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Review Article

β-Thalassemia heterozygote state detrimentally affects health expectation

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ABSTRACT

Background: Thalassemia minor (Tm) individuals, are generally considered healthy. However, the prognosis of Tm individuals has not been extensively studied.

The aim of this study was to evaluate the prognosis of Tm versus controls without β-thalassemia carrier state.

Methods: A total of 26,006 individuals seeking thalassemia screening at the AOOR Villa Sofia-V. Cervello, Palermo (Italy) were retrospectively studied. Logistic penalised regression model was used to estimate risk of potential complications and survival techniques were used to study mortality.

Results: We identified a total of 4943 Tm and 21,063 controls. Tm was associated with significantly higher risks of hospitalisation for cirrhosis (OR 1·94, 95% CI 1·30 to 2·90, $p = 0·001$), kidney disorders (OR 2·11, 95% CI 1·27 to 3·51, $p = 0·004$), cholelithiatis (OR 1·39, 95% CI 1·08 to 1·79, $p = 0·010$), and mood disorders (OR 2·08, 95% CI 1·15 to 3·75, $p = 0·015$). No statistically difference in life expectancy between thalassemia minor and control group was found (HR 1·090, 95% CI 0·777 to 1·555, $p < 0·590$; log-rank test $p = .426$).

Conclusion: This study shows that Tm affects the prognosis of Tm carriers regarding health expectation. Probably, iron overload and anaemia for several years may be at the basis of these effects.

1. Introduction

β-thalassemia is a hereditary blood disorder decreasing haemoglobin synthesis. β-thalassemia is classified into three phenotypes, depending on the severity of symptoms: 1) thalassemia major (TM) (also known as Cooley's anaemia); 2) thalassemia intermedia (TI); and 3) β-trait state or thalassemia minor (Tm) [1]. In TM, signs and symptoms appear within the first two years of life and patients develop life-threatening anaemia (haemoglobin(Hb) < 7·0 g/dl) [1]. TM patients are transfusion-dependent the rest of their life. Over time, chronic blood transfusions can lead to severe body iron accumulation that, in spite of chelation treatments, may result in liver, cardiac, and endocrinological complications [2]. In TI, the signs and symptoms appear after the first two year of life [1]. Affected individuals have mild to moderate anaemia (Hb 7·0 to 9·0 g/dl) and they may need occasionally blood transfusions [3]. The clinical consequences may include endocrinopathies, bone disease, thromboembolism, pulmonary hypertension, cerebrovascular and neuronal damage, liver fibrosis or cirrhosis, and increased risk of hepatocellular carcinoma [3, 4]. Tm individuals are usually considered healthy and they do not need blood transfusions because of this condition. They are even informed that their heterozygote carrier state provides advantages, like protective effects against malaria and coronary heart disease [5]. Moreover, Tm individuals will not know if they are carriers unless they have a specific blood test to detect this condition [6]. Tm has been described as a potential risk factor for liver, kidney, metabolic, cardiovascular, neurological, and vascular complications, although the findings remain controversial [7–29]. As the prognosis of Tm individuals could be affected by long-term enhanced iron absorption and by negative effects of long-standing anaemia, the topic needs further study [8, 15, 29, 30].

Abbreviations: AIC, Akaike Information Criterion; CVD, Cardio-vascular disease; DHSEO, Department Health Services and Epidemiological Observatory; Hb, haemoglobulin; HDRS, Hamilton Depression Rating scores; Hosp, hospitalization; ICD-9-CM, International Classification of Diseases 9th revision; IQR, Interquartile range; LIC, liver iron concentration; LPRM, Logistic penalised regression model; OR, Odds ratio; TI, Thalassemia Intermedia; TM, Thalassemia major; Tm, Thalassemia minor

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Table 1
Causes of hospital admissions for different complications captured as diagnosis codes of the hospital discharge records (SDO), according to the International Classification of Diseases 9th revision (ICD-9-CM).

ICD-9-CM diagnosis codes	Description
427	Arrhythmia
574	Cholelithiasis
571	Cirrhosis
250	Diabetes
296	Mood disorders
580–589	Kidney diseases
414	Ischaemic cardiomiopathy

The aim of this paper is to evaluate the prognosis regarding hospitalisations and mortality in Tm individuals compared to a control group without β-thalassemia carrier state.

2. Materials and methods

Data were retrospectively studied. They refer to all subjects, registered in our database, at the Regional Centre for Thalassemia, Azienda Ospedali Riuniti Villa Sofia-V. Cervello, Palermo (Italy) from January 2000 to July 2014. In particular, subjects were sent by the family doctors following a national screening program aiming at preventing hemoglobinopathies. Thalassemia screening was performed according to standard recommendations, described elsewhere [6]. The whole cohort of subjects was divided into individuals positive for the test (Tm) and individuals negative for the test (without β-thalassemia carrier state, called "Controls"). We determined prognosis as hospital admissions for different complications, according to the ICD-9-CM [31] (Table 1), from January 2004 until December 2013. Hospital admissions and mortality data were, kindly, provided by Department for Health Activities and Epidemiological Observatory (DHAEO) of Sicilian Region, and they refer to people who have had hospitalisation or were dead in Sicily or in other parts of Italy since DHAEO can match, via identity fiscal Code, information entered on the National Register. Information on hospital admission and mortality before January 2004, for all individuals included in the study, were not available at the DHAEO because data were not recorded.

Descriptive analyses were presented as mean ± standard deviation, median with IQR, and percentages. Since the two studied groups had very similar distributions of the follow up, Logistic Penalised Regression Model (LPRM) was used to estimate the risk to develop different complications [32] instead of a hazard model. These models, one for each complication, include the effect of group, sex, age, and interaction between sex and age. The variable *group* was set to *zero* for the *control group* and *1* for the *Tm group*. Moreover, the model was also used for evaluating the interaction of a single complication compared to hospitalisation for other causes (Hosp), following the ICD-9-CM classification [31]. The variable *hospitalisation* was set to *1* when the individual have had at least one hospitalisation for causes that differ from the complication under study, and was set to *zero* otherwise.

The choice of the best model was based on penalised AIC (Akaike Information Criterion) [32].

Moreover, Kaplan-Meier curves and Cox regression model were used to investigate difference in survival between the two groups of interest.

3. Results

Overall, 26,006 individuals participated. A total of 4943 were Tm individuals; the controls numbered 21,063 individuals without β-thalassemia carrier state. The median time from inclusion and until censoring was 2348 days (IQR, 1359–3613 days).

Table 1 describes causes of hospital admissions for different complications. These were selected according to the previous papers on small cohorts or case reports of Tm individuals [7–30]. Therefore, we assessed the risk of hospital admissions for arrhythmia, cholelithiasis, cirrhosis, diabetes, mood disorders, kidney diseases, and ischaemic cardiomyopathy for the Tm and Control groups.

Table 2
Main characteristics of studied groups.

	Total	Tm	Control
Demographics			
N (%)	26,006	4943 (19·00)	21,063 (81·00)
Sex, Females, n (%)	17,438 (67·00)	2869 (58·00)	14,569 (69.17)
Age, mean ± sd	37·00 ± 11·10	39·00 ± 12·40	36·60 ± 10·70
Age_Test, mean ± sd	31·40 ± 10·30	32·20 ± 11·90	31·20 ± 9·80
Death, n (%)	152 (0·58)	51 (1·03)	101 (0·48)
Hematology, mean ± sd			
RBC	4·80 ± 2·23	5·63 ± 0·78	4·65 ± 2·37
Hb	13·05 ± 2·72	11·75 ± 1·57	13·28 ± 2·82
MCV	81·61 ± 10·45	65·11 ± 10·54	84·60 ± 7·13
MCH	27·51 ± 4·26	21·00 ± 2·51	28·69 ± 3·36
RDW	13·71 ± 4·04	15·44 ± 1·52	13·40 ± 4·27
HbA2	3·29 ± 2·05	5·23 ± 2·40	2·94 ± 1·77

All data are referred to follow-up.

Table 2 describes demographics and haematological parameters of the Tm and Control groups.

Table 3 shows the causes in which a statistical significant difference was found in hospital admissions between the Tm and the Control group. The risks of hospital admissions for cholelithiasis, cirrhosis, mood disorders, and kidney diseases were statistically significant higher in Tm group compared to the control group (Table 3).

The Tm group did not seem to differ from the Control group regarding hospital admissions for arrhythmia, diabetes, and ischaemic cardiomyopathy. The risk of hospital admissions for cholelithiasis, cirrhosis, mood disorders, and kidney diseases increases with age and

Table 3
Logistic penalised regression model for hospitalisation for cholelitiasis, cirrhosis, mood disorders, or kidney diseases.

Covariates	OR	95% CI	*p*-Value
Cholelithiasis – 574 code			
Intercept	0·003	(0·002;0·004)	0.000
SEX	0·612	(0·473;0·792)	0·000
GROUP	1·393	(1·083;1·792)	0·010
HOSP	1·937	(1·540;2·436)	< 0·001
AGE	1·031	(1·022;1·040)	< 0·001
Cirrhosis - 571			
Intercept	0·000	(0·000;0·000)	< 2e-16
SEX	12·000	(3·230;44·581)	0·000
GROUP	1·943	(1·298;2·906)	0·001
HOSP	2·849	(1·857;4·370)	< 0·001
AGE	1·067	(1·046;1·090)	< 0·001
SEX × AGE	0·976	(0·952;1·002)	0·068
Mood disorders - 296			
Intercept	0·000	(0·000;0·001)	< 0·001
SEX	0·626	(0·312;1·257)	0·187
GROUP	2·076	(1·149;3·750)	0·015
HOSP	2·105	(1·242;3·569)	0·005
AGE	1·035	(1·016;1·054)	< 0·001
SEX × AGE	0·329	(0·074;1·459)	0·143
Kidney diseases 580–589			
Intercept	0·000	(0·000;0·000)	< 2e-16
SEX	2·022	(1·224;3·340)	0·006
GROUP	2·111	(1·270;3·509)	0·004
HOSP	6·231	(3·116;12·459)	< 0·001

AGE: age of patient in years; GROUP: No-Tm = 0. Tm = 1; HOSP: 0 = no hospitalisation or no hospitalisation differently from the studied complication, 1 = hospitalisation for other complication differently from the studied complication; SEX: F = 0, M = 1; SEX × AGE: interaction effect between sex and age. OR = odds ratio.