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Original Article

# Thalassemia and risk of dementia: A nationwide population-based retrospective cohort study☆

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ABSTRACT

*Background:* This study is a nationwide population-based retrospective cohort study to investigate the risk for developing dementia in thalassemia population.
*Methods:* In a longitudinal cohort of 1 million insured people, we identified 871 thalassemia patients who were newly diagnosed between 2000 and 2004 and selected a comparison cohort of 3484 subjects without thalassemia. We analyzed the risks for thalassemia and dementia using Cox proportional hazard regression models to assess the dementia risk in thalassemia patients after adjusting for age, gender, insured amount, urbanization and comorbidities.
*Results:* The overall risks for developing dementia were 1.88-fold (95% CI = 1.10–3.21) in patients with thalassemia compared with the comparison cohort after adjusting for age, sex, insured amount, urbanization and comorbidities. The combined effects measured for patients afflicted with thalassemia and the comorbidities of diabetes, hypertension, CAD, head injury, depression, CKD, or substance-related disorder exhibited a significant association with hyperlipidemia risk compared with that measured for patients without thalassemia and without any counterpart comorbidities. In subgroup analysis, the HRs of dementia increased, from 1.69 (95% CI = 0.93–3.07) for those who had not undergone transfusion to 2.72 (95% CI = 1.09–6.78) for those experienced transfusion compared with the no thalassemia cohort (p for trend < 0.01).
*Conclusion:* Our long-term cohort study result showed that thalassemia should be considered a crucial risk factor for developing dementia.


## 1. Introduction

Thalassemia is a common hereditary hemoglobinopathy resulting from significantly impaired synthesis of one or more globin subunits of normal hemoglobins. Clinical classification of thalassemia is based on a mutation or a deficient amount of globin numbers. The data bank of the World Health Organization has indicated a recent prevalence of hemoglobinopathies reported in approximately 5% of the global population [1]. Diverse clinical characteristics varying from asymptomatic to transfusion-dependent severe ineffective erythropoiesis have been documented in thalassemia patients, typically resulting from severe hemoglobinopathies. Mainstay pathophysiology in thalassemia patients includes ineffective erythropoiesis and peripheral hemolytic anemia caused by membrane destruction [2]. Several chronic complications and subsequent end-organ damage have been observed with disease severity, repeated blood transfusions, and impaired gastrointestinal iron absorption contributing to abnormal iron deposition [3]. Because of advances in prenatal screening and diagnostic methods, the severe genotypes of thalassemia have declined gradually, and most cases are silent carriers or have a mildly lower hemoglobin value without any symptoms, and are transfusion-independent or transfusion-naïve population [4].

Based on DSM-5 classification, neurocognitive disorders included delirium, mild cognitive impairment and dementia. Dementia is a major neurocognitive disorder characterized by impaired function of learning and memory, executive function, perceptual motor, complex attention, social cognition and language that can result in severe disabilities in daily activities, leading to a great health care burden in the

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general population worldwide [5]. Several defined risk factors included aging, presence of apolipoprotein E4 allele, socioeconomic status, and vascular factors such as hypertension, diabetes, head injury, and depression [6]. Based on recent studies, anemia is another strong risk factor for dementia pathogenesis [7,8]. A large systematic review also revealed that anemia is significantly associated with cognitive performance [9]. A population-based cohort study has also shown a positive correlation of iron deficiency anemia with dementia [10]. However, these studies have focused on acquired anemia, whereas few studies have focused on hereditary anemia. Previous studies with small sample sizes have demonstrated a trend of developing cognitive dysfunction in severe types of thalassemia and the hemoglobin mutations associated with β thalassemia minor [11–13]. However, studies elucidating the relationship between thalassemia and long-term dementia incidence are rare. This nationwide population-based cohort study clarified the association between thalassemia and dementia in Taiwan population.

## 2. Methods

### 2.1. Data source

The National Health Insurance (NHI) Program implemented on March 1, 1995 covers more than 99% of the 23.74 million population of Taiwan. The current study was a retrospective cohort study that used the Longitudinal Health Insurance Database 2000 (LHID 2000), released by the National Health Research Institutes (NHRI). The NHRI established a National Health Insurance Research Database (NHIRD) to record all beneficiary medical services, including inpatient and outpatient demographics, primary and secondary diagnoses, procedures, prescriptions, and medical expenditures. The LHID 2000 includes one million insurants randomly selected from the 2000 Registry of NHI beneficiaries, which contains all medical records of each insurant from 1996 to 2011. No significant difference exists in sex, age, or health care costs between cohorts in LHID 2000 and all insurance enrollees, as reported by the NHRI in Taiwan [14]. Disease was identified based on the International Classification of Diseases, 9th Revision (ICD-9 codes).

### 2.2. Sampled participants

We conducted a cohort analysis to determine the association between thalassemia (ICD-9-CM code 282.4) and dementia (ICD-9-CM codes 290.0–290.4, 294.1, and 331.0–331.2). Patients aged more than 20 years who were identified with newly diagnosed thalassemia during January 1, 2000 and December 31, 2004, and who had no history of dementia, low B12 (ICD-9-CM codes 281.1 and 281.2), folic acid anemia (ICD-9-CM codes 280.0, 280.1, 280.8, and 280.9), or receiving transfusion (ICD-9 code for procedure 990), were included as the thalassemia cohort. The index date for each thalassemia case was the date of thalassemia diagnosis. To increase statistical power, for each patient with thalassemia, 4 study subjects without history of anemia (ICD-9-CM codes 280–285), dementia, or receiving transfusion were selected from the LHID 2000 as the no thalassemia cohort, and frequency-matched for sex, age (per 1 year) and the year of thalassemia diagnosis. Overall, 871 patients were included as the thalassemia cohort and 3484 patients as the no thalassemia cohort.

### 2.3. Outcome and comorbidities

Person-years of follow-up were calculated for each patient until dementia diagnosis, death, withdrawal from the insurance system, or until the end of 2011. Baseline comorbidities associated with dementia were also analyzed. These included diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), coronary artery disease (CAD, ICD-9-CM codes 410–414), head injury (ICD-9-CM codes 850–854 and 959.01), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), chronic kidney disease (CKD, ICD-9-CM code 585), stroke (ICD-9-CM codes 430–438) and substance-related disorder (ICD-9-CM codes 291–299 and 303–305). We also used the transfusion as the severity marker of thalassemia to evaluate thalassemia disease status. Transfusion in the follow-up period served as a clinical relative-severity manifestation for thalassemia patients. In addition, patients had received a diagnosis of dementia on two separate occasions, and the diagnoses was made by an Neurologist clinical evaluation, serial imaging and laboratory investigations during the period between 2001 and 2011.

### 2.4. Statistical analysis

The distributions of age and histories of comorbidities were compared between the thalassemia and no thalassemia cohorts. The differences of categorical variables were analyzed using the chi-square test, and differences of continuous variables were estimated using *t*-tests. The gender-, age- and comorbidity-specific incidence density rates of dementia were calculated in follow-up period until the end of 2011 or the date of the first diagnosis of dementia, death, and loss to follow-up. We used the Kaplan–Meier method to compare the cumulative incidence rates of dementia in cohort of participants without thalassemia, with thalassemia and with transfusion, and with thalassemia and without transfusion, and used the log-rank test to examine the differences among the survival curves. The Cox proportional hazard models were used to determine the association of thalassemia and dementia. Hazard ratios (HRs) and their respective 95% confidence intervals (CIs) after adjusting for gender, age, insured amount, urbanization, diabetes, hypertension, CAD, head injury, depression, CKD, stroke and substance-related disorder were reported. All data analyses were performed using SAS 9.3 statistical package (SAS Institute Inc., NC, USA), with $p < 0.05$ in 2-tailed tests considered significant.

### 2.5. Data availability statement

All data and related metadata were deposited in an appropriate public repository. The data on the study population that were obtained from the NHIRD (http://w3.nhri.org.tw/nhird//date_01.html) are maintained in the NHIRD (http://nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established by the government.

### 2.6. Ethics statement

The NHIRD encrypts patient's personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board (IRB) of China Medical University (CMU-REC-101-012). The IRB specifically waived the consent requirement.

## 3. Results

In total, 871 patients with thalassemia and 3484 subjects without thalassemia were enrolled in our study, with similar age and sex distributions in both. Among the study patients, 8.96% were 65 years of age or older (Table 1). The mean age in the thalassemia and no thalassemia cohorts was 38.91 years [standard deviation (SD) = 15.45 years] and 38.92 years (SD = 15.46 years), respectively. In addition, we observed much higher urbanization level in non-thalassemia patient than thalassemia patients ($p = 0.004$) However, we didn't find any significant difference in insured amount between cohort with and without thalassemia ($p = 0.10$). The thalassemia cohort had a higher prevalence of diabetes (7.12% vs 4.91%), CAD (11.60% vs 7.29%), depression (5.05% vs 2.15%), and CKD (1.95% vs 0.43%) than did the no thalassemia cohort. The mean follow-up years were 8.84 years (SD = 2.20 years) and