Transfusion-naïve Thalassemia Pediatric Patients have Higher Incidence of Asthma: A Nationwide Population-based Retrospective Cohort Study

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Abstract

Background: Few studies have studied the association between asthma and pediatric transfusion naïve thalassemia.

Methods: A nationwide population-based retrospective cohort study was conducted using medical records of selected children from the 2010 Registry for Beneficiaries of the Taiwan National Health Insurance Research Database, with a follow-up period extending to the end of 2013. One thalassemia patient was matched with four control patients without thalassemia according to year of birth, sex, and the propensity score model based on comorbidities.

Results: In this study, 794 patients with thalassemia and 3176 controls were included. Transfusion-naïve thalassemia children had higher rates to develop asthma (41.03 vs 36.69 per 1000 person-y; P = 0.032) than the non-thalassemia controls with an adjusted hazard ratio of 1.16 (95% confidence interval (CI) = 1.01–1.33). Boys in the thalassemia cohort had a significantly higher adjusted hazard ratio of asthma than those in the non-thalassemia cohort (adjusted hazard ratio = 1.20, 95% CI = 1.02–1.42). In thalassemic patients without atopic dermatitis, the risk of asthma was 1.25-fold higher than in the non-thalassemic ones (95% CI=1.07–1.47).

Conclusions: Transfusion-naïve thalassemia children are more likely to have asthma. We need to pay more attention to it in order to diagnosis asthma earlier and to prevent asthma attacked earlier.

Background

Thalassemia is an autosomal recessive hereditary hemoglobinopathy and has complex genotypes associated with various broad clinical manifestations ranging from asymptomatic to severe lethal complications (1). According to epidemiologic results provided by the World Health Organization, patients with thalassemia account for approximately 5% of the world population (2) and up to 6.2% in our country (3–6). We frequently classified thalassemia into silent carrier, trait, intermedia and thalassemia major (7). Transfusion related chronic complications, for example cardiovascular diseases, are typically found in the patients with thalassemia (7). However, it is still not very clear whether transfusion-naïve thalassemia pediatric patients have higher incidence of chronic illness or complications.

Asthma is the most common chronic inflammatory illness in childhood and a major cause of morbidity in adults, affecting 9.3% of children in the United States (8) and 20.7% of school children in recent Taiwan epidemiological study (9, 10).

The incidence or prevalence of asthma among patients with transfusion-naïve thalassemia pediatric patients are uncertain. The objective of the present study is to determine whether transfusion-naïve thalassemia pediatric patients have higher incidence of asthma than populations without thalassemia and related risk factors.

Methods

1.1 Data source

The Taiwan National Health Insurance (NHI) program is a singlepayer system instituted on March 1, 1995, which, according to the Bureau of the National Health Insurance (BHNI), covers approximately 99% of the 23.74 million citizens of Taiwan. The BNHI has authorized the National Health Research Institutes (NHRI) to create the National Health Insurance Research Database (NHIRD) for medical research; this database contains administrative and health claims data collected through the NHI program. In this study, we used the Longitudinal Health Insurance Database 2010 (LHID2010), which is a subset of the NHIRD comprising patient data from 1996 to 2013. The LHID2010 comprises data on 1,000,000 beneficiaries randomly sampled from the original NHIRD.

1.2. Sampled patients

Patients who was diagnosed with thalassemia (ICD-9-CM code 282.4) and born between 1997 and 2010 were included in our study cohort. We excluded patients with a history of transfusion (ICD-9-CM code: 990 or treatment code 990) or a history of partial or total splenectomy (ICD-9 treatment code 70001B, 70003B, and 70006B), immunodeficiency (ICD-9-CM: 279), iron deficiency and other deficiency anemias (ICD-9-CM: 280 ~ 281), myelodysplastic syndrome (ICD-9-CM: 238.7), primary or secondary hemochromatosis (ICD-9-CM: 275.0), and hematological malignancies (ICD-9-CM: 200 ~ 208), or for whom age or sex information at the baseline was missing.

One thalassemia patient was matched with four control patients without thalassemia (1:4 matching) according to year of birth, sex, and the propensity score model based on comorbidities. The comorbidities included were atopic dermatitis (ICD-9-CM code 691.xx), allergic rhinitis (ICD-9-CM code 477.xx), and enteroviral infections including enteroviral infection (ICD-9-CM code: 008.67); meningitis due to enterovirus, coxsackievirus, and echovirus (ICD-9-CM code: 047, 047.0, and 047.1); other enterovirus diseases of central nervous system (ICD-9-CM code: 048); specific diseases related to coxsackievirus (ICD-9-CM code: 074, 074.1, 074.2, 074.20, 074.21, 074.23 and 074.8); herpangina (ICD-9-CM code: 074.0); hand-foot-and-mouth disease (ICD-9-CM code: 074.3); and echovirus and coxsackievirus infection (ICD-9-CM code 079.1 and 079.2). The propensity score was calculated using the Statistical Analysis System 9.4 program (SAS Institute, Cary, North Carolina, USA).

1.3. Outcome and comorbidities

The patients in both the thalassemia and non-thalassemia cohorts were followed up until they were diagnosed with asthma (ICD-9-CM: 493.xx); or death; or the end of 2013. The index date was defined as the date of the first visit for asthma. To improve data accuracy, the selection criteria of thalassemia, atopic dermatitis, allergic rhinitis and enteroviral infections required all cases ICD-9 code to be diagnosed once at hospitalization or at least thrice in the outpatient department in one year. Enteroviral infections were identified according to diagnoses in the claims records data before the index date while atopic dermatitis and allergic rhinitis were enrolled no matter they were diagnosed before or after the diagnosis of asthma.

1.4. Statistical analysis

The distributions of categorical demographics and clinical characteristics between the thalassemia and non-thalassemia cohorts were compared using the chi-square test. The incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated using Poisson regression. Univariate and multivariate Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% CIs for asthma. All statistical analyses were performed using SAS software, Version 9.3 (SAS Institute, Cary, NC, USA). A P value < 0.05 in 2-tailed tests was considered statistically significant.

Results

One million people were randomly selected from LHID 2010, and those whose years of birth were between 1998 and 2007 were selected for further analysis. People who had ever received blood transfusion, splenectomy or a diagnosis of immunodeficiency or hematologic disorders except for thalassemia were excluded. The remaining people were separated into a group with thalassemia and a group with non-thalassemia, with 1:4 matching according to birth year, sex, and propensity score. Details of these processes are shown in Fig. 1. Finally, 794 patients were identified in the thalassemia group and 3176 controls in the non-thalassemia group.

Table 1 shows the incidence rate rations of asthma in thalassemia patients versus non-thalassemia patients. The overall incidence of asthma was 11.8% higher in the thalassemia cohort than in the non-thalassemia cohort (41.03 vs 36.69 per 1000 person-y), with an adjusted HR of 1.16 (95% CI = 1.01–1.33). In an analysis in which the patients were stratified according to sex, male patients in the thalassemia cohort had a significantly higher adjusted HR of asthma than did those in non-thalassemia cohort (adjusted HR = 1.20, 95% CI = 1.02–1.42). In patients whose birth year were 1997–2000, the risk of asthma was 1.31-fold higher in the thalassemia cohort than in the non-thalassemia cohort (95% CI = 1.05–1.64). About comorbidity, in patients without atopic dermatitis, the risk of asthma was 1.25-fold higher in the thalassemia cohort than in the non-thalassemia cohort (95% CI = 1.07–1.47).

Table 1
Incidence rate ratio of asthma in thalassemia patients versus non-thalassemia patients

THA (n = 794)						Non-THA (n = 3176)								
	N	Times	PY	Rate (per 1000 PY)[a]		N	Times	PY	Rate (per 1000 PY)		IRR (95% CI)		Adjusted IRR (95% CI)	
Overall	794	263	6409.23	41.03	(36.36–46.31)	3176	988	26927.54	36.69	(34.47–39.05)	1.12	(0.98–1.28)	1.16	(1.0 1.33
Female	327	88	2867.63	30.69	(24.90-37.82)	1308	339	11739.25	28.88	(25.96–32.12)	1.06	(0.84–1.34)	1.08	(0.8 1.36
Male	467	175	3541.6	49.41	(42.61–57.30)	1868	649	15188.29	42.73	(39.57–46.15)	1.16	(0.31–1.16)	1.20	(1.0 1.42
Birth year 1997–2000	273	100	2988.64	33.46	(27.50-40.71)	1092	341	12861.02	26.51	(23.84–29.48)	1.26	(1.01–1.58)	1.31	(1.0 1.64
2001–2005	277	104	2178.46	47.74	(39.39–57.86)	1108	387	9156.89	42.26	(38.26–46.69)	1.13	(0.91–1.40)	1.19	(0.9 1.48
2006–2010	244	59	1242.14	47.50	(36.80-61.31)	976	260	4909.63	52.96	(46.90–59.80)	1.11	(0.96–1.28)	0.92	(0.6 1.22
No comorbidity	288	35	2755.13	12.70	(9.12–17.69)	1152	108	11308.38	9.55	(7.91–11.53)	1.19	(1.01–1.39)	1.33	(0.9 1.95
Comorbidity[b]	506	228	3654.1	62.40	(54.80-71.04)	2024	880	15619.16	56.34	(52.74–60.19)	0.96	(0.74–1.25)	1.09	(0.9 1.27
w/o AD	606	193	5134.24	37.59	(32.64–43.29)	2424	686	21645.28	31.69	(29.41–34.16)	1.15	(0.87–1.52)	1.25	(1.0 1.47
with AD	188	70	1274.99	54.90	(43.44–69.40)	752	302	5282.26	57.17	(51.07-64.00)	1.13	(0.96–1.32)	0.97	(0.7 1.25
w/o AR	384	65	3429.54	18.95	(14.86–24.17)	1536	232	14095.47	16.46	(14.47–18.72)	1.15	(0.87–1.52)	1.09	(0.8 1.44
with AR	410	198	2979.7	66.45	(57.81–76.38)	1640	756	12832.07	58.91	(54.86–63.27)	1.13	(0.96–1.32)	1.16	(0.9 1.36
w/o HPF	712	181	6085.61	29.74	(25.71–34.41)	2848	660	25435.22	25.95	(24.04–28.01)	1.15	(0.97–1.35)	1.15	(0.9 1.35
with HPF	82	82	323.62	253.38	(204.07-314.62)	328	328	1492.32	219.79	(197.25-244.91)	1.15	(0.91–1.47)	1.14	(0.9 1.46

[a] Rate, incidence rate, per 1000 person years

[b] Individuals with any comorbidity of atopic dermatitis, allergic rhinitis, any morbidity of enteroviral infection, meningitis due to enterovorus, coxsackievirus, o enterovirus diseases of central nervous system, echovirus and coxsackievirus infection, herpangina and hand-food-and-mouth disease.

Next, we analyzed HR of thalassemia to non-thalassemia patients having asthma. Cox regression showed similar results to Table 1. In addition to factors of male gender, year of birth, without atopic dermatitis, we found patients lived in urban 2 area (HR: 1.31) and with allergic rhinitis (HR: 1.19) had higher ratio to have asthma in the thalassemia cohort than in the non-thalassemia cohort (Table 2). If we put thalassemia as an independent factor for further analysis, crude and adjusted hazards ratio of factors for asthma proved thalassemia to be a risk factor to have asthma (HR: 1.17) besides male (HR: 1.19), comorbidity (HR: 5.33), atopic dermatitis (HR: 1.32), allergic rhinitis (HR: 2.64) and previous enteroviral infections (HR: 5.31) (Table 3).

Table 2
Hazard ratio of thalassemia to non-thalassemia patients had asthma

			Univariate		Multivariate		
		N	HR (CI)		HR (CI))		*P*
Overall		3970	1.11	(0.97–1.28)	1.17*	(1.03–1.35)	0.021*
Gender	Female	1635	1.06	(0.84–1.35)	1.08	(0.85–1.36)	0.524
	Male	2335	1.15	(0.97–1.36)	1.23*	(1.04–1.45)	0.016*
Birth year	1997–2000	1365	1.26*	(1.01–1.57)	1.30*	(1.04–1.63)	0.020*
	2001–2005	1385	1.14	(0.92–1.42)	1.23	(0.99–1.53)	0.059
	2006–2010	1220	0.90	(0.68–1.19)	0.93	(0.70–1.24)	0.636
Urban	1 (City)	1340	1.12	(0.89–1.42)	1.18	(0.93–1.49)	0.172
	2	1855	1.19	(0.99–1.44)	1.31*	(1.08–1.58)	0.006*
	3	515	0.85	(0.55–1.31)	0.77	(0.50–1.19)	0.238
	4 (Country)	260	1.03	(0.57–1.86)	1.05	(0.58–1.89)	0.868
Comorbidity	none	1440	1.33	(0.91–1.95)	1.33	(0.91–1.95)	0.138
	yes	2530	1.10	(0.95–1.27)	1.10	(0.95–1.28)	0.190
w/o AD		3030	1.17*	(1.01–1.39)	1.26*	(1.08–1.48)	0.004*
with AD		940	0.95	(0.73–1.23)	0.98	(0.76–1.28)	0.902
w/o AR		1920	1.14	(0.87–1.51)	1.11	(0.85–1.47)	0.433
with AR		2050	1.13	(0.97–1.32)	1.19*	(1.02–1.40)	0.027*
w/o HPF		3560	1.14	(0.97–1.34)	1.15	(0.98–1.35)	0.098
with HPF		410	1.33*	(1.04–1.30)	1.23	(0.97–1.57)	0.091

Univariate: without adjust any covariate

Multivariate: adjust covariate by *PY = gender + birth year + urban + AD + AR + HPF + Thalassemia (no asthma as ref)

Table 3
Crude and adjusted hazards ratio of factors for asthma

		Univariate		Multivariate	
		HR (CI)		HR (CI))	
Gender	Female	1		1	
	Male	1.44*	(1.28–1.62)	1.19*	(1.05–1.34)
Birth year	1997–2000	1		1	
	2001–2005	1.20*	(1.06–1.37)	1.14	(1.00-1.30)
	2006–2010	1.14	(0.98–1.32)	1.28*	(1.10–1.48)
Urban	1 (City)	1		1	
	2	1.09	(0.96–1.23)	1.13	(0.99–1.27)
	3	0.83	(0.69–1.01)	0.95	(0.79–1.16)
	4 (Country)	0.83	(0.64–1.07)	1.18	(0.91–1.53)
Comorbidity	none	1			
	yes	5.33*	(4.48–6.34)		
Comorbidity (no as 1)	AD	1.59*	(1.41–1.79)	1.32*	(1.16–1.49)
	AR	3.43*	(3.01–3.90)	2.64*	(2.31–3.03)
	HPF	7.02*	(6.21–7.93)	5.31*	(4.68–6.03)
	Thalassemia	1.11	(0.97–1.28)	1.17*	(1.02–1.34)

Discussion

This is a nationwide population-based cohort study based on an extremely large database and adjusted for numerous typical risk factors for asthma. The results suggested that thalassemia patients who didn't receive any blood transfusion had an increased risk of developing asthma. In addition, male thalassemic patients had higher risk for asthma than non-thalassemia patients. About comorbidity, thalassemic patients without atopic dermatitis had higher risk of asthma than the non-thalassemia ones, while in thalassemic patients with allergic rhinitis, the risk of asthma was higher than in the non-thalassemia ones.

Ramakrishnan and Borade (11) reported that anemia was a risk factor for childhood asthma. They found asthma was present in 74% children in the anemic group and 33% children in the nonanemic group and stated that anemic children were 5.75 times more susceptible to asthmatic attacks when compared with nonanemic children. However, in their study, most causes of anemia were iron-deficiency anemia (85%). and thalassemia was not mentioned. Palma-Carlos et al. (12) collected 4.000 patients in an out-patient allergy clinic in a 5 years period. Of them 63 cases had thalassemia and 41/63 (65%) cases had asthma compared to 57% had asthma in control group of 491 respiratory allergic patients without thalassemia. However, this data was only collected in allergy clinics, and there were only 63 patients with thalassemia. Thalassemia is high prevalent in Taiwan that about 6.2% of the population are patients with thalassemia (3–5). If patients with thalassemia are really prone to asthma, then we need to detect asthma earlier so that we can prevent asthma attacked and/or give treatments earlier.

As regards the possible mechanisms of thalassemic patients had higher risk to have asthma, Palma-Carlos et al. (12) stated that the hemorheological changes in thalassemia may be a greater rigidity of red blood cells in capillary bed which can contribute to changes in bronchial circulation and bronchial hyperactivity, but no solid evidence supported yet. Recently, we found thalassemic patients had higher incidence of low respiratory tract infection (Yuu et al., just submitted) which may link to higher incidence of asthma or asthma exacerbation (13, 14).

In our study, thalassemic boys had higher rate of asthma than control cohorts. This was compatible with previous reports. Boys are reported to have an increased incidence of asthma compared to girls. Around puberty the frequency of asthma starts to change from being higher in males to higher in females (15, 16). The development of atopic dermatitis in infancy and subsequent allergic rhinitis and asthma in later childhood is known as the atopic march (17). In our study, thalassemic patients had allergic rhinitis had higher rate to have asthma than non-thalassemia cohorts with allergic rhinitis seemed that these two

factors may interact and influence the incidence. While thalassemic patients without atopic dermatitis had higher rate to have asthma than non-thalassemic ones. Whether thalassemic patients had more nonatopic asthma e.g. infection related asthma or other unknown causes still needed further study.

Our study has a few limitations. First, our ICD codes cannot differentiate type or severity e.g. silent carrier, minor trait, intermediate or major. Although we excluded all thalassemia major patients by blood transfusion ICD codes, few cases of thalassemia intermedia or Hb H disease that didn't require any blood transfusion may exist in our study population. However, the proportion of thalassemia intermedia and Hb H disease are less than 5 percent among the thalassemia patients in our population (18, 19).We had also excluded cases ever received blood transfusion and/or splenectomy, thus, the effect of thalassemia intermedia in our study was very small. Second, although we used ICD-9 codes to screen out thalassemia patients, some asymptomatic patients were missed because the physicians did not include thalassemia in the diagnostic lists for this population. There might have been some thalassemia patients in the control group. Thus, the asthma rate in the control group may be overestimated. In other words, in real condition, the thalassemic group had more chance to have asthma than non-thalassemic group.

The major strength of our study lies in the high number of patients selected from a nationwide population-based database that contains data on numerous thalassemia cases. Although the detailed pathophysiology of the relationship between asthma and thalassemia may require further examination, we recommend that physicians consider the possibility for developing asthma in transfusion-naïve thalassemia populations.

Conclusions

The phenomenon that transfusion-naïve thalassemia patients have higher risk to have asthma than non-thalassemia patients was observed in our study. We need to pay more attention to it in order to make earlier diagnosis and earlier prevention. Further studies should be designed to obtain more details on the pathophysiology.

Abbreviations

AD: atopic dermatitis, AR: allergic rhinitis, CI: confidence interval, HPF: any morbidity of enteroviral infection, meningitis due to enterovorus, coxsackievirus, other enterovirus diseases of central nervous system, echovirus and coxsackievirus infection, herpangina and hand-food-and-mouth disease, HR: hazard ratio, IRR: incidence rate ratio, PY: person-year, THA: thalassemia

Declarations

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Author Contributions

HYH and LHH: wrote the first draft of the manuscript. HRY, KCK, and YCL: revised the subsequent drafts. HYH and CHS: performed statistical analyses. YHY and JMS: critically reviewed the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). Any researcher interested in accessing this dataset can submit an application form to the MOWH requesting access. Please contact the staff of MOHW (Email: wt.vog.whom@uwloracts) for further assistance. Taiwan MOHW address: No. 488, Sec. 6, Zhongxiao E. Road, Nangang District, Taipei City 115, Taiwan. Phone: + 886 2 8590 6848.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kaohsiung Chang-Gung Memorial Hospital (Permit No CGMF- 201801200B0), Taiwan. Because this was a secondary data analysis, all identifications of patients and institutions in NHIRD have been removed before data release, the informed consent was not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

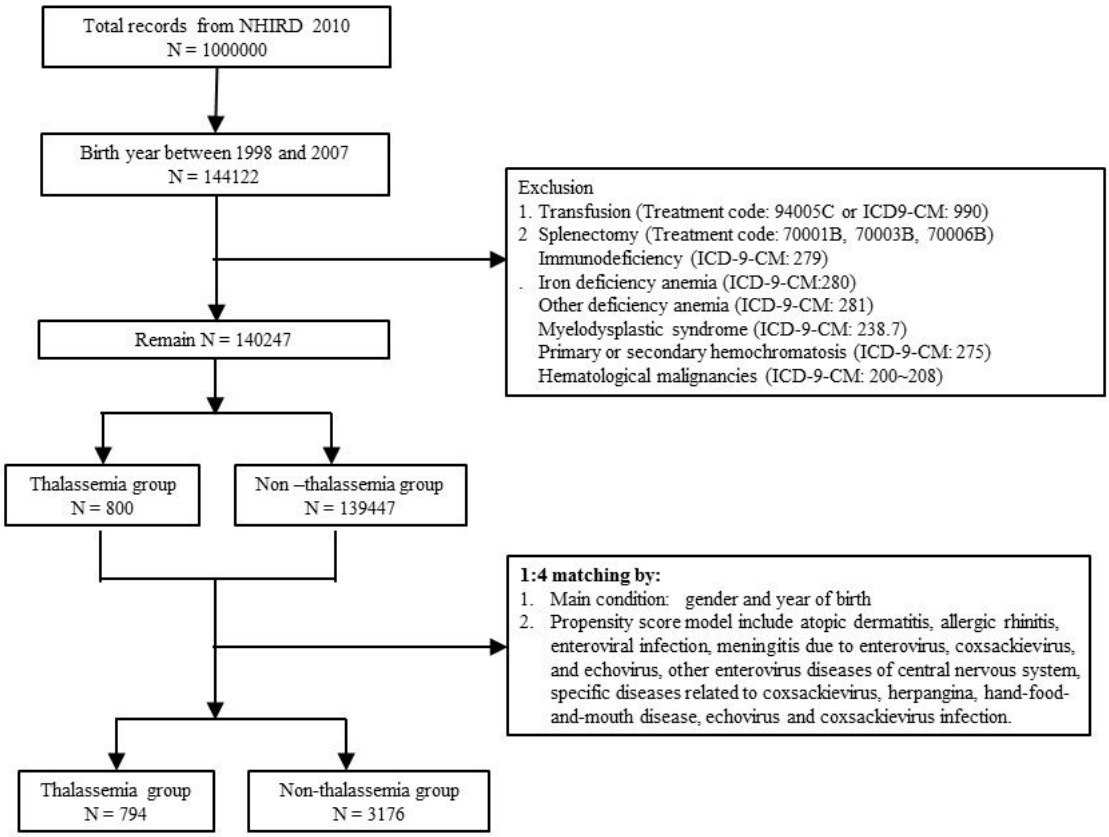

Figure 1

Flow chart of matched cohorts selection. One million people were randomly selected from the Longitudinal Health Insurance Database 2010 (LHID 2010). After the screening process, 794 persons in the thalassemia group and 3176 persons in the non-thalassemia group were analyzed.