Healthcare Resource Utilization Among Patients with Transfusion-Dependent β-Thalassemia in the Netherlands

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BACKGROUND

- β-thalassemia is a rare, inherited blood disorder characterized by chronic hemolytic anemia. Patients with the most severe form, transfusion-dependent β-thalassemia (TDT), require regular, lifelong red blood cell transfusions (RBCTs) to survive.[1,2,3]
- TDT is associated with significant burden on patients and results in high rates of healthcare resource utilization (HCRU).[4,5,6]
- Complications of TDT include iron overload, end-organ damage, and increased infections all of which contribute to morbidity and early mortality.[7]
- In the Netherlands, there is limited information on the HCRU of patients with TDT.

OBJECTIVE

- To describe the HCRU of patients with TDT in the Netherlands.

METHODS

Study Design & Database

- This longitudinal, retrospective cohort study utilized healthcare data form from the PHARMO Data Network.
- The PHARMO Data Network is a population-based data source with combined anonymous electronic healthcare data from different primary and secondary healthcare settings in the Netherlands.
  - The different data sources, including data from general practitioners, inpatient/outpatient pharmacies, clinical laboratories, hospitals, the Netherlands cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms.
- The PHARMO Data Network covers 20%-25% of 17 million active persons in the Netherlands.[8]
- The study was conducted from January 1, 2013 to December 31, 2021 and included a 6-year patient selection period (January 1, 2014 to December 31, 2020), and a minimum of 1 year of data availability before and after patient inclusion in the study

Patient Identification

- Patients were included in the analysis if they met the following inclusion criteria:
  1. At least one diagnosis of β-thalassemia between January 1, 2014 to December 31, 2020
  2. At least eight RBCTs in one 12-month period in the selection period
  3. At least 12 months of data availability before and after the index date (date of the eighth RBCT in one 12-month period)
- Patients were excluded if they met the following exclusion criteria:
  - Evidence of hematopoietic stem cell transplant (HSCT), diagnosis of hereditary persistence of fetal hemoglobin, or diagnosis of alpha-thalassemia or SCD during baseline, index, or follow-up
- All patients were followed for at least 12 months from the index date to death, loss to follow-up, or the end of the study period (December 31, 2021).

Study Measures and Analysis

- Descriptive analyses were conducted for demographics and HCRU for patients with TDT.
  - Mean (standard deviation [SD]) values were reported for continuous variables and frequencies/proportions (n,%) for categorical variables. Median (Q1-Q3) was also reported for age.
  - All values with a count of less than 5 patients were suppressed according to data protection requirements.
- Demographics were assessed at the index date, including sex, age, and socioeconomic status.
- Rate of HCRU (per patient per year [PPPY]) was calculated over the variable-length follow-up period.
- Rate of RBCTs (PPPY) was calculated over the variable-length follow-up period.

Subgroup Analyses

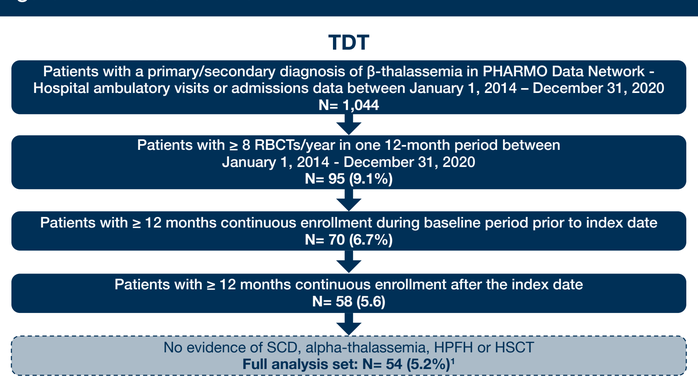
- Two subgroup analyses were conducted for HCRU: age at index date and number of RBCTs PPPY in the follow-up period.
  - Age at index date: 0 – 11 years, 12 – 35 years, and ≥ 36 years
  - Rate of RBCTs in the follow-up period: < 8 PPPY and ≥ 8 PPPY

RESULTS

Patient Demographics

- A total of 54 patients with TDT were identified in PHARMO Data Network. (**Figure 1**)
- The mean age of patients with TDT was 17.7 years (SD: 15.2) and 57.4% of patients were male. (**Table 1**)
- Data on socio-economic status was reported in a small proportion of patients (8 patients, 14.8%); among these patients, 50% were of low socio-economic status. (**Table 1**)
- The mean duration of follow-up was 3.3 years (SD: 1.4). (**Table 1**)

Figure 1. Patient Attrition



TDT, transfusion-dependent β-thalassemia; **SCD,** sickle cell disease; **HPFH,** hereditary persistence of fetal hemoglobin; **HSCT,** hematopoietic stem cell transplant
[1]Subset with treatment data was too sparse to include in the analysis (n=8)

Table 1. Baseline Demographics

Patient characteristics	TDT, N=54
Sex, n (%)	
Male	31 (57.4%)
Female	23 (42.6%)
Age at index date	
Mean (SD)	17.7 (15.2)
Median (Q1-Q3)	13.5 (4.0-27.0)
Min-Max	0.0 - 62.0
Socio-economic status, N (%)[1]	8 (14.8%)
Low	4 (50.0%)
Middle	2 (25.0%)
High	2 (25.0%)
Years of follow-up, mean (SD)	3.3 (1.4)

TDT, transfusion-dependent β-thalassemia; **SD,** standard deviation; **Q,** quartile
[1] Socio-economic status is a relative measure based on scores of the Netherlands Institute for Social Research, which aggregates mean household income, percentages of households with a low income, inhabitants without a paid job, and households with a low mean education. Based on social-economic status data, patients in the PHARMO database are categorized as low, middle, and high. Furthermore, percentage of patients with low, middle, and high in Table 1 were calculated among patients with available data on social-economic status.

HCRU

- Patients with TDT on average received 13.0 (SD: 12.4) RBCTs PPPY in the follow-up period.
- Patients had a mean 11.3 (SD: 11.3) inpatient hospitalizations, 15.1 (SD: 12.6) days spent in the hospital, and 8.4 (SD: 7.2) outpatient specialist visits (all PPPY). (**Table 2**)
- 98.1% of patients with TDT had inpatient hospitalizations with < 1 day of stay, with a mean of 10.8 PPPY (SD: 11.3) (**Table 2**)
  - 87.0% of inpatient hospitalizations <1 day were RBCT-related with a mean of 7.4 PPPY (SD: 6.2).
- 63.0% had inpatient hospitalizations with ≥ 1 day of stay, with mean of 0.5 PPPY (SD: 0.6). (**Table 2**)

Table 2. HCRU

Healthcare Resource Utilization (N=54)	Prevalence, n (%)	Rate (PPPY), Mean (SD), (95% CI)
Outpatient specialist visits	51 (94.4)	8.4 (7.2), (6.4-10.4)
RBCT-related	3 (5.6)	0.1 (0.6), (0.0-0.3)
Not RBCT-related	48 (88.9)	8.2 (7.3), (6.2-10.2)
Inpatient hospitalizations	54 (100.0)	11.3 (11.3), (8.2-14.3)
RBCT-related	49 (90.7)	7.6 (6.1), (5.9-9.2)
Not RBCT -related	43 (79.6)	3.7 (8.7), (1.3-6.1)
Total number of hospital days	NA	15.1 (12.6), (11.7-18.6)
Inpatient hospitalizations with < 1 day	53 (98.1)	10.8 (11.3), (7.7-13.9)
RBCT-related	47 (87.0)	7.4 (6.2), (5.7-9.1)
Not RBCT-related	39 (72.2)	3.4 (8.8), (1.0-5.8)
Inpatient hospitalizations with ≥ 1 day	34 (63.0)	0.5 (0.6), (0.3-0.6)
RBCT-related	14 (25.9)	0.1 (0.2), (0.1-0.2)
Not RBCT-related	30 (55.6)	0.3 (0.4), (0.2-0.5)

CI, confidence interval; **PPPY,** per patient per year; **NA,** not applicable; **RBCT,** red blood cell transfusion; **SD,** standard deviation; Scores were categorized across tertiles using all patients with available data in the PHARMO Database Network as low, middle, or high.

Subgroup Analysis: HCRU by Age and Transfusion Subgroups

- Inpatient hospitalizations, and total number of hospital days increased with increasing age. (**Table 3**)
  - Outpatient specialist visits were highest among those aged 12 to 35 years.
- Children aged 0-11 years had the highest average length of stay of hospital visits with overnight admissions (≥ 1 day) compared to individuals in the older age groups.
- Patients with ≥ 8 RBCTs PPPY in the follow-up period had higher rates of HCRU than those < 8 RBCTs PPPY in the follow-up period. (**Table 3**)
  - Mean rate of outpatient specialist visits was higher among patients with TDT with ≥8 RBCTs (9.3 visits PPPY) compared to patients with <8 RBCTs per year (7.6 visits PPPY).
  - Mean rate of inpatient hospitalizations was higher among patients with TDT with ≥8 RBCTs (17.4 hospitalizations PPPY) compared to patients with <8 RBCTs per year (5.9 hospitalizations PPPY).
  - Mean rate of total number of hospital days was higher among patients with TDT with ≥8 RBCTs (19.2 days PPPY) compared to <8 RBCTs per year (11.6 days PPPY).

Table 3. HCRU by Age and RBCT Frequency Subgroups

Healthcare Resource Utilization	Age Groups			Transfusion Frequency	
	0-11 Years (N=25)	12-35 Years (N=23)	≥ 36 Years (N=6)	< 8 RBCTs (N=29)	≥ 8 RBCTs (N=25)
	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)	Rate (PPPY) Mean (SD), (95% CI)
Outpatient specialist visits	7.1 (5.4), (4.9 - 9.4)	9.7 (9.1), (5.7 - 13.6)	8.7 (5.6), (2.8 - 14.6)	7.6 (5.6), (5.4 - 9.7)	9.3 (8.7), (5.7 - 13.0)
RBCT-related	0.1 (0.5), (-0.1 - 0.3)	0.2 (0.8), (-0.1 - 0.6)	NA	0.2 (0.7), (-0.1 - 0.4)	0.1 (0.5), (-0.1 - 0.3)
Not RBCT-related	7.0 (5.5), (4.7 - 9.3)	9.5 (9.3), (5.4 - 13.5)	8.7 (5.6), (2.8 - 14.6)	7.4 (5.8), (5.2 - 9.6)	9.2 (8.8), (5.6 - 12.9)
Inpatient hospitalizations	8.1 (5.7), (5.8 - 10.5)	11.9 (7.1), (8.8 - 14.9)	22.0 (27.9), (-7.3 - 51.2)	5.9 (3.6), (4.6 - 7.3)	17.4 (13.8), (11.7 - 23.1)
RBCT-related	6.0 (5.8), (3.6 - 8.4)	9.0 (6.6), (6.2 - 11.9)	8.4 (5.0), (3.2 - 13.6)	3.0 (2.2), (2.2 - 3.9)	12.8 (4.9), (10.8 - 14.8)
Not RBCT-related	2.1 (2.2), (1.2 - 3.0)	2.8 (3.0), (1.5 - 4.1)	13.6 (24.8), (-12.4 - 39.6)	2.9 (2.9), (1.8 - 4.0)	4.6 (12.5), (-0.6 - 9.8)
Total number of hospital days	14.0 (11.3), (9.3 - 18.7)	14.1 (7.3), (11.0 - 17.3)	23.8 (27.0), (-4.5 - 52.2)	11.6 (10.5), (7.6 - 15.6)	19.2 (13.7), (13.6 - 24.9)
Inpatient hospitalizations with < 1 day	7.7 (5.7), (5.3 - 10.0)	11.4 (7.1), (8.3 - 14.4)	21.7 (28.0), (-7.8 - 51.1)	5.4 (3.5), (4.1 - 6.8)	17.0 (13.9), (11.3 - 22.7)
RBCT-related	5.8 (5.8), (3.4 - 8.2)	9.0 (6.7), (6.1 - 11.9)	8.4 (4.9), (3.2 - 13.5)	2.8 (2.2), (2.0 - 3.7)	12.8 (4.9), (10.7 - 14.8)
Not RBCT-related	1.8 (2.1), (1.0 - 2.7)	2.4 (3.1), (1.1 - 3.7)	13.3 (24.9), (-12.9 - 39.5)	2.6 (2.9), (1.5 - 3.7)	4.2 (12.6), (-1.0 - 9.4)
Inpatient hospitalizations with ≥ 1 day	0.5 (0.6), (0.2 - 0.7)	0.5 (0.6), (0.2 - 0.7)	0.3 (0.4), (-0.1 - 0.7)	0.5 (0.7), (0.2 - 0.8)	0.4 (0.4), (0.3 - 0.6)
RBCT-related	0.2 (0.3), (0.1 - 0.3)	0.1 (0.2), (0.0 - 0.2)	0.0 (0.1), (-0.1 - 0.1)	0.2 (0.3), (0.1 - 0.3)	0.1 (0.1), (0.0 - 0.1)
Not RBCT-related	0.3 (0.4), (0.1 - 0.5)	0.4 (0.5), (0.2 - 0.6)	0.3 (0.3), (0.0 - 0.6)	0.3 (0.5), (0.1 - 0.5)	0.4 (0.4), (0.2 - 0.5)

SD, standard deviation; **CI,** confidence interval; **PPPY,** per patient per year; **RBCT,** red blood cell transfusion; **NA,** not applicable

Limitations

- The data analyzed in this study are based on administrative medical records. Therefore, measurement errors and possible inaccuracy of diagnostic and procedural codes could happen.
- Given the minimum 12-month post-index period for patients with TDT, individuals who were not continuously enrolled for at least 12 months post-index date were excluded, which potentially could lead to underestimation of HCRU.
- Socio-economic status results should be interpreted with caution due to the limited number of patients who had socio-economic status reported.
- Prevalence of HCRU should be interpreted with caution due to the variable length of the follow-up period.

CONCLUSIONS

- **Patients with TDT in the Netherlands continue to have substantial HCRU.**
- **Consistent with progressive disease, a higher number of RBCTs and older age was associated with most measures of HCRU.**
- **These findings among patients with TDT highlight the need for novel therapies that can reduce the number of RBCTs and the associated HCRU.**

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