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Economic and healthcare burden of blood transfusions in transfusion-dependent ß-thalassemia in Thailand, Brazil, and India

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Introduction

- ß-thalassemia is a genetic blood disorder caused by a mutation in the hemoglobin (Hb) *HBB* gene, which leads to reduced erythropoiesis due to a decrease in, or total absence of, ß-hemoglobin chain synthesis[1]
- The need for chronic transfusions may lead to transfusion-dependent ß-thalassemia (TDT), the most severe form of the disease[2]
- Patients with TDT require lifelong treatment with red blood cell (RBC) transfusions and iron chelation therapy (ICT)[2]
- Numerous transfusion and disease-related complications can make management of TDT challenging and create substantial economic burden for patients and healthcare providers[3]
- It is estimated that 1.5% of the world population, or up to 80 million individuals, are carriers for ß-thalassemia[1]
- There is a high prevalence of ß-thalassemia in Thailand (23 cases per 100,000 population in 2017) and in India (1250–1660 per 100,000 persons between 2005 and 2015, respectively), while the prevalence of suspected TDT in Brazil was 803 per 100,000 people in 2015[4-6]
- Despite such a high prevalence, the economic burden of ß-thalassemia has not been well characterized in these countries

Objective

- The aim of this study was to estimate the clinical and treatment pathways, and economic burden of TDT in Thailand, Brazil, and India

Methods

- This study used a pragmatic literature review (PLR) to map the current clinical and treatment pathways, and to quantify the economic burden from the published evidence of TDT
- The PLR was performed in Thailand and Brazil (on November 12, 2022) and in India (on June 29, 2023) using the PICOS (Patient, Intervention, Comparison, Outcomes, Study)-based search strategy to identify observational studies for adults with TDT published in English in the past 10 years from Embase®, MEDLINE®, evidence-based medicine (EBM) Reviews-Health Technology Assessment (HTA), and EconLit (**Table 1**)

Table 1. PICOS search criteria

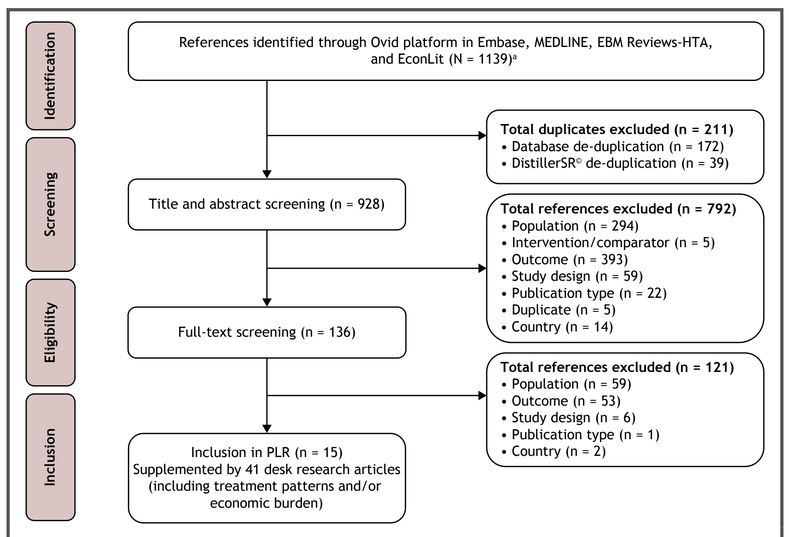
PICOS search criteria	Search 1: patient pathways	Search 2: economic burden
Population	Adults (≥ 18 years of age) with TDT	
Intervention/ comparator	Not applicable	
Outcomes	• Patient pathways • Treatment patterns • Associated complications	• Healthcare (transfusion) burden due to blood shortage • Economic burden
Study design	Any observational study	
Sources	• Embase • MEDLINE	• Embase • MEDLINE • EBM reviews-HTA • EconLit
Limitations	• Language: English • Timeframe: past 10 years • Geography: Thailand, Brazil, India	

- Exclusion criteria were: patients < 18 years of age; publications not reporting outcomes listed in the inclusion criteria; animal studies, books, chapters, notes, news, letters, short surveys, and editorials; geographic locations other than those mentioned in the inclusion criteria; non-English publications; publications for which free full-text was unavailable
- The search strategy included thalassemia population search terms, study design search terms, and limitations
- The PLR was supplemented by a hand search of the local clinical guidelines, relevant websites, and local medical journals for additional evidence, which could be in a language other than English
- Clinical pathway and treatment patterns included, but were not limited to: current treatments, duration of treatment, discontinuation rates, and treatment switches
- Associated complications included shortage of blood supplies, complications due to frequent RBC transfusions, and iron overload
- Economic burden outcomes included, but were not limited to, economic burden of TDT, healthcare (transfusion) burden due to blood shortage (estimate), proportion of blood supply required for patients with TDT
- Direct costs included costs related to RBC transfusions and ICT
  - Costs of RBC transfusions included cost of: patient transportation, blood transportation, blood collection procedure, hemovigilance, hemocomponent separation, units of RBC transfused, RBC transfusion equipment per transfusion, blood and instrumental monitoring (blood group and laboratory tests), management of complications associated with RBC transfusions (iron overload complications, transfusion-transmitted infections, antibody formation, other acute complications)
  - Costs of ICT included cost of: the drug and its administration to avoid iron overload and healthcare expenditure for drug acquisition, traditional or alternative treatment/services, disposable healthcare equipment, outpatient and day care, hospital visits, and annuitized durable medical equipment
- Indirect costs included: productivity loss/absenteeism for blood donors, patients, and/or caregivers, and time spent for transportation, transfusion, and monitoring by the blood donors, patients and/or caregivers

Results

- Among the 1139 articles identified, 136 were assessed for full-text review, and 15 studies were included
  - These articles were supplemented by 41 desk references (**Figure 1**)

Figure 1. Literature selection and review



[a]The identification stage also includes myelodysplastic syndromes (MDS) search terms as this project has been part of combined MDS and TDT studies.

Epidemiology: definition of TDT

- Between the countries studied, there was no consensus on the definition of TDT (**Figure 2**), making it difficult to compare outcomes across the 3 countries

Figure 2. Definitions of TDT

Thailand[7,8]	Brazil[9]	India[10]
• Onset of anemia at < 2 years of age • First blood transfusion at < 4 years of age • Height and body weight below normal • Baseline Hb < 7.0 g/dL • Genotype: B0/B0, B0/ß+, or ß+/ß+ (some severe B0/BE or ß+/BE)	• Hb levels < 7.0 g/dL on 2 occasions at an interval of > 2 weeks • RBC transfusions every 2–4 weeks from the first months of life • Hb > 7.0 g/dL with facial changes, growth compromised, fractures, or extramedullary hematopoiesis • Genotype: B0/B0, B0/ß+, or ß+/ß+	• Severe microcytic anemia with target cells (typical Hb 3–4 g/dL) • Hb analysis by high performance liquid chromatography or electrophoresis showing Hb A2 (≥ 5%) • Hb F ≤ 95% • No Hb A

Hb A, normal adult hemoglobin; Hb A2, minor adult hemoglobin; Hb F, fetal hemoglobin.

Patient pathway

- The patient pathway for TDT is shown in **Figure 3**
- A typical patient journey included screening, diagnosis, treatment, and follow-up
- All 3 countries have some national program/guidelines for ß-thalassemia diagnosis at birth/maternal screening
- TDT is mainly managed at tertiary or secondary hospitals by specialist hematologists, and routine surveillance is needed for disease complications and iron overload
- RBC transfusions and ICTs remained the standard of care for patients with TDT (**Figure 4**)
- Splenectomies could be used to reduce the transfusion requirements of patients, while HSCT was a potential ß-thalassemia treatment (**Figure 4**)

Figure 3. Patient pathway identified in Thailand, Brazil, and India

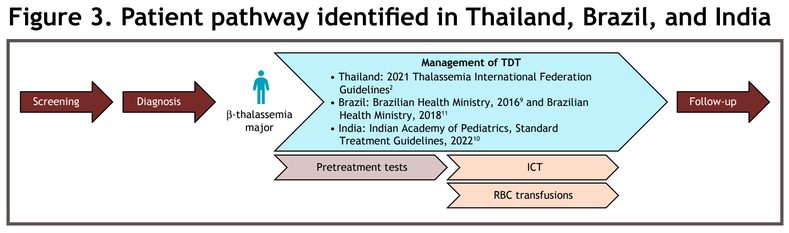
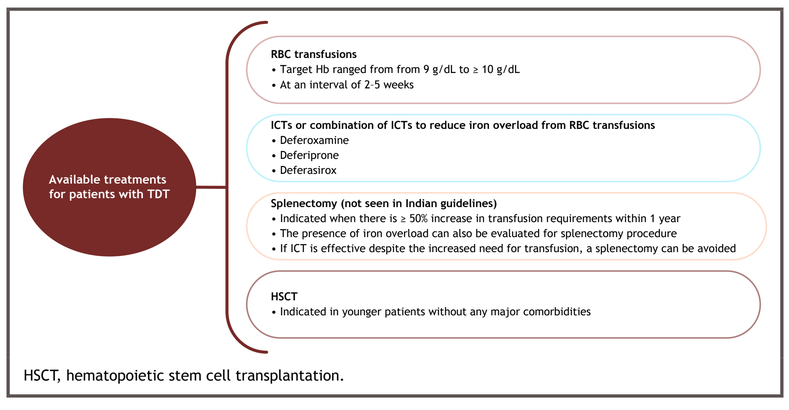


Figure 4. Available TDT treatments across Thailand, Brazil, and India



HSCT, hematopoietic stem cell transplantation.

Complications of TDT disease and treatment

- Across the 3 countries, reported complications of TDT were: liver dysfunction/hepatitis C, osteopenia/osteoporosis, gallstones, decreased vitamin D levels, cardiorenal syndrome, hypogonadism, growth disorders, diabetes, and splenomegaly
- Across the countries, reported complications due to TDT treatment were infection complications due to febrile neutropenia from deferiprone treatment, and iron overload (cardiac, liver, or pancreas)

ICT

- Patients reported issues like high cost and experienced lack of immediate results from ICT[12]
- In a study conducted in India, 10.7% of patients with TDT were non-adherent to ICT (ie, patients were taking < 75% of the prescribed doses)[13]

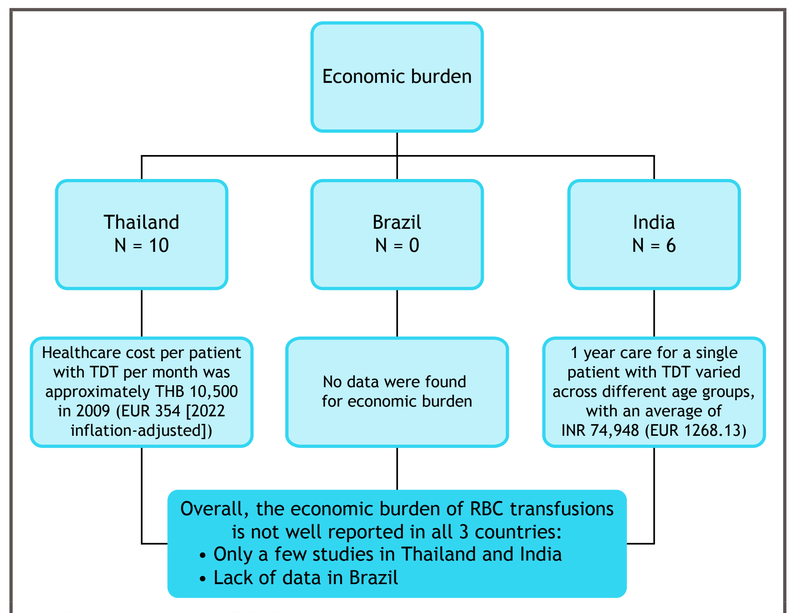
Blood-supply shortages

- As the mainstay of TDT treatment is lifelong RBC transfusions, blood-supply shortages can have a significant impact
- Inadequate transfusions due to blood shortages were reported across all 3 countries
  - In Thailand, the Red Cross could supply only 28% of the blood units requested by hospitals per day[14]
  - In Brazil, approximately 41% of patients faced barriers to scheduling RBC transfusions, and the most common reasons were blood shortage (35%), lack of phenotype-matched blood (31%), and delays in blood preparation (21%)[15]
  - Although not specifically for patients with TDT, in India, the annual blood supply is estimated at 31.9 per 1000 eligible population against the 34.3 per 1000 eligible population of donation required to meet clinical demand[16]

Economic burden

- Overall economic burden data were limited to Thailand and India, and data were fragmented (**Figure 5**)
- There was a lack of literature to understand the direct and indirect costs of RBC transfusions and ICTs in all 3 countries

Figure 5. Economic burden



EUR, Euro; INR, Indian rupee; THB, Thai baht.

Conclusions

- There is a lack of literature to understand the healthcare resource use and costs associated with RBC transfusions and ICTs in all 3 countries
  - A cross-sectional survey among Thai, Brazilian, and Indian healthcare stakeholders, which is currently in progress, will help to address these evidence gaps
- Although RBC transfusions and ICTs remain the standard of care for patients with TDT, inadequate transfusions or transfusion delays due to blood-supply shortages were commonly reported in Thailand, Brazil, and India
  - As such, there is a compelling need to improve adequate RBC transfusion support in each country
- Alternative solutions are required to address inadequate provision of RBC transfusions, and novel therapies may have the potential to reduce transfusion requirements

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