Clinical and Economic Burden in Pediatric Patients With Transfusion-Dependent β-Thalassemia in the United States

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BACKGROUND

- β-thalassemia, a rare hereditary blood disorder affecting ~3,670 people in the United States, is characterized by reduced or absent β-globin production, leading to ineffective red blood cell (RBC) production and anemia[1-5]
- The most severe and common form of the disease is transfusion-dependent β-thalassemia (TDT), in which patients depend on regular RBC transfusions (RBCTs) for survival[1,2]
- Individuals with TDT experience reduced life expectancy, increased morbidity, and iron overload resulting from frequent RBCTs[1,2]; iron overload adversely affects nearly all organ systems in patients with TDT, such as the heart, liver, and the endocrine system, with organ damage beginning in childhood and worsening over time[6-8]
- Standard treatments, including regular RBCTs and daily iron chelation therapies (ICTs), are necessary throughout a patient's lifetime[1,2]
- Lifelong transfusion dependence and iron overload lead to significant healthcare resource utilization (HCRU) and lifetime costs[6,9,10]

OBJECTIVE

- To characterize the clinical and economic burden of disease among pediatric patients with TDT in the United States

METHODS

Study Design and Database

- The Merative™ MarketScan® Commercial, Medicare, and Multi-State Medicaid Databases contain de-identified inpatient, outpatient medical, and outpatient prescription drug data
- A retrospective cohort study design was used to identify patients with TDT in the MarketScan Databases between January 1, 2014, and December 31, 2024

TDT Patient Identification

- Patients were included if they met the following inclusion criteria:
  - At least 1 inpatient claim with a principal diagnosis of β-thalassemia or ≥2 non-diagnostic outpatient claims of β-thalassemia within 365 days of each other between January 1, 2014, and December 31, 2024
  - At least 8 claims (on separate dates ≥3 days apart) with a procedure code for a RBCT during any 12-month period after and including the date of the earliest qualifying β-thalassemia diagnosis claim
  - At least 12 months of continuous enrollment with medical and pharmacy benefits after and including the index date, and ending on the earliest date of either inpatient death, end of continuous enrollment, or end of the study period (December 31, 2024)
    - The index date was the date of the first RBCT among the ≥8 discrete RBCT events
  - **Primary cohort:** Patients were required to be 5 to 11 years old at index
  - **Secondary cohort:** Patients were required to be ≥12 years old at index
    - This cohort was compared to the primary cohort to evaluate the clinical burden, treatment patterns, HCRU, and costs associated with TDT patients across different age groups
- Patients were excluded if they met the following exclusion criteria:
  - Evidence of sickle cell disease (SCD) from the beginning of pre-index continuous enrollment through the follow-up period
  - Evidence of hematopoietic stem cell transplantation (HSCT) during the follow-up period

Matched Control Identification

- Individuals in the MarketScan Databases without a claim for SCD, β-thalassemia, or any other blood disorder at any time during their MarketScan enrollment were included in the general population
- Matched controls from the general population were compared with the primary cohort to contextualize the clinical and economic burden of patients with TDT aged 5 to 11 years
- Five controls were matched on age, sex, region, payer type, and duration of follow-up data to each patient with TDT
- Index dates for controls were assigned based on the distribution of index dates among patients with TDT
- Consistent with the TDT cases, matched controls were required to have ≥12 months of continuous enrollment with medical and pharmacy benefits after and including the index date

Study Measures and Analyses

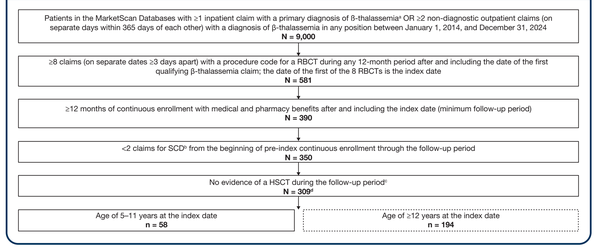
- Demographics, including age, sex, payer type, and duration of follow-up, were reported at the index date
- The proportion of individuals with clinical complications was reported through the presence of non-diagnostic claims during the follow-up period
- The proportion of individuals with treatments of interest in the follow-up period was captured using medical or pharmacy claims
- The annualized rate of treatment regimens (drugs and procedures per patient per year [PPPY]) was reported among all patients; annualized rates of discrete RBCTs and ICT were characterized separately
- Annualized rates of all-cause HCRU included inpatient admissions, emergency room (ER) visits, outpatient visits, and pharmacy prescriptions
- The proportion of patients with ≥1 inpatient admission and outpatient visit was also reported
- Annualized inpatient, outpatient, prescription, ICT, and RBCT costs (PPPY) were based on the paid amounts of adjudicated claims, including insurer and health plan payments, as well as patient cost-sharing in the form of co-payment, deductibles, and co-insurance
- Costs were inflated to 2024 US dollars using the Medical Care Component of the Consumer Price Index
- All study measures were summarized using descriptive statistics
  - Mean (standard deviation [SD]) values were reported for continuous variables, and frequencies (n)/proportions (%) were reported for categorical variables
- Comparative analyses were conducted between patients with TDT and matched controls for HCRU and annual costs
  - Chi-square tests were used to evaluate differences in categorical variables, and *t* tests were used for continuous variables
  - *P*<0.05 was considered statistically significant

RESULTS

Patient Demographics

- Three hundred and nine patients met the criteria for TDT and other inclusion/exclusion criteria; the group included 58 patients aged 5 to 11 years at the index date (primary cohort) and 194 patients aged ≥12 years at the index date (secondary cohort) (**Figure 1**)
- Fifty-eight patients aged 5 to 11 years at the index date were matched to 290 individuals from the general population (**Table 1**)
- Demographics are provided for 3 cohorts: patients with TDT aged 5 to 11 years, controls aged 5 to 11 years, and patients with TDT aged ≥12 years (**Table 1**)

Figure 1. TDT Attrition Table



CPT, Current Procedural Terminology; HSCT, hematopoietic stem cell transplant; ICD, International Classification of Diseases; RBCT, red blood cell transfusion; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.
[a]ICD-9: 282.44, 282.47; ICD-10: D56.1, D56.5.
[b]ICD-9: 282.41, 282.42, 282.6x; ICD-10: D57.x (except D57.3: sickle cell trait); SCD diagnosis codes must be accompanied by CPT codes for physician evaluation and management.
[c]Follow-up begins with the index date and ends with the earliest of inpatient death, end of continuous enrollment, or end of the study period (December 31, 2024).
[d]57 patients aged 0 to 4 years at the index date were not included in the analyses.

Table 1. Patient Demographics by Age Group

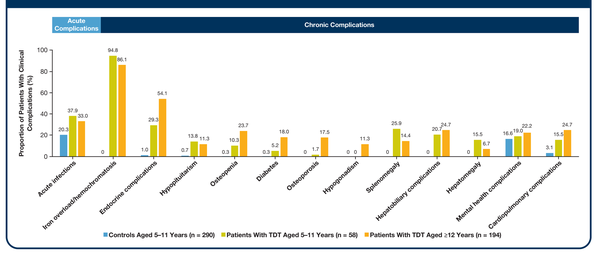
Patient Demographics	Primary Cohort: Patients With TDT Aged 5–11 Years (n = 58)	Matched Controls: Controls Aged 5–11 Years (n = 290)	Secondary Cohort: Patients With TDT Aged ≥12 Years (n = 194)
Age at index date (years)			
Mean (SD)	8.1 (2.0)	8.1 (2.0)	32.0 (15.7)
Min–max	5–11	5–11	12–96
Sex, n (%)			
Male	28 (48.3)	140 (48.3)	81 (41.8)
Female	30 (51.7)	150 (51.7)	113 (58.2)
Payer, n (%)			
Commercial	37 (63.8)	185 (63.8)	147 (75.8)
Medicaid	21 (36.2)	105 (36.2)	39 (20.1)
Medicaid FFS	4 (6.9)	20 (6.9)	16 (8.2)
Medicare	0 (0)	0 (0)	8 (4.1)
Duration of follow-up (years)			
Mean (SD)	4.5 (2.6)	4.5 (2.6)	3.7 (2.5)

FFS, fee-for-service; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.

Clinical Complications

- Complications are pronounced from childhood (**Figure 2**)
  - The most common acute complications in the 5 to 11 years cohort were acute infections (37.9%)
  - The most common chronic complications in the 5 to 11 years cohort were iron overload/hemochromatosis (94.8%), endocrine complications (29.3%), splenomegaly (25.9%), hepatobiliary complications (20.7%), mental health complications (19.0%), and cardiopulmonary complications (15.5%)
  - Hypopituitarism, osteopenia, and diabetes were the most common endocrine complications in the 5 to 11 years cohort
- Acute and chronic complications were substantially more prevalent in patients with TDT aged 5 to 11 years compared with the control group (**Figure 2**)
- The prevalence of complications was generally higher in the ≥12 years cohort than the 5 to 11 years cohort, although some complications were more common in patients aged 5 to 11 years than in those aged ≥12 years (**Figure 2**)

Figure 2. Clinical Complications by Age Group

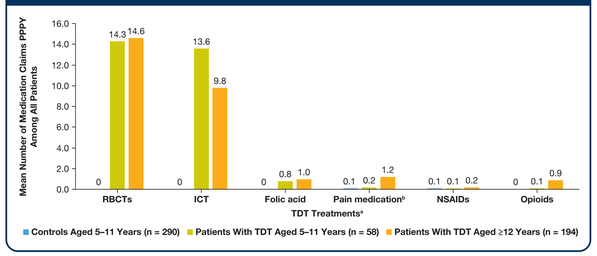


TDT, transfusion-dependent β-thalassemia.

Treatment Regimens

- RBCTs were comparable between the 5 to 11 years and ≥12 years TDT cohorts
  - RBCTs PPPY: 14.3 versus 14.6 (**Figure 3**)
  - Average days between RBCTs: 26.4 versus 27.7 days
- The majority of patients in the 5 to 11 years and ≥12 years TDT cohorts utilized ICT
  - Proportion of patients receiving ICT: 94.8% versus 88.7%
  - ICT claims PPPY: 13.6 versus 9.8 (**Figure 3**)

Figure 3. Treatments by Age Group



ICT, iron chelation therapy; NSAID, nonsteroidal anti-inflammatory drug; PPPY, per patient per year; RBCT, red blood cell transfusion; TDT, transfusion-dependent β-thalassemia.
[a]Treatments reported included those with ≥10% prevalence in the TDT cohort aged 5 to 11 years. The prevalence of treatments in the TDT cohort aged 5 to 11 years included RBCTs: 100%; ICT: 94.8%; folic acid: 13.8%; pain medications: 37.9%; NSAIDs: 19.0%; and opioids: 29.3%.
[b]Pain medications included opioids, NSAIDs, and gabapentin.

HCRU

- Patients with TDT aged 5 to 11 years had significantly higher HCRU than matched controls (**Table 2**)
  - Inpatient admissions PPPY: 0.4 versus 0.01
  - Outpatient visits PPPY: 75.2 versus 9.3
  - Outpatient prescriptions PPPY: 21.2 versus 4.4
- HCRU was similar between the TDT cohorts aged 5 to 11 years and ≥12 years (**Table 2**)
  - Inpatient admissions PPPY: 0.4 versus 0.3
  - ER visits PPPY: 0.4 versus 0.8
  - Outpatient prescriptions PPPY: 21.2 versus 22.2

Table 2. Annual HCRU by Age Group

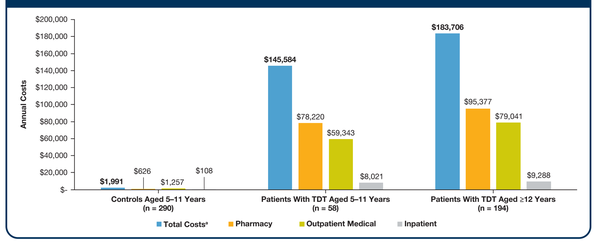
Annual HCRU	Primary Cohort: Patients With TDT Aged 5–11 Years (n = 58)	Matched Controls: Controls Aged 5–11 Years (n = 290)	*P* Value	Secondary Cohort: Patients With TDT Aged ≥12 Years (n = 194)
Inpatient				
Patients with an admission, n (%)	14 (24.1)	10 (3.4)	<0.001	59 (30.4)
Inpatient admissions PPPY, mean (SD)	0.4 (1.3)	0.01 (0.1)	<0.001	0.3 (1.0)
Outpatient				
Patients with any outpatient visit, n (%)[a]	58 (100.0)	283 (97.6)	0.606	194 (100.0)
Outpatient visits PPPY, mean (SD)	75.2 (33.2)	9.3 (10.3)	<0.001	89.6 (58.1)
ER visits PPPY, mean (SD)	0.4 (0.6)	0.3 (0.5)	0.048	0.8 (1.9)
Office visits PPPY, mean (SD)[b]	14.2 (7.6)	2.9 (2.6)	<0.001	14.8 (12.1)
Laboratory visits PPPY, mean (SD)[c]	28.4 (12.3)	1.3 (1.8)	<0.001	33.3 (17.5)
Other outpatient visits PPPY, mean (SD)[d]	32.2 (23.0)	4.8 (7.6)	<0.001	40.8 (44.8)
Pharmacy				
Prescriptions PPPY, mean (SD)	21.2 (16.0)	4.4 (9.5)	<0.001	22.2 (17.7)

ER, emergency room; HCRU, healthcare resource utilization; PPPY, per patient per year; RBCT, red blood cell transfusion; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.
[a]Outpatient visits were denoted as a unique patient seeing a distinct provider type (eg, primary care provider) on a distinct date. ER, outpatient office visits, laboratory visits, and other outpatient visits were included in this total.
[b]Outpatient office visits were denoted as a patient visiting an office setting at a unique provider type on a distinct date (eg, visits usually associated with being screened by a physician).
[c]Laboratory visits were denoted as a patient visiting a laboratory setting at a unique provider type on a unique date.
[d]Other outpatient visits were denoted as a patient visiting a non-office setting at a unique provider type on a unique date (eg, visits for screening, X-ray, RBCTs, intravenous iron chelation administration, etc.).

Annual Costs

- Patients with TDT aged 5 to 11 years had significantly higher total costs PPPY than matched controls (TDT: $145,584 [SD: $83,879] versus controls: $1,991 [SD: $5,275]) (**Figure 4**)
  - Differences in costs were driven by outpatient costs (**Table 3**) and outpatient prescription costs
- Cost burden was evident from childhood, total costs PPPY were higher in the ≥12 years cohort than the 5 to 11 years cohort (**Figure 4**)
- For patients with TDT aged 5 to 11 years, the majority of costs were attributable to ICT and RBCTs (**Table 3**)

Figure 4. Annual Total Costs by Age Group



TDT, transfusion-dependent β-thalassemia.
[a]Total costs were the sum of pharmacy, outpatient medical, and inpatient costs.

Table 3. Outpatient Medical Cost Breakdown, ICT, and RBCT Costs by Age Group

Annual Costs	Primary Cohort: Patients With TDT Aged 5–11 Years (n = 58)	Matched Controls: Controls Aged 5–11 Years (n = 290)	*P* Value	Secondary Cohort: Patients With TDT Aged ≥12 Years (n = 194)
Outpatient medical costs PPPY, mean (SD)[a]	$59,343 ($44,898)	$1,257 ($2,147)	<0.001	$79,041 ($73,556)
ER visit costs	$509 ($1,135)	$136 ($434)	<0.001	$1,163 ($7,614)
Outpatient office visit costs	$2,427 ($1,841)	$314 ($368)	<0.001	$2,272 ($1,863)
Laboratory service costs	$29,430 ($25,030)	$102 ($344)	<0.001	$24,367 ($29,066)
Other outpatient visit costs	$26,978 ($23,429)	$705 ($1,605)	<0.001	$51,240 ($65,318)
ICT costs PPPY, mean (SD)[b]	$75,141 ($53,620)	$0 ($0)	<0.001	$92,487 ($83,848)
RBCT costs PPPY, mean (SD)[c]	$27,805 ($25,325)	$0 ($0)	<0.001	$32,837 ($31,936)

ER, emergency room; ICT, iron chelation therapy; PPPY, per patient per year; RBCT, red blood cell transfusion; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.
[a]Transfusion costs may be included if the transfusion was given in the outpatient setting, and ICT costs may be included if they were billed to the patient's medical benefit.
[b]ICT costs included costs for outpatient pharmacy ICT prescriptions and costs for ICT administered by a provider in an outpatient setting.
[c]RBCT costs included costs for both inpatient and outpatient RBCTs.

Limitations

- This study used administrative claims data collected for reimbursement purposes and is therefore subject to potential misclassification bias; only direct costs are included in this analysis, which likely underestimate the burden of disease associated with TDT
- Given the minimum 12-month post-index period for patients with TDT, those who died, went on long-term disability, or were not continuously enrolled for ≥12 months were excluded from the analysis and might have systematically different outcomes than patients who met enrollment criteria

CONCLUSIONS

- **Starting in childhood, patients with TDT require intensive RBCTs and ICT as part of disease management**
- **Despite standard treatments (eg, frequent RBCTs), pediatric patients aged 5 to 11 years still experience a substantial burden of TDT-related complications**
- **Beginning in childhood, TDT is associated with considerable HCRU and costs**
- **From a young age, TDT imposes substantial clinical and economic burden, underscoring the need for potentially curative therapies early in the disease course**

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Disclosures

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