Risk of Erectile Dysfunction in Transfusion-naive Thalassemia Men
A Nationwide Population-based Retrospective Cohort Study

Yu-Guang Chen, MD, Te-Yu Lin, MD, Cheng-Li Lin, MSc, Ming-Shen Dai, MD, Ph.D, Ching-Liang Ho, MD, and Chia-Hung Kao, MD

Abstract: Based on the mechanism of pathophysiology, thalassemia major or transfusion-dependent thalassemia patients may have an increased risk of developing organic erectile dysfunction resulting from hypogonadism. However, there have been few studies investigating the association between erectile dysfunction and transfusion-naive thalassemia populations. We constructed a population-based cohort study to elucidate the association between transfusion-naive thalassemia populations and organic erectile dysfunction.

In this study, 588 transfusion-naive thalassemia men and 2337 controls were included. Total 12 patients were identified within the thalassemia group and 10 within the control group. The overall risks for developing organic erectile dysfunction were 4.56-fold in patients with transfusion-naive thalassemia men and organic erectile dysfunction by using Cox proportional hazards regression models.

Our long-term cohort study results showed that in transfusion-naive thalassemia men, there was a higher risk for the development of organic erectile dysfunction, particularly in those patients with comorbidities.

INTRODUCTION

Male sexual dysfunction can be classified as erectile dysfunction (ED), diminished sexual desire disorders, or abnormal ejaculation. ED, defined as difficulty in achieving or maintaining an erection during sexual intercourse, is the most common form of sexual dysfunction in adult men. The risk factors for ED are complex and can generally be classified into 2 distinct groups, namely systemic organic and psychological causes. The major risk factors resulting in organic ED include chronic cardiovascular and metabolic causes such as diabetes, coronary artery disease, hypertension, stroke, and hyperlipidemia. In a previous study, 26.5% of patients with ED were anemic. Therefore, anemia of any cause may contribute to ED. In addition, age is an independent risk factor for ED, and the prevalence of complete ED increases with age. In particular, approximately 30% to 40% of men in their 80s have complete ED.

Thalassemia is an autosomal recessive hereditary hemoglobinopathy that manifests as microcytic hypochromic anemia and has varied clinical presentations ranging from asymptomatic to severe lethal complications caused by hemolytic anemia, ineffective hematopoiesis, or transfusion dependence. Although thalassemia has various clinically distinct phenotypes and complex genotypes, transfusion dependence may be considered as a marker of severity to distinguish between thalassemia major and other types of thalassemia. Recently, thalassemia has been classified into 3 distinct groups according to clinical characteristics and transfusion dependence as follows: asymptomatic thalassemia trait/minor, nontransfusion-dependent thalassemia (NTDT), and thalassemia major.

Patients with α/β thalassemia major usually require repeated blood transfusions because of ineffective hematopoiesis and severe hemolytic anemia. Secondary iron overload frequently results in target-organ toxicity such as heart failure, osteoporosis, or hypogonadism. In patients with thalassemia major or transfusion-dependent thalassemia, ED is a possible complication predominantly due to iron overload as a result of recurrent blood transfusion leading to hypogonadism. However, most thalassemia populations are...
usually transfusion-naive and asymptomatic, with much fewer having NTDT syndromes or thalassemia major. Although these patients have less severe clinical manifestations and have not received blood transfusions, they may also have a risk of developing ED via the pathophysiological mechanisms of anemia and chronic hemolysis. However, studies investigating the relationships between these groups and the incidence of ED are rare. The purpose of this nationwide population-based cohort study was to clarify the relationship between transfusion-naive thalassemia populations and ED in a multiethnic male population.

METHODS

Data Source

The National Health Insurance (NHI) Program was implemented on March 1, 1995, and this program covers >99% of the 23.72 million people in Taiwan. The Longitudinal Health Insurance Database 2000 (LHID 2000), which was released by the National Health Research Institutes (NHRI), was used in this retrospective cohort study. The NHRI established a National Health Insurance Research Database (NHIRD) to record the medical services of all beneficiaries, including inpatient and outpatient demographics, primary and secondary diagnoses, procedures, prescriptions, and medical expenditures. The LHID 2000 includes 1 million insurers randomly selected from the 2000 Registry for Beneficiaries, which contains all medical records of each insurer from 1996 to 2011. The LHID 2000 was released by the NHRI, of which the institute claims detailed examinations of each International Classification of Diseases, Ninth Revision (ICD-9-CM) coding. The NHRI has also reported no significant difference in age, or health care costs between cohorts in the LHID 2000 and all insurance enrollees. Disease was identified based on the ICD-9-CM codes registered in the LHID 2000. We used secondary data with deidentified analysis; therefore, no informed consent was required. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012).

Sampled Participants

We selected male patients aged 20 years and older with a first diagnosis of thalassemia (ICD-9-CM code 282.4) between 1998 and 2010 from the LHID 2000 to be the thalassemia cohort. The index date for each thalassemia case was the date of diagnosis. To increase statistical power, for each case of thalassemia, 4 male control subjects without thalassemia were selected from the LHID 2000 as the nonthalassemia cohort, and were frequency-matched for age (in 5-year bands) and the year of diagnosis. Patients from both cohorts with organic ED (ICD-9-CM code 607.84) or sickle cell, iron deficiency anemia (ICD-9-CM codes 280), other deficiency anemias (ICD-9-CM codes 281), aplastic, hemolytic, or sideroblastic anemia, anemia of chronic disease (ICD-9-CM codes 282.6–285.8), myelodysplastic syndrome (ICD-9-CM codes 238.7), primary or secondary hemochromatosis (ICD-9-CM codes 275.0), or hematological malignancies (ICD-9-CM codes 200–208), before the index date, were excluded. In addition, we excluded cases with a history of transfusion (ICD-9 procedure codes 990) or with missing age or sex information at the baseline. There were no patients in whom age information was lacking.

Outcome and Comorbidities

Follow-up was calculated in person-years for each patient until organic ED was diagnosed, death occurred, the patient withdrew from the insurance system, or until the end of 2011. Organic ED was diagnosed based on the results of a self-administered International Index of Erectile Dysfunction (IIEF-5) questionnaire. The questionnaire was given to patients who complained of ED symptoms or had a clinical impression of ED. In addition, patients had received a diagnosis of ED on 2 separate occasions, and at least one of the diagnoses was made by an Urologist during the period between 2001 and 2011. We also analyzed baseline comorbidities thought to be associated with organic ED: anemia (ICD-9-CM code 285.9), anxiety (ICD-9-CM code 300.00), coronary artery disease (ICD-9-CM codes 410–414), cirrhosis (ICD-9-CM code 571), chronic kidney disease (CKD) (ICD-9-CM codes 580–589), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–496), diabetes (ICD-9-CM code 250), depression (ICD-9-CM codes 296.2, 296.3, 300.4, 311), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), and peripheral artery disease (ICD-9-CM codes 443.81, 443.9, 440.2, 444.2, 444.89).

Statistical Analysis

The distributions of age and history of comorbidities were compared between the thalassemia and nonthalassemia cohorts. The differences between categorical variables were analyzed using the chi-square test, and differences in continuous variables were estimated using t tests. The incidence densities rate of organic ED was calculated by age and comorbidity for each cohort. Univariable and multivariable Cox proportional hazard regression models were used to assess the risk of organic and psychogenic ED associated with thalassemia, compared with the nonthalassemia cohort. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in the Cox model. Multivariate models were adjusted for age and comorbidities of cirrhosis, CAD, CKD, COPD, diabetes, hypertension, hyperlipidemia, and anxiety. We used the Kaplan–Meier method to compare the cumulative incidence of organic and psychogenic ED events between the 2 cohorts, and used the log-rank test to examine the differences. All data analyses were performed using the SAS 9.3 statistical package (SAS Institute Inc, NC), with P < 0.05 in 2-tailed tests considered significant.

RESULTS

A total of 588 thalassemia male and 2337 male controls without thalassemia were included in our study. The mean ages in the thalassemia and nonthalassemia cohorts were 38.1 ± 16.1 years and 37.7 ± 16.2 years, respectively. The thalassemia cohort had more prevalence of comorbidities including cirrhosis (23.8% vs 14.0%), CKD (6.80% vs 3.25%), COPD (22.6% vs 16.8%), hyperlipidemia (15.3% vs 9.16%), anxiety (4.93% vs 2.35%), coronary artery disease (9.01% vs 5.26%), hypertension (16.0% vs 12.7%), and anemia (20.1% vs 0.56%) than did the nonthalassemia cohort (all P < 0.05). (Table 1)

The mean follow-up years were 7.27 (SD = 3.51) and 7.22 (SD = 3.48) for the thalassemia cohort and the nonthalassemia cohort, respectively (data not shown). Figure 1 shows that the cumulative incidence of organic and psychogenic ED was higher in the thalassemia cohort than in the nonthalassemia cohort by 1.88% (log-rank test ⪯ 3.001) at the end of follow-up. The overall incidence of organic ED was 4.73-fold higher in the thalassemia cohort than in the nonthalassemia cohort (2.81 and 0.59 per 1000 person-years, respectively), with an adjusted HR (aHR) of 4.56 (95% CI = 1.88–11.1) (Table 2). The organic ED incidence increased with age and with comorbidity in both
Table 1. Demographic Characteristics and Comorbidities in Cohorts With and Without Thalassemia

| Variable          | No       | Yes      | P     |
|-------------------|----------|----------|-------|
| Age, y            |          |          | 0.99  |
| 20–34             | 1249 (53.4) | 313 (53.2) |       |
| 35–49             | 565 (24.2)   | 142 (24.2)  |       |
| ≥50               | 523 (22.4)   | 133 (22.6)  |       |
| Mean ± SD         | 37.7 ± 16.2 | 38.1 ± 16.1 | 0.64  |

Comorbidity

| Comorbidity | No       | Yes      | P     |
|-------------|----------|----------|-------|
| Cirrhosis   | 326 (14.0) | 140 (23.8) | <0.001|
| CKD         | 76 (3.25)  | 40 (6.80)  | <0.001|
| COPD        | 392 (16.8) | 133 (22.6) | 0.001 |
| Hyperlipidemia | 214 (9.16) | 90 (15.3)  | <0.001|
| Anxiety     | 55 (2.35)  | 29 (4.93)  | <0.001|
| CAD         | 123 (5.26) | 53 (9.01)  | <0.001|
| Hypertension| 297 (12.7) | 94 (16.0)  | 0.04  |
| Anemia      | 13 (0.56)  | 118 (20.1) | <0.001|

Chi-square test. CAD = denotes coronary artery disease, CKD = denotes chronic kidney disease, COPD = denotes chronic obstructive pulmonary disease, SD = standard deviation.

DISCUSSION

This is the first nationwide population-based cohort study based on an extremely large database and adjusted for numerous classic organic ED risk factors. This study suggests that transfusion-naive thalassemia men have an increased risk of developing ED. This risk was increased by 4.56-fold compared with the nonthalassemia controls after adjusting for age and medical comorbidities. According to the previous epidemiological results of thalassemia in Taiwan (our cohort database), the prevalence rates of α- and β-thalassemia were approximately 3% to 5% and 1% to 3%, respectively. Most patients with α- and β-thalassemia had hereditary traits or were carriers of borderline asymptomatic anemia or minimal symptoms, and were not transfusion-dependent. In addition, to purify our population using ICD procedure codes, we initially excluded male populations with transfusion-dependent thalassemia. This means that we excluded patients with thalassemia major, who were likely to have hypogonadism as a result of abnormal iron deposition.

Overall, according to our study results, the incidence rate of ED was higher among transfusion-naive thalassemia older men than among younger healthy men. In the patients with transfusion-naive thalassemia and chronic medical comorbidities, we also found that the incidence rate of organic ED was higher than among normal populations without chronic comorbidities. These results indicate that age and medical comorbidities play crucial roles in the development of ED in patients with transfusion-naive thalassemia. However, it is not clear from this study whether the thalassemia magnifies this risk.

Most patients with thalassemia in our country were silent thalassemia carriers or had concealed thalassemia traits. Although relatively more cases were included in the present study than in other previous studies, it is likely that the patients in our study who were diagnosed with thalassemia had more severe clinical features and presented to medical services with complications, which led to the diagnosis of their thalassemia; or that these patients presented with nonhematological diagnoses and were subsequently found to also have thalassemia during blood tests performed to investigate the presenting condition. Although more thalassemia patients were included in this study, still very small numbers of these had ED. Only 12 patients had both diagnoses of thalassemia and ED, and only 10 patients in the nonthalassemic group had ED. Our results suggest that the small number of cases could lead to overemphasis of the results in this study. Therefore, in view of the small numbers, caution should be used in interpreting the findings of this study. Further studies, ideally prospective, should be done to investigate whether there is a true relationship between thalassemia trait/NTDT and ED.

The process of erection is complex and involves numerous vascular structures. Two major mechanisms that may affect the pathophysiological mechanism of ED are systemic organ and psychological effects. Penile vascular disease is the hallmark of the pathophysiological mechanism of organic ED. Vascular abnormalities include decreased arterial blood flow, ischemia-induced vascular hypoperfusion, subsequent increased cavernosal smooth-muscle contraction, or veno-occlusive dysfunction. These effects may result in eventual endothelial dysfunction. Therefore, traditional risk factors that impair
the vascular system include several systemic diseases such as diabetes mellitus, hypertension, dyslipidemia, end-stage kidney disease, cirrhosis of the liver, and coronary artery disease.18–20 Several studies have also indicated that ED could be an early sign of endothelial dysfunction and microvascular disease.21–23 Several hypothetical effects may explain the association between organic ED and transfusion-naive thalassemia. In patients with thalassemia who have less severe clinical manifestations, anemic status is a possible contributory factor to ED. However, although the patients in our study had transfusion-naive thalassemia, few NTDT patients who did not require any blood transfusions to maintain activities of daily life existed in our study populations. NTDT patients exhibit ineffective erythropoiesis and hemolytic anemia, which results from an imbalance of the ratio between $\alpha$ and $\beta$ associated with membrane damage. 24,25 Despite disease genetic polymorphisms

### TABLE 2. Incidence of Organic Erectile Dysfunction by Age and Comorbidity and Cox Model Measured Hazards Ratio for Patients With Thalassemia Compared With Those Without Thalassemia

| Variables | Thalassemia | Thalassemia to Nonthalassemia |
|-----------|-------------|-------------------------------|
|           | No          | Yes                          |                          |
|           | Event PY Rate | Event PY Rate | Crude HR (95% CI) | Adjusted HR (95% CI) |
| All       | 10 16864 0.59 | 12 4277 2.81 | 4.73 (2.04, 10.9)** | 4.56 (1.88, 11.1)** |
| Stratify age |           |                               |                          |
| 20–49     | 4 13764 0.29 | 5 3515 1.42 | 4.88 (1.31, 18.2)* | 4.76 (1.24, 18.2)* |
| ≥50       | 6 3100 1.94 | 7 762 9.18 | 4.75 (1.60, 14.1)** | 4.29 (1.31, 14.1)* |
| Comorbidity |           |                               |                          |
| No        | 4 11356 0.35 | 1 1808 0.55 | 1.49 (0.17, 13.4) | 1.66 (0.18, 15.0) |
| Yes       | 6 5508 1.09 | 11 2469 4.46 | 4.18 (1.55, 11.3)** | 5.06 (1.86, 13.7)** |

CI = confidence interval, HR = hazard ratio, PY = person-years.

* $P < 0.05$.
* * $P < 0.01$.
* * * $P < 0.001$.

† Incidence rate, per 1000 person-years.

‡ Relative hazard ratio.

§ Multivariable analysis including age, and comorbidities of cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, anxiety, coronary artery disease, hypertension, and anemia.

| Variables | Age, y | N | Event | Adjusted HR (95% CI) |
|-----------|--------|---|-------|---------------------|
| Thalassemia |         |   |       |                     |
| No        | 20–49  | 1814 | 4 | 1 (Reference)* |
| No        | ≥50    | 523  | 6 | 4.14 (1.05, 16.4)* |
| Yes       | 20–49  | 455  | 5 | 4.49 (1.18, 17.2)* |
| Yes       | ≥50    | 133  | 7 | 17.7 (4.27, 73.5)** |
| Thalassemia | Comorbidity | No | 1505 | 4 | 1 (Reference)* |
| No        | Yes    | 832  | 6 | 1.39 (0.37, 5.27) |
| Yes       | No     | 232  | 1 | 1.84 (0.21, 16.5) |
| Yes       | Yes    | 356  | 11 | 7.12 (2.17, 23.3)** |

N indicates the total number of patients in each study group; for example, 1814 patients aged 20–49 years did not have thalassemia. CI = confidence interval, HR = hazard ratio.

* $P < 0.05$.
* * $P < 0.01$.
* * * $P < 0.001$.

† Model was adjusted for comorbidities of cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, anxiety, coronary artery disease, hypertension and anemia.

‡ Patients with any one of the comorbidities (cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, hyperlipidemia, anxiety, coronary artery disease, hypertension, and anemia) were classified as the comorbidity group.

§ Model was adjusted for age.
related to various clinical manifestations and disease severity, persistent membrane destruction related to hemolysis results in low arginine and nitric oxide (NO) bioavailability, as well as superoxide production with oxidative stress and endothelial inflammation.26 A recent study with β-thalassemic mice showed a decrease in NO bioavailability in vascular endothelial cells and impairment in preserved smooth muscle cell reactivity to NO. In addition, Butthep et al found vascular endothelial cell injury/dysfunction in patients with α- and β-thalassemia and a relative decrease in protein C and S levels but an increased plasma thrombomodulin circulation of endothelial cells, vascular endothelial growth factor concentration, and tumor necrosis factor-alpha in circulation.27,28 These effects could result in vascular endothelial dysfunction, and subsequently decrease wall stress and cause softening of the vessel wall.29 Moreover, hemolytic anemia-related persistent endovascular dysfunction played a more crucial role in the vasculopathy of organic ED. This may explain why elderly thalassic patients experienced higher rates of organic ED than younger patients. In addition, NTDT patients could have abnormal iron metabolism and hyperferritinemia with iron overload-related complications, including hypogonadism and endocrine abnormalities.30 This study has several limitations. First, the NHIRD does not contain detailed information regarding patients’ current use of medications such as psychological agents or hormonesuppressive therapy, smoking habits, or obesity, all of which might increase ED, whether in thalassemia or nonthalassemia populations, and are confounding factors in this study. Second, the NHIRD database uses ICD-9 CM codes that do not reflect specific genotypes and associated hemoglobinopathies, which might have led to heterogeneous clinical manifestations. Certain detailed information of the patients with thalassemia, including hemoglobin level, clinical manifestations, and chronic complications, was not available. Detailed individual differences should be elucidated through further studies. Third, because the diagnosis of ED resulted from data collected from a self-administered IIEF-5 questionnaire, the incidence rate of ED might have been underestimated. ED patients in Taiwan are less likely to visit sexual specialists because of cultural taboos. Fourth, the evidence derived from retrospective cohort studies is typically lower in statistical quality than that derived from randomized trials because of potential biases related to adjustments for confounding variables. Fifth, more chronic comorbidities were observed in the thalassemic group, and the cause of organic ED might have been these comorbidities rather than thalassemia itself. The detailed causes were not clear, and further studies are necessary to elucidate the clinical correlation. This study does not provide strong evidence to differentiate between the relationship of thalassemia and ED, or comorbidities and ED. Sixth, in the analysis of comorbidities, the psychological causes of ED (ie, anxiety and depression) were particularly likely to be underdiagnosed due to under-reporting. Seventh, although the control groups selected were from those populations without the diagnosis of thalassemia, it does not mean that there were no thalassemia cases in the control group. It could mean either that they have been tested and found not to have it, or that they have not been tested for it. Finally, only 20.1% of patients with thalassemia cohort have anemia. It did not contain the detailed information regarding those remainder patients were either with hematological featuring microcytosis only or anemia not being recorded in the diagnostic list.

The main contribution of our study is its use of a nationwide population-based database that contains data on a high number of thalassemia cases, and the results indicate that patients with transfusion-naive thalassemia exhibited a 4.56-fold risk of developing organic ED when compared with the general population. Higher incidence rates of organic ED were also observed in elderly patients with transfusion-naive thalassemia and chronic comorbidities. Although the detailed pathophysiological mechanism between organic ED and thalassemia may require further examination, we recommend that physicians consider the possibility of organic ED. In addition, more detailed longitudinal cohort studies are necessary to elucidate whether healthy carriers of thalassemia, including those with thalassemia minor/trait, may still be at risk of developing ED.

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