Economic Burden of Transfusion-Dependent β-Thalassemia in the United States

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INTRODUCTION

- β-thalassemia, a rare hereditary blood disorder affecting ~2,600 people in the United States, is characterized by reduced or absent β-globin production, leading to ineffective red blood cell (RBC) production and anemia[1-4]
- The most severe 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 blood transfusions, which are required to sustain life[1,2]
- Standard treatments, including regular RBCTs and iron chelation therapies (ICTs), are necessary throughout a patient's lifetime[1,2]
- There are limited data on total health care resource utilization (HCRU) and costs associated with TDT, including key cost drivers

OBJECTIVE

- To describe the economic burden of patients with TDT in the United States

METHODS

Study Design

- The IBM® MarketScan® Commercial, Medicare Supplemental, and Multi-State Medicaid Databases contain de-identified inpatient, outpatient medical, and outpatient prescription drug data for ~198.9 million commercially insured individuals and their dependents between 1995 and 2020, ~14.4 million Medicare Supplemental individuals between 1995 and 2020, and ~52 million Medicaid enrollees between 1999 and 2020
- A retrospective cohort study design was used to identify patients with TDT in the IBM® MarketScan® Commercial, Medicare Supplemental, and Multi-State Medicaid Databases between 1 March 2010 and 1 March 2019
- Each patient with TDT was matched to 5 controls from the general population; comparison of patients with TDT and controls was used to contextualize TDT HCRU and costs

Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  - At least 1 non-diagnostic inpatient or ⩾2 outpatient claims of β-thalassemia (ICD-9 282.44, 282.47; ICD-10 D56.1, D56.5) within 365 days of each other between 1 March 2010 and 1 March 2019
  - At least 8 discrete RBCTs during any 12-month period after and including the date of the earliest qualifying β-thalassemia diagnosis claim
    - At least 3 days between the service dates of transfusion claims were required to be considered discrete transfusions
  - At least 12 months of continuous enrollment with medical and pharmacy benefits after and including the index date (study period was 1 March 2010 to 1 March 2020)
- Identified patients with TDT were excluded if they met the following exclusion criteria:
  - Evidence of sickle cell disease (SCD) during the study period
  - Evidence of hematopoietic stem cell transplant (HSCT) during the follow-up period
- The index date was the date of the first transfusion
- All patients were followed for ⩾12 months from the index date to the earliest of the last date of continuous enrollment, inpatient death, or end of the study period (1 March 2020)

Matched Controls

- Patients in the IBM® 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
- Five controls from the general population 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
- 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 Analysis

- Demographics including age, sex, and payer type were assessed on the index date
- Annualized rates of all-cause HCRU included inpatient admissions, emergency room (ER) visits, physician office visits, and medication use
  - The proportion of patients with ⩾1 inpatient admission and ER visit was also reported
- Annualized rates of RBCTs and ICT were characterized separately
- Annualized inpatient, outpatient, and prescription health care costs (per patient per year [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, deductible, and co-insurance
- Costs were inflated to 2020 dollars using the Medical Care Component of the Consumer Price Index
- Lifetime costs were estimated by summing the average total cost for each age category multiplied by the number of years per category, up to the patient's estimated life expectancy (LE)
  - Age categories for TDT lifetime costs included 0 to 11, 12 to 17, 18 to 35, and 36+
  - $TDT\ lifetime\ costs = \sum_{0}^{LE} Age\ category * Cost_{Age\ category}$
- All study measures were summarized using descriptive statistics
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (%) for categorical variables
- Comparative analysis was conducted between patients with TDT and matched controls for HCRU and annual cost
  - Chi-squared tests were used to evaluate the statistical significance of differences for categorical variables, and t-tests were used for continuous variables
  - A P value of <0.05 was considered statistically significant

RESULTS

Patient Demographics

- A total of 4,504 patients with claims for β-thalassemia were identified; 207 met the criteria for TDT and other inclusion/exclusion criteria (**Figure 1**) and were matched to 1,035 individuals from the general population
- Demographics are provided in **Table 1**
- The mean age of patients with TDT was 21.9 years (SD: 16.4 years; range: 0 to 85 years) and 57.5% of patients were female
- Most patients included were on commercial insurance (80.7%)
- Demographics were generally similar between patients with TDT and matched controls

Figure 1. TDT Attrition Table

⩾1 inpatient OR ⩾2 outpatient claims[a] with a diagnosis of β-thalassemia between 1 March 2010 and 1 March 2019
N = 4,504

↓

⩾8 claims[b] with a procedure code for a blood transfusion during any 12-month period after and including the date of the first qualifying β-thalassemia claim
N = 418

↓

⩾12 months of continuous enrollment from index date
N = 291

↓

No evidence of SCD or HSCT
N = 207

HSCT, hematopoietic stem cell transplant; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.
[a]Within 365 days of each other; [b]⩾3 days between the service dates of transfusion claims were required to be considered discrete transfusions.

HCRU

- Patients with TDT had significantly higher HCRU than matched controls (**Table 2**)
  - A higher proportion of patients with TDT had inpatient admissions (TDT: 28.5% vs Controls: 7.1%; $P<0.0001$) and ER visits (55.6% vs 38.0%; $P<0.0001$) compared to matched controls
- Patients with TDT had an average of 14.2 discrete transfusions PPPY; the average time between transfusions was 27.7 days
  - The total number of transfusion days for patients with TDT was 15.2 PPPY
- A substantial proportion of patients with TDT (91.3%) were on iron chelators; patients on iron chelators averaged 12.1 ICT claims PPPY

Table 1. Baseline Demographics

Parameter	TDT (N = 207)	Controls (N = 1,035)
Age (years), mean (SD; range)	21.9 (16.4; 0–85)	22.7 (17.5, 0–87)
Age categories (years), n (%)		
0 to 11	72 (34.8)	350 (33.8)
12 to 35	95 (45.9)	485 (46.9)
36+	40 (19.3)	200 (19.3)
Sex, n (%)		
Male	88 (42.5)	440 (42.5)
Female	119 (57.5)	595 (57.5)
Payer, n (%)		
Commercial	167 (80.7)	835 (80.7)
Medicaid	38 (18.4)	190 (18.4)
Medicare Supplemental	2 (1.0)	10 (1.0)
Insurance plan type, n (%)		
Comprehensive/indemnity	21 (10.1)	81 (7.8)
EPO/PPO	95 (45.9)	485 (46.9)
POS/POS with capitation	20 (9.7)	85 (8.2)
HMO	38 (18.4)	216 (20.9)
CDHP/HDHP	28 (13.5)	144 (13.9)
Other/unknown	5 (2.4)	24 (2.3)
Years of follow-up, mean (SD)	3.3 (1.9)	3.5 (2.0)

CDHP, consumer-driven health plan; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; POS, point-of-service; PPO, preferred provider organization; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.

Table 2. Overall Annual HCRU

Annual HCRU	TDT (N = 207)	Controls (N = 1,035)	P Value
Inpatient			
Patients with an admission in entire follow-up, n (%)	59 (28.5)	74 (7.1)	<0.0001
Inpatient admissions PPPY, mean (SD)	0.2 (0.6)	0.03 (0.1)	<0.0001
Outpatient visits PPPY, mean (SD)[a]	81.8 (41.4)	11.4 (16.2)	<0.0001
ER visits	0.7 (1.8)	0.3 (0.8)	<0.0001
Office visits[b]	15.0 (9.9)	3.4 (3.2)	<0.0001
Laboratory visits[c]	28.2 (13.7)	1.8 (2.6)	<0.0001
Other outpatient visits[d]	38.0 (31.3)	5.9 (13.6)	<0.0001
Outpatient pharmacy			
Prescriptions PPPY, mean (SD)	18.6 (14.4)	6.8 (10.8)	<0.0001

ER, emergency room; HCRU, health care resource utilization; IV, intravenous; PCP, primary care provider; PPPY, per patient per year; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.
[a]Outpatient visits were denoted as a unique patient seeing a distinct provider type (e.g., PCP, podiatrist, etc.) on a distinct date. ER, outpatient office visits, laboratory visits, and other outpatient visits are 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 (e.g., visits usually associated with being screened by a physician); [c]Laboratory visits were denoted as a patient visiting a lab 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 (e.g., visits for screening, X-ray, transfusions, IV iron chelation administration, etc.)

HCRU by Payer Type

- Compared to those with commercial insurance, a greater proportion of patients on Medicaid had an inpatient admission (Medicaid: 36.8% vs Commercial: 26.3%) and ER visit (71.1% vs 51.5%)
- Patients on Medicaid received a higher number of outpatient prescriptions PPPY (Medicaid: 22.5 vs Commercial: 17.5) but had a lower number of lab visits PPPY (22.1 vs 29.9) (**Table 3**)

Table 3. Annual TDT HCRU by Payer Type

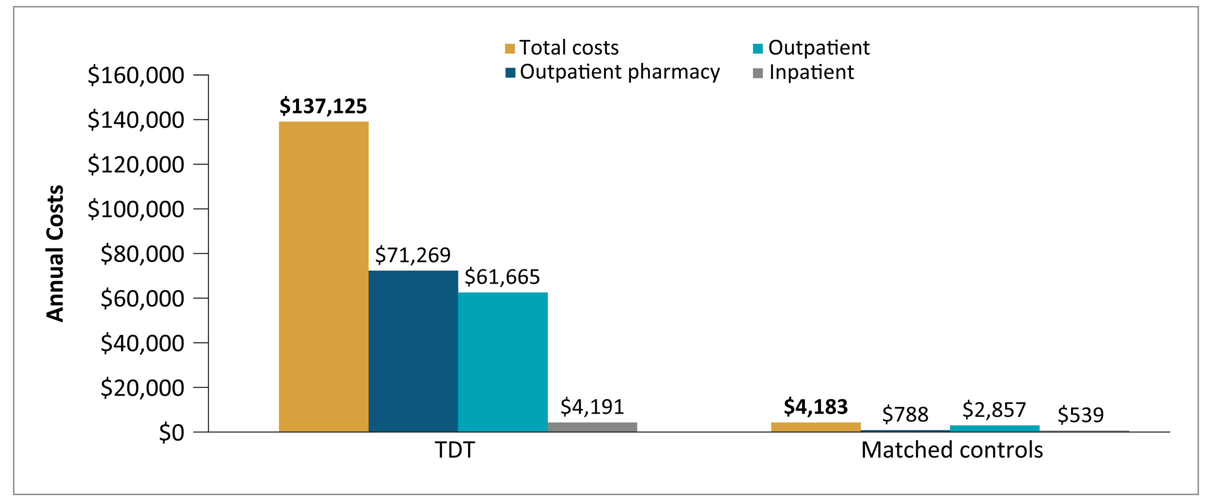
Annual HCRU	Commercial (N = 167)	Medicaid (N = 38)
Inpatient		
Patients with an admission in entire follow-up, n (%)	44 (26.3)	14 (36.8)
Inpatient admissions PPPY, mean (SD)	0.2 (0.6)	0.3 (0.5)
Outpatient visits PPPY, mean (SD)[a]	83.4 (39.9)	75.7 (48.3)
ER visits	0.7 (2.0)	0.8 (1.0)
Office visits[b]	15.2 (10.1)	13.2 (8.7)
Laboratory visits[c]	29.9 (14.0)	22.1 (9.4)
Other outpatient visits[d]	37.6 (28.7)	39.6 (41.9)
Outpatient pharmacy		
Prescriptions PPPY, mean (SD)	17.5 (14.2)	22.5 (14.1)

ER, emergency room; HCRU, health care resource utilization; IV, intravenous; PCP, primary care provider; PPPY, per patient per year; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.
[a]Outpatient visits were denoted as a unique patient seeing a distinct provider type (e.g., PCP, podiatrist, etc.) on a distinct date. ER, outpatient office visits, laboratory visits, and other outpatient visits are 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 (e.g., visits usually associated with being screened by a physician); [c]Laboratory visits were denoted as a patient visiting a lab 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 (e.g., visits for screening, X-ray, transfusions, IV iron chelation administration, etc.)

Annual Costs

- Patients with TDT had significantly higher total costs PPPY than matched controls (TDT: $137,125 [SD: $84,847] vs Controls: $4,183 [SD: $10,619]; $P<0.0001$) (**Figure 2**)
  - Differences in costs were driven by outpatient costs (**Table 4**) and outpatient prescription costs
- Annual transfusion costs for patients with TDT were $32,325 PPPY (SD: $28,285) and annual ICT costs were $71,506 (SD: $60,050)
  - Transfusion costs included costs for the inpatient and outpatient setting in which the transfusion occurred
  - ICT costs included costs for outpatient prescriptions and the outpatient setting in which the physician-administered ICT occurred

Figure 2. TDT and Matched Control Annual Costs



TDT, transfusion-dependent β-thalassemia.

Table 4. TDT Outpatient Cost Breakdown

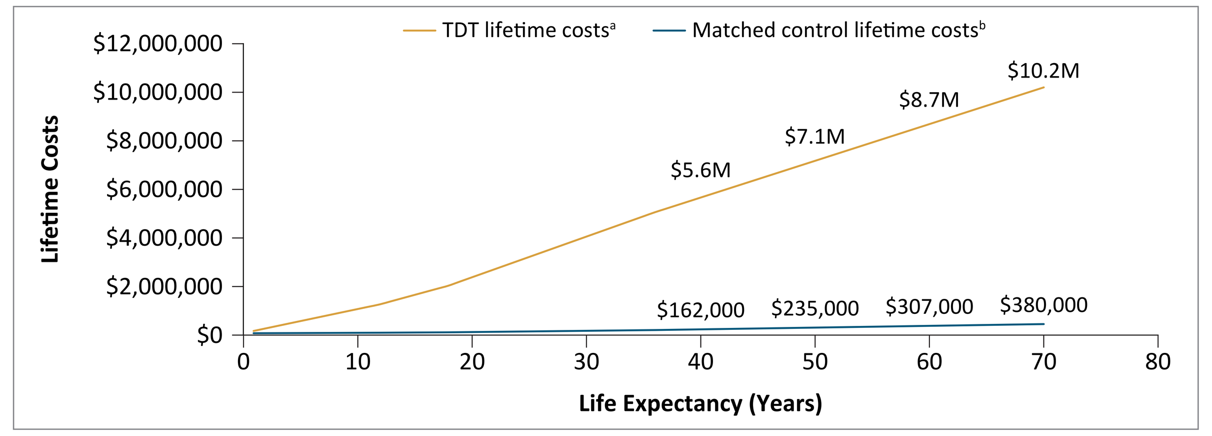
Annual Costs	TDT (N = 207)
Total outpatient costs PPPY, mean (SD)	$61,665 ($46,942)
ER visit costs	$1,364 ($9,041)
Outpatient office visit costs	$2,444 ($1,810)
Laboratory services costs	$15,537 ($16,994)
Other outpatient visit costs[a]	$42,320 ($35,966)

ER, emergency room; HCRU, health care resource utilization; IV, intravenous; PPPY, per patient per year; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.
[a]Other outpatient costs included those for transfusions and IV chelation therapy.

Lifetime Costs

- Extrapolation of annual costs suggests patients with TDT incur substantial costs over their lifetimes. By age 50, patients have an expected lifetime cost of ~$7.1 million compared to ~$235,000 in matched controls (**Figure 3**)
  - After age 36, each additional year of life adds $152,482 and $7,258 to lifetime costs for patients with TDT and matched controls, respectively

Figure 3. TDT and Matched Control Lifetime Costs



M, million; TDT, transfusion-dependent β-thalassemia.
[a]Annual costs for patients with TDT per age group were $99,931 (Age 0 to 11 [n = 72]); $129,259 (Age 12 to 17 [n = 24]; $168,848 (Age 18 to 35 [n = 71]); and $152,482 (Age 36+ [n = 40]); [b]Annual costs for controls per age group were $1,927 (Age 0 to 11 [n = 350]); $2,803 (Age 12 to 17 [n = 130]); $5,181 (Age 18 to 35 [n = 355]); and $7,258 (Age 36+ [n = 200]).

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 economic outcomes than patients who met enrollment criteria
- Cost of blood donations, blood testing/matching, and time spent undergoing RBCTs are not included in RBCT costs; RBCT costs derived from claims likely underestimated the health system impact of regular transfusions in patients with TDT
- This study does not account for the recently approved TDT therapies including luspatercept and its impact on TDT HCRU and costs and therefore likely underestimates the overall costs
- This study may not be generalizable to patients without commercial health coverage, private Medicare supplemental coverage, or Medicaid eligibility
- There is no validated algorithm for diagnosis of β-thalassemia in claims and the positive predictive values for ICD-9/10 codes are unknown; however, the specificity of TDT is likely to be high, as it requires an additional set of criteria

CONCLUSIONS

- Patients with TDT have significant HCRU and annual health care costs associated with the disease
- TDT costs are driven by outpatient costs and outpatient prescriptions, specifically RBCTs and ICT
- Over patients' lifetimes, TDT is associated with a substantial economic burden on the health care system in the United States

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DISCLOSURES

This study was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics AG. CU and YY are employees of Vertex Pharmaceuticals Incorporated and may hold stock/stock options. RM was an employee of IBM Watson Health at the time of study completion and may hold stock/stock options. KE and PS are employees of IBM Watson Health and may hold stock/stock options. BA has received research funding from the American Society of Hematology, CT Department of Public Health, Forma Therapeutics, Global Blood Therapeutics, Hemanext, HRSA, Imara, Novartis, and PCORI; and has served as an advisory board member or consultant for Agios, Aruvant, bluebird bio, CRISPR Therapeutics AG, CVS / Accordant, Cyclerion, Emmanaus, Forma Therapeutics, GBT, Hemanext, Novartis, NovoNordisk, Roche, Terumo, and Vertex Pharmaceuticals Incorporated.

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