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Predicting factors of survival rates among alpha- and beta-thalassemia patients: a retrospective 10-year data analysis

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Background: Thalassemia is a genetic hemoglobinopathy in which a defective globin chain can cause transfusion-dependent anemia and other complications. As genotype interactions lead to variations in the clinical course among patients with thalassemia, clinical factors may help predict survival in the types of thalassemia complicated by gene interactions.

Aim: This study aimed to determine the clinical factors associated with survival in patients with thalassemia. We retrospectively reviewed the medical records of patients with thalassemia older than 15 years between 2002 and 2020 that were available at the Rajavithi Hospital. Data on the clinical parameters, laboratory tests, treatments, and survival status were collected and analyzed.

Results: Of the 478 thalassemia patients included, 68.8% were women, and the mean age was 41 ± 17 years. The most common type of thalassemia was β-thalassemia (53.3%). Male sex, low body mass index, the thalassemia type, comorbidities, low hemoglobin level, high ferritin level, and regular blood transfusion were significantly associated with short-term survival. However, only the thalassemia type (β-thalassemia, $p = 0.048$) and the co-inheritance of the α- and β-thalassemia genotypes ($p = 0.03$) were independently associated with death. The overall survival rates among patients with α-thalassemia, β-thalassemia, and co-inheritance of the α- and β-thalassemia genotypes were 98.1%, 90.6%, and 75.0%, respectively. The death rate was 6.3%, and the most common cause of death was infection.

Conclusion: The thalassemia genotype was a predictive factor of survival, and co-inheritance of the α- and β-thalassemia genotypes results in a shorter-term survival compared with other types, especially transfusion-dependent thalassemia. These results can be applied in clinical settings to predict and possibly extend the life expectancy of patients with thalassemia.

KEYWORDS

alpha-thalassemia, beta-thalassemia, causes of death, survival rate, risk factor

1 Introduction

Thalassemia is a genetic hemoglobinopathy and is considered to be among the global public health issues (1–4). Mutations in the globin gene result in abnormal globin chain synthesis, ultimately leading to chronic hemolytic anemia. Thalassemia has alpha (α) and beta (β) forms, and the disease severity is categorized based on the transfusion dependency and complications. Moreover, it can be classified based on its clinical severity and the degree of anemia. The standard phenotype-based classification that is widely applied is transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT). Furthermore, while thalassemia major manifests as severe anemia in the neonatal period, some patients with thalassemia intermedia only have asymptomatic anemia (5). The severity of thalassemia is determined by the number of mutated genes—four in α-thalassemia and two in β-thalassemia (6). In Thailand, while approximately 40% of the Thai population carries either α- or β-thalassemia (7, 8), only 1% of patients with thalassemia have TDT (7).

Patients with TDT suffer from chronic anemia, which leads to short life expectancy. Furthermore, although life expectancy can be improved by regular blood transfusions, multiple side effects occur both during (allergic reaction) or after transfusion (such as iron overload or hemochromatosis). In hemochromatosis, iron deposits in the visceral organs (the myocardium, liver, and endocrine glands) lead to organ dysfunction (e.g., congestive heart failure, cirrhosis, and endocrinopathies associated with diabetes mellitus) (9). Thus, novel treatment strategies for thalassemia have been developed to balance the necessary blood transfusion and iron accumulation to increase the survival rate (7, 8). Numerous studies have demonstrated that an optimization of the blood transfusions/iron chelation protocols induces a high survival rate that is close to the life expectancy of the general population (8–12). However, the survival rate of thalassemia is also dependent on several other factors, including disease severity, adequate blood transfusion, blood quality, and preventive iron deposition. The prevalence of cardiopulmonary and bone deformities remains high among western thalassemia patients with high ferritin levels, whereas among eastern TDT patients, infection is the main cause of complications (8, 12–15). It has been hypothesized that different clinical outcomes are the results of the interaction between the α- and β-thalassemia genotypes, which can compensate to yield a normal lifespan in patients with minimal complications (8, 16). The co-inheritance of the α- with β-thalassemia genotypes can affect genotype-based categorization, similar to that observed in other hemoglobinopathy combinations, such as α-thalassemia and sickle cell anemia-sickle hemoglobin (HbS) (17). However, only a few studies have investigated the survival and predictive factors that can influence the outcomes during the clinical course of the α- and β-thalassemia genotypes. Thus, the present study aimed to identify the clinical factors that determine the survival rate in patients with α- and β-thalassemia and in those with co-inheritance of the α- and β-thalassemia genotypes.

2 Method

2.1 Study setting

This retrospective study reviewed the medical records of adult patients (aged >18 years) with thalassemia at the Rajavithi Hospital, Bangkok, Thailand, between 2002 and 2020. The eligibility criteria were thalassemia diagnosed using a high-performance liquid column chromatography (HPLC)-based hemoglobin analysis for β-thalassemia and the gap-PCR method for α-thalassemia (18). The primer sequences used were suitable for diagnosing 5 α^0-thalassemia deletions and 2 α^+-thalassemia deletions. In addition, for α-thalassemia, molecular diagnosis of α^0-thalassemia (category Southeast Asian or Thai deletion) and Hemoglobin Constant Spring (HbCS) was performed in patients with hemoglobin H (HbH) disease. Based on the risk of death (19), the sample size was calculated as at least 300 patients, ensuring that the study achieved 95% confidence interval and 5% significance level the risk of death hazard ratio equal to 2.8 in a prior study.

2.2 Recruitment and data collection method

The information collected included demographic characteristics and diagnosis based on hemoglobin analysis, first diagnosis with follow-up period, body mass index (BMI) [calculated as BMI = Wt/$(Ht)^2$, where weight (Wt) was in kilograms and height (Ht) was in meters], comorbidities, treatment-related thalassemia, and cause of death. Comorbidities during the follow-up period were categorized according to the guidelines provided in the OPTIMAL CARE study (14). Thalassemia patients were divided into two groups: TDT, which consisted of patients requiring regular blood transfusions every 2–6 weeks for survival, and NTDT, which consisted of patients who may or may not require an occasional transfusion (12, 20). Data analysis was conducted to determine the clinical characteristics, treatments, causes of death, and the survival rates.

2.3 Ethical consideration

The study was approved by and carried out in accordance with the Ethics Committee of the Rajavithi Hospital, no. 050/2562 (Rajavithi Hospital). The Ethics Committee of the Rajavithi Hospital has granted a waiver for informed consent. All patient data were de-coded, and written informed consent was not required as this was a retrospective study.

2.4 Data management and statistical analysis

Categorical data were expressed as number and percentages. Continuous parameters were demonstrated as the mean with standard deviation if the parameters were normally distributed

and as median if the parameters were not normally distributed. The Cox proportional hazards model was utilized to evaluate the relationship between risk factors and survival time, whereas the Kaplan–Meier method was used for survival analysis. Data were analyzed using SPSS Statistics version 22.0 (license 22.0; IBM, Armonk, NY, USA). A *p*-value less than 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

The data of 478 patients with thalassemia who matched our inclusion criteria were included in this study. Of these patients, 329 (68.8%) were women, the mean age was 41 ± 17 years (range, 16–91 years), and the median BMI was 19.9 kg/m^2 (range, 12.8–40.4 kg/m^2). The distribution of the thalassemia types was as follows: 51.9% had β-thalassemia/HbE, 29.7% had HbH, 8.4% had combined HbH CS disease, 4.6% had HbAE Bart's disease, 1.6% had homozygous HbCS, 1.5% had Hb EF Bart's disease and homozygous β-thalassemia, and 0.8% had Hb AE with CS disease. Men predominantly had β-thalassemia (21.1%), while women constituted the majority of those with α-thalassemia (35.4%). Individuals with combined α- and β-thalassemia were primarily women (6 out of 8). The baseline clinical characteristics of all patients are presented in Table 1. The pre-transfusion ferritin level was 1,052 ng/mL (range, 17–41,677 ng/mL), and 20.3% of the patients had ferritin levels >2,500 ng/mL. The last ferritin level was lower by 875 ng/mL (range, 34–25,034 ng/mL), whereas 18.6% of the patients had ferritin levels >2,500 ng/mL. The pre-transfusion hemoglobin level was 7.3 g/dL (range, 1.8–12 g/dL), and the last hemoglobin level was 7.6 g/dL (range, 2.2–14.9 g/dL). Hypertension

TABLE 1 Characteristics of 478 thalassemia patients.

Characteristics	n (%)	Median (range)
Gender		
Woman	329 (68.8)	
Man	149 (31.2)	
Age (years), mean ± SD		41 ± 17
Body mass index (kg/m^2)		19.9 (12.8–40.4)
<18.5	144 (30.1)	
≥18.5	334 (69.9)	
Thalassemia type		
Alpha-thalassemia	215 (45.0)	
Beta-thalassemia	255 (53.3)	
Alpha- and beta-thalassemia	8 (1.7)	

(Continued)

TABLE 1 Continued

Characteristics	n (%)	Median (range)
Comorbidities		
No	383 (80.1)	
Yes	95 (19.9)	
Hypertension	32 (33.7)	
Chronic kidney disease	17 (17.9)	
Malignancy	16 (16.8)	
Diabetes mellitus	14 (14.7)	
Dyslipidemia	14 (14.7)	
Others	46 (48.4)	
Splenectomy		
Yes	91 (19.0)	
Cholecystectomy		
Yes	49 (10.3)	
Pre-transfusion hemoglobin level (g/dL)		7.3 (1.8–12.0)
≤7	267 (55.9)	
>7	211 (44.1)	
Last hemoglobin level (g/dL)		7.6 (2.2–14.9)
≤7	290 (60.7)	
>7	188 (39.3)	
Pre-transfusion ferritin level (ng/mL)		1,052 (17–41,677)
<2,500	381 (79.7)	
≥2,500	97 (20.3)	
Last ferritin level (ng/mL)		875 (34–25,034)
<2,500	389 (81.4)	
≥2,500	89 (18.6)	
Transfusion status		
Yes	280 (58.6)	
Transfusion-dependent (TDT)	58 (20.7)	
Non-transfusion dependent (NTDT)	222 (79.3)	
Iron chelation therapy		
Yes	217 (45.4)	
Deferiprone	167 (77.0)	
Deferasirox	22 (10.1)	
Deferoxamine	15 (6.9)	
Combined deferoxamine + deferiprone	11 (5.1)	
Combined deferoxamine + deferasirox	2 (0.9)	

(33.7%) was the most common comorbid condition. Most of the patients (79.3%) had NTDT, almost half of all patients (45.4%) required iron chelator therapy for iron overload, and 19% of the patients underwent splenectomy. The mean age of the patients in the death group was 39.2 ± 2.7 years, and the time to developing complications did not differ statistically between the death and survival groups. Complications occurred in 19.2% of patients with thalassemia, which included liver disease, endocrinopathies, and cardiac disease. All patients were followed up in the hospital for at least 10 years (median follow-up of 16.1 years; range, 9.8–16.1 years).

3.2 Risk factors for death

Factors were classified using incidence death rate per 1,000 person-years and are presented in Table 2. The following factors were statistically significant in the model male sex ($p = 0.02$), BMI <18.5 kg/m^2 ($p = 0.013$), co-inheritance of the α- and β-thalassemia genotypes ($p < 0.001$), comorbidities ($p = 0.02$), pre-transfusion hemoglobin ≤7 g/dL ($p = 0.01$), last hemoglobin ≤7 g/dL ($p = 0.001$), pre-transfusion ferritin level ≥2,500 ng/mL ($p = 0.004$), last ferritin level ≥2,500 ng/mL ($p < 0.001$), and requirement of blood transfusion ($p = 0.013$). The univariate analyses identified the following variables as associated with death: gender [male: hazard ratio (HR) = 2.28, 95%CI = 1.11–4.66, $p = 0.024$]; BMI <18.5 kg/m^2 (HR = 2.40, 95%CI = 1.17–4.91, $p = 0.017$); thalassemia type (β-thalassemia: HR = 5.31, 95%CI = 1.84–15.29, $p = 0.002$; co-inheritance of the α- and β-thalassemia genotypes: HR = 14.45, 95%CI = 2.65–78.90, $p = 0.002$); blood transfusion (HR = 2.93, 95%CI = 1.20–7.18, $p = 0.018$); and pre-transfusion ferritin level >2,500 ng/mL (HR = 2.79, 95%CI = 1.34–5.79, $p = 0.006$) (Table 3). Subsequently, the multivariate logistic regression analyses revealed that the thalassemia type was independently associated with increased risk of death (β-thalassemia type: adjusted HR = 3.21, 95%CI = 1.01–10.21, $p = 0.048$; co-inheritance of the α- and β-thalassemia genotypes: adjusted HR = 13.17, 95%CI = 2.40–72.44, $p = 0.003$).

After treatment, the overall survival rate among patients with thalassemia was 93.7%, and the survival rates of patients with α-

TABLE 2 Incidence death rate per 1,000 person-years classified by factors.

Factors	Dead	Person-years	IDR/1,000 person years	p-value
Gender				0.02*
Male	15	2,344.12	6.40	
Female	15	5,250.30	2.86	
Body mass index (kg/m^2)				0.013*
<18.5	15	2,261.42	6.63	
≥18.5	15	5,333.00	2.81	
Thalassemia type				<0.001*
Alpha-thalassemia	4	3,458.31	1.16	
Beta-thalassemia	24	4,011.88	5.98	
Alpha- and beta-thalassemia	2	124.23	16.10	
Comorbidities				0.02*
No	19	6,090.03	3.12	
Yes	11	1,504.39	7.31	
Splenectomy				0.553
No	23	6,150.54	3.74	
Yes	7	1,443.88	4.85	
Cholecystectomy				0.942
No	27	6,811.75	3.96	
Yes	3	782.67	3.83	
Pre-transfusion hemoglobin level (g/dL)				0.01*
>7	10	4,272.18	2.34	
≤7	20	3,322.25	6.02	

(Continued)

TABLE 2 Continued

Factors	Dead	Person-years	IDR/1,000 person years	p-value
Last hemoglobin level (g/dL)				0.001*
>7	10	4,636.09	2.16	
≤7	20	2,958.33	6.76	
Pre-transfusion ferritin level (ng/mL)				0.004*
<2,500	18	6,084.84	2.96	
≥2,500	12	1,509.58	7.95	
Last ferritin level (ng/mL)				<0.001*
<2,500	15	6,225.28	2.41	
≥2,500	15	1,369.14	10.96	
Transfusion status				0.013*
No	6	3,175.35	1.89	
Yes	24	4,419.07	5.43	
Iron chelation therapy				0.585
No	15	4,158.46	3.61	
Yes	15	3,435.96	4.37	
Complications				0.013*
No	19	6,147.33	3.09	
Yes	11	1,447.09	7.60	

IDR, incidence death rate per 1,000 person year.
* means statistically significant.

TABLE 3 Cox proportional hazards model for the risk factors associated with death.

| Factors	Crude HR (95%CI)	p-value	Adjust HR (95%CI)	p-value
Gender (ref = female)	2.28 (1.11–4.66)	0.024*	1.73 (0.84–3.58)	0.138
Body mass index (ref ≥ 18.5)	2.40 (1.17–4.91)	0.017*	1.72 (0.82–3.62)	0.151
Thalassemia type				
Alpha-thalassemia	1		1	
Beta-thalassemia	5.31 (1.84–15.29)	0.002*	3.21 (1.01–10.21)	0.048*
Alpha- and beta-thalassemia	14.45 (2.65–78.90)	0.002*	13.17 (2.40–72.44)	0.003*
Transfusion status (ref = no)	2.93 (1.20–7.18)	0.018*	1.31 (0.47–3.65)	0.608
Pre-transfusion ferritin level (ng/mL) (ref < 2,500)	2.79 (1.34–5.79)	0.006*	1.89 (0.87–4.10)	0.106

* means statistically significant.

thalassemia, β-thalassemia, and co-inheritance of the α- and β-thalassemia genotypes were 98.1%, 90.6%, and 75.0%, respectively (Figure 1). A comparison of the overall survival rates classified by thalassemia genotype and phenotype indicated that the survival rate among α-thalassemia-TDT patients was 100%, whereas that for the NTDT group was 98.5%. In β-thalassemia, the survival rate among TDT patients was 92.3%, which was higher than that of NTDT patients (88.3%). The overall survival rates of patients with co-inheritance of the α- and β-thalassemia genotypes were 66.7% in the TDT group and 50.0% in the NTDT group (Figure 2). We recorded 30 deaths (15 men and 15 women) during the follow-up period, with the most common cause of death being infection (50.0%), followed by heart failure (23.3%), and then hepatocellular carcinoma, upper gastrointestinal bleeding, and
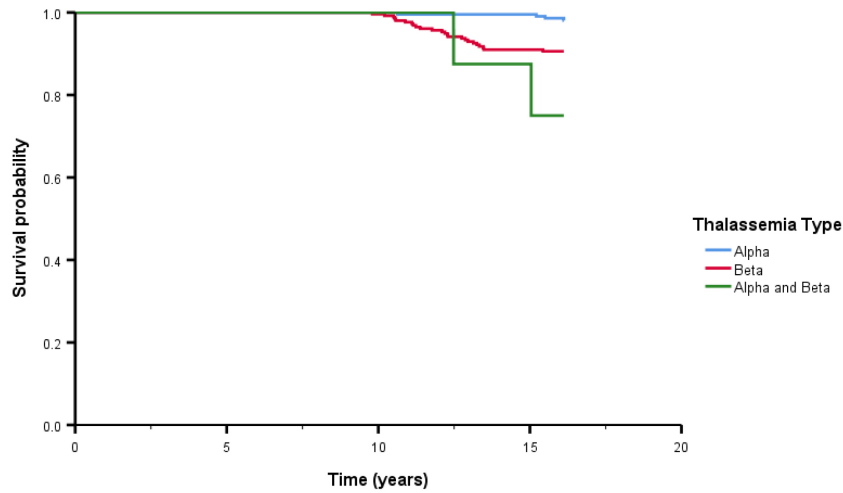
FIGURE 1
The overall survival after treatment among thalassemia patients classified by thalassemia type. Alpha means alpha thalassemia genotype, Beta means beta thalassemia genotype.
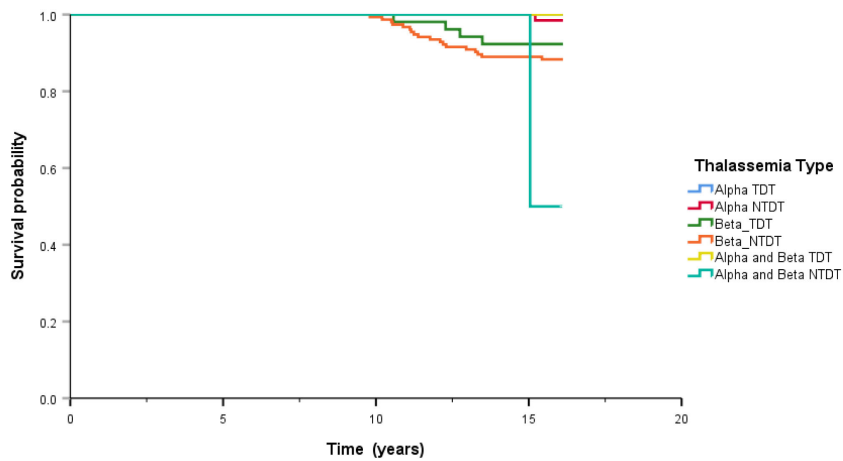
FIGURE 2
Comparison of overall survival classified by genotype of thalassemia. Alpha means alpha thalassemia genotype, Beta means beta thalassemia genotype, TDT means transfusion dependence thalassemia, and NTDT means non-transfusion dependence thalassemia.

cancers (6.7% in each). Among the death-related infection cases, five patients died from gut-associated organisms (*Vibrio* and *Escherichia coli*), followed by four with *Pseudomonas* septicemia, and one each with *Klebsiella* spp. and *Acinetobacter* infection. Two patients died with tuberculosis and one from advanced AIDS infection. The remaining cases had unidentified organisms. Patients with cancer had gynecologic malignancies ($n = 4$), hepatocellular carcinoma ($n = 3$), lung cancer ($n = 2$), breast cancer ($n = 2$), thyroid cancer ($n = 1$), prostate cancer ($n = 1$), cholangiocarcinoma ($n = 1$), leukemia ($n = 1$), and lymphoma ($n = 1$). Intracerebral hemorrhage and severe metabolic acidosis each accounted for 3.3% of all deaths (Table 4). Thalassemia survival patients were shown in Table 5.

TABLE 4 Causes of death among 30 thalassemia patients.

Causes of death	n (%)
Infection	15 (50.0)
Heart failure	7 (23.3)
Hepatocellular carcinoma	2 (6.7)
Upper gastrointestinal bleeding	2 (6.7)
Cancer (ovarian and breast)	2 (6.7)
Intracerebral hemorrhage	1 (3.3)
Severe metabolic acidosis	1 (3.3)

TABLE 5 Characteristics of 448 thalassemia survival patients.

Characteristics	n (%)	Median (range)
Gender		
Female	314 (70.1)	
Male	134 (29.9)	
Age (years), mean ± SD		41 ± 17
Body mass index (kg/m^2)		20.0 (12.8–40.5.)
<18.5	129 (28.8)	
≥18.5	319 (71.2)	
Thalassemia type		
Alpha-thalassemia	211 (47.1)	
Beta-thalassemia	231 (51.6)	
Alpha- and beta-thalassemia	6 (1.3)	
Comorbidities		
No	364 (81.3)	
Yes		
Hypertension	29 (6.5)	
Chronic kidney disease	13 (2.9)	
Malignancy	15 (3.3)	
Diabetes mellitus	11 (2.5)	
Dyslipidemia	14 (3.1)	
Splenectomy		
Yes	84 (18.9)	
Cholecystectomy		
Yes	46 (10.3)	
Pre-transfusion hemoglobin level (g/dL)		7.4 (1.8–12.0)
≤7	257 (57.4)	
>7	191 (42.6)	
Last hemoglobin level (g/dL)		7.6 (2.2–14.9)
≤7	168 (37.5)	
>7	280 (62.5)	
Pre-transfusion ferritin level (ng/mL)		1,027 (17–41,677)
<2,500	363 (81.0)	
≥2,500	85 (19.0)	
Last ferritin level (ng/mL)		824 (34–14,249)
<2,500	374 (83.5)	
≥2,500	74 (16.5)	
Transfusion status		
Yes	256 (57.1)	
Transfusion-dependent (TDT)	54 (21.1)	
Non-transfusion dependent (NTDT)	202 (78.9)	

(Continued)

TABLE 5 Continued

Characteristics	n (%)	Median (range)
Iron chelation therapy		
Yes		
Deferiprone	156 (77.2)	
Deferasirox	20 (9.9)	
Deferoxamine	20 (9.9)	
Combined deferoxamine + deferiprone	10 (5.0)	
Combined deferoxamine + deferasirox	2 (1.0)	

4 Discussion

This retrospective cohort study aimed to identify the clinical predictors of death and survival rates in Thai patients with thalassemia and to compare the results of this study with those of other studies (8, 9, 14). It is interesting to note that our cohort comprised predominately older women (aged >40 years), similar to another study (14), and that only 19% of the patients underwent splenectomy. This indicates that the availability of blood transfusion has reduced the need for splenectomy. Severe anemia was observed in about half of the cohort, both initially and during follow-up, a finding similar to that of other Thai studies (8, 9). A balance between blood transfusion and iron depletion has been proposed to increase the survival rates among patients with thalassemia (12, 21).

We demonstrated seven clinical factors that were significantly associated with death rate, namely, male sex, low BMI, thalassemia type, comorbidities, low hemoglobin level, high ferritin level, and requirement of regular blood transfusion. These findings are in agreement with those of multiple studies of clinical factors associated with survival rates in thalassemia (22–25). The greater risk due to male sex may be explained by the fact that thalassemia in women might be associated with lower oxidative stress, which in turn affects the cardiac function and incidence of infections (24). This effect is similar to that observed in hemochromatosis, which may also require regular blood transfusion and is associated with greater incidence of cardiac dysfunction and infection. In addition, several studies have demonstrated that high ferritin levels (>2,500 ng/mL) are associated with short-term survival in patients with thalassemia (13, 26). A low BMI typically reflects nutritional deficiencies among patients with thalassemia, and malnutrition can lead to anemia that requires regular blood transfusion (22). Thus, malnutrition is associated with TDT and is thereby related to iron overload, cardiac dysfunction, and increased infection rate. However, it should be noted that most published studies have been conducted on patients with thalassemia major, and it is possible that the type of thalassemia is significantly associated with complications and death. We demonstrated that thalassemia major (β-thalassemia) had a more severe clinical course than α-thalassemia. As blood transfusions are needed to treat anemia,

high ferritin levels can be commonly observed among TDT patients (8, 12, 15). This observation potentially reflects the association between transfusion dependence and more severe thalassemia conditions. The difference in the survival rates among various studies may be attributed to sample size disparities or the methods used for calculating the survival rate, which are based on the thalassemia major or thalassemia intermedia types. Similarly, the higher overall survival rate observed in our cohort may be attributed to the thalassemia type, which has also been reported by other studies (27, 28). Patients with thalassemia major are at a higher risk of mortality than those with other types of thalassemia, and the underlying etiology is the need for regular blood transfusions and consequent iron accumulation, leading to organ dysfunction (29). Other factors that may influence the survival of patients with thalassemia include time to diagnosis, availability of healthcare services, regular monitoring, proper treatment, and early iron chelation therapy. Contrary to the results presented here, a study from Great Britain found that 50% of patients with thalassemia intermedia died at a young age (<35 years) (6). Limitations in the study design and data analysis may have influenced the non-significant finding for age of complication onset.

There were hypotheses of the deletion of the α-globin gene with the β-thalassemia genotype affecting the hyperunstable globin variant, leading to easy hemolytic condition (30–32). The pathophysiology of co-inheritance is not clear to explain this phenomenon related to the survival rate. Interestingly, our data showed support that the co-inheritance of the α- and β-thalassemia genotypes with TDT reduced the survival rate. This combined hemoglobinopathy (α- and β-thalassemia) is contradictory to that of another study in patients with co-inheritance of α-thalassemia and other hemoglobinopathy types (HbS), especially with respect to improving the survival rate (17). Some studies have mentioned other clinical factors that might be related to the prognosis of α-thalassemia (10, 33, 34). Similarly to β-thalassemia leading to anemia that needs regular blood transfusions, complications might develop earlier among patients with co-inheritance of the α- and β-thalassemia types. It has been known that co-inheritance of the α- and β-thalassemia genotypes is relatively common in Southeast Asia (35). Blood transfusion with concordant iron chelation therapy was prescribed for the patients in our study. Iron overload due to long-term blood transfusion among patients with thalassemia is the major cause of complications, such as cardiac dysfunction, and 92 patients experienced complications (e.g., liver dysfunction, endocrinopathies, and cardiac disease). In our cohort, more than half were categorized as TDT, and iron chelation therapy, given twice in a 3-month interval, was advised when high serum ferritin levels were >1,000 ng/mL (14). While a few patients used deferasirox owing to its low cost, most patients (77%) received deferiprone and did not develop cardiac problems. This can be explained by the cardioprotective effect of deferiprone, which exhibits greater iron mobilization. This increases the heart signal and improves heart function in patients with iron overload (36). Surprisingly, we found a high incidence of infection (50% of the study population). This observation is different from the results of a previous study (27). In another study, it was demonstrated that thalassemia patients with iron overload predominantly suffered

from cardiac complications, including heart failure and arrhythmia (29). We hypothesized that the high ferritin levels in our cohort have rendered the patients susceptible to bacterial infection, with the underlying mechanism involving impaired phagocytic function of macrophages and neutrophils, alternated T lymphocytes, lower numbers and function of natural killer cells, increased numbers and function of B lymphocytes, impaired secretion of immunoglobulin, and suppression of the complement system function (11). In support of this hypothesis, Teawtrakul et al. have demonstrated that a high ferritin level is a significant risk factor to bacterial infection in patients with TDT (15). The strength of this study lies in our observational study supporting the hypothesis of co-inherited thalassemia patients having low survival rates. The limitations of this study include its retrospective design and the fact that the cohort was recruited from a tertiary care center with a small sample size for subgroup analysis. Although we demonstrated poor survival among patients with co-inheritance of the α- and β-thalassemia genotypes and TDT, future studies on a larger population are required to validate the results of the present study. A case–control study may be needed to make conclusions on clinical parameters for use in the global medical fraternity, including exploring potential differences in the efficacy and compliance between the various iron chelators used in clinical practice.

5 Conclusion

The overall survival rate among patients with thalassemia was 93.7%, and it was higher in those with α-thalassemia-TDT. However, the co-inheritance of the α- and β-thalassemia genotypes with TDT led to poor survival, and it was found that the most common cause of death was infection. Our results suggest the usefulness of clinical parameters in estimating the survival rates among patients with thalassemia.

Data availability statement

Available data and materials upon request, please directly contact correspondence author for data request according to the regulation of the Ethical Committees. Requests to access the datasets should be directed to Supat.cha@mahidol.ac.th.

Ethics statement

The studies involving humans were approved by The Ethics Committee of the Rajavithi Hospital-Number 050/2562 (Rajavithi Hospital). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because all patient data were decoded and this was a retrospective study, written informed consent was not required.

Author contributions

KI-a: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. SC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TS: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Writing – review & editing. PT: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Writing – review & editing. SF: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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