Overall survival and morbidity among adults with thalassemia in England: a retrospective analysis using routinely collected healthcare data from 2008 to 2020

PS2183

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BACKGROUND

- Thalassemia is a group of recessively inherited disorders caused by an imbalance of globin chains, which, in turn, leads to ineffective erythropoiesis, hemolysis, chronic anemia, and complications that can impact life expectancy[1–2]
- Lower hemoglobin (Hb) levels among patients with non-transfusion-dependent thalassemia (NTDT) have been associated with higher morbidity and mortality[3,4]
- Limited studies have compared mortality in patients with NTDT, including both non-transfusion-dependent (NTD) α-thalassemia and NTD β-thalassemia, or transfusion-dependent thalassemia (TDT) with non-thalassemia populations[5–8]

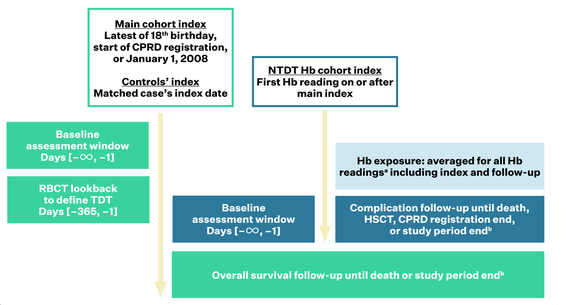
AIMS

- **To compare overall survival (OS) between patients with thalassemia and the non-thalassemia population in England**
- **To assess the association of Hb with complications in patients with NTDT in England**

STUDY DESIGN

- Primary care electronic health records from the Clinical Practice Research Datalink (CPRD) Aurum database linked to secondary care reimbursement data from the Hospital Episode Statistics and the Office for National Statistics death registrations were used to identify adults with TDT or NTDT from January 1, 2008 to December 31, 2019 (i.e. the eligibility period) to allow at least 12 months of follow-up (**Figure 1**)
  - Patients were indexed on the latest of the following 3 dates: their 18th birthday, start of CPRD registration, or January 1, 2008
  - Patients were followed retrospectively until the earliest of the following events: death, hematopoietic stem cell transplantation (HSCT), transfer out of primary care practice, last data collection from primary practice, or December 31, 2020
  - For OS analysis, patients were followed retrospectively until the earliest of the following events: death or December 31, 2020
- Patients with TDT or NTDT were matched to non-thalassemia controls (1:5 ratio) on age, sex, geography, and ethnicity to assess OS from birth; cohort definitions are outlined in **Table 1**
- Patients with NTDT and ≥1 Hb reading (**Figure 1**) were re-indexed at their earliest Hb reading to assess the association of Hb with complications

Figure 1: Study design for cohort index and follow-up



[a]Hb readings within 8 weeks after an RBCT were excluded from analysis, and this applied to Hb readings during baseline, at index, and during follow-up. [b]Study period ended on December 31, 2020 to allow a minimum follow-up period of 12 months. CPRD, Clinical Practice Research Datalink; Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; NTDT, non-transfusion-dependent thalassemia; RBCT, red blood cell transfusion; TDT, transfusion-dependent thalassemia.

Study population

- TDT was defined based on RBCTs from the 12 months pre-index (**Table 1**)
- Among patients with NTDT, to limit the possible inclusion of trait/carriers, 4 definitions were developed. The study population flowchart of the creation of each cohort is outlined in **Supplementary Figure 1**

Table 1: Cohort definitions

Study population	Inclusion criteria	Exclusion criteria
Patients with thalassemia	Diagnosis code of thalassemia	Signifying traits of thalassemia OR sickle cell disease at any time OR non-α- or β-thalassemia at any time OR HSCT prior to index OR <12 months of follow-up post-index (unless censored due to death)
TDT	≥8 RBCTs, all of which are ≤42 days apart, in the 12 months before index	
Suggestive NTDT	Patients with NTDT (i.e. <8 RBCTs in the 12 months before index OR ≥8 RBCTs and at least 2 of them are >42 days apart) that meet any of the 4 definitions shown below	As above AND patients with non-specific (i.e. not major or intermedia) thalassemia inclusion AND ≥1 trait code Additional criteria for NTDT definition 1 only: Patients with specific (i.e. major or intermedia) thalassemia inclusion code AND ≥1 trait code OR patients with only non-specific thalassemia inclusion codes
Definition 1 (based on diagnosis code certainties)	Patients with NTDT	
Definition 2 (based on thalassemia-related care)	Patients with NTDT AND 1) ≥1 hematology outpatient appointment in 3 years prior to index date OR 2) ≥1 inpatient admission with primary diagnosis of thalassemia (ever) prior to index date	
Definition 3	Meeting the criteria for definition 1 AND definition 2	
Definition 4	Meeting the criteria for definition 1 OR definition 2	
NTD α-thalassemia[a]	α-thalassemia specified in diagnosis code	
NTD β-thalassemia[a]	β-thalassemia specified in diagnosis code	
Non-thalassemia controls	Registration period at CPRD contributing practice is inclusive of matched case's index date	Any hemoglobinopathy or hemolytic anemia at any time OR HSCT prior to index date OR <12 months of follow-up post-index (unless censored due to death)

[a]Subgroups by NTDT definition and genotype/Hb level are summarized in **Supplementary Figure 1**.
CPRD, Clinical Practice Research Datalink; Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; NTD, non-transfusion-dependent; NTDT, non-transfusion-dependent thalassemia; RBCT, red blood cell transfusion; TDT, transfusion-dependent thalassemia.

Statistical analysis

- OS from birth to death from any cause for patients with thalassemia and their matched controls was assessed using the Kaplan–Meier method and compared using log-rank test and Cox proportional hazards regression
  - Hazard ratios (HRs) were adjusted for deprivation
  - OS from index to death was assessed in a sensitivity analysis
- Subgroups of patients with thalassemia were evaluated separately, including TDT, NTDT, NTD α-thalassemia, NTD β-thalassemia, NTDT with pre-index Hb ≤10 g/dL, and NTDT with pre-index Hb >10 g/dL
  - For NTDT subgroups, each of the previously mentioned definitions of NTDT was used (**Table 1**)
  - Patients with TDT were not stratified by genotype due to the limited α-thalassemia sample size
- Among patients with NTDT who had ≥1 Hb reading:
  - Hb level was averaged for all Hb readings including index and follow-up; Hb readings within 8 weeks after an RBCT were excluded from the analysis
  - The association between each 1 g/dL increment in Hb and the number of complications present by the end of follow-up was evaluated using multivariable Poisson regression to generate incidence rate ratios adjusted for age and sex, with follow-up time included in the model as an offset
  - The association between each 1 g/dL increment in Hb and presence of new thalassemia-related complications (osteopathy, heart disease, chronic endocrine complications, chronic renal disease, acute liver or gallbladder disease, acute vascular events, and arrhythmias) was assessed using multivariable logistic regression to generate odds ratios adjusted for age, sex, and follow-up

RESULTS

Baseline demographic and clinical characteristics

- The demographic and clinical characteristics are displayed in **Table 2** and full data are available in **Supplementary Table 1**

Table 2: Baseline demographic and clinical characteristics in patients with TDT or NTDT vs. matched controls

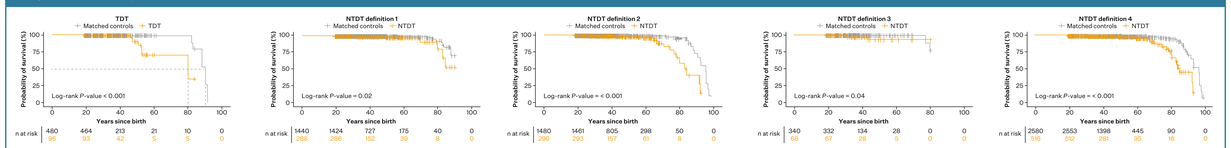
Characteristic	TDT		NTDT definition 1		NTDT definition 2		NTDT definition 3		NTDT definition 4	
	Cases (n=96)	Controls (n=480)	Cases (n=288)	Controls (n=1440)	Cases (n=296)	Controls (n=1480)	Cases (n=68)	Controls (n=340)	Cases (n=516)	Controls (n=2580)
Age at index (years), mean (SD)	31.9 (12.2)	31.9 (12.2)	35.8 (13.3)	35.8 (13.3)	37.8 (15.6)	37.8 (15.5)	32.1 (11.6)	32.1 (11.5)	37.4 (14.8)	37.4 (14.7)
Female, n (%)	40 (41.7)	200 (41.7)	166 (57.6)	830 (57.6)	191 (64.5)	955 (64.5)	36 (52.9)	180 (52.9)	321 (62.2)	1605 (62.2)
Hb reading available[a], n (%)	S[b]	91 (19.0)	73 (25.3)	349 (24.2)	100 (33.8)	368 (24.9)	18 (26.5)	63 (18.5)	155 (30.0)	654 (25.3)
Hb g/dL[a], mean (SD)	S[b]	13.5 (1.5)	11.5 (1.9)	13.5 (1.6)	11.1 (2.0)	13.0 (1.6)	10.6 (2.0)	13.1 (1.6)	11.3 (1.9)	13.2 (1.6)
Follow-up (years), mean (IQR)	5.6 (3.3–9.6)	5.9 (3.1–11.1)	7.3 (2.9–13.0)	5.8 (2.9–11.0)	6.0 (2.7–11.8)	6.6 (3.3–12.6)	5.2 (2.5–12.4)	5.2 (2.5–10.7)	6.6 (2.8–12.7)	6.5 (3.2–12.1)

[a]Most recent prior to index, limited to a 12-month lookback. [b]Counts <5 are suppressed in accordance with CPRD guidelines.
CPRD, Clinical Practice Research Datalink; Hb, hemoglobin; IQR, interquartile range; NTDT, non-transfusion-dependent thalassemia; S, suppressed; SD, standard deviation; TDT, transfusion-dependent thalassemia.

Overall survival in patients with TDT or NTDT

- OS was significantly shorter for adults with either TDT or NTDT (all NTDT definitions) compared with matched controls during the follow-up period based on log-rank test (**Figure 2**); similar trends were seen in the sensitivity analysis (**Supplementary Figure 2**)

Figure 2: OS in patients with TDT or NTDT vs. matched controls



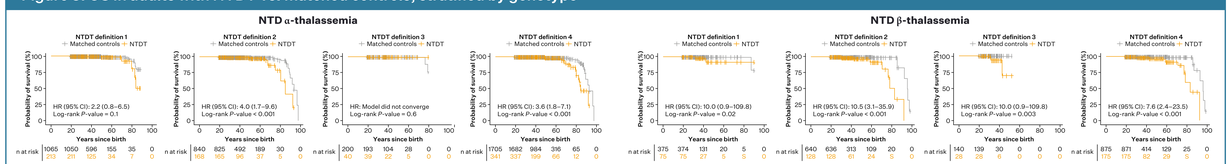
NTDT, non-transfusion-dependent thalassemia; OS, overall survival; TDT, transfusion-dependent thalassemia.

- Based on Cox regression model, results were similar for patients with TDT or NTDT definitions 1, 2, and 4, respectively, during the follow-up period (**Table 3**); the trend was similar for NTDT definition 3, but the result was not significant due to the low number of events

Overall survival in patients with NTDT stratified by genotype

- Similar trends were observed for NTD α-thalassemia or NTD β-thalassemia subgroups vs. matched controls during the follow-up period, respectively (**Figure 3**)

Figure 3: OS in adults with NTDT vs. matched controls, stratified by genotype



[a]Counts <5 are suppressed in accordance with CPRD guidelines. CI, confidence interval; HR, hazard ratio; NTD, non-transfusion-dependent; NTDT, NTD thalassemia; OS, overall survival; S, suppressed.

Table 3: Cox regression analysis in patients with TDT or NTDT vs. matched controls

	Patients with TDT/NTDT	TDT/NTDT events, n (%)	Matched control, n	Matched control events, n (%)	Adjusted HR[a] (95% CI)	*P*-value
TDT	96	6 (6.3)	480	7 (1.5)	11.7 (3.0–45.5)	< 0.001
NTDT definition 1	288	7 (2.4)	1440	11 (0.8)	2.9 (1.1–7.4)	0.031
NTDT definition 2	296	17 (5.7)	1480	22 (1.5)	5.6 (2.8–11.0)	< 0.001
NTDT definition 3	68	S[b]	340	S[b]	6.6 (0.9–49.5)	0.066
NTDT definition 4	516	22 (4.3)	2580	31 (1.2)	4.3 (2.5–7.7)	< 0.001

[a]HR adjusted for deprivation, and matched control was the reference group in the model. [b]Counts <5 are suppressed in accordance with CPRD guidelines.
CI, confidence interval; CPRD, Clinical Practice Research Datalink; HR, hazard ratio; NTDT, non-transfusion-dependent thalassemia; S, suppressed; TDT, transfusion-dependent thalassemia.

Overall survival in patients with NTDT with pre-index Hb ≤10 g/dL or >10 g/dL

- Among patients with pre-index Hb ≤10 g/dL, the adjusted HRs (95% confidence intervals) for NTDT definitions 1 and 4 were 4.5 (0.2–85.8, *P* = 0.316) and 22.4 (1.9–264.8, *P* = 0.014), respectively; for definitions 2 and 3, the models failed to converge due to low event count
- Patients under NTDT definition 1, 2, or 4 with pre-index Hb >10 g/dL had significantly shorter OS during the follow-up period than controls (**Table 4**); for definition 3, the model failed to converge due to low event count

Table 4. Mortality among patients with NTDT with pre-index Hb >10 g/dL vs. matched controls

	Patients with NTDT, n	NTDT events, n (%)	Matched control, n	Matched control events, n (%)	Adjusted HR[a] (95% CI)	*P*-value
NTDT definition 1	123	S[b]	615	S[b]	4.6 (1.1–18.5)	0.033
NTDT definition 2	130	11 (8.5)	650	14 (2.2)	6.1 (2.6–14.4)	< 0.001
NTDT definition 3	21	S[b]	105	S[b]	Did not converge[c]	
NTDT definition 4	232	15 (6.5)	1160	18 (1.6)	5.6 (2.7–11.7)	< 0.001

[a]HR adjusted for deprivation, and matched control was the reference group in the model. [b]Counts <5 are suppressed in accordance with CPRD guidelines.
[c]A model failing to converge means it could not reach a stable solution to provide an accurate prediction, in this instance, due to low event count.
CI, confidence interval; CPRD, Clinical Practice Research Datalink; Hb, hemoglobin; HR, hazard ratio; NTDT, non-transfusion-dependent thalassemia; S, suppressed.

Association of Hb with complications in NTDT

- For each 1 g/dL incremental increase in Hb, the number of complications significantly decreased for NTDT definitions 2 and 4 during the follow-up period (**Supplementary Table 2**)
- At the individual complication level, for each 1 g/dL incremental increase in Hb, osteopathy was the only complication where the odds of development significantly decreased, and only for NTDT definitions 2 and 4 (**Supplementary Figure 3**)
  - Results for other complications and NTDT definitions were likely affected by low event counts

CONCLUSIONS

- **In this study, adults with TDT or NTDT had significantly shorter OS compared with respective matched controls without thalassemia**
  - **Subgroup analysis by genotype indicates that patients with NTD α- and NTD β-thalassemia are both more likely to have shorter OS than those without thalassemia**
  - **Subgroup analysis by pre-index Hb level indicates that patients with NTDT with pre-index Hb >10 g/dL are more likely have shorter OS than those without thalassemia; among patients with NTDT with pre-index Hb ≤10 g/dL, similar trends are observed but are only significant for NTDT definition 4, perhaps due to the small sample size**
- **In adults with NTDT, higher Hb was generally associated with lower occurrence of thalassemia-related complications, especially osteopathy**
- **There remains a critical unmet need for novel therapies for all patients with thalassemia across genotypes (α- and β-thalassemia) and transfusion requirements (NTDT and TDT) that can also address patient burden, including reducing serious morbidities and premature mortality risk**

LIMITATIONS

- The potential survivor bias among the selected cases may lead to an underestimation of the OS effects observed in this study
  - The study design may introduce left truncation bias, as only patients who were alive by 2008 had a chance to be assessed in the study, which can lead to an overestimation of survival times
- Patients with α- or β-thalassemia traits could not be definitively excluded, as identification of patients relied on accurate diagnostic coding by providers rather than recorded genetic test results
- There was limited power to associate Hb with complications due to a low observed number of events in the NTDT population, in part driven by the sample size of patients with NTDT available for inclusion

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References: 1. Kattamis A, et al. Lancet 2022;399(10343):2310–24. 2. Taher AT, et al. N Engl J Med 2021;384(8):727–43. 3. Musallam KM, et al. Ann Hematol 2021;100(7):1903–5. 4. Taher AT, et al. Blood Cells Mol Dis 2015;55:108–9. 5. Udeze C, et al. J Med Econ 2023;26(1):924–32. 6. Langer AL, et al. HemaSphere 2023;7(S3):e33315lf. 7. Musallam KM, et al. Haematologica 2021;106(9):2489–92. 8. Gianesin B, et al. Haematologica 2025;110(5):1211–6.

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