# Mortality and Clinical Complications Among Patients With Transfusion-Dependent β-Thalassemia in France

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## INTRODUCTION

- β-thalassemia is a rare hereditary hemoglobinopathy characterized by reduced or absent β-globin production, which leads to ineffective erythropoiesis[1-3]
- The most severe form of the disease is transfusion-dependent β-thalassemia (TDT), wherein patients depend on frequent, regular red blood cell transfusions (RBCTs) and iron chelation therapy (ICT) for survival[1,2]
- In addition, individuals with TDT experience significant clinical complications that impact all organ systems, especially the hepatobiliary, cardiopulmonary, and endocrine systems, which can lead to early mortality[3-5]
- There are limited contemporary data on the clinical burden and mortality in patients with TDT in France[4]

## OBJECTIVE

- To describe the mortality and clinical complications associated with TDT in France

## METHODS

### Study Design and Database

- A longitudinal, retrospective cohort study design utilized the French National Health Data System database, Système National des Données de Santé (SNDS), to identify patients with TDT in France
- The SNDS is a national claims database that captures pseudonymized, longitudinal data for ~99% of the French population, inclusive of overseas territories and reports claims data for 65 million insurees[6]
  - The SNDS contains details of all primary care, hospital, and pharmacy records reimbursed in France
- The study was conducted from January 1, 2012, to March 1, 2020, and included a 7-year eligibility period (from January 1, 2012, to March 1, 2019) and a minimum follow-up of 1 year after inclusion

### Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  - An inpatient claim or registration in the long-term disease (LTD) database with a diagnosis of β-thalassemia between January 1, 2012, and March 1, 2019
  - At least 8 RBCTs/year in any 2 consecutive years after the first qualifying β-thalassemia diagnosis record between January 1, 2012, and March 1, 2019
  - At least 12 months of follow-up data after and including the index date
- Patients were excluded if they met the following exclusion criterion:
  - Evidence of sickle cell disease, α-thalassemia, hereditary persistence of fetal hemoglobin, or hematopoietic stem cell transplant at any time in their medical records
- The index date was the date of the eighth RBCT record in the second year of 2 consecutive years
- All patients were followed for at least 12 months from the index date until death or the end of the study period (March 1, 2020)

### Study Measures and Analysis

- Descriptive analyses were conducted for demographics, number of RBCTs, mortality, and clinical complications (acute and chronic) for patients with TDT
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (n [%]) for categorical variables
  - In all cases where data were available for <10 patients, values were masked to protect patient confidentiality
- Demographics, including age, sex, and area of residence, were assessed at the index date
- Mortality rates (deaths per 100 person-years), mortality proportion (% of total population), and mean age of death were calculated during follow-up
- The proportion of patients with clinical complications (% of total population) was calculated during follow-up
  - To avoid immortal time bias in mortality rate estimates, person-years were measured starting from 1 year after the index date

### Subgroup Analyses

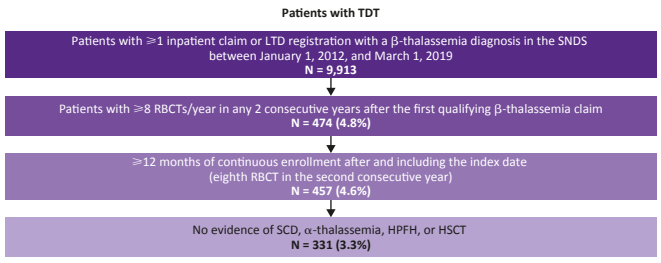
- Descriptive analyses for mortality and clinical complications during follow-up were conducted based on patient age (years) at the index date
  - Age subgroups were: <18 years and ≥18 years

## RESULTS

### Patient Demographics

- A total of 331 patients with TDT were identified in the SNDS database (**Figure 1**)

*Figure 1. Patient Attrition[a]*




*HSCT, hematopoietic stem cell transplant; HPFH, hereditary persistence of fetal hemoglobin; LTD, long-term disease; RBCT, red blood cell transfusion; SCD, sickle cell disease; SNDS, Système National des Données de Santé; TDT, transfusion-dependent ß-thalassemia.*

*[a]Values presented in parentheses represent the proportion of patients with ≥1 inpatient claim or LTD database registration during the study period.*

### Patient Demographics (Continued)

- The mean age of patients with TDT was 26.1 years (SD: 18.0; range: 1–88), and 49.6% of patients were female (**Table 1**)
- Nearly all patients (95%) lived in Metropolitan France, while 3.9% lived in Overseas France (**Table 1**)
- Of the 331 patients, 87% had an LTD registration with a diagnosis of β-thalassemia (**Table 1**)

*Table 1. Baseline Demographics*

| | Patients With TDT (N = 331) |
|---|---|
| **Age, years, mean (SD; range)** | 26.1 (18.0; 1–88) |
| **Age categories (years), n (%)** | |
| 0–11 | 88 (26.6) |
| 12–35 | 146 (44.1) |
| ≥36 | 97 (29.3) |
| **Female, n (%)** | 164 (49.6) |
| **Broad area of residence, n (%)** | |
| Metropolitan France | 314 (94.9) |
| Overseas France | 13 (3.9) |
| Unknown | <10 |
| **LTD registration, n (%)[a]** | 309 (93.4) |
| With β-thalassemia code | 289 (87.3) |
| **Follow-up time, years, mean (SD; range)** | 4.9 (1.9; 1.0–6.9) |

*LTD, long-term disease; SD, standard deviation; TDT, transfusion-dependent ß-thalassemia.*

*[a]Patients were registered to this database with the corresponding ICD-10 code for the disease that required long-term and/or expensive treatment due to its severity and/or chronic nature.*

### Mortality

- The overall mortality rate for patients with TDT was 1.16 deaths per 100 person-years (**Table 2**)
- During follow-up, 15 (4.5%) patients with TDT died (**Table 2**)
  - The mean age of death for patients with TDT who died was 52.5 years (SD: 22.0), which is ~30 years lower than the life expectancy of the French general population (males and females: 82.3 years; females: 85.5 years; males 79.3 years[7])

*Table 2. Mortality*

| | Patients With TDT (N = 331) |
|---|---|
| **Overall mortality rate, deaths per 100 person-years** | 1.16 |
| **Deaths, n (%)** | 15 (4.5) |
| **Age at death, years, mean (SD)** | 52.5 (22.0) |

*SD, standard deviation; TDT, transfusion-dependent ß-thalassemia.*

### Clinical Complications

- The most common clinical complications in patients with TDT were endocrine (26%), hepatobiliary (23%), cardiopulmonary (19%), and renal (9%) (**Table 3**)

*Table 3. Acute and Chronic Clinical Complications*

| Clinical Complication, n (%) | Patients With TDT (N = 331) |
|---|---|
| **Cardiopulmonary complications[a]** | 62 (18.7) |
| Arrythmia | 38 (11.5) |
| Atrial fibrillation | 34 (10.3) |
| Heart failure | 27 (8.2) |
| **Endocrine complications** | 86 (26.0) |
| Diabetes | 35 (10.6) |
| Hypogonadotropic hypogonadism | 30 (9.1) |
| Hypoparathyroidism | 25 (7.6) |
| Infertility | 14 (4.2) |
| Osteoporosis | 22 (6.7) |
| **Hepatobiliary complications** | 75 (22.7) |
| **Hypercoagulable state** | 15 (4.5) |
| **Infections[b]** | 17 (5.1) |
| **Malignancy** | 14 (4.2) |
| **Mental health complications** | 17 (5.1) |
| **Renal complications** | 31 (9.4) |
| **Splenomegaly** | 29 (8.8) |
| **Urinary tract complications** | 14 (4.2) |

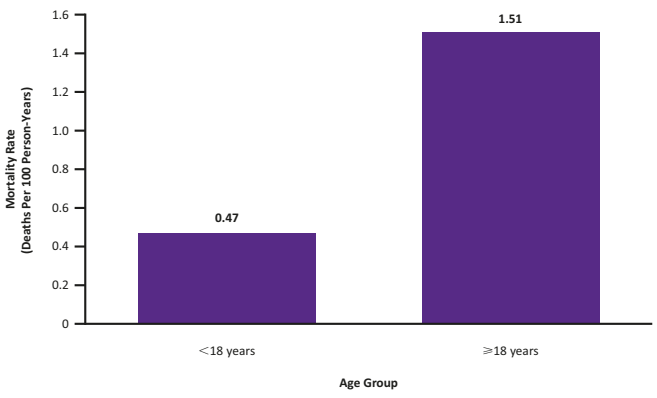
*TDT, transfusion-dependent ß-thalassemia.*

*[a]Inclusive of arrythmia, atrial fibrillation, pericarditis, heart failure, and pulmonary hypertension; [b]Inclusive of septicemia/sepsis, pneumococcal sepsis, and bacteremia.*

### Subgroup Analysis: Mortality

- Older patients with TDT (aged ≥18 years) had over a 3-fold higher mortality rate (1.51) than younger patients (aged <18 years: 0.47) (**Figure 2**)

*Figure 2. Subgroup Analysis: Mortality Rate by Age*




### Subgroup Analysis: Clinical Complications

- A substantially higher proportion of older patients with TDT (aged ≥18 years) had clinical complications compared to younger patients (aged <18 years)
  - Among older patients, the most common clinical complications were endocrine (37.6%), hepatobiliary (28.8%), and cardiopulmonary (26.8%) (**Table 4**)
  - Blinding for younger patients made it difficult to interpret trends in clinical complications for this patient group

*Table 4. Subgroup Analysis: Acute and Chronic Clinical Complications by Age*

| Clinical Complication, n (%)[a] | Age Group | |
|---|---|---|
| | <18 Years (n = 126) | ≥18 Years (n = 205) |
| **Cardiopulmonary complications[b]** | - | 55 (26.8) |
| Arrythmia | - | 31 (15.1) |
| Atrial fibrillation | - | 33 (16.1) |
| Heart failure | - | 26 (12.7) |
| Pulmonary hypertension | - | 10 (4.9) |
| **Endocrine complications** | - | 77 (37.6) |
| Diabetes | - | 34 (16.6) |
| Hypogonadotropic hypogonadism | - | 25 (12.2) |
| Hypoparathyroidism | - | 23 (11.2) |
| Infertility | - | 13 (6.3) |
| Osteoporosis | - | 19 (9.3) |
| **Hepatobiliary complications** | 16 (12.7) | 59 (28.8) |
| **Hypercoagulable state** | - | 14 (6.8) |
| **Infections[c]** | - | 15 (7.3) |
| **Malignancy** | 0 | 14 (6.8) |
| **Mental health complications** | 0 | 17 (8.3) |
| **Renal complications** | - | 25 (12.2) |
| **Splenomegaly** | 12 (9.5) | 17 (8.3) |
| **Urinary tract complications** | - | 13 (6.3) |

*[a]Patient numbers <10 were masked (i.e., "-") to protect patient confidentiality; [b]Inclusive of arrythmia, atrial fibrillation, pericarditis, heart failure, and pulmonary hypertension; [c]Inclusive of septicemia/sepsis, pneumococcal sepsis, and bacteremia.*

## LIMITATIONS

- As with any claims study, the use of ICD-10 codes and Classification Commune des Actes Médicaux (CCAM) procedure codes to identify patients could lead to misclassification bias; however, the effect of this bias was limited in this study, given the significant requirements for identifying patients with TDT (e.g., 8 RBCTs/year in 2 consecutive years)
- The subgroup analysis by age had substantial blinding for patients <18 years of age and was limited by small sample sizes
- Given the minimum 12-month post-index period for patients with TDT, individuals who died during this period were excluded, which may have further led to an underestimation of mortality

## CONCLUSIONS

- Despite available care, patients with TDT in France experience numerous TDT-related clinical complications and increased mortality, underscoring the need for innovative therapies in this space
- Older age was associated with higher mortality and number of clinical complications

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## AUTHOR DISCLOSURES

JB, CU, NL and LD are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. LB is a former employee of Vertex Pharmaceuticals and may hold stock or stock options in the company. GP, NQ, and HJ are employees of Certara France and may hold stock or stock options in the company. FG is an employee of the Sickle Cell Referral Center, Henri Mondor Hospital Paris, France. Approval for use of SNDS data was granted by all relevant authorities and governing bodies. Analyses for this study were performed through remote access on the Caisse Nationale de L'assurance Maladie (CNAM) portal to comply with national security guidance (Le Référentiel de Sécurité). The final protocol was reviewed and approved by a scientific committee and the National Informatics and Liberty Commission (CNIL, decision DR-2022-065, March 2, 2022). All patient data were pseudonymized, which according to applicable legal requirements renders the data exempt from privacy laws; therefore, obtaining informed consent from patients was not required. The interpretation and conclusions contained in this study are those of the authors alone.

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