Increased risk of arterial thromboembolic events in transfusion-naïve thalassemia: a nationwide population-based study

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ABSTRACT

Transfusion-naïve thalassemia minor/trait is often associated with decreased risk of coronary artery diseases. The present study aimed to evaluate the effect of transfusion-naïve thalassemia on the incidence of arterial thromboembolic events using the National Health Insurance Research Database, Taiwan (2001–2010). Data from patients with transfusion-naïve thalassemia (n=2356) frequency matched with non-thalassemia subjects (n=9424) according to sex, age, and index year at a ratio of 1:4 were included. The risk of arterial thromboembolic events, cerebrovascular ischemic events, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, and angina pectoris in transfusion-naïve thalassemia were analyzed using Cox proportional hazard regression models. The transfusion-naïve thalassemia group had significantly higher risk of arterial thromboembolic events (aHR=1.28, 95% CI 1.07 to 1.52) and myocardial ischemia (aHR=1.41, 95% CI 1.13 to 1.76) as compared with the non-thalassemia group. In addition, they also had a significantly higher cumulative incidence of arterial thromboembolic event and myocardial ischemia. Interestingly, a higher risk of arterial thromboembolic events (aHR=1.58, 95% CI 1.22 to 2.04) and myocardial ischemia (aHR=1.73, 95% CI 1.25 to 2.41) was observed in men with thalassemia as compared with those without. Furthermore, patients with comorbidities had an increased risk of arterial thromboembolic events than did those without comorbidities. The effect of thalassemia on arterial thromboembolic events may be mainly attributed to the influence of thalassemia on myocardial ischemia, as no significant differences were observed in other outcomes evaluated in the present study. In conclusion, the present study confirms the increased risk of arterial thromboembolic events, mainly attributed to the dramatic increase in myocardial ischemia, inminor patients with transfusion-naïve thalassemia.

Significance of this study

What is already known about this subject?

- Transfusion dependence is a key factor in differentiating the various phenotypes of thalassemia and their severity.
- Thalassemia minor is associated with decreased prevalence of arterial hypertension.
- Transfusion-naïve thalassemia minor/trait is often associated with decreased risk of coronary artery diseases.

What are the new findings?

- Patients with transfusion-naïve thalassemia had a significantly higher risk of arterial thromboembolic events and myocardial ischemia.
- Men with thalassemia had a higher risk of arterial thromboembolic events and myocardial ischemia compared with those without thalassemia.
- The effect of thalassemia on arterial thromboembolic events may be mainly attributed to the influence of thalassemia on myocardial ischemia.

How might these results change the focus of research or clinical practice?

- The present results may provide insights in the understanding and management of cardiovascular events and its association with comorbidities in the transfusion-naïve thalassemia population.

INTRODUCTION

Thalassemia is a hereditary disorder of hemoglobin synthesis that results in ineffective hematopoiesis and variable degrees of hemolytic anemia.[1] This condition is characterized by an absence of or reduction in the α-globin and/or β-globin polypeptide chains of the hemoglobin tetramer. Such aberrant globin chain synthesis leads to an imbalance in the number of α and β subunits of hemoglobin.[2 3]

β-thalassemia, caused by deletional or non-deletional mutations in one or more of the four β-globin genes, results in an array of phenotypes ranging from severe anemia to an absence of clinical symptoms. This condition affects multiple organs and is associated with considerable morbidity and mortality.[3] The incidence of β-thalassemia is high in Mediterranean

countries, the Middle East, Central Asia, India, Southern China, and the Far East, as well as in countries along the north coast of Africa and in South America.[4 5] The highest carrier frequencies are reported in Cyprus (14%), Sardinia (10.3%), and South-East Asia.[6] Reports estimate that the global prevalence of abnormal hemoglobin and thalassemia is 270 million people, of which 80 million have β-thalassemia.[7]

While less common than β-thalassemia, α-thalassemia is also a common human monogene disorder.[8] The most common cause of α-thalassemia is deletional mutation of the α-globin gene. The normal complement of four functional α-globin genes may be decreased by one, two, three, or all four copies, explaining the clinical variation and increasing severity of the disease.[9] Individuals who carry only one such mutation are often asymptomatic.[10] Compound heterozygotes and some homozygotes have a moderate-to-severe form of α-thalassemia known as **hemoglobin H diseas** (HbH) disease,[9] characterized by hemolytic anemia, splenomegaly, mild jaundice, and sometimes bone changes.[11] The most severe deficiency in α-globin production is observed in infants who inherit no α-globin genes from either parent, a condition known as Hb Bart's hydrops fetalis syndrome. Symptoms include fetal onset of generalized edema, pleural and pericardial effusions, severe hypochromic anemia, marked hepatosplenomegaly, extramedullary erythropoiesis, hydrocephalus, and cardiac and urogenital defects. Death usually occurs during the neonatal period. Patients with non-deletional mutations in the α-globin genes often have more severe symptoms than do those with deletional mutations.[8 12] An example is the hemoglobin constant spring variant of the α-2 globin gene. Patients homozygous for this mutation have a more serious clinical phenotype than do those who are homozygous for deletional α-thalassemia.[13]

Based on the quantity of α-globin and β-globin produced and the severity of clinical symptoms, thalassemias are classified as either the carrier state (also termed 'minor' or 'trait), thalassemia intermedia, or thalassemia major. Transfusion dependence is a key factor in differentiating the various phenotypes and their severity.[14] Patients with thalassemia major with severe anemia often require regular blood transfusions, while heterozygous carriers are clinically asymptomatic and are identified only by specific hematological features. Thalassemia intermedia comprises a heterogeneous group both clinically and genotypically, with features ranging from the asymptomatic carrier state to the severe transfusion-dependent type.[15]

The underlying pathophysiology of thalassemia is the accumulation of α-globin (in β-thalassemia) or β-globin (in α-thalassemia) and premature apoptotic destruction of erythroblasts, causing oxidative-stress-induced ineffective erythropoiesis, bone marrow hyperplasia, splenomegaly, and increased intestinal iron absorption with progressive iron overload.[16] Ineffective hematopoiesis and chronic transfusions can lead to secondary iron overload and target organ damage, including heart failure.[17] Transfusion-related chronic complications like cerebral thrombosis, myocardial infarction, and coronary artery diseases (CADs) are generally reported in patients with transfusion-dependent thalassemia with severe clinical manifestations.[18 19] In contrast, non-transfusion-dependent patients show no clinical symptoms but may have a type of microcytic hypochromic anemia, seldom requiring blood transfusion (transfusion-naive).[19 20]

Studies have shown that β-thalassemia minor plays a protective role in preventing cardiovascular events including CAD and ischemic cerebrovascular accidents.[21–24] Moreover, thalassemia minor is associated with a decreased prevalence of arterial hypertension. These protective effects could be attributed to the lower total cholesterol and LDL levels and low blood viscosity seen in patients with thalassemia minor.[18 23] However, the cardioprotective effects attributed to the carriers of β-thalassemia have been challenged in recent years. Results of a population-based study demonstrated that patients with transfusion-naïve thalassemia had a higher risk of CAD than did those without thalassemia.[19] Other studies have reported that thalassemia trait may act as a protective factor against the development of arterial cardiovascular and cerebrovascular disease in men.[23] The present study evaluates the effect of transfusion-naïve thalassemia on the incidence of arterial thromboembolic events in patients registered in the National Health Insurance Research Database (NHIRD) in Taiwan.

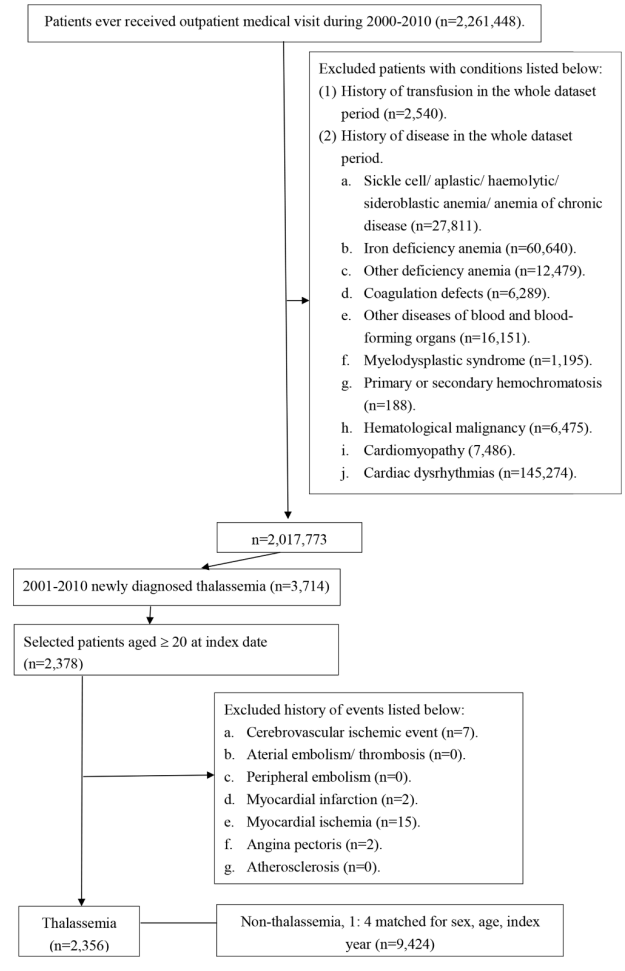

Figure 1 Flow chart for the selection of the thalassaemia and non-thalassaemia study population.

Table 1 Demographic and baseline characteristics in the transfusion-naïve thalassemia group and controls

	Thalassemia n = 2356	Non-thalassemia n= 9424	P values
Male	922 (39.1)	3688 (39.1)	1.00
Age, years	38.4 (14.99)	38.4 (15.12)	0.90
Socioeconomic status			
Low	955 (40.5)	4355 (46.2)	<0.0001
Moderate	923 (39.2)	3582 (38.0)	
High	478 (20.3)	1487 (15.8)	
Urbanization level			
Urban	607 (25.8)	2158 (22.9)	0.007
Suburban	809 (34.3)	3191 (33.9)	
Rural	413 (17.5)	1738 (18.4)	
Unknown	527 (22.4)	2337 (24.8)	
Comorbidities			
Diabetes	149 (6.3)	311 (3.3)	<0.0001
COPD	115 (4.9)	217 (2.3)	<0.0001
Hyperlipidemia	128 (5.4)	294 (3.1)	<0.0001
Hypertension	218 (9.3)	524 (5.6)	<0.0001
Chronic kidney disease	19 (0.8)	10 (0.1)	<0.0001

COPD, chronic obstructive pulmonary disease.

METHODS

Data source

The National Health Insurance (NHI) program in Taiwan is a universal insurance system established by the Bureau of National Health Insurance in the Department of Health and was implemented in 1995. The insurance program provides healthcare to 99% of the 23.74 million people in Taiwan, and has a contract with 97% of hospitals and clinics in Taiwan.[25] NHIRD includes original claims data of inpatient expenditures by admission, ambulatory care expenditures by visits, as well as details of admission and ambulatory care orders. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Informed consent was not obtained as the patient database contained only deidentified data.

Study population

Patients aged ≥20 years diagnosed with thalassemia (ICD-9-CM code 282.4) between 2001 to 2010 were included in our study cohort. The index date was defined as the date of the first clinical visit for thalassemia after 2000. We excluded patients with a history of arterial thromboembolic events (ICD-9-CM codes 410–414, 433–435, 443.9, 444, 445, 449).

We further excluded patients with a history of transfusion (ICD-9-CM code 990), sickle cell/aplastic/hemolytic/sideroblastic anemia/anemia of chronic disease (ICD-9-CM codes 282.6–285.8), iron deficiency anemia (ICD-9-CM code 280), other deficiency anemia (ICD-9-CM code 281), coagulation defects (ICD-9-CM code 286), other diseases of blood and blood-forming organs (ICD-9-CM code 289), myelodysplastic syndrome (ICD-9-CM code 238.7), primary or secondary hemochromatosis (ICD-9-CM code 275.0), hematological malignancy (ICD-9-CM codes 200–208), cardiomyopathy (ICD-9-CM code 425), and cardiac dysrhythmias (ICD-9-CM code 427).

Patients in the non-thalassemia cohort were selected using a simple random sampling method in which four insured people among the NHI data set without thalassemia were randomly selected and matched with each person with thalassemia in the same period according to age, sex, and index year.

OUTCOMES AND COVARIATES

The outcomes analyzed were arterial thromboembolic events, which included cerebrovascular ischemic events (ICD-9-CM codes 433–435), arterial embolism/thrombosis (ICD-9-CM codes 444, 445, 449), peripheral embolism (ICD-9-CM code 443.9), myocardial infarction (ICD-9-CM codes 410, 412), myocardial ischemia (ICD-9-CM codes 411, 414), and angina pectoris (ICD-9-CM code 413).

Table 2 Association of risk factors for arterial thromboembolic events in the total study population

	Arterial thromboembolic event† Crude HR (95% CI)	Cerebrovascular ischemic event Crude HR (95% CI)	Arterial embolism/ thrombosis Crude HR (95% CI)	Peripheral embolism Crude HR (95% CI)
Socioeconomic status (vs low)				
Moderate	1.45 (1.23 to 1.71)***	1.46 (1.09 to 1.95)*	0.45 (0.14 to 1.41)	2.84 (1.52 to 5.33)*
High	1.10 (0.88 to 1.38)	1.08 (0.72 to 1.61)	0.25 (0.03 to 1.94)	1.18 (0.46 to 3.08)
Urbanization level (vs urban)				
Suburban	1.14 (0.93 to 1.40)	1.44 (0.99 to 2.09)	0.88 (0.24 to 3.28)	1.41 (0.66 to 3.01)
Rural	1.76 (1.42 to 2.17)***	2.42 (1.66 to 3.52)***	1.33 (0.33 to 5.30)	2.66 (1.25 to 5.69)*
Comorbidities (yes vs no)				
Diabetes	8.92 (7.37 to 10.80)***	8.04 (5.77 to 11.21)***	4.27 (0.97 to 18.84)	16.50 (9.29 to 29.30)***
COPD	3.63 (2.77 to 4.76)***	3.91 (2.49 to 6.13)***	5.11 (1.16 to 22.49)*	1.44 (0.35 to 5.93)
Hyperlipidemia	6.36 (5.11 to 7.90)***	4.03 (2.61 to 6.21)***	–	9.22 (4.72 to 17.99)***
Hypertension	10.31 (8.74 to 12.16)***	9.86 (7.44 to 13.07)***	5.97 (1.92 to 18.57)*	6.73 (3.64 to 12.46)***
Chronic kidney disease	4.50 (1.87 to 10.84)**	2.79 (0.39 to 19.90)	39.85 (5.22 to 304.10)**	–

*p<0.05, **p<0.001, ***p<0.0001.
†Including cerebrovascular ischemic event, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, angina pectoris.
COPD, chronic obstructive pulmonary disease.

Table 3 Association of risk factors for arterial thromboembolic events in the total study population

	Myocardial infarction Crude HR (95% CI)	Myocardial ischemia Crude HR (95% CI)	Angina pectoris Crude HR (95% CI)
Socioeconomic status (vs low)			
Moderate	1.14 (0.53 to 2.42)	1.35 (1.08 to 1.68)*	1.15 (0.81 to 1.62)
High	0.59 (0.17 to 2.04)	1.20 (0.90 to 1.60)	0.83 (0.50 to 1.37)
Urbanization level (vs urban)			
Suburban	1.53 (0.58 to 4.02)	0.99 (0.76 to 1.28)	1.43 (0.92 to 2.21)
Rural	1.76 (0.61 to 5.06)	1.61 (1.23 to 2.12)**	1.67 (1.04 to 2.70)*
Comorbidities (yes vs no)			
Diabetes	20.43 (9.81 to 42.54)***	9.07 (7.10 to 11.60)***	9.24 (6.29 to 13.58)***
COPD	5.54 (1.93 to 15.87)*	4.36 (3.13 to 6.07)***	1.24 (0.51 to 3.03)
Hyperlipidemia	14.30 (6.53 to 31.32)***	6.95 (5.29 to 9.14)***	6.48 (4.18 to 10.05)***
Hypertension	20.48 (9.97 to 42.08)***	11.27 (9.13 to 13.92)***	8.79 (6.22 to 12.42)***
Chronic kidney disease	22.16 (3.00 to 163.52)*	4.70 (1.51 to 14.66)*	4.04 (0.56 to 28.87)

*p<0.05, **p<0.001, ***p<0.0001.
COPD, chronic obstructive pulmonary disease.

The patients were followed up until the events happened. The baseline comorbidity histories of diabetes (ICD-9-CM code 250), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 490–496), hyperlipidemia (ICD-9-CM codes 272.0–272.4), hypertension (ICD-9-CM code 401), and chronic kidney disease (CKD, ICD-9-CM code 585) before the index date were identified. Patient socioeconomic status was stratified into three groups: low, moderate, and high, based on the minimum monthly wage for the year 2006 (NT $15,840).[26] Urbanization levels were classified into three groups: urban (urbanization level 1), suburban (urbanization levels 2–3), and rural (urbanization levels 4–7).[27] Data were censored due to patient withdrawal from insurance, lost-to-follow-up, death, or the end of 2012.

STATISTICAL ANALYSIS

Numerical variables were presented as mean and SD, while the categorical variables were presented as frequency and percentage. Difference in the outcomes measured between the thalassemia and non-thalassemia groups were analyzed using either Student's t-test for numerical variables or Pearson's χ^2 test for categorical variables. Cox proportional hazards model was used to estimate the risk for observed events, including arterial thromboembolic events, cerebrovascular ischemic events, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, angina pectoris and other risk factors for thalassemia. The risk estimates of factors other than thalassemia were calculated separately for each observed event in univariate Cox's proportional hazards model, and factors with statistical significance in the univariate model were further included in multiple Cox proportional hazards models for adjustment. In addition, subgroup analyses stratified by gender were conducted for each observed event in this study. Cumulative incidence function and log-rank tests were also performed to estimate the difference in the risk of arterial thromboembolic events and myocardial ischemia between the thalassemia and non-thalassemia groups. All statistical analyses were conducted using the SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA) and a p value <0.05 (two-tailed) was considered statistically significant.

RESULTS

The flow chart for the selection of the thalassemia and non-thalassemia study population is shown in figure 1. After selecting subjects in a ratio of 1:4, matched for sex, age, and index year, the study cohort included 2356 patients with thalassemia and 9424 non-thalassemia subjects (figure 1). In the thalassemia group 39.1% of patients were men, and the overall average age in this group was about 38.4 years. Distributions of socioeconomic status (p<0.0001),

Table 4 Arterial thromboembolic events in transfusion-naïve thalassemia and non-thalassemia groups

	Thalassemia n=2356	Non-thalassemia n=9424	Crude HR (95% CI)	Adjusted HR (95% CI)†
Arterial thromboembolic event‡	177 (7.5)	485 (5.2)	1.52 (1.28 to 1.80)***	1.28 (1.07 to 1.52)*
Cerebrovascular ischemic event	49 (2.1)	169 (1.8)	1.18 (0.86 to 1.62)	0.97 (0.70 to 1.34)
Arterial embolism/thrombosis	6 (0.3)	10 (0.1)	2.45 (0.89 to 6.73)	1.95 (0.69 to 5.51)
Peripheral embolism	12 (0.5)	40 (0.4)	1.22 (0.64 to 2.33)	0.96 (0.50 to 1.84)
Myocardial infarction	8 (0.3)	22 (0.2)	1.48 (0.66 to 3.33)	0.97 (0.43 to 2.20)
Myocardial ischemia	113 (4.8)	269 (2.9)	1.74 (1.39 to 2.16)***	1.41 (1.13 to 1.76)*
Angina pectoris	42 (1.8)	106 (1.1)	1.62 (1.13 to 2.32)*	1.32 (0.92 to 1.90)

*p<0.05, **p<0.001, ***p<0.0001.
†Model adjusted for socioeconomic status, urbanization level, comorbidities at significance in an univariate model.
‡including cerebrovascular ischemic event, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, angina pectoris.

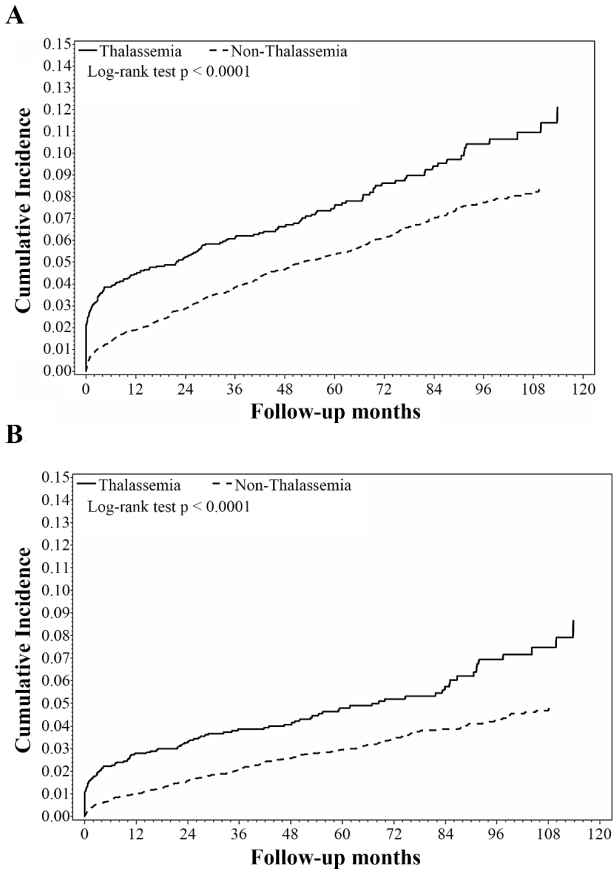

Figure 2 Cumulative incidences in thalassemia and non-thalassemia groups. (A) Cumulative incidence for arterial thromboembolic event. (B) Cumulative incidence for myocardial ischemia.

urbanization (p=0.007), and all comorbidities (p<0.0001) (including diabetes, COPD, hyperlipidemia, hypertension, CKD) in the thalassemia group were significantly different from those in the non-thalassemia group (table 1).

Univariate logistic regression analysis was performed to identify risk factors for arterial thromboembolic events, which included cerebrovascular ischemic event, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, and angina pectoris. The results showed that patients with comorbidities were at a higher risk of arterial thromboembolism than patients without comorbidities (tables 2 and 3). After adjusting for risk factors in the univariate model, the risk for arterial thromboembolic event (aHR=1.28, 95% CI 1.07 to 1.52) and myocardial ischemia (aHR=1.41, 95% CI 1.13 to 1.76) was significantly higher in the thalassemia group as compared with the non-thalassemia group (table 4).

Log-rank tests for cumulative incidence indicate significant differences in arterial thromboembolic events (p<0.0001) and myocardial ischemia (p<0.0001) between the thalassemia and non-thalassemia groups (figure 2A,B). Furthermore, the influence of gender on the risk for arterial thromboembolic events was analyzed and presented in table 5. After stratification of all eligible patients based on gender, male patients in the thalassemia group had a higher risk for arterial thromboembolic event (aHR=1.58, 95% CI 1.22 to 2.04) and myocardial ischemia (aHR=1.73, 95% CI 1.25 to 2.41) compared with male subjects in the non-thalassemia group (table 5). On the other hand, no significant differences were observed between women in the thalassemia and non-thalassemia groups.

Table 5 Arterial thromboembolic event in transfusion-naïve thalassemia and non-thalassemia groups by gender

	Adjusted HR (95% CI)†	
	Male	Female
Arterial thromboembolic event‡	1.58 (1.22 to 2.04)**	1.09 (0.86 to 1.38)
Cerebrovascular ischemic event	1.22 (0.76 to 1.96)	0.84 (0.54 to 1.32)
Arterial embolism/thrombosis	2.13 (0.35 to 12.98)	1.70 (0.45 to 6.40)
Peripheral embolism	0.92 (0.29 to 2.90)	0.91 (0.41 to 2.02)
Myocardial infarction	1.07 (0.34 to 3.40)	0.94 (0.29 to 3.10)
Myocardial ischemia	1.73 (1.25 to 2.41)*	1.20 (0.88 to 1.63)
Angina pectoris	1.71 (0.99 to 2.93)	1.10 (0.67 to 1.79)

*p<0.05, **p<0.001, ***p<0.0001.
†Model adjusted for socioeconomic status, urbanization level, comorbidities at significance in an univariate model.
‡Including cerebrovascular ischemic event, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, angina pectoris.

DISCUSSION

The present study analyzed the effect of transfusion-naïve thalassemia on the incidence of arterial thromboembolic events in patients registered in the NHIRD of Taiwan. In this study, arterial thromboembolic event is defined to include cerebrovascular ischemic event, arterial embolism/thrombosis, peripheral embolism, myocardial infarction, myocardial ischemia, and angina pectoris. The results indicate that subjects in the thalassemia group had higher odds of developing arterial thromboembolic events and myocardial ischemia than those in the non-thalassemic group. In addition, the transfusion-naïve thalassemia group had significantly higher cumulative incidence of arterial thromboembolic events (figure 2A) and myocardial ischemia (figure 2B). However, no difference in the incidence of cerebrovascular ischemic events, arterial or peripheral embolism, thrombosis, myocardial infarction, and angina pectoris were observed between the groups (table 4). Furthermore, the risk for arterial thromboembolic event and myocardial ischemia was higher in male patients with thalassemia as compared with men in the non-thalassemia group (table 5). No such difference was observed in women between the two groups. The present study confirms the increased risk of arterial thromboembolic events, mainly attributed to the dramatic increase in myocardial ischemia, in minor patients with transfusion-naïve thalassemia.

Our current results are in agreement with a similar population-based cohort study in patients with transfusion-naïve thalassemia, where the risk of CAD was 1.5 times higher than that of non-thalassemia controls after adjustment for age, sex, and medical comorbidities.[19] Moreover, the overall risk of developing CAD was significantly greater in

patients with both thalassemia and multiple comorbidities as compared with the normal population. Similarly, our results also reveal that patients with comorbidities were at higher risk for developing arterial thromboembolic events (tables 2 and 3).

Thalassemia minor is often reported to be associated with decreased prevalence of arterial hypertension, myocardial infarction and might offer protection against cerebrovascular accidents.[24] Thalassemia heterozygosity is found to be a favorable factor in reducing the risk of advanced CAD, defined as the presence of atheroma in coronary arteries resulting in at least 70% stenosis. Hypolipidemia, mild anemia, and microcytosis caused by the β-thalassemia trait alters the red blood cell rheology, improves blood filterability and viscosity, thus conferring its cardioprotective effect.[21] A systematic review and meta-analysis on the association of thalassemia minor and arterial cardiovascular disease reveal that the thalassemia trait may act as a protective factor against the development of arterial cardiovascular and cerebrovascular disease in male subjects, but not in women.[23]

In line with these reports, we also hypothesized that transfusion-naïve thalassemia might be associated with a reduced risk of arterial thromboembolic events. However, the present results do not support the protective role of thalassemia minor in myocardial ischemia and arterial thromboembolic events. In effect, the protective effect of transfusion-naïve thalassemia has been challenged recently in literature. Reports indicate that the cardioprotective prevalence of heterozygous thalassemia was not significantly different among patients with or without CAD, nor does it affect the likelihood of atherosclerotic plaque formation.[20] Yet another study had shown that a transfusion-naïve thalassemia population is a crucial risk factor for CAD, even in patients with relatively mild clinical manifestations of thalassemia. Bodzar *et al* have suggested that the β-thalassemia trait may offer protection against ischemic heart disease, though it is not absolute cardioprotection due to the role of other risk factors.[28] Significant differences in comorbidities including diabetes, COPD, hyperlipidemia, hypertension, and CKD were observed in our study cohort, and patients with comorbidities were at higher risk of arterial thromboembolic events (tables 1–3). Based on our results and previous reports, it becomes more evident that patients with transfusion-naïve thalassemia with chronic comorbidities must be made aware of the influence of comorbidities and must be clinically managed, if feasible, to delay the onset of cardiovascular events.

A major strength of this study is that it consists of subjects selected from a nationwide registry covering 99% of the 23.74 million people in Taiwan, providing a high number of patients with transfusion-naïve thalassemia (n=2356). Patients with transfusion-naïve thalassemia were matched with controls in a 1:4 ratio to minimize the effect of confounding factors like sex, age, and index year. However, we acknowledge that this study has several limitations, the major one being that the evidence is derived from a retrospective cohort study. Another limitation is that information about lifestyle and personal behavior, such as smoking, body mass index, physical activity, and family history were not included in the NHIRD. Thus, the possible effects of these confounding variables could not be ruled out. Further, the diagnostic criteria of thalassemia and comorbidities were not specified in the NHIRD and were identified based on ICD codes only. Coding errors and misclassification might exist. Moreover, the severity of the comorbidities was unknown based on the ICD codes, which might potentially impact the outcomes evaluated. Although we excluded all patients with thalassemia major by blood transfusion ICD codes, few cases of non-transfusion-dependent thalassemia (NTDT) or thalassemia intermedia who did not require blood transfusion might still exist in the study cohort. The carrier frequency of NTDT is high, up to 80% in tropical and subtropical regions and has a variable presentation that can go unnoticed.[29] It is also important to note that the complications associated with NTDT, including ineffective erythropoiesis, thrombosis, pulmonary hypertension, and right heart failure, can be severe if not properly managed and awareness of NTDT is important in early detection of cardiovascular complications.[30] The incidental inclusion of patients with NTDT in our study cohort might have led to the higher incidence of thromboembolic events observed. Similarly, people with thalassemia minor/trait have no clinical manifestations usually and might go undiagnosed and hence not included in the study cohort. Finally, the maximum length of follow-up was 10 years, which might not be long enough to identify the incidence of arterial thromboembolic events and myocardial ischemia. Well-designed prospective studies should be conducted to validate the present results. Nevertheless, our study provides further evidence for the increased risk of CAD in transfusion-naïve patients and its association with comorbidities in this population.

In conclusion, this large-scale, longitudinal cohort study underscores the increased risk of myocardial ischemia and arterial thromboembolic events in patients with transfusion-naïve thalassemia. Male patients with thalassemia were at a higher risk than the normal male population. The increase in arterial thromboembolic events are mainly attributed to the increased incidence of myocardial ischemia in the thalassemia group as compared with the non-thalassemia group. In addition, patients with comorbidities had a higher risk of developing arterial thromboembolic events irrespective of their thalassemia carrier status. The present results, once validated, may drive a significant shift in the understanding and management of cardiovascular events and its association with comorbidities in the transfusion-naïve thalassemia population.

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