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Original article

Mortality and complications in Omani patients with beta-thalassemia major: a long-term follow-up study

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Abstract. *Background and aim:* Beta thalassemia major (β-TM) is a genetic blood disorder requiring lifelong blood transfusions. The resulting iron overload damages multiple organs, particularly the heart and endocrine organs. This study aimed to describe and assess the predictors of survival and complications in Omani patients with β-TM. *Methods:* All β-TM patients registered in the day care of Sultan Qaboos University Hospital were included in this retrospective study. *Results:* There were 187 patients with β-TM with a median follow-up of 24.9 years. The median ages at diagnosis and the start of chelation were 0.7 and 4.8 years, respectively. The following complications developed at different time points [Median (age in years), Complication Free Probability at 20 years]: Death (20.0 years;85%), hypogonadism (15.9 years;50%), insulin-dependent or non-insulin dependent diabetes (20.0 years;88%), cardiac complications (20.3 years;91%), osteoporosis (20.7 years;96%), hypothyroidism (25.7 years;97%), liver complications (7.3 years;54%). The number of complications predicted death ($P = 0.0038$). Those born after 1980 had a lower risk of death ($P = 0.005$), hypogonadism ($P = < 0.0001$), and cardiac complications ($P = 0.004$). Higher serum ferritin at the start of chelation was associated with the development of diabetes ($P = < 0.001$). *Conclusions*: This long-term study shows complications development at different ages, and the number of complications is associated with survival. Later birth cohorts had a lower risk of death, hypogonadism, and cardiac complications. There was a persistent negative impact of delay in the start of iron chelation that is present even after a long follow-up. (www.actabiomedica.it)

Key words: β -thalassemia major, Oman, mortality, morbidity, long-term follow-up

Introduction

The prognosis for β-thalassemia major (β-TM) patients has markedly improved over the past four decades as shown by studies from the United Kingdom (UK), Italy, Greece and Cyprus, particularly in β-TM patients born after 1990 (1-4). This has been attributed to better transfusion policies, improved access to a wider range of iron chelators and the use of T2* magnetic resonance imaging (T2*MRI) to identify and appropriately treat patients at risk of cardiac death (5). Currently, almost all the published data on long-term survival and complications in β-TM are from the western population, particularly Europe and the USA, with some data available from other countries such as Lebanon, Hong Kong and Iran (1-4, 6-10). There have

been no long-term survival studies published from the countries in the Arabian Peninsula, which have a relatively younger health care system.

The current modern healthcare system in the Sultanate of Oman only dates back to the 1970s, and standard treatment of β-TM was not readily available until the late 1980s. In 1991, almost all patients (age range 2yrs-18yrs) with β-TM in Oman were transferred to the day care unit of the newly commissioned Sultan Qaboos University Hospital (SQUH). It currently remains the largest unit, although smaller centres are now present in all regional hospitals. We report here our experience of survival and complications in a cohort of Omani patients with β-TM followed and treated in the same unit over nearly 3 decades.

Methods

This is a retrospective study from a prospectively collected database with long-term follow-up. A total of 187 patients with β-TM were treated in the day care unit of SQUH, Muscat, Oman, from April 1991 to Jan 2020. All patients with β-TM, based on Hb electrophoresis or HPLC, who started regular blood transfusion before the age of 5 years (yrs) and were registered in SQUH day care from April 1991 onwards, were included. For the purposes of this study, we limited the start of follow-up to 1991, as there was inadequate data on deaths and causes of death prior to this date. The last follow-up before data lock was 1st of January 2020. All patients had been transfused with packed red cells 2-4 weekly, and iron chelation had been started either when patients were transferred from other institutions if they were not on regular chelation, or when the serum ferritin (SF) was 1000 ng/ml.

SF was measured using the immuno-turbidimetry method (Roche), and mean yearly SF was calculated. Yearly endocrine assessment after the age of 10 years included 2-hour oral glucose tolerance test (OGTT), pubertal assessment (physical and biochemical), and biochemical assessment of thyroid and parathyroid function. Growth hormone was tested in pubertal patients if the growth velocity/year was ≤ 3rd centile for age and sex or below the target height. All patients over the age of 20 yrs had regular dual-energy X-ray absorptiometry (DEXA) scans. DEXA scan was not performed on younger patients as no control data were available for Omani children and adolescents.

Additional data included age at diagnosis of β-TM, age at starting regular iron chelation, age at onset of endocrine complications or other complications, splenectomy status, hepatitis B, C and HIV data, past history of severe infections, date and cause of death. From September 2006, cardiac and liver MRI T2* were available. Liver fibrosis was assessed using two-dimensional shear wave elastography (2-D SWE) imaging (GE LOGIQ E9 XD clear 2.0; GE Healthcare, Milwaukee, WI, USA). Liver elastography of ≥ 8 KPas represents stage 2 fibrosis (F2) which is considered significant (11).

Chelation therapy

Only 4 patients of the first group transferred in 1991 to the day care unit of SQUH were on regular chelation due to a lack of portable infusion pumps. Thereafter, pumps were freely available, and all patients were offered subcutaneous (s.c.) iron chelation with deferoxamine (DFO) for 8 hours/day, 5 days/week. However, compliance in the early years was poor, particularly with older patients, and some families refused chelation. In 2000 the oral chelator, deferiprone (DFP), became available, and by 2001 most patients were either on combination DFO and DFP or monotherapy with DFP if SF levels dropped markedly. Deferasirox (DFX) became available to our patients in 2010.

Statistical analysis

Continuous variables were described using medians and interquartile ranges (IQR), while categorical variables were described using frequencies and percentages. Overall Survival (OS) was estimated from the date of the centre registration till the date of death or last follow-up. The probability of OS was estimated using the Kaplan-Meier curve. The impact of predictors was assessed using univariable and multivariable Cox-Regression analyses. Birth cohorts were categorized using the following: born before 1980 (BC1), 1980 - 1989 (BC2), 1990 - 1999 (BC3), and

2000 - 2009 (BC4). An alpha threshold of 0.05 was used for statistical significance and no correction for multiple testing was performed. All descriptive and analytical statistics were performed using R program version 3.5.2 (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

Ethics

The study was approved by the Medical Research Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (June 2020, MREC#2133).

Results

Baseline characteristics

A total of 187 patients with β-TM (Table 1) were included in this study with a median follow-up duration of 24.9 years (IQR: 15.2 – 27.3) for all patients, and 26.6 years (IQR: 24.0 – 27.9) for those alive. The median ages of diagnosis and start of chelation were 0.7 and 4.8 years, respectively. At the start of chelation, the median SF was 2276 ng/ml (IQR: 1372 - 4516) compared to 2177 ng/ml (IQR: 1152 - 4882) at last follow-up (P = 0.85). The majority of patients (55%) were homozygous for the IVS1,5 G>C mutation, followed by homozygous cod 44-C. Other mutations included IVS1-3'end -25 bp deletion, IVS 11-1 G>A and the 619 bp deletion. We were unable to identify 12 alleles as patients had died and DNA samples were either too degraded or not available. A total of 67 patients underwent splenectomy before transferring to our unit or during follow-up.

Overall survival (OS)

During the study period, 51 patients died. Causes of death (Figure 1) included cardiac complications in 24 (47%), infections in 14 (27.4 %), including 6 patients with acquired immunodeficiency syndrome (AIDS) in the first 6 yrs of follow-up, bone marrow transplant-related in 5 (9.8 %), liver disease in 5 (9.8 %) and other causes in 3 (5.9%). The OS probability at 20 years was 85% (95% CI: 80 - 90). After censoring for a bone marrow transplant, the OS probability at 20 years was 84% (95% CI: 79 - 90). Table 2 details the results of the univariable and multivariable analyses of OS and the other study outcomes. The probability of OS according to the birth cohorts is shown in Figure 2.

Table 1. Baseline Characteristics (n = 187).

Characteristic	Value
Age, median (IQR), years	
Diagnosis	0.7 (0.4 - 1.2)
Seen at Thalassemia Centre	4.1 (1.4 - 8.3)
Start of chelation	4.8 (2.9 - 8.0)
Gender, n (%)	
Male	99 (53)
Female	88 (47)
Genotype, n (%)	
homozygous IVS1,5 G>C (β^+/β^+)	103 (55)
homozygous COD 44 -C (β^o/β^o)	23 (12)
heterozygous IVS1,5 G>C (β^+/β^0)	26 (14)
heterozygous COD 44 -C (β^o/β^+)	4 (2)
Others	19 (10)
Missing	12 (7)
Pre-transfusion Hb, g/dL	9.3 (9.0 - 9.7)
Splenectomized, n (%)	67 (36%)
Serum Ferritin, ng/ml (IQR)	
Start of chelation	2276 (1372 - 4516)
Last follow-up	2177 (1152-4882)
Highest	4736 (3118 - 7845)
Mean	2238 (1524 - 3779)
Annual blood requirement, median (IQR), ml/Kg/year (IQR)	217 (186 - 250)

Abbreviations: IQR: Interquartile range; n: number; IVS: intervening sequence; Cod: codon; g/l: grams per decilitre.

Development of complications

A total of 146 (78.1%) patients developed at least one complication related to β-TM or therapy. The probability of developing one, two and three or more complications during the follow-up was 21.9% (41 patients), 16.0% (30 patients), and 40.1% (75 patients), respectively. The number of complications developed predicted the OS of these patients (P = 0.0038, Figure 3).

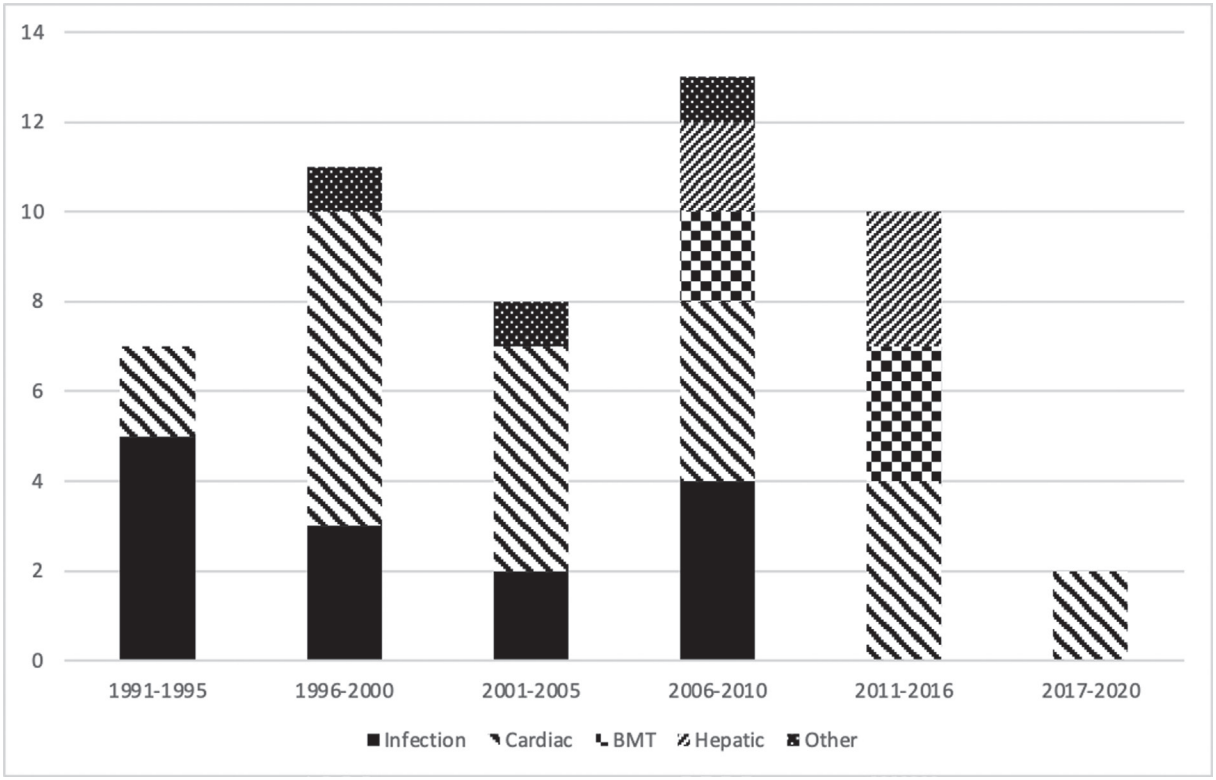

Figure 1. Causes of Death in the Total Cohort April 1991- January 2020 (51 patients).

Table 2. Impact of baseline factors on the risk of complications.

	Overall survival (n=51 died)		**Cardiac Complications (n=29)**		**Hypogonadism (n =103)**	
Median age of complication (IQR), years	20.0 (16.0 - 24.0)		20.3 (16.4 -23.8)		15.9 (15.0 - 17.3)	
Model	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Gender (M vs. F), HR (*p*-value)	1.1 (0.66)	NA	0.999 (0.997)	NA	0.5 (0.0004)	0.5 (0.0007)
Age at the center, HR	1.1 (0.003)	1.03 (0.7)	1.06 (0.0076)	0.95 (0.55)	1.06 (<0.0001)	0.96 (0.4)
Birth Cohort, HR (*p*-value), (Ref: BC1)						
BC2	0.5 (0.04)	0.5 (0.4)	0.4 (0.047)	0.4 (0.2)	0.6 (0.035)	0.5 (0.1)
BC3	0.2 (0.0004)	0.5 (0.4)	0.1 (0.0007)	0.2 (0.2)	0.3 (<0.0001)	0.3 (0.08)
BC4	0.6 (0.47)	2.4 (0.4)	0.4 (0.42)	0.9 (0.92)	0.1 (0.005)	0.2 (0.06)
Serum Ferritin at start of chelation, HR (*p*-value)	1.0002 (0.001)	1.0001 (0.2)	1.0003 (<0.0001)	1.0003 (0.026)	1.0002 (<0.0001)	1.0001 (0.1)
Probability of Complication free survival At 20 years (95%CI)	85% (80-90)		91% (87-96)		50% (43-58)	

	Overall survival (n=51 died)		**Cardiac Complications (n=29)**		**Hypogonadism (n =103)**	
	Diabetes (n = 38)		**Hypothyroidism (n = 24)**		**Hypoparathyroidism (n = 12)**	
Median age complication (IQR), years	20.0 (16.8 -25.1)		25.7 (21.4 -31.4)		22.3 (18.8 -24.8)	
Model	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Gender (M vs. F), HR (*p*-value)	0.8 (0.5)	NA	0.45 (0.07)	NA	1.96 (0.3)	NA
Age at the center, HR	1.1 (0.0003)	1..03 (0.67)	0.97 (0.5)	NA	0.99 (0.8)	NA
Birth Cohort, HR (*p*-value), (Ref:BC1) BC2 BC3 BC4	 0.4 (0.02) 0.1 <(0.0001) 0.3 (0.3)	 0.9 (0.9) 0.1 (0.1) 1.5 (0.8)	 1.5 (0.5) 0.7 (0.6) $1.04x10^{-7}$ (0.998)	NA	 2.1 (0.48) 1.1 (0.93) 1.5×10^{-7} (0.998)	NA
Serum Ferritin at start of chelation, HR (*p*-value)	1.0003 (<0.001)	1.0002 (0.02)	1.00001 (0.9)	NA	1.0002 (0.3)	NA
Probability of Complication free survival At 20yrs (95%CI)	88% (83-93)		97% (94-99.6)		97% (94-99.6)	
	Osteoporosis (n = 50)		**Liver complications (n = 104)**			
Median age of complication (IQR), years	20.7 (20.3 -23.1)		7.3 (3.4 -17.6)			
Model	Univariable	Multivariable	Univariable	Multivariable		
Gender (M vs. F), HR (*p*-value)	1.3 (0.4)	NA	1.1 (0.51)	NA		
Age at the center, HR	0.99 (0.8)	NA	1.1 (<0.0001)	1.05 (0.32)		
Birth Cohort, HR (*p*-value), (Ref:BC1) BC2 BC3 BC4	 1.9 (0.14) 1.001 (0.999) 3.6×10^{-7} (0.997)	NA	 0.6 (0.045) 0.1 (<0.0001) 0.3 (0.0049)	 1.05 (0.9) 0.4 (0.1) 0.8 (0.7)		
Serum Ferritin at start of chelation, HR (*p*-value)	1.00003 (0.7)	NA	1.0002 (<0.0001)	1.0001 (0.09)		
Probability of Complication free survival At 20 years (95%CI)			54% (47-62)			

Abbreviations: IQR: interquartile range; NA: not available; HR: hazard ratio; BC: birth cohort (BC1: born <1980, BC2: born 1980-1989, BC3: born 1990-1999, BC4: born 2000-2009); CI: confidence interval.

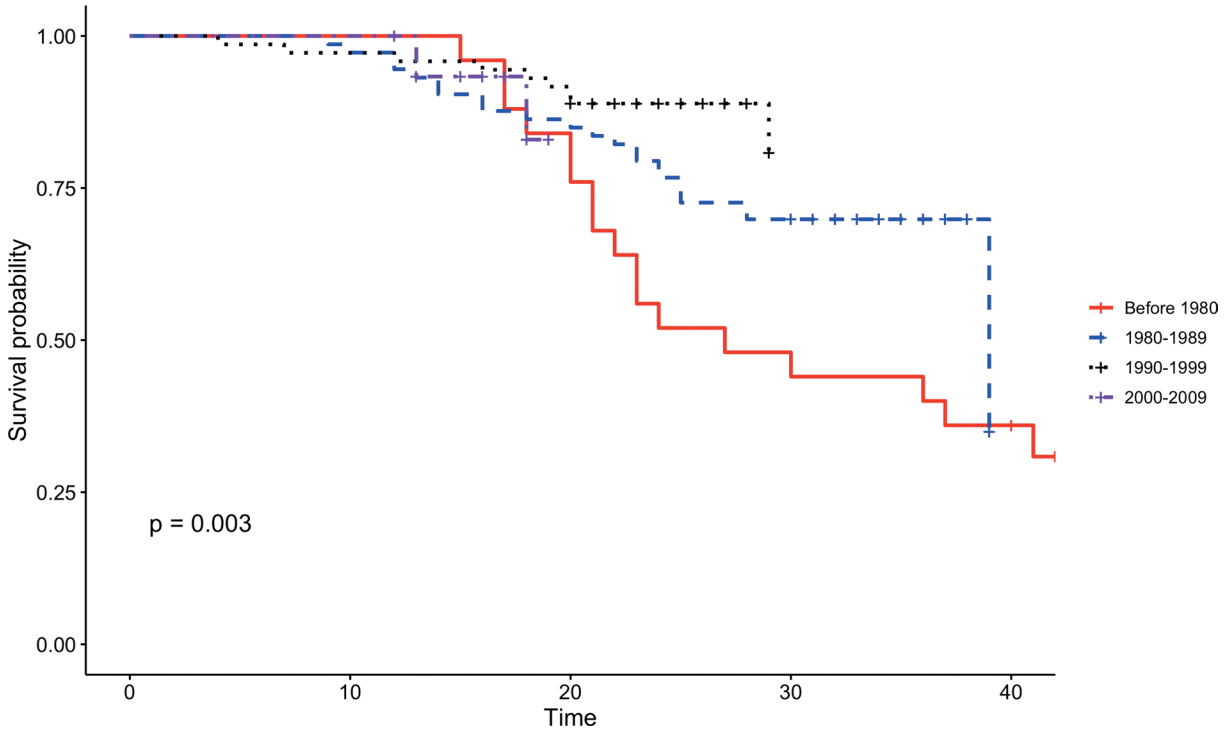

Figure 2. Overall Survival according to the birth cohort.

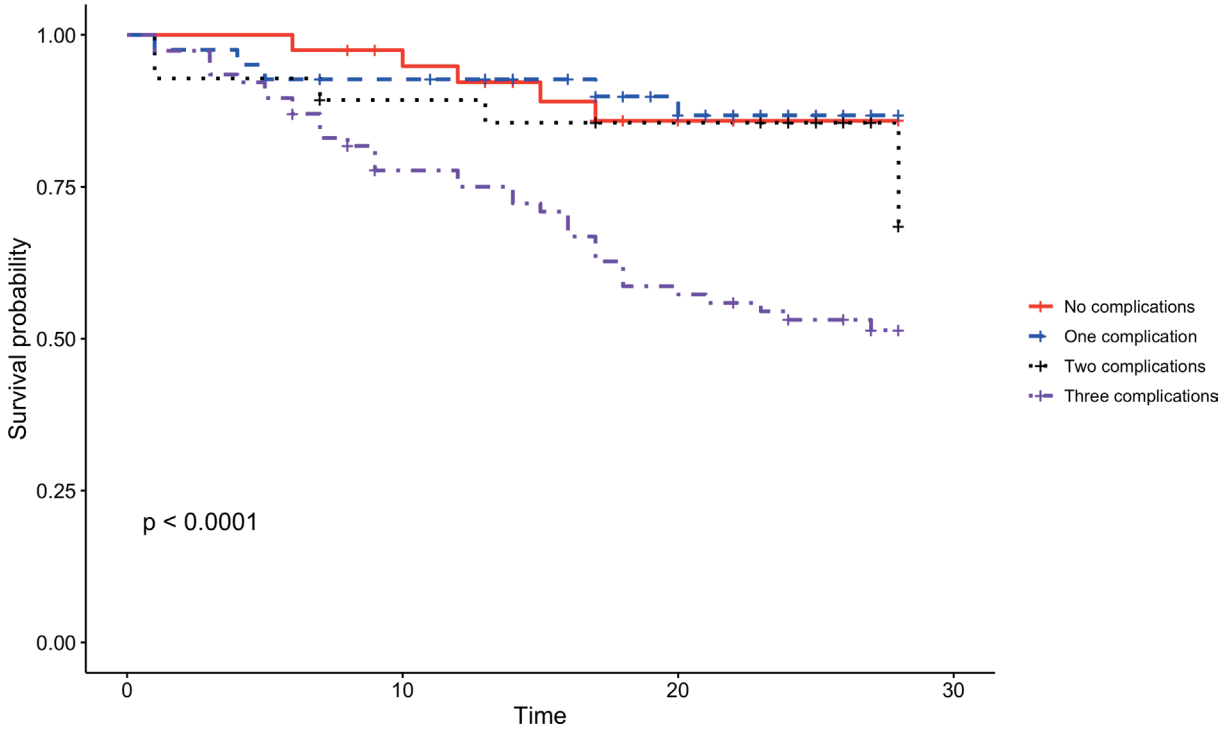

Figure 3. Overall survival according to the number of complications.

Infections

There were 40 severe infections in which the causative organism was documented. *Plasmodium falciparum* malaria accounted for 14 infections, the majority occurring before the year 2000. Of the remaining 26 infections, 19 (73.1%) were caused by gram negative organisms, mainly *Klebsiella pneumoniae*; 14 (73%) of those patients were splenectomized, seven were diabetic, and six were both splenectomized and diabetic. Six patients had been infected by the Human Immunodeficiency virus (HIV) before transfer to our unit.

Cardiac complications

Twenty-nine patients developed cardiac complications. The median of the last cardiac T2* that these patients had was 5.5 milliseconds (ms) (IQR: 4.7 – 18.9). The median SF before the development of cardiac complication was 2793 ng/ml (IQR: 2052 - 6486). All 29 patients developed congestive cardiac failure, and 24 (82.7%) of them died.

Endocrine complications

Hypogonadism developed in 103 (55%) patients during the study period. The median SF, during pubertal age, before the development of hypogonadism was 3500 ng/ml (IQR: 2161 - 5079). Patients with hypogonadism had a significantly higher median SF when compared to those who were eugonadal (2703 vs. 1858 ng/ml, *P*= < 0.0001) and had a higher risk of developing osteoporosis (OR 3, *P* = 0.007).

Thirty-eight (20.3%) patients developed diabetes mellitus (DM) during the follow-up; 27 patients presented with insulin-dependent diabetes (IDDM), and 15 first developed non-insulin-dependent diabetes (NIDDM). The median SF before the development of IDDM and NIDDM were 3776 ng/ml (IQR: 2637 - 6263) and 2738 ng/ml (IQR: 2242 - 5728), respectively. Patients with diabetes were more likely to have hypothyroidism (OR 5, *P* = 0.0004), hypogonadism (OR 13, *P* = < 0.0001), liver disease (OR 5, *P* = 0.0004), and to have been splenectomized (OR 17, *P*= < 0.0001). All patients who had cardiac complications also had diabetes. Patients with diabetes had a significantly higher median SF than those without (3602 vs. 2036 ng/ml, *P* = 0.0002).

Twenty-four (12.8%) patients developed hypothyroidism and 12 (6.4%) developed hypoparathyroidism. The median SF before the development of primary hypothyroidism was 2473 ng/ml (IQR: 1897 - 3660) while it was 3954 ng/ml (IQR: 2484 - 4244) before the onset of hypoparathyroidism.

A total of 100 adult patients had DEXA scan and 50 (50%) were found to be osteoporotic. The probability of being free from osteoporosis at 25 years was 73% (95% CI: 65-80). There was no statistically significant predictor of these complications in the univariable model (Table 2). One patient was treated for growth hormone deficiency for 5 years.

Hepatic complications

A total of 104 (55.6%) patients developed at least one hepatic complication. This was hepatitis C virus infection (HCV) in 76 patients (40.6 %), hepatitis B virus infection (HBV) in 3 patients (1.6%), and liver abscess in 2 patients (1%). Significant liver fibrosis (KPa>8.8) was found in 45 patients with or without HCV. The median liver elastography value was 8.8 kPa (IQR: 7.4 - 10.3). The median highest LIC in the cohort was 13.6 g/gram dry weight (g.d.w.) (IQR: 6.9 - 21.4).

Discussion

This study, encompassing 187 β-TM patients treated in a single unit between 1991-2019 for a median follow-up of 24.9 years, is the longest reported from the Middle East. Fifty-one patients (27.3%) died over the study period, a relatively high number compared to some published reports, e.g., Italy 8.47%, Cyprus 10.9%, and Iran 8-23.3% (2-4,9,10). However, one of the Iranian studies also included patients with thalassemia intermedia, which would almost certainly have affected their results. Both Italy and Cyprus started good management of β-TM early, which may explain their better survival, whereas many of our patients did not start iron chelation until their second decade. On the other hand, reports from both the UK

and Greece have shown overall mortality of >20% (1,3). In both these latter studies, the highest percentage of deaths was due to cardiac complications, and the risk of cardiac death improved after 2000. This has been attributed to improved chelation availability and the use of MRI T2* to better identify patients most at risk. At least two studies have demonstrated that cardiac T2* <10 ms increases the risk of heart failure, and cardiac T2* of < 6 ms is even more strongly associated with the risk of cardiac arrhythmia (12,13). After MRI T2* became available for our patients in 2006, there were 20 deaths; all 8 cardiac-related deaths had T2* ≤ 10 ms at the time of death, and 6 of them had T2* < 6 ms.

Intravenous (IV) or s.c. iron chelation has been shown to reverse cardiac disease, and home delivery of disposable infusers with DFO is regularly provided in the UK to high-risk patients (14,15). Our study showed no improvement in the number of deaths due to cardiac iron load in the 13 years following the availability of cardiac MRI T2*. In our unit, patients identified as high risk had T2*MRI performed 3-4 monthly and were given increased, focused counseling. We attempted to provide 24-hour chelation, with continuous DFO and oral DFP in divided doses. Although DFO infusers (to be used with a port-a-cath) are available to our patients, home delivery of newly filled infusers is not currently an option in our setting. Therefore, these patients are advised to either use continuous s.c. DFO chelation at home or be admitted long-term to the hospital or, if using infusers, asked to come three times a week for refills. The latter two strategies were not sustainable for the long time it takes to improve severe cardiac iron load. This lack and continued noncompliance in most patients has continued to result in deaths due to cardiac iron load.

It has also been postulated that females tolerate iron toxicity better than males (16). However, published data on the impact of gender on survival has been variable, with studies from Italy, Greece and Cyprus showing improved survival in females with β-TM (2,4,17,18). In contrast, other studies from Lebanon and Iraq showed no difference between the genders (7,19). We found no significant difference in overall survival between males and females in our cohort, but this may change as our cohorts get older.

Some studies have shown that the β-globin genotype can affect cardiac function and organ iron overload (20,21). On the contrary, we found that genotype had no impact on OS or morbidity in our cohort, most of whom had either β^0 or β^+ mutations. The commonest mutation in our patients is IVS1,5 G>C which is known to be a severe β^+ mutation and our findings agree with a recently published large study on 2019 patients by Musallam et al that showed that β^+ mutations have the same severe risk profile as β^0 mutations (22).

Twenty-nine patients had cardiac failure at some point during follow-up. Low SF has been shown to be a predictor of improved survival, and an early report by Olivieri et al. (23) identified the majority of SF values being < 2500 ng/ml as a factor affecting cardiac disease-free survival (2,7). We found that age at referral to our centre and SF at the start of iron chelation were significant factors (univariable analysis) in the development of cardiac complications. In addition, the median SF was 2793 ng/ml before cardiac disease occurred.

Deaths due to infection decreased after 2010 (Figure 1). AIDS accounted for 6 deaths; all patients were infected before the availability of routine blood donor testing for HIV and no patient became infected after 1991. Over the nearly three decades of the study period there was a marked reduction in patients dying of bacterial infections. We attribute this improvement to sensitization and increased awareness of doctors in the regional hospitals (where patients are most likely to present first) of the high likelihood of gram-negative infections in β-TM patients, as well as to continued education of patients themselves.

Endocrinopathies, secondary to organ iron overload, are major complications in β-TM and are common worldwide (24). Studies have shown that older Italian β-TM patients and over 80% of Iranian patients have at least one endocrinopathy (24,25). In North America, the incidence rate for new onset of endocrine disturbance was 14% for each of 5 years of advancing age (6). The commonest endocrinopathy in all β-TM populations is hypogonadism, with studies reporting a prevalence of 23-78% (Table 3) (6,7,25-31). Fifty-five percent of our cohort had hypogonadism. Gender and birth cohort were significant in the multivariable

Table 3. Comparison of endocrinopathies in thalassemia major between countries.

Country, number of patients	Hypogonadism (%)	Diabetes (%)	Hypothyroidism (%)	Hypoparathyroidism (%)	Osteoporosis (%)
Oman, 187 (current study)	55	19.7	8.5	5.9	50[¶]
Lebanon, 214 (7)	27.9	7	20.9	N.A.	
USA, 342 & 236 (6, 26)	35, 51.3	10, 14.1	9, 12	4, 2.1	
Italy,720 (27)	44-78	4.7-18	17-39	2-17	16.3-69.7
Hong Kong, 232 (8)	29.7	8.6	6.9		
Taiwan, 454 (28)	23.1	21.2	8.8	2	
Iran, 713 & 613 (25,29)	44.5 and 46.8	15.9,7.8	10.7 and 8.3	13.2 and 22	
Cyprus, 435 (30)	32.5	9.4	5.9	1.2	
UK[§], 612 (31)		34			39.7

Legend: [§]UK reported that the sum of patients who had hypopituitarism, hypothyroidism, hypoparathyroidism was 40%; [¶]Dexascan only performed on patients ≥ 20 years age. N.A. not available.

analysis, with males having a lower incidence. The high percentage of patients with hypogonadism in our total cohort may possibly be due to late start in chelation in older patients, as cohorts born after 1980 had a lower incidence.

Diabetes, both NIDDM and IDDM, was the next commonest endocrinopathy in our cohort, with a prevalence of 20.3%. An earlier report on 30 adult Omanis with β-TM showed a similarly high prevalence (32). A meta-analysis by He et al. has shown a high prevalence of glucometabolic disorders in β-TM, with the highest prevalence in the Middle East (33). An association between splenectomy and impaired glucose tolerance or diabetes has also been reported (24,25,34). It has been suggested that removal of the spleen decreases total body iron storage capacity, thus increasing iron load in other organs, including the pancreas (24). Our results show that patients with diabetes were more likely to have been splenectomized and to have hypogonadism, cardiac disease and liver disease. However, this correlation is confounded by the fact that most of our older patients started iron chelation late, and, before 2010, splenectomy was performed more frequently at a relatively young age (Table 1). In addition, splenomegaly, with increased transfusion requirements, is the commonest reason for performing a splenectomy in thalassemia, and so these patients already had a high iron load. Our data analysis shows that SF at the start of chelation, birth cohort and age at entry to our centre were all significant predictors for the development of diabetes in the univariable analysis. However, only SF at the start of chelation was significant in the multivariable model. In addition, patients with hypogonadism or diabetes had a significantly higher median SF than those without. It is notable that no patient reverted to normoglycaemic status despite some patients achieving persistent SF <1000 ng/ml and some <500 ng/ml. Iron removal from the pancreas has been shown to be difficult and Calleja et al. showed that early chelation could prevent diabetes, thus emphasizing the need for early and adequate iron chelation (34,35).

Hypothyroidism and hypoparathyroidism were present in 12.8% and 6.4% of patients, respectively, but no significant predictors were associated with these two endocrinopathies. These are similar findings to a major Italian study where SF was also not associated with hypothyroidism (2). It is noticeable that hypothyroidism appears to be less common in our patients than that reported in Italy (17-39%) and Lebanon (20.9%), although comparable to that reported in the USA, Iraq, Iran and Cyprus (Table 3). The reason for this needs further exploration. Osteoporosis developed in 50% of patients over the age of 20 yrs, and, as expected, was more prevalent in those individuals with

hypogonadism. Longer term studies are needed to see if younger cohorts who have a lower incidence of hypogonadism are similarly affected.

HCV infection among multi-transfused patients is known to enhance liver fibrosis. Angelucci et al. (36) reported a high risk of liver fibrosis progression in the presence of chronic HCV and high LIC > 22 mg/g d.w. In contrast, the median highest LIC seen in our cohort was 13.6 mg/g d.w. (IQR: 6.9 - 21.4), and the median liver elastography Kpa was 8.8 (IQR: 7.4 - 10.3), indicating significant liver fibrosis of more than F2 in the METAVIR staging system but with a much lower LIC. Similar findings of a lower level of LIC associated with cirrhosis have been reported in 51 Egyptian β-TM patients, of whom 82% were anti-HCV positive with a median LIC of 12 mg/g d.w. (37). Two of our patients died of advanced hepatocellular carcinoma (HCC), and two died secondary to decompensated liver cirrhosis. The most common etiology of HCC is liver cirrhosis secondary to chronic viral hepatitis and iron overload. With the development of direct anti-viral agents to treat chronic hepatitis C, most thalassemia patients will be successfully treated. However, older patients with cirrhosis remain at risk for HCC even after treatment and sustained virological response (38).

Finally, our data show that the number of complications developed impacted overall survival in our cohort, with those patients having more than two complications having a poorer outcome. Data from a single tertiary care centre and lack of data before 1991 are limitations of the current study. However, we present a long follow-up with prospectively collected data, and the advantage of a single centre is uniformity of treatment.

Conclusions

This is the first long term evaluation of morbidity and mortality in β-TM patients from the Arab world. Complications secondary to iron overload remain a major challenge in Omani β-TM patients and there is a strong association between the number of complications and mortality despite the universal availability of chelators. Cardiac disease remains a significant cause of morbidity, although the youngest cohort is showing an improvement in this respect. European countries have shown a marked decrease in cardiac-related deaths over the past two decades, whereas our cohort shows no such reduction, and it is clear that our current chelation strategy for patients with heavy cardiac iron load needs to be improved. Infections have been a major cause of death, but 3rd and 4th generation antibiotics to treat septicaemia, particularly in splenectomized patients, have improved survival. Liver-related morbidity and mortality should improve in the coming years due to the effective treatment of HCV.

The importance of starting early chelation has multiple aspects, the most important being to prevent irreversible damage to the endocrine organs, particularly the pancreas and pituitary. In addition, our experience has been that, despite freely available chelation and persistent focused counseling, families and patients are very resistant to regular chelation if they have not been started in early childhood.

Our data shows a that delay in the start of iron chelation has a persistent impact on morbidity and mortality that is present even after a long follow-up.

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