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TRANSFUSION COMPLICATIONS

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# Relationship between transfusion burden, healthcare resource utilization, and complications in patients with beta-thalassemia in Taiwan: A real-world analysis

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## Abstract

**Background:** This study utilized a population-based claims database to identify patients with beta-thalassemia and evaluate associations between transfusion burden, healthcare resource utilization (HCRU), and complications.

**Study design and methods:** Taiwan's National Health Insurance Research Database was used to identify patients with beta-thalassemia (ICD-10 D56.1) in 2016. Patients with a beta-thalassemia claim in 2016 were indexed into the study at their first claim on or after January 1, 2001 in the dataset through to December 31, 2016 and followed until the end of study. During the follow-up period, red blood cell transfusion (RBCT) units, HCRU, iron chelation therapy use, and beta-thalassemia-related complications incidence were recorded. Patients were grouped into transfusion burden severity cohorts based on average number of RBCT units per 12 weeks during follow-up: 0 RBCT units, >0 to <6 RBCT units (mild), ≥6 to <12 RBCT units (moderate), and ≥12 RBCT units (severe).

**Results:** A total of 2984 patients were included with mean follow-up of 6.95 years. Of these, 1616 (54.2%) patients had no claims for RBCT units, 1112 (37.3%) had claims for >0 to <6 RBCT units, 112 (3.8%) for ≥6 to <12 RBCT units, and 144 (4.8%) for ≥12 RBCT units per 12 weeks. Transfused patients had significantly more all-cause HCRU and iron chelation therapy compared with non-transfused patients during follow-up. Thalassemia-related HCRU and risk of liver, endocrine, cardiac, and renal complications were significantly and positively correlated with increases of RBCT units.

**Discussion:** Clinical and healthcare resource burden of patients with beta-thalassemia is closely related to transfusion burden.

KEYWORDS

hemoglobinopathies, morbidity, outcomes, red blood cell transfusion

## 1 | INTRODUCTION

The thalassemias are a group of genetic disorders with reduced production of adult hemoglobin.[1] In patients with beta-thalassemia, the deficient production of beta-globin chains leads to an alpha-to-beta globin chain imbalance and ineffective erythropoiesis. This subsequently leads to chronic anemia of varying degrees of severity, based on the underlying genotype and modifier mutations.[1] Patients can be in an asymptomatic "carrier state" that is often referred to as beta-thalassemia minor.[2] Patients with beta-thalassemia minor can experience mild anemia, especially during pregnancy and situations of acute stress, but usually do not require treatment. The homozygous and compound heterozygous states of beta-thalassemia can lead to two clinically distinct forms, beta-thalassemia intermedia and beta-thalassemia major with mild–moderate and severe anemia, respectively.[2] More recently, classification of beta-thalassemia became more closely related to transfusion requirement, and the terms transfusion-dependent (TD) and non-transfusion-dependent (NTD) beta-thalassemia are more widely used. Patients with TD beta-thalassemia are commonly diagnosed in early childhood and require lifelong transfusion therapy for survival. Patients with NTD beta-thalassemia are diagnosed in later childhood or adolescence and may only require occasional or temporary transfusions to manage growth or specific clinical morbidities.[3]

The global annual incidence of symptomatic individuals with beta-thalassemia is around 1 in 100,000 with significant regional variations.[4] Beta-thalassemia is more common in the Mediterranean, Southeast Asia, India, Africa, and the Middle East.[1] However, recent migrations have led these conditions to become more highly encountered in large multi-ethnic cities in Europe and North America.[1]

The incidence of beta-thalassemia major has generally decreased over time in some regions, especially following the introduction of national screening programs and adoption of multidisciplinary preventive measures. In Taiwan, where a national screening program was introduced in 1993, the prevalence of beta-thalassemia major per 100,000 births decreased from 5.6 in 1994 to 1.2 in 2002.[5]

Patients with beta-thalassemia are now living longer due to earlier diagnosis, improved understanding of the disease, and increased access to conventional care.[1] This, however, does not come without its own side effect considering longer survival may allow long-term disease morbidities to manifest. In patients with NTD beta-thalassemia, a wide range of complications in critical organ systems can develop due to ineffective erythropoiesis, hemolysis, and primary iron overload attributed to increased intestinal absorption.[3] Patients with NTD beta-thalassemia can go on to become TD later in life. In TD beta-thalassemia, transfusion therapy leads to secondary iron overload in vital organs, such as the liver, heart, and endocrine glands, which, if left untreated, can result in significant morbidity, mortality, and diminished quality of life.[6] Despite iron chelation therapy availability, a considerable proportion of patients with TD beta-thalassemia continue to live with high iron burden in such vital organs.[7]

The presence of significant comorbidities and frequent transfusions has been found to significantly increase costs and healthcare resource utilization (HCRU) in patients with beta-thalassemia compared with the general population.[8] In the United States (US), the mean 1-year healthcare cost for patients with TD beta-thalassemia was $128,062 (standard deviation [SD] = 62,260) compared with $5438 (SD = 11,855) for a matched cohort of non-thalassemia patients ($p < 0.001$). A study by Paramore et al. of US commercially insured or Medicaid patients with beta-thalassemia reported similar results, with mean annual per patient costs of $127,553.[9]

New therapies currently being studied and/or under review by regulatory agencies have shown promise in reducing the number of red blood cell transfusion (RBCT) units in TD beta-thalassemia. While the real-world incidence of iron-related complications and their subsequent outcomes have been well studied in beta-thalassemia, less is known about the direct relationship between RBCT units, complications, and HCRU. Such information could prove vital in further understanding the benefit of transfusion reduction in patients with beta-thalassemia, whether mediated by reduction in iron overload and associated complications, iron chelator use, or alternate causal pathways.

This study is a retrospective database analysis of beta-thalassemia patients in Taiwan. The primary objective was to understand the relationship between transfusion burden and the development of complications and HCRU within beta-thalassemia. The results of the study can help stakeholders and decision-makers understand the implications associated with a high transfusion burden in beta-thalassemia and the potential benefits of transfusion burden reduction.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source

Taiwan's single-payer healthcare system covers over 99% of the population and has been in place since 1995. The Ministry of Health and Welfare maintains the Health and

Welfare Data Center, which houses the population-level claims-based National Health Insurance Research Database (NHIRD) for all of Taiwan.[10] The de-identified longitudinal NHIRD includes claims data for all reimbursed healthcare goods and services, such as ambulatory care, inpatient care, and prescription drugs in Taiwan.[10] All claims in the database are accompanied by diagnosis codes, such as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, which were available in the database from January 1, 2001 to December 31, 2015. The database introduced International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) coding starting on January 1, 2016 and running through to the end of the study period. The study was granted an exemption from ethical review by the Taipei Medical University-Joint Institutional Review Board.

## 2.2 | Study design

This retrospective cohort study included all claims for patients with thalassemia from January 1, 2001 to December 31, 2016 (the last year available at the time of the data application). As beta-thalassemia is a rare genetic condition, the index period spanned the entire study period (January 1, 2001 to December 31, 2016) to maximize the number of patients included in the study.

The database only included four-digit ICD-9-CM coding until December 31, 2015, which presented a challenge in identifying patients with beta-thalassemia. The ICD-9-CM code of 282.4 includes all patients with thalassemia and the database did not include the five-digit code of 282.44, which is specifically for beta-thalassemia. The introduction of ICD-10-CM coding in 2016 allowed for the identification of patients with beta-thalassemia using the D56.1 code after this point.

Patients were included in the study if they had ≥2 outpatient or ≥1 inpatient healthcare claim(s) within a calendar year during the index period, associated with either:

1. Thalassemia (ICD-9-CM 282.4) between January 1, 2001 and December 31, 2015, or
2. Beta-thalassemia (ICD-10-CM D56.1) between January 1, 2016 and December 31, 2016.

In the outpatient setting, ≥2 claims were required to prevent the possibility of miscoding and to confirm diagnosis. Patients were excluded from the study if they did not have any healthcare claim (inpatient, outpatient, or emergency room) associated with beta-thalassemia (ICD-10-CM D56.1) between January 1, 2016 and December 31, 2016. This exclusion criterion was used to confirm the patients indexed using ICD-9 coding (prior to 2016) were correctly identified by checking if they had the ICD-10 code for beta-thalassemia, which was introduced in the last year of the study (2016).

Patients were indexed on the date of their first interaction (claim) with the database during the study period, regardless of the claim or diagnosis code associated with the claim, as beta-thalassemia is a genetic disease. Patients were followed from index until either the end of the study period (December 31, 2016) or the patient left the database because of death or disenrollment from National Health Insurance (NHI). There was no mandatory minimum follow-up period required for inclusion.

## 2.3 | Study groups

The number of RBCT units received during the follow-up period was measured. Patients were categorized according to the average number of RBCT units per 12 weeks during follow-up to evaluate transfusion burden severity. Patients were grouped by transfusion burden and included those with 0 RBCT units received, patients with mild transfusion burden averaging >0 to <6 RBCT units, patients with moderate transfusion burden averaging ≥6 to <12 RBCT units, and patients with severe transfusion burden averaging ≥12 RBCT units. The number of units for each severity threshold was informed by a clinical expert.

## 2.4 | Statistical analysis

Baseline demographics including age and sex were measured at index. Clinical characteristics such as number of RBCT units received in the 24 weeks post-index were also assessed and described. During follow-up, RBCT units, HCRU, and complications were summed.

### 2.4.1 | Descriptive analysis

A descriptive analysis was undertaken to examine the relationship between average RBCT units per 12 weeks received during follow-up, and HCRU, iron chelation therapy use, and complications.

HCRU included the number of hospital admissions, hospital inpatient days, outpatient visits, and emergency room visits per 12 weeks during follow-up. All healthcare resources were measured as both all-cause and thalassemia-related. Thalassemia-related resources included only claims with a primary ICD-9-CM code of 282.4 or an ICD-10-CM code of D56.1. The utilization rates of the included healthcare resources were reported for patients with 0 RBCT

units and compared with those of all patients with >0 RBCT units during follow-up. A one-way analysis of variance (ANOVA) test was used to test for statistical significance at a level of 0.05 for each HCRU category between patients with and without RBCT units received during follow-up. HCRU was also reported for mild, moderate, and severe patient groups based on RBCT units per 12 weeks during follow-up.

Iron chelation therapy utilization rates were also measured during the follow-up period. Included iron chelation therapies were deferoxamine, deferiprone, and deferasirox. The percentage of patients with ≥1 claim during follow-up for each of the included iron chelation therapies was reported for patients with 0 RBCT units received and for patients averaging >0 RBCT units per 12 weeks during follow-up.

The incidence of complications was assessed during the follow-up period and included cardiac (congestive heart failure and cardiac arrhythmias), liver (liver disease), endocrine (hypogonadism, hypothyroidism, hypoparathyroidism, and diabetes), and renal (renal disease) complications. Complications were determined to be present in patients with one or more ICD-9-CM codes associated with a healthcare claim in the inpatient, outpatient, or emergency room setting for a specific complication. See Table S1 for coding details. Using the same RBCT categories from the HCRU analysis, the total number of patient-years during follow-up and the number of patient-years during follow-up after a claim for a complication were reported. Subsequently, for each of the included complications and RBCT categories, the percentage of follow-up period with the complication was calculated.

### 2.4.2 | Panel regressions

To quantify the relationship between transfusion burden and HCRU and complications, panel regressions were conducted with a patient-level observation. For each complication, logistic regressions of presence of complication on contemporaneous RBCT were used while controlling for patient age, sex, and availability of deferasirox. Then, generalized estimating equations were used to estimate the relationship between transfusion intensity and HCRU (all-cause and thalassemia-related) while controlling for age, sex, and availability of deferasirox.

The logistic regression equation used was:

$$\text{Complications}i,t = \text{Covariates}i,t + \text{RBCT}i,t + \text{EXJADE} + \text{error}i,t$$

The generalized estimating equation used was:

$$\text{HCRU}i,t = \text{Covariates}i,t + \text{RBCT}i,t + \text{EXJADE} + \text{error}i,t$$

To clarify, the logistic regression was conducted with the occurrences of complications as the dependent variable, and the other was performed with HCRU as the dependent variable using a pooled ordinary least squares (OLS) approach. Contemporaneous RBCT was a continuous variable of the number of RBCT units as the main explanatory variable in the model. Both models were estimated with longitudinal data that included repeated measurements of patients over the study period. To account for the correlation within patients, generalized estimating equations, a type of generalized linear model with unknown dependence between outcomes, were used to fit both types of model. Note that deferasirox was the first oral iron chelation therapy approved in Taiwan and was available in 2007.

**TABLE 1** Baseline characteristics of patients with beta-thalassemia

| Characteristic | Patients with beta-thalassemia ($N = 2984$) | |
|---|---|---|
| | ***n*** | **%** |
| Sex | | |
| Male | 1061 | 35.6 |
| Female | 1903 | 63.8 |
| Missing | 20 | 0.7 |
| Age (at index) | | |
| Mean ± SD | 37.8 ± 23.7 | |
| Median (IQR) | 37 (19–56) | |
| Min | 0 | |
| Max | 85 | |
| Age groups (at index) | | |
| 0–6 | 386 | 12.9 |
| 7–12 | 144 | 4.8 |
| 13–17 | 169 | 5.7 |
| 18–32 | 620 | 20.8 |
| 33–50 | 709 | 23.8 |
| 51–60 | 348 | 11.7 |
| 61+ | 608 | 20.4 |
| 24 weeks[a] RBCT units | | |
| Mean ± SD | 2.7 ± 7.1 | |
| Median (IQR) | 0 (0–0) | |
| Min | 0 | |
| Max | 51 | |

Abbreviations: IQR, interquartile range; RBCT, red blood cell transfusion; SD, standard deviation.

[a]24 weeks immediately following the index date.

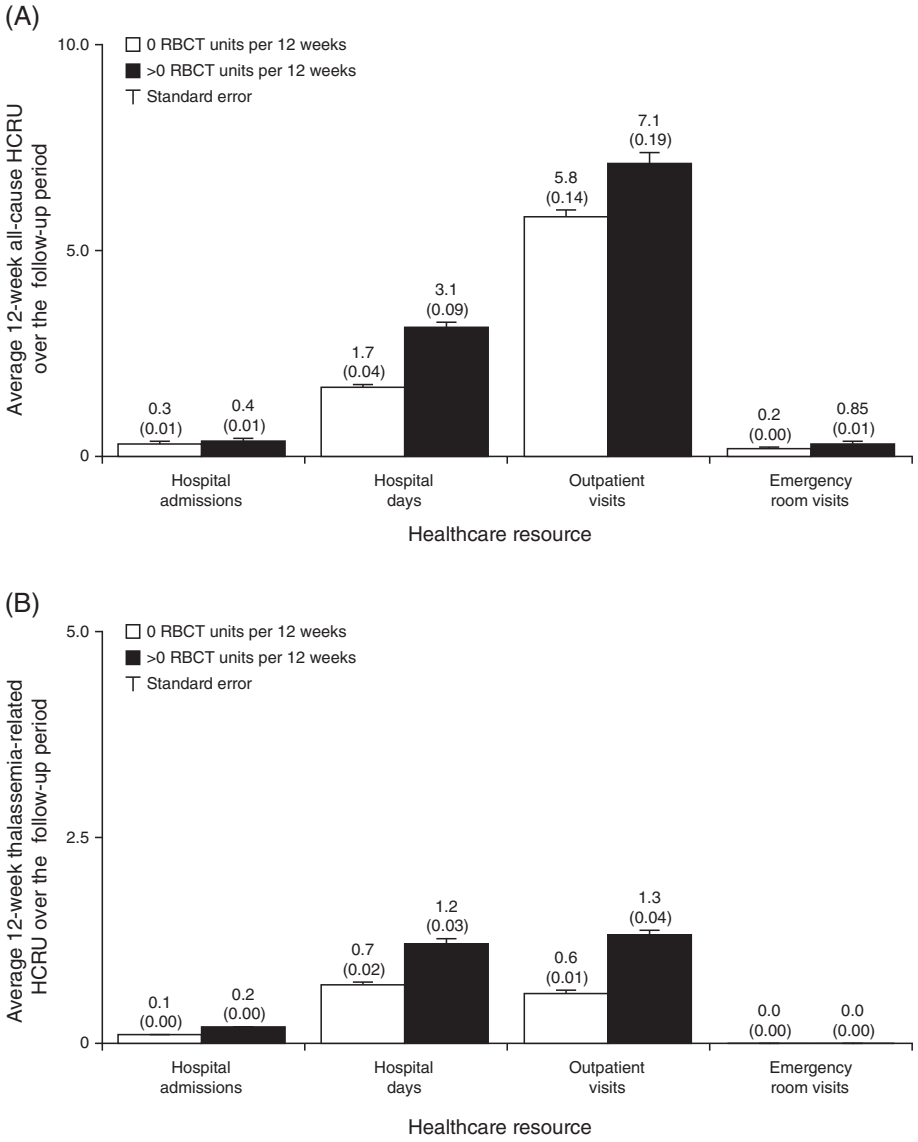


**FIGURE 1** Average 12-week RBCT units and HCRU during follow-up. (A) All-cause; (B) thalassemia-related. HCRU, healthcare resource utilization; RBCT, red blood cell transfusion

The estimates of both models were performed in SAS 9.4 (SAS Institute Inc., Cary, North Carolina) using PROC LOGISTIC and PROC GENMOD.

## 3 | RESULTS

### 3.1 | Patient characteristics

There were a total of 2984 patients with beta-thalassemia included in the study. The mean (SD) age was 37.8 (23.7) years and 63.8% ($n = 1903$) were female (Table 1). The average follow-up time was 6.95 years from index through to end of the study period. Patients with >0 RBCT units had a higher average follow-up time (8.9 patient-years) compared with patients with 0 RBCT units (5.3 patient-years).

The mean (SD) number of RBCT units received in the 24 weeks immediately following index was 2.7 (7.1). During the follow-up period, there were 1616 (54.2%) patients with no claims for RBCT units, 1112 (37.3%) with claims for >0 to <6 RBCT units per 12 weeks, 112 (3.8%) with claims for ≥6 to <12 RBCT units per 12 weeks, and 144 (4.8%) with claims for ≥12 RBCT units per 12 weeks.

### 3.2 | Descriptive analysis

#### 3.2.1 | HCRU

All-cause HCRU for patients with and without RBCT units during the follow-up period are shown in Figure 1 (A). Patients averaging >0 RBCT units compared with 0 RBCT units per 12 weeks had significantly ($p < 0.0001$)

**TABLE 2** Average 12-week all-cause and thalassemia-related HCRU by average 12-week RBCT unit categories during follow-up

| | 0 RBCT units ($N = 1616$) | | | >0 to <6 RBCT units ($N = 1112$) | | | ≥6 to <12 RBCT units ($N = 112$) | | | ≥12 RBCT units ($N = 144$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Resource** | **Mean** | **SD** | **SE** | **Mean** | **SD** | **SE** | **Mean** | **SD** | **SE** | **Mean** | **SD** | **SE** |
| Patient-years, mean (SD) | 5.3 | 4.7 | — | 8 | 5.1 | — | 10.3 | 6.3 | — | 14.3 | 4.5 | — |
| Inpatient | | | | | | | | | | | | |
| Hospital admissions | | | | | | | | | | | | |
| All-cause | 0.3 | 0.6 | 0.01 | 0.4 | 0.5 | 0.01 | 0.6 | 1.0 | 0.06 | 0.5 | 1.6 | 0.04 |
| Thalassemia-related | 0.1 | 0.4 | 0.00 | 0.1 | 0.3 | 0.00 | 0.4 | 0.8 | 0.04 | 0.5 | 1.5 | 0.04 |
| Hospital days | | | | | | | | | | | | |
| All-cause | 1.7 | 6.1 | 0.04 | 2.9 | 6.0 | 0.09 | 4.5 | 8.4 | 0.43 | 4.0 | 13.1 | 0.33 |
| Thalassemia-related | 0.7 | 3.1 | 0.02 | 1.0 | 2.9 | 0.03 | 1.9 | 4.0 | 0.18 | 2.5 | 9.4 | 0.21 |
| Outpatient | | | | | | | | | | | | |
| Outpatient visits | | | | | | | | | | | | |
| All-cause | 5.8 | 3.9 | 0.14 | 7.0 | 4.4 | 0.21 | 7.9 | 3.2 | 0.75 | 7.6 | 2.5 | 0.63 |
| Thalassemia-related | 0.6 | 1.3 | 0.01 | 0.7 | 1.1 | 0.02 | 3.2 | 2.0 | 0.30 | 4.9 | 1.9 | 0.41 |
| Emergency room | | | | | | | | | | | | |
| Emergency room visits | | | | | | | | | | | | |
| All-cause | 0.2 | 0.4 | 0.00 | 0.3 | 0.9 | 0.01 | 0.5 | 0.7 | 0.05 | 0.4 | 0.5 | 0.03 |
| Thalassemia-related | 0.0 | 0.1 | 0.00 | 0.0 | 0.1 | 0.00 | 0.2 | 0.4 | 0.02 | 0.1 | 0.2 | 0.01 |
| Iron chelation therapy | | | | | | | | | | | | |
| Deferoxamine | | | | | | | | | | | | |
| Utilization (≥1 claim), *n* (%) | 6 | 0.37 | — | 93 | 8.36 | — | 71 | 63.39 | — | 129 | 89.58 | — |
| Mg per patient-year, mean (SD) | 15306 | 19470 | — | 14320 | 20364 | — | 82719 | 64717 | — | 158929 | 79016 | — |
| Deferiprone | | | | | | | | | | | | |
| Utilization (≥1 claim), *n* (%) | 3 | 0.19 | — | 32 | 2.88 | — | 51 | 45.54 | — | 98 | 68.06 | — |
| Mg per patient-year, mean (SD) | 35174 | 31686 | — | 183023 | 127303 | — | 434900 | 369523 | — | 539355 | 414757 | — |
| Deferasirox | | | | | | | | | | | | |
| Utilization (≥1 claim), *n* (%) | 9 | 0.56 | — | 146 | 13.13 | — | 82 | 73.21 | — | 119 | 82.64 | — |
| Mg per patient-year, mean (SD) | 39471 | 41270 | — | 43534 | 45682 | — | 135931 | 85798 | — | 204549 | 117351 | — |

*Note*: National Health Insurance drug codes: Deferoxamine = BC11917277/BC22483277; Deferiprone = XC00084100; Deferasirox = BC24603100.

Abbreviations: HCRU, healthcare resource utilization; IQR, interquartile range; Mg, milligram; RBCT, red blood cell transfusion; SD, standard deviation; SE, standard error.

**TABLE 3** Complications by average 12-week RBCT unit categories during follow-up

| Complication | 0 RBCT units per 12 weeks (PYs = 8634.6) | | >0 to <6 RBCT units (PYs = 8921.8) | | ≥6 to <12 RBCT units (PYs = 1157.8) | | ≥12 RBCT units (PYs = 2053.8) | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | PYs w/complication | % of PYs w/complication | PYs w/complication | % of PYs w/complication | PYs w/complication | % of PYs w/complication | PYs w/complication | % of PYs w/complication | |
| Cardiac complications | | | | | | | | | |
| Congestive heart failure | 245.5 | 2.84 | 1043.6 | 11.70 | 228.2 | 19.71 | 358.2 | 17.44 | <0.0001 |
| Cardiac arrhythmias | 716.1 | 8.29 | 1383.6 | 15.51 | 191.0 | 16.50 | 385.3 | 18.76 | <0.0001 |
| Any cardiac complication | 893.5 | 10.35 | 1926.9 | 21.60 | 340.4 | 29.40 | 613.8 | 29.89 | <0.0001 |
| Endocrine | | | | | | | | | |
| Hypogonadism | 0.8 | 0.01 | 7.9 | 0.09 | 15.9 | 1.37 | 261.9 | 12.75 | 0.0104 |
| Hypothyroidism | 244.0 | 2.83 | 235.8 | 2.64 | 79.6 | 6.88 | 120.1 | 5.85 | <0.0001 |
| Hypoparathyroidism | 4.9 | 0.06 | 6.5 | 0.07 | 23.6 | 2.04 | 76.3 | 3.72 | 0.0239 |
| Diabetes | 889.2 | 10.30 | 1846.3 | 20.69 | 313.6 | 27.09 | 691.5 | 33.67 | <0.0001 |
| Any endocrine complication | 1085.5 | 12.57 | 2023.7 | 22.68 | 379.5 | 32.78 | 835.0 | 40.66 | <0.0001 |
| Liver | | | | | | | | | |
| Liver disease | 1658.1 | 19.20 | 2876.3 | 32.24 | 351.7 | 30.38 | 740.8 | 36.07 | <0.0001 |
| Renal | | | | | | | | | |
| Renal disease | 351.9 | 4.08 | 1264.6 | 14.17 | 109.9 | 9.49 | 64.1 | 3.12 | <0.0001 |
| Renal failure | 183.1 | 2.12 | 903.4 | 10.13 | 95.5 | 8.25 | 47.5 | 2.31 | <0.0001 |
| Any renal complication | 374.3 | 4.33 | 1285.7 | 14.41 | 109.9 | 9.49 | 64.1 | 3.12 | <0.0001 |

Abbreviations: PY, patient-year; RBCT, red blood cell transfusion.

**TABLE 4** Relationship between utilization (all-cause) and RBCT utilization estimated with PROC GENMOD

| | All-cause ($N = 40,678$) | | | | | | Thalassemia-related ($N = 40,678$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | | | 95% CI | | | |
| **Utilization** | **Coefficient** | **SE** | **Lower** | **Upper** | **Z** | ***p*-value** | **Coefficient** | **SE** | **Lower** | **Upper** | **Z** | ***p*-value** |
| Hospital admissions | | | | | | | | | | | | |
| Age | −0.0011 | 0.0014 | −0.0039 | 0.0016 | −0.81 | 0.4187 | −0.004 | 0.0011 | −0.0062 | −0.0017 | −3.48 | 0.0005 |
| Sex | 0.1036 | 0.0838 | −0.0607 | 0.2679 | 1.24 | 0.2167 | 0.0736 | 0.0766 | −0.0765 | 0.2237 | 0.96 | 0.3365 |
| RBCT | 0.0183 | 0.0054 | 0.0077 | 0.0289 | 3.4 | 0.0007 | 0.0189 | 0.0053 | 0.0086 | 0.0292 | 3.59 | 0.0003 |
| Deferasirox available | 0.4586 | 0.0357 | 0.3886 | 0.5286 | 12.85 | <0.0001 | 0.1849 | 0.0304 | 0.1253 | 0.2445 | 6.08 | <0.0001 |
| Inpatient days | | | | | | | | | | | | |
| Age | 0.0208 | 0.0118 | −0.0024 | 0.0439 | 1.75 | 0.0794 | −0.0126 | 0.0039 | −0.0203 | −0.005 | −3.24 | 0.0012 |
| Male | 1.363 | 0.8394 | −0.2823 | 3.0082 | 1.62 | 0.1044 | −0.0391 | 0.2646 | −0.5577 | 0.4796 | −0.15 | 0.8827 |
| RBCT | 0.054 | 0.016 | 0.0226 | 0.0854 | 3.37 | 0.0008 | 0.0517 | 0.0082 | 0.0357 | 0.0677 | 6.33 | <0.0001 |
| Deferasirox available | 4.4084 | 0.4444 | 3.5374 | 5.2794 | 9.92 | <0.0001 | 1.4797 | 0.2311 | 1.0268 | 1.9326 | 6.4 | <0.0001 |
| Outpatient visits | | | | | | | | | | | | |
| Age | 0.1891 | 0.015 | 0.1597 | 0.2185 | 12.6 | <0.0001 | −0.0374 | 0.0042 | −0.0455 | −0.0292 | −9 | <0.0001 |
| Male | −2.5606 | 0.6772 | −3.8879 | −1.2333 | −3.78 | 0.0002 | 0.0746 | 0.2015 | −0.3202 | 0.4695 | 0.37 | 0.7111 |
| RBCT | 0.2306 | 0.0138 | 0.2035 | 0.2577 | 16.68 | <0.0001 | 0.3202 | 0.0097 | 0.3012 | 0.3392 | 33.07 | <0.0001 |
| Deferasirox available | 3.0000 | 0.3125 | 2.3876 | 3.6125 | 9.6 | <0.0001 | 1.1465 | 0.1214 | 0.9085 | 1.3845 | 9.44 | <0.0001 |
| Emergency room visits | | | | | | | | | | | | |
| Age | 0.0004 | 0.0017 | −0.003 | 0.0038 | 0.22 | 0.8256 | −0.0021 | 0.0006 | −0.0032 | −0.001 | −3.83 | 0.0001 |
| Male | −0.0844 | 0.0994 | −0.2792 | 0.1105 | −0.85 | 0.3962 | −0.0066 | 0.0215 | −0.0488 | 0.0356 | −0.31 | 0.7576 |
| RBCT | 0.0093 | 0.0024 | 0.0045 | 0.014 | 3.83 | 0.0001 | 0.0064 | 0.0009 | 0.0046 | 0.0082 | 6.85 | <0.0001 |
| Deferasirox available | 0.4653 | 0.0968 | 0.2756 | 0.655 | 4.81 | <0.0001 | 0.0588 | 0.0152 | 0.0291 | 0.0886 | 3.88 | 0.0001 |

Abbreviations: CI, confidence interval; RBCT, red blood cell transfusion; SE, standard error.

higher average all-cause hospital admissions (0.4 vs 0.3), hospital days (3.1 vs 1.7), outpatient visits (7.1 vs 5.8), and emergency room (0.85 vs 0.2) visits per 12 weeks during follow-up. Similar trends were observed for thalassemia-related HCRU (Figure 1(B)).

When HCRU was further stratified by the average number of RBCT units received per 12 weeks during follow-up (Table 2), patients averaging ≥6 to <12 RBCT units per 12 weeks had the highest average all-cause HCRU rates between all measured RBCT unit categories. Thalassemia-related HCRU was highest for patients averaging ≥12 RBCT units compared with those averaging >0 to <6 RBCT units. Patients averaging ≥12 RBCT units per 12 weeks had 7 times higher mean thalassemia-related 12-week outpatient visits (4.9 vs 0.7), 5 times higher hospital admissions (0.5 vs 0.1), and 2.5 times higher hospital days (2.5 vs 1.0) compared with patients averaging >0 to <6 RBCT units.

During the follow-up period, the overall rate of iron chelation therapy utilization (≥1 claim) regardless of RBCT units during follow-up was 10.0% for deferoxamine, 6.2% for deferiprone, and 11.9% for deferasirox. Patients averaging >0 RBCT units compared with those averaging 0 RBCT units per 12 weeks during follow-up had higher rates of iron chelation therapy utilization for deferoxamine (21.42% vs 0.37%), deferiprone (13.23% vs 0.19%), and deferasirox (25.37% vs 0.56%). Utilization and the average number of milligrams (mg) per patient-year of iron chelation therapy increased across the included RBCT unit groups for all included therapies (Table 2).

### 3.2.2 | Complications

The percentage of patients with any cardiac, endocrine, liver, or renal complication during the follow-up period was higher for patients with >0 RBCT units than patients with 0 RBCT units. The percentage of patients with any cardiac complication was 2.58 times higher (13.30% vs 34.36%), any endocrine complication was 2.33 times higher (16.09% vs 37.43%), any liver disease was 1.85 times higher (21.04% vs 38.96%), and any renal complication was 3.71 times higher (6.19% vs 22.95%).

The percentage of total patient-years that were after the first claim for a complication was compared across the RBCT groups to adjust for differences in follow-up time (Table 3). The percentage of patient-years following a cardiac or endocrine comorbidity diagnosis increased as each of the RBCT groups increased in severity. The percentage of patient-years following a cardiac diagnosis was 10.35% for patients with 0 RBCT units during follow-up, 21.60% for patients averaging >0 to <6 RBCT units per 12 weeks, 29.40% for patients averaging ≥6 to <12 RBCT units per 12 weeks, and 29.89% for patients averaging ≥12 RBCT units during the follow-up period.

Renal complications were most prevalent for patients averaging >0 to <6 RBCT units per 12 weeks (14.41% of patient-years) followed by patients averaging ≥6 to <12 RBCT units per 12 weeks (9.49% of patient-years). The percentage of patient-years following a liver disease diagnosis was 19.20% for patients with 0 RBCT units during follow-up, 32.24% for patients averaging >0 to <6 RBCT units per 12 weeks, 30.38% for patients averaging ≥6 to <12 RBCT units per 12 weeks, and 36.07% for patients averaging ≥12 RBCT units per 12 weeks (Table 3).

## 3.3 | Panel regression

### 3.3.1 | RBCT units and HCRU

Table 4 shows the regression results for the inpatient days, outpatient visits, hospital admissions, and emergency room visits for all-cause and thalassemia-related

**TABLE 5** Relationship between complications and RBCT utilization estimate with PROC LOGISTIC

| | | 95% CI | | |
|---|---|---|---|---|
| (*N* = 40,678) | OR | Lower | Upper | *p*-value |
| Cardiac | | | | |
| Age | 1.05 | 1.05 | 1.05 | <0.0001 |
| Male | 0.87 | 0.78 | 0.97 | 0.014 |
| RBCT | 1.04 | 1.03 | 1.04 | <0.0001 |
| Deferasirox available | 1.68 | 1.47 | 1.92 | <0.0001 |
| Liver | | | | |
| Age | 1.02 | 1.02 | 1.02 | <0.0001 |
| Male | 1.51 | 1.38 | 1.66 | <0.0001 |
| RBCT | 1.02 | 1.01 | 1.02 | <0.0001 |
| Deferasirox available | 1.37 | 1.23 | 1.52 | <0.0001 |
| Endocrine | | | | |
| Age | 1.04 | 1.04 | 1.04 | <0.0001 |
| Male | 0.81 | 0.74 | 0.88 | <0.0001 |
| RBCT | 1.04 | 1.04 | 1.04 | <0.0001 |
| Deferasirox available | 1.5 | 1.37 | 1.64 | <0.0001 |
| Renal | | | | |
| Age | 1.04 | 1.04 | 1.05 | <0.0001 |
| Male | 1.25 | 1.1 | 1.41 | 0 |
| RBCT | 1.02 | 1.01 | 1.02 | <0.0001 |
| Deferasirox available | 2.87 | 2.39 | 3.45 | <0.0001 |

Abbreviations: CI, confidence interval; OR, odds ratio; RBCT, red blood cell transfusion.

utilization. For all-cause utilization, the RBCT coefficient was statistically different from 0 for inpatient days ($p = 0.0008$), outpatient visits ($p < 0.0001$), hospital admissions ($p = 0.0007$), and emergency room visits ($p = 0.0001$). One additional unit of RBCT utilization was associated with additional outpatient visits (0.2306), inpatient days (0.054), hospital admissions (0.0183), and emergency room visits (0.0093).

For thalassemia-related utilization, RBCT was statistically significant and positively correlated with all utilization measures.

### 3.3.2 | RBCT units and complications

Table 5 shows the estimated RBCT on complications. An increase in contemporaneous RBCT was associated with a higher risk of liver, endocrine, cardiac, and renal complications ($p < 0.0001$). Patients' age and the availability of deferasirox are also positively correlated with complications.

## 4 | DISCUSSION

To the authors' knowledge, this is the first real-world claims-based study examining the differences in HCRU and incidence of complications according to transfusion burden in terms of RBCT units for patients with beta-thalassemia. The descriptive analysis showed HCRU burden and percentage of patients with complications generally increased as the severity of the RBCT unit cohorts increased. Each RBCT unit increase was significantly and positively correlated with thalassemia-related HCRU and a higher risk of liver, endocrine, cardiac, and renal complications as demonstrated in the panel regressions.

Our study included 256 patients averaging ≥6 RBCT units per 12 weeks throughout the follow-up period and was consistent with previously published literature in Taiwan, suggesting this study is representative of the TD beta-thalassemia population in Taiwan. In 2002, there were 361 patients with TD thalassemia in the Taiwan Thalassemia Association Registry.[5] Furthermore, the 2016 study by Wu et al. found 454 patients with TD thalassemia major between 2007 and 2011.[11]

The HCRU outcomes and comorbidities of our study population in this study are in-line with the literature. An analysis by Weiss et al. estimated outpatient visits, inpatient visits, and emergency room visits per person-year in TD beta-thalassemia in the US.[8] Although the care-seeking patterns are different between the US and Taiwan due to differences in the health system, these results are generally in-line with our study. The Wu et al. analysis of 454 patients with TD thalassemia major identified similar prevalence rates of comorbidities to this analysis.[11]

The results of this study demonstrate that transfused patients have increased rates of HCRU, iron chelation therapy, and complications compared with non-transfused patients. As this was a claims-based analysis absent of clinical information pertaining to hemoglobin levels and genotype, we cannot attribute the increase in burden solely to transfusions. It is possible patients receiving transfusions could need additional transfusions to counterbalance the underlying disease and improve outcomes.

In addition to transfused patients having worse outcomes, within the transfused cohort additional RBCT units led to an increase in HCRU, iron chelation therapy, and complications. As with the previously discussed analysis of transfused versus non-transfused, without clinical information such as genotype and hemoglobin levels, it cannot be certain that the observed outcomes were solely due to transfusions or if they were caused by the underlying disease. The all-cause HCRU results of this study suggest patients with possibly more severe disease and receiving more RBCT units could have better outcomes. Patients in the ≥6 to <12 RBCT units per 12 weeks group had higher average all-cause HCRU for all measured categories compared with the most severe group (≥12 RBCT units).

Iron-related complications were significantly correlated with a per unit increase in RBCT units among patients in this analysis. The descriptive analysis also showed an increasing rate in percentage of patients with iron-related complications as the severity of the RBCT unit cohorts increased. Rather than HCRU, the increase in iron-related complications is likely due to the additional RBCT units rather than the underlying disease. This is supported by similar trends in the increase of iron-related complications and iron chelation therapy utilization rates and dosing within the RBCT unit cohorts as they increase in severity. One outlier was that renal complications were higher for the >0 to <6 RBCT units per 12 weeks group compared with the ≥6 to <12 RBCT units per 12 weeks group. One explanation for this could be that the relationship between renal complications and transfusions in transfused patients might be non-linear, which is probably because renal disease per se is also a function of anemia (not only iron overload), and hence there might be a protective effect of transfusions for heavily transfused patients.[12]

There were a few study results that may require additional analysis. For example, 63% of patients were female, which is higher than expected. Taiwan started a national screening program in 1993; one possible explanation is

that a sizable portion of the patient population consisted of immigrant workers, who were predominantly female. Chern et al. noted the following: "A total of 224,196 female immigrants were living in Taiwan in interracial marriages at the end of August 2003. They have changed the epidemiology of thalassemia."[13] These immigrants could contribute to the skew toward the sex differential in the study. Another issue is that there were almost 3 times as many 0–6 year-olds as there were 7–12 year-olds. This is because the study design examined age at index rather than cross-sectionally at a single point in time. The high percentage of patients 0–6 years old was due to the study design of indexing patients upon their first interaction (claim) within the database. Any patient included in the study who had their first claim during the index period (2001–2016) or within 6 years of the index period would be included in the 0–6 years classification. Only patients born and with claims prior to 1996 were included in the age categorizations above 0–6 years.

The results of this study also highlight an unmet need in patients with beta-thalassemia receiving regular transfusions. The current treatment paradigm for patients with beta-thalassemia only offers RBCTs and subsequently iron chelation therapy to counteract iron overload. Upstream interventions reducing transfusions or RBCT units per transfusion event could lead to lower complications and HCRU. There are several new and innovative therapies being developed for patients with beta-thalassemia. Several of these therapies seek to reduce or eliminate the need for transfusions in patients. The results of this study could aid in the development of health economic evidence supporting the use of new therapies in beta-thalassemia.

There are several limitations to this study. First, the restriction in ICD-10-CM coding to 2016 only may have led to a cohort of patients with beta-thalassemia that was not reflective of the real world during the study period. However, the authors feel these restrictions would, if anything, have led to a more conservative patient population that was less severe. Current data availability does not allow for sensitivity analysis of including patients in the study exclusion criteria. Second, deferasirox was reimbursed by the NHI in 2007, which was in the middle of our analysis period. While the panel regressions controlled for deferasirox, the treatment patterns and outcomes before and after reimbursement could have skewed the descriptive results. Lastly, this was a retrospective database analysis of a claims-based database without any clinical data. Without information regarding the genotype of the disease or hemoglobin level, we could not assess the severity of the underlying disease or differentiate between the effect of the disease itself compared with transfusions on the outcomes being measured. As it was a claims-based database, any HCRU not reimbursed by the NHI would have been excluded from this study, which suggests the analysis may be underestimating the burden of transfusions in the beta-thalassemia population.

Our study shows a significant relationship between RBCT units and the development of beta-thalassemia-related complications as well as HCRU. Patients consuming more RBCT units were more likely to develop heart, endocrine, or renal complications as well as to have more HCRU.

The findings of this study quantify the downstream burden experienced by patients with beta-thalassemia who receive transfusions. The ability to reduce the number of transfusions and subsequently the number of RBCT units would reduce the clinical and economic burden of patients with beta-thalassemia in Taiwan.

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## CONFLICT OF INTEREST

Wesley Furnback, Bruce C.M. Wang, and Jackson Tang are paid consultants of Bristol Myers Squibb. Vicky W.-H. Huang and Derek Tang are employees of Bristol Myers Squibb. Khaled M. Musallam received consulting fees from Bristol Myers Squibb. Chao-Hsiun Tang and Meng-Yao Lu have no conflicts of interest to disclose.

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## ENDNOTE

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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