapy who had no complications and their serum ferritin was ≤ 2000 ng/ml were switched to Deferasirox. Deferasirox was given 2 mg/kg initially, rising dose within 4 weeks to 30 mg /kg if patient maintain normal hematological, hepatic and renal laboratory indices. In addition to that Deferasirox was used for all 41 newly registered patients at 2 year of age or earlier if serum ferritin was >2000ng/ml, those patients named Deferasirox group. No patient was treated with combination therapy. As Deferasirox was used in the last 2

years of study, no comparison was conducted among those different treatment groups regarding mortality cause and survival rate. One patient had

congenital heart disease. No other patients had documented hepatic endocrine, renal or neurological complications at start of chelation therapy after 1997. A staff physician examined all patients at approximately one-month interval. Monthly hemoglobin level, bimonthly serum ferritin (available since 2010) while six monthly calcium, thyroid stimulating hormone, parathyroid hormone, and echocardiography were analyzed and at shorter period if abnormalities ensued. Results were kept in case sheets along with the electronic data records. All patients were investigated for Hepatitis B and Hepatitis C; hepatologist opinion was requested for any seropositive patients. Complicated cases were checked by diverse subspecialties for management. Mean yearly serum ferritin levels were computed for a subgroup of patients who survive after 2010. Patients underwent splenectomy after 5 years of age if the volume of blood transfused exceeded 250 ml/kg/year, they were fully immunized preoperatively against encapsulated bacteria, postsplectomty they were on long-term penicillin prophylaxis with proper instructions about fever management. Local research authority approved this study .Survival probabilities were estimated by the Kaplan-Meier method; independent sample T test was used to test the differences between means. A p-value of equal or less than 0.05 was defined as statistically significant. Data analysis was executed using version 17 SPSS program.

RESULTS

A total of 718 patients with B thalassemia major on chelator therapy were studied, 374 (52.1%) of whom were male and 349(47.9%) were female; The median age at death was 15 years, maximum age at death was 46 years in females and 36 years in males. Table 1 showed that 160(22.3%) of patients died. Approximately one third (32%) of patients of age group 11-20 years and 27.1% of 21-30 years age group patients fail to survive, which was significantly different from other age groups (*p=0.000*). Splenectomy did not significantly affect death rate. Kaplan-Meier survival curves showed that 5-, 10-, 15-, 20-, 25-,30-,35, 40-,45-year survival rate was 98.7%, 95.1%, 81.6%, 61.6%, 49.8% 44.4%, 42.2% .42.1% and 36.9% respectively (Figure1). No statistical difference in the survival time was observed between the genders (Figure 2), though the median survival time of female with beta thalassemia patients was longer than that of males (median survival in female 29 years versus 24 years in male). Table 2 displayed that cardiac cause was the predominant cause of death, ensued in 130(81.3%) of 160 cases. Heart failure was the cause in 122/130 (93.8%) of cases which was secondary to cardiomyopathy (based on echocardiographic diagnosis), in all of cases apart from one patient with complex congenital heart disease, the remaining eight patients died due to arrhythmias. Nine (5.6%) out of 160 patients died due to accidents caused by car accidents in four of them, car explosion in two patients, fall from height in other two patients and by burn in another patient at 2 years of age. Acute renal failure secondary to dehydration owing to gastroenteritis was responsible for death of 6(3.8%) of patients. Diabetes mellitus with its fluid and electrolytes complications terminated another 3.8% of patients. One case of meningitis and 2 cases of central nervous system stroke resulted in death of 1.9% of cases, similar percentage of death caused by liver failure secondary to liver cirrhosis proven by biopsy, no one of them had positive test for hepatitis viral study (Table 2). In 7(4.4%) out of 160 patients died due to causes associated with infections, six patients with gastroenteritis leading to renal failure and one patient with meningitis. Heart failure was responsible for death of sixteen (94.1%) out of the 17 splenectomized dead patients. Onset of complications among dead patients occurred at mean±SE of age was 13.28±0.47 year. Mean±SE of interval between onset of complication and death was 2.33 ± 0.145 year. Analysis of variance (ANOVA) test demonstrated that there was no significant difference (p=0.715) of mean serum ferritin level in relation to different causes of death (Table 2). No statistical difference in mean serum ferritin levels was found between dead males and females.

Table 1*:* Characteristics of 718 patients with β-thalassemia major on iron chelation therapy in Mosul, Iraq (2014)

Variable		Alive		Dead		Total	P value
		No	%	No	%		
Number of patients		558	77.7	160	22.3	718	
Sex	Male	285	76.2	89	23.8	374	0.310
	Female	273	79.4	71	20.6	344	
Age group(years)	≤10	237	89.1	29	10.9	266	0.000*
	11-20	225	68.0	106	32	331	
	21-30	62	72.9	23	27.1	85	
	31-40	18	94.7	1	5.3	19	
	>40	16	94.1	1	5.9	17	
Splenectomy	Yes	48	73.8	17	26.2	65	0.432
	No	510	78.1	143	21.9	653	

Table 2: Causes of death among 160 patients with β- thalassemia major in relation to age at onset of complications, age at death, and ferritin level in Mosul city, Iraq (2014).

Cause of death	No.	%	Age at death (year) minimum-maximum)	Mean±SE of ageat onset of complication (year)	Mean ± SE of age at death(year)	Mean ±SE of ferritin level *
Cardiac causes	130	81.3	3-36	13.24± 0.449	15.75 ± 0.449	3189.28± 556.33
Accidents†	9	5.6	2-24	13.33±2.309	13.44±2.328	3007.75± 341.44
Diabetes mellitus	6	3.8	5-29	11.00±3.141	14.00±3.483	2033.71 ±579.43
Acute renal failure	6	3.8	4-21	11.17± 2.676	11.67± 2.940	2405.49± 721.74
Liver failure	3	1.9	12-46	25.67± 8.413	28.67± 9.821	2316.57± 419.16
CNS causes	3	1.9	4-24	12.00± 6.110	12.00± 6.110	1110.25± 603.51
Others §	3	1.9	10-18	12.33±2.848	12.67±2.667	2118.71 ±229.59
Total	160	100	2-46	13.28± 0 .466	15.52 ± 0.48	2916.57±419.16

Figure 1. Kaplan-Meier survival curves of 718 patients with β-thalassemia major in Mosul city /Iraq (2014)

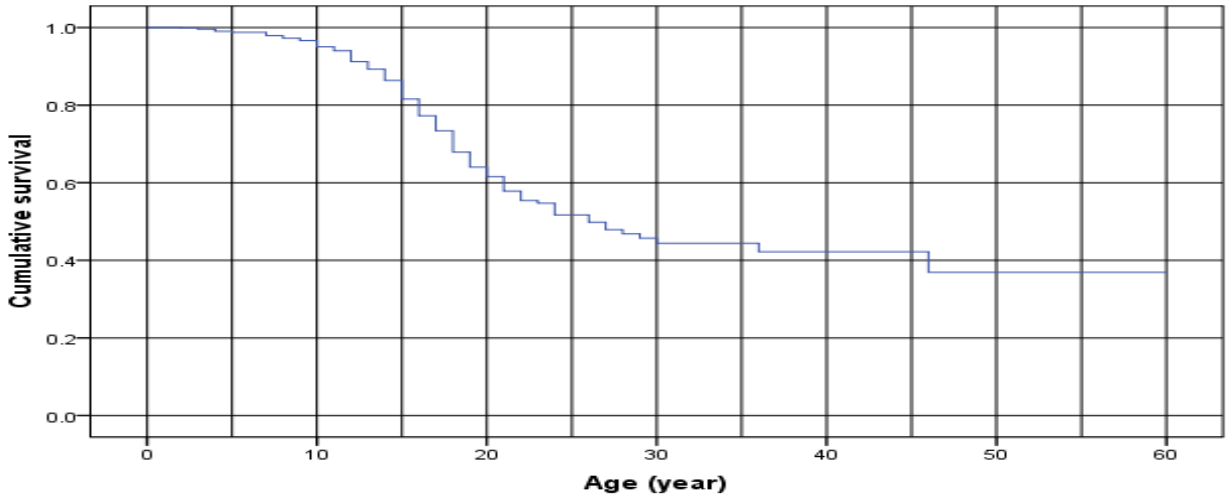
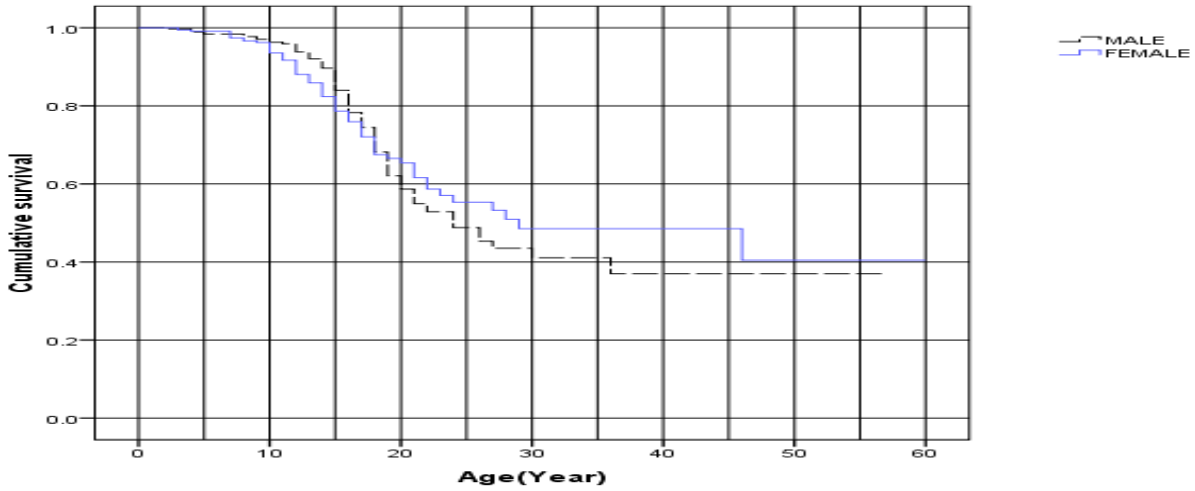


Figure 2: Kaplan-Meier survival curves of 718 β- thalassemia patients stratified according to sex. Log rank (mantel-cox) = 0.918, Baserlow (Generalized Wilcoxon) = 0.349, Tarone-Ware= 0.601.



DISCUSSION

Overall, 23.3% of thalassemia patients in Shiraz, Iran died[6], which is comparable to our finding of 22.3% of death among studied thalassemia patients. The median survival time in our study is 16.15 years, which is lower than median survival time of 20.0 years in Hamadan[7]. The 5-, 10-, 15-, 20-,25-,30-,35, 40-,45-year survival rate were 98.7%, 95.1%, 81.6%, 61.6%, 49.8% 44.4%, 42.2% .42.1% and 36.9% respectively (Figure 1). A study conducted in Shiraz, Iran showed that the 20-year, 40-year, and 60-year survival rates were 85%, 63%, and 54%, respectively[6]. At age of 40 years, 42.1% of our patients survived. The differences between these results reported from different countries could be due to less uniform pattern of management and different rates of drug compliance.

No statistical difference in the survival time is observed between the genders (Figure 2) this is in consistent with other studies[7], both genders having a similar risk of accumulating iron[8], in agreement with our findings. The median survival time of studied females with beta thalassemia was none significantly longer than that of males; (median survival in female 29 years versus 24 years in male). Female patients may have a better tolerance for iron toxicity[8].

Heart disease, including heart failure and arrhythmia, continues to be the leading cause of death[9,10]. Iron overload cardiomyopathy, is the chief cause of mortality in patients with thalassemia[11,12]. In 81.3% of all analyzed death certificates reported a cardiac cause of mortality (Table 2). Cardiac complications were the most frequent sequela in patients >15 years old[13]. Onset of cardiac complications among studied dead patients occurred at mean age ± SE of 13.24± 0.449 year. Most complications of thalassemia commenced after 10 years of age[8].

Diabetes complications are very common in multi-transfused thalassemia patients affecting 4.9–9.4% of patients in different geographical areas[14,15]**.** Diabetes was the cause of death in 3.8% of our patients. Thrombosis-related cerebrovascular event and left hemiplegia was detected at 1.5% of thalassemia patients**[14]**. Central nervous system stroke results in death of 1.3% of our cases. Iron overload disorder, such as β-thalassemia, interfere with iron-restrictive host responses, and thereby increased susceptibility to infections**[16]**. Infection was responsible for death of 4.4% of analyzed patients. Hepatic complications cause 1.9% of studied death, 0.5% of Saudi thalassemia patients died from liver diseases[8].

The median serum ferritin in analyzed dead cases was 2916.57± 419.163ng/ml. However, the mean serum ferritin in studied patient with cardiac mortality was 3189.3±556.3ng/ml, which is not significantly higher than its level in another mortality causes. In Turkish study mean ferritin level was 2212±1370ng/ml for 4.5 years, there was no statistically significant relationship between complications and mean ferritin levels and there was no statistically significant relationship between mean ferritin levels and occurrence of cardiac complications ($p > 0.05$)[17], in concordance with our findings.

A number of limitations were present in this study being a retrospective study, including lack of evidences about treatment adherence, moreover the small number of dead patients who had measurement of serum ferritin constituting around a quarter of total dead patient's sample. On the other hand, being the first demonstration of thalassemia survival rate in our locality represents a strong point in this study.

CONCLUSION

The survival rate of patients with β- thalassemia major in Nineveh governorate is comparatively unsatisfactory. A greater attention to management of thalassemia and its complications is recommended in order to improve survival rate of thalassemia.

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Ethical approval: The study was approved by the Ethics Committee at Mosul Health Directorate.

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