Clinical Burden of Alpha- and Beta-Thalassemia Compared to Matched Controls in the Real-World Setting

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BACKGROUND

- Thalassemia is a hereditary disorder caused by diminished globin chain synthesis[i] leading to ineffective erythropoiesis and chronic hemolytic anemia (HA) with subsequent clinical complications.[ii, iii, iv]
- Alpha (α) and beta (β) thalassemia result from defective synthesis of α- or β-globin, respectively.
- Limited research in the US regarding the burden of comorbidities associated with thalassemia, particularly
  - Non-transfusion dependent thalassemia (NTDT)
  - α-thalassemia

OBJECTIVE

- Describe the burden of disease and complications in:
  - Patients with α- and β-thalassemia; and
  - TDT and NTDT patients
- Compared to matched controls
- 12-month period

METHODS

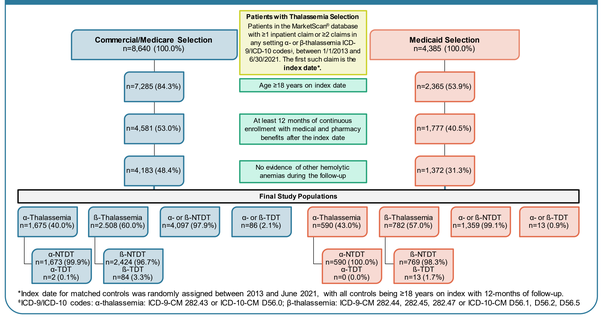
- Patients and controls were selected from the Merative MarketScan® Commercial & Medicare and Multi-State Medicaid claims databases
  - *Patients with thalassemia:* Patient selection criteria are outlined in Figure 1
  - *Controls:* Subjects with no history of thalassemia or other hemolytic anemias were matched 5:1 to patients with thalassemia on age, sex, payer, race and ethnicity (Medicaid only), and follow-up time

Definition of thalassemia cohorts:

Thalassemia type (α or β), transfusion dependence status (TDT or NTDT)*, or by both characteristics (α-NTDT, α-TDT, β-NTDT, or β-TDT)

*TDT was defined as ≥8 transfusions within 12 months of follow-up, with <42 days between any 2 transfusions

Figure 1: Patient Selection

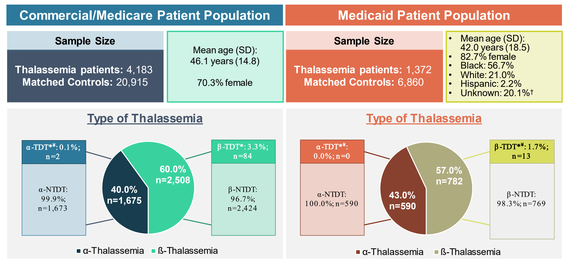


*Index date for matched controls was randomly assigned between 2013 and June 2021, with all controls being ≥18 years on index with 12-months of follow-up.
#ICD-9/ICD-10 codes: α-thalassemia: ICD-9-CM 282.43 or ICD-10-CM D56.0; β-thalassemia: ICD-9-CM 282.44, 282.45, 282.47 or ICD-10-CM D56.1, D56.2, D56.5

- Clinical outcomes compared during defined 12-month follow-up period
  - Charlson comorbidity index (CCI), number and proportion of patients with each comorbidity of interest (both thalassemia-related and non-thalassemia related), and mean number of comorbidities of interest
- Summary statistics
  - Categorical variables (e.g., a comorbidity of interest): number and proportion of participants in each category
  - Continuous variables (e.g., CCI): mean and standard deviation (SD)
- Chi-square (categorical variables) and t-tests (continuous variables) were used for outcome comparisons between patients with thalassemia and matched controls with a significance level of 0.05

RESULTS

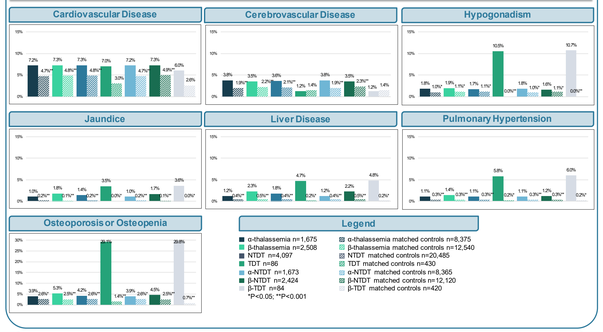
Figure 2



† Race and ethnicity is only reported in Medicaid
*Sensitivity analysis without the 42-day requirement between transfusions had minimal impact on TDT numbers
#Due to small sample size, further results on Commercial/Medicare α-TDT and Medicaid α- or β-TDT patients are not reported

Figure 3: Comorbidity burden in the Commercial/Medicare population

A significantly higher proportion of patients with thalassemia had thalassemia-related comorbidities compared to their matched controls, across all stratifications (all p <0.05)



*P<0.05; **P<0.001

Figure 4: Comorbidity burden in the Medicaid population

A significantly higher proportion of Medicaid patients with thalassemia had thalassemia-related comorbidities compared to their matched controls, across all stratifications (all p <0.05)

*P<0.05; **P<0.001

Comorbidity burden in the Commercial/Medicare population

- Thalassemia patients were also generally more likely to have other comorbidities, significantly more comorbidities per patient, and a higher CCI than controls (**Tables 1 & 2**)
  - There were too few patients with α-TDT to report on this sub-stratification

Table 1. Other complications and comorbidities in thalassemia by genotype OR transfusion status vs. matched controls (Commercial/Medicare; 12-month follow-up)

	α-Thalassemia N=1,675	α-Thalassemia Control Cohort N=8,375	β-Thalassemia N=2,508	β-Thalassemia Control Cohort N=12,540	NTDT (Any) N=4,097	NTDT Control Cohort N=20,485	TDT (Any) N=86	TDT Control Cohort N=430
CCI, Mean (SD); Median	**0.9 (1.6)**; 0.0**	0.4 (1.1); 0.0	**0.8 (1.5)**; 0.0**	0.4 (1.2); 0.0	**0.8 (1.6)**; 0.0**	0.4 (1.1); 0.0	**0.7 (1.5)**; 0.0**	0.2 (0.7); 0.0
# of unique comorbid conditions (Mean, SD); Median	**1.7 (1.5)**; 1.0**	1.1 (1.2); 1.0	**1.8 (1.5)**; 2.0**	1.1 (1.3); 1.0	**1.7 (1.5)**; 2.0**	1.1 (1.2); 1.0	**3.3 (1.6)**; 3.0**	0.9 (1.0); 1.0
Select Non-Thalassemia Related Complications and Comorbidities (N, %)								
Hypertension	**660 (39.4)****	2,031 (24.3)	**759 (30.3)****	2,980 (23.8)	**1,411 (34.4)****	4,961 (24.2)	8 (9.3)	50 (11.6)
Abnormal growth	**549 (32.8)****	2,290 (27.3)	**866 (34.5)****	3,514 (28.0)	**1,364 (33.3)****	5,601 (27.3)	50 (58.1)	203 (47.2)
Diabetes	**288 (17.2)****	770 (9.2)	**319 (12.7)****	1,135 (9.1)	**591 (14.4)****	1,890 (9.2)	**16 (18.6)****	15 (3.5)
Anxiety	195 (11.6)	959 (11.5)	**401 (16.0)****	1,470 (11.7)	**585 (14.3)****	2,389 (11.7)	11 (12.8)	40 (9.3)
Depression	153 (9.1)	810 (9.7)	**327 (13.0)****	1,129 (9.0)	**473 (11.5)****	1,907 (9.3)	7 (8.1)	32 (7.4)
Hypothyroidism	**160 (9.6)***	675 (8.1)	**283 (11.3)****	953 (7.6)	**436 (10.6)****	1,611 (7.9)	7 (8.1)	17 (4.0)
Malignancy	**147 (8.8)****	295 (3.5)	**193 (7.7)****	463 (3.7)	**333 (8.1)****	753 (3.7)	**7 (8.1)***	5 (1.2)

*p<0.05; **p<0.001
[i]α-thalassemia: ICD-9-CM 282.43 or ICD-10-CM D56.0; β-thalassemia: ICD-9-CM 282.44, 282.45, 282.47 or ICD-10-CM D56.1, D56.2, D56.5

Table 2. Other complications and comorbidities in thalassemia by genotype AND transfusion status vs. matched controls (Commercial/Medicare; 12-month follow-up)

	α-NTDT N=1,673	α-NTDT Control Cohort N=8,365	β-NTDT N=2,424	β-NTDT Control Cohort N=12,120	β-TDT N=84	β-TDT Control Cohort N=420
CCI, Mean (SD); Median	**0.9 (1.6)**;0.0**	0.4 (1.1); 0.0	0.8 (1.5); 0.0	0.5 (1.2); 0.0	**0.6 (1.5)**; 0.0**	0.2 (0.6); 0.0
# of unique comorbid conditions (Mean, SD); Median	**1.7 (1.5)**; 1.0**	1.1 (1.2); 1.0	1.8 (1.5)**; 2.0	1.1 (1.3); 1.0	**3.3 (1.6)**; 3.0**	0.9 (1.0); 1.0
Select Non-Thalassemia Related Complications and comorbidities (N, %)						
Hypertension	**659 (39.4)****	2,027 (24.2)	**752 (31.0)****	2,934 (24.2)	7 (8.3)	46 (11.0)
Abnormal growth	**549 (32.8)****	2,290 (27.4)	**815 (33.6)****	3,311 (27.3)	50 (59.5)	203 (48.3)
Diabetes	**288 (17.2)****	770 (9.2)	**303 (12.5)****	1,120 (9.2)	**16 (19.0)****	15 (3.6)
Anxiety	193 (11.5)	958 (11.5)	**392 (16.2)****	1,431 (11.8)	9 (10.7)	39 (9.3)
Depression	152 (9.1)	808 (9.7)	**321 (13.2)****	1,099 (9.1)	6 (7.1)	30 (7.1)
Hypothyroidism	159 (9.5)	674 (8.1)	**277 (11.4)****	937 (7.7)	6 (7.1)	16 (3.8)
Malignancy	**145 (8.7)****	292 (3.5)	**188 (7.8)****	461 (3.8)	**5 (6.0)***	2 (0.5)

*p<0.05; **p<0.001; Note: α-TDT data not presented due to small sample size.
[i]α-thalassemia: ICD-9-CM 282.43 or ICD-10-CM D56.0; β-thalassemia: ICD-9-CM 282.44, 282.45, 282.47 or ICD-10-CM D56.1, D56.2, D56.5

Comorbidity burden in the Medicaid population

- Among thalassemia patients, other comorbidities were also generally more common in patients with thalassemia, and had a higher mean CCI than matched controls (**Table 3**)
  - In the Medicaid population, the ability to adjust for race did not eliminate differences in conditions, such as hypertension, associated with race and racial bias

Table 3. Other complications and comorbidities in thalassemia by genotype, transfusion status, or genotype AND transfusion status vs. matched controls (Medicaid; 12-month follow-up)

	α-Thalassemia N=590	α-Thalassemia Control Cohort N=2,950	β-Thalassemia N=782	β-Thalassemia Control Cohort N=3,910	NTDT Thalassemia (Any) N=1,359	NTDT Thalassemia Control Cohort N=6,795	α-NTDT N=590	α-NTDT Control Cohort N=2,950	β -NTDT N=769	β -NTDT Control Cohort N=3,845
CCI, Mean (SD); Median	**1.4 (2.2)**, 1.0**	0.5 (1.4), 0.0	**1.4 (2.2)**, 1.0**	0.6 (1.4), 0.0	**1.4 (2.2)**, 1.0**	0.6 (1.4), 0.0	**1.4 (2.2)**, 1.0**	0.5 (1.4), 0.0	**1.4 (2.2)**, 1.0**	0.6 (1.4), 0.0
# of unique comorbid conditions (Mean, SD); Median	**2.3 (1.8)**, 2.0**	1.1 (1.4), 1.0	**2.7 (1.8)**, 2.0**	1.3 (1.5), 1.0	**2.5 (1.8)**, 2.0**	1.2 (1.5), 1.0	**2.3 (1.8)**, 2.0**	1.1 (1.4), 1.0	**2.7 (1.8)**, 2.0**	1.3 (1.5), 1.0
Select Non-Thalassemia Related Complications and comorbidities (N, %)										
Hypertension	**242 (41.0)****	661 (22.4)	**326 (41.7)****	937 (24.0)	**567 (41.7)****	1,583 (23.3)	**242 (41.0)****	661 (22.4)	**661 (22.4)****	325 (42.3)
Abnormal growth	**284 (48.1)****	1060 (35.9)	**457 (58.4)****	1615 (41.3)	**732 (53.9)****	2,638 (38.8)	**284 (48.1)****	1,060 (35.9)	**1,060 (35.9)****	448 (58.3)
Diabetes	**129 (21.9)****	302 (10.2)	**189 (24.2)****	455 (11.6)	**317 (23.3)****	751 (11.1)	**129 (21.9)****	302 (10.2)	**302 (10.2)****	188 (24.4)
Anxiety	**100 (16.9)****	331 (11.2)	**191 (24.4)****	530 (13.6)	**290 (21.3)****	852 (12.5)	**100 (16.9)****	331 (11.2)	**331 (11.2)****	190 (24.7)
Depression	**136 (23.1)****	356 (12.1)	**199 (25.4)****	577 (14.8)	**334 (24.6)****	921 (13.6)	**136 (23.1)****	356 (12.1)	**356 (12.1)****	198 (25.7)
Hypothyroidism	**46 (7.8)****	86 (2.9)	**112 (14.3)****	176 (4.5)	**158 (11.6)****	258 (3.8)	**46 (7.8)****	86 (2.9)	**86 (2.9)****	112 (14.6)
Malignancy	**35 (5.9)****	50 (1.7)	**52 (6.6)****	84 (2.1)	**85 (6.3)****	132 (1.9)	**35 (5.9)****	50 (1.7)	**50 (1.7)****	50 (6.5)

*p<0.05; **p<0.001; Note: TDT data not presented due to small sample.
[i]α-thalassemia: ICD-9-CM 282.43 or ICD-10-CM D56.0; β-thalassemia: ICD-9-CM 282.44, 282.45, 282.47 or ICD-10-CM D56.1, D56.2, D56.5

STRENGTHS AND LIMITATIONS

Strengths

- Large multi-year retrospective analysis to provide burden of disease data on α-thalassemia
- Billing claims allowed for rigorous code-based definitions for transfusion dependence considering lack of chart review

Limitations

- Relied on diagnosis codes, procedure codes, and pharmacy prescriptions in claims, which are subject to data coding limitations and data entry error, to identify patient clinical profile and study outcomes (No chart review)
- Matched to address observable imbalances, but residual differences may remain
- A smaller and geographically non-random population limited the ability to assess certain stratifications of the Medicaid population, affecting generalizability of the results for all US Medicaid patients
- Some patients with thalassemia minor may have been coded incorrectly by physicians and included in the NTDT group, suggesting that NTDT estimates in this study provide a lower boundary for the impact of NTDT
- Databases were limited to only those individuals with commercial, Medicare, or Medicaid coverage. Consequently, results of this analysis may not be generalizable to thalassemia patients with other insurance or without health insurance coverage

CONCLUSIONS

- Serious comorbidities and unmet needs persist for patients with thalassemia, even in thalassemia types that have historically been considered less severe such as NTDT and α-thalassemia
- Both α-NTDT and β-NTDT had significantly higher clinical burden than matched controls including endocrinopathies, cardiovascular disease, liver disease and pulmonary hypertension – conditions associated with considerable morbidity and mortality
- Likely inclusion of some thalassemia minor patients in the NTDT group, suggests that NTDT comorbidities may be underestimated
- Across insurance types, cardiovascular and cerebrovascular disease were more frequent in the Medicaid population than the Commercial/Medicare population, with an opposite finding among osteoporosis and hypogonadism
- Additional therapies are needed to address the underlying cause of the disease in an effort to decrease these serious complications

Abbreviations: CCI: Charlson Comorbidity Index; NTDT: non-transfusion dependent; TDT: transfusion dependent.

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