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β-thalassemia as a progressive disease: age-related morbidity in the de-LIGHT study

Short title: Age-related morbidity in β-thalassemia

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DATA AVAILABILITY STATEMENT

Data will be made available to qualified researchers upon reasonable request to the corresponding author.

AUTHORSHIP

Study conceptualization and design: KMM, AM. Data collection: AV, AI, RDM, RB, AGian, MCR, EF, AT, AGiam, GBR, EV, TMV, PR, BZ, MS, EC, FL, MC. Data analysis: KMM. Manuscript Drafting: KMM. Data interpretation and manuscript review for intellectual content: KMM, AV, AI, RDM, RB, AGian, MCR, EF, AT, AGiam, GBR, EV, TMV, PR, BZ, MS, EC, FL, MC, AM. All authors gave final approval for submission.

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CONFLICTS OF INTEREST

KMM reports consultancy fees from Novartis, Bristol Myers Squibb (Celgene Corp), Agios Pharmaceuticals, CRISPR Therapeutics, Vifor Pharma, Pharmacosmos, Novo Nordisk, NewBridge Pharmaceuticals, Avanzanite, and Vertex Pharmaceuticals; and research funding from Agios Pharmaceuticals and Pharmacosmos. **RDM** reports membership of advisory boards for Novo Nordisk. GBR reports membership of advisory boards for Novartis, Bristol Meyers Squibb, Bluebird Bio, and Vertex Pharmaceuticals. **PR** reports membership of advisory boards and honoraria from Agios Pharmaceuticals, Vertex Pharmaceuticals, and Bristol Myers Squibb. **FL** reports membership of advisory boards and honoraria from Bristol Myers Squibb, Vertex Pharmaceuticals, and Avanzanite Bioscience; and consultancy fees from Agios Pharmaceuticals. **AM** reports membership of advisory boards for Novartis, Celgene Corp (Bristol Meyers Squibb), Bluebird Bio, and Vertex Pharmaceuticals; and research funding from Agios Pharmaceuticals. The remaining authors have no conflicts of interest to disclose.

Advances in transfusion support, iron chelation, and more recently disease-modifying and curative therapies have substantially improved survival in patients with β -thalassemia, resulting in an expanding and aging patient population.^{1, 2} Although the pathophysiology of thalassemia is fundamentally determined by the underlying genetic defect and does not inherently progress with age in the manner of malignant or degenerative disorders, persistent exposure to ineffective erythropoiesis, chronic anemia, iron overload, and other disease-related abnormalities inevitably leads to the accumulation of organ damage over time when these processes are not fully controlled. In addition, age-related physiological changes and comorbidities may further amplify disease burden in later life.^{3, 4} Despite this, relatively few epidemiologic studies have systematically characterized age-related morbidity in thalassemia or provided age-specific estimates of morbidity prevalence and incidence in both patients with non-transfusion-dependent β -thalassemia (NTDT) and transfusion-dependent β -thalassemia (TDT).^{2, 5-7} Such information is important for patient education, surveillance strategies, and treatment planning across the lifespan.

The full details of the de-LIGHT study were previously reported.⁸ In summary, it was a retrospective longitudinal cohort study conducted at six centers in Italy and Greece. The study included all thalassemia patients who have ever attended participating centers since their establishment with a confirmed diagnosis of a clinically significant form of β -thalassemia and available clinical information since diagnosis. Patients were further classified as NTDT or TDT based on a calculated lifetime proportion spent on transfusion therapy.⁸ Data were retrieved from medical records from the date of diagnosis until death, loss to follow-up, or 31 December 2020, whichever occurred earlier. The Ethics

Committee/Institutional Review Board at each participating center approved the study and written informed consents for data collection and use were obtained for each patient at participating centers.

For each patient, we collected data on age at last follow-up, sex, history of splenectomy, history of hepatitis C virus infection, and lifetime hemoglobin (pretransfusion in TDT patients) and serum ferritin levels to reflect adequacy of management and disease control, calculated as the average of all available values throughout the entire period of observation. Age was further stratified into groups of clinical relevance (<18, 18 to <35, 35 to <50, 50 to <65, and ≥65 years). We also retrieved data on the development of morbidities including first documented event of cardiac morbidity (left-sided heart failure, right-sided heart failure, arrhythmia), vascular morbidity (myocardial infarction, pulmonary hypertension, peripheral vascular disease, venous thrombosis, non-cardiac arterial thrombosis, stroke), hepatic morbidity (liver fibrosis or cirrhosis, hepatocellular carcinoma [HCC], other liver disease), endocrine morbidity (diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadism), osteoporosis, renal morbidity (nephropathy, end-stage renal disease on dialysis), sepsis, leg ulcers, extramedullary hematopoiesis (EMH) masses, and cancer (other than HCC) - defined per standard local practice which is largely comparable at participating centers.

A total of 557 patients were included in the analyses. This included a total of 150 patients with NTDT and 407 patients with TDT. The median age at last follow-up was 40.6 years (interquartile range [IQR]: 31.5-49.0, range: 2.4-87.4) for the overall population, 48.0

years (IQR: 38.1-58.1, range: 11.0-87.4) for NTDT, and 38.8 years (IQR: 28.5-45.0, range: 2.4-84.1) for TDT. Patients had the following age group distribution: <18 (all: n = 45, 8.1%; NTDT: n = 1, 0.7%; TDT: n = 44, 10.8%), 18 to <35 (all: n = 142, 25.5%; NTDT: n = 30, 20%; TDT: n = 112, 27.5%), 35 to <50 (all: n = 244, 43.8%; NTDT: n = 49, 32.7%; TDT: n = 195, 47.9%), 50 to <65 (all: n = 103, 18.5%; NTDT: n = 51, 34%; TDT: n = 52, 12.8%), and ≥65 years (all: n = 23, 4.1%; NTDT: n = 19, 12.7%; TDT: n = 4, 1%). A total of 298 patients (53.5%, 56.7% in NTDT and 52.3% in TDT) were female, 301 (54% [at median age 10.3 years], 63.3% [at median age 13.3 years] in NTDT and 50.6% [at median age 9.9 years] in TDT) had a history of splenectomy, and 210 (37.7%, 40% in NTDT and 36.9% in TDT) had a history of hepatitis C virus infection. The median lifetime hemoglobin level was 9.6 g/dL (IQR: 9.2-9.9) in the overall population, 9.2 g/dL (IQR: 8.8-9.6) in NTDT, and 9.7 g/dL (IQR: 9.3-10.0) in TDT. The median lifetime serum ferritin level was 1289.6 ng/mL (IQR: 811-1923.6) in the overall population, 728.6 ng/mL (IQR: 486.0-1314.4) in NTDT, and 1472.1 ng/mL (IQR: 1016.8-2023.2) in TDT.

There was a significant and positive correlation between higher age at last follow-up and the number of experienced morbidities (Spearman's r : 0.636, p <0.001), with an incremental increase in the mean number of morbidities in ascending age groups for the overall population and for both patients with NTDT and TDT (**Figure 1A**). There was also a significant variation with ascending age groups in the prevalence of cardiac morbidity (both NTDT: Chi-squared p = 0.009 and TDT: p <0.001), vascular morbidity (both NTDT: p <0.001 and TDT: p <0.001), hepatic morbidity (mainly TDT: p <0.001), endocrine morbidity (mainly TDT: p <0.001), osteoporosis (both NTDT: p = 0.001 and TDT: p <0.001),

renal morbidity (mainly TDT: $p = 0.012$), sepsis (mainly TDT: $p = 0.012$), leg ulcers (both NTDT: $p = 0.048$ and TDT: $p = 0.008$), EMH masses (mainly TDT: $p = 0.001$), and cancer (mainly TDT: $p = 0.151$) (**Figures 1B-D**). The prevalence rates for individual morbidities (and risk factors) are summarized in **Supplementary Tables S1-S3**. Because multiple morbidity outcomes were evaluated, individual p -values should be interpreted cautiously in the absence of adjustment for multiple comparisons.

On logistic regression analysis and following adjustment for potential confounders and mediators (center of treatment, sex, splenectomy, hepatitis C infection, lifetime hemoglobin, and lifetime serum ferritin), each 10-year increase in age was significantly and independently associated with increased odds of cardiac morbidity (both NTDT: 34.9% increase, $p = 0.034$ and TDT 132.1%, $p < 0.001$), vascular morbidity (both NTDT: 53.8%, $p = 0.002$ and TDT: 124.8%, $p < 0.001$), hepatic morbidity (both NTDT: 46.5%, $p = 0.028$ and TDT: 198.4%, $p < 0.001$), endocrine morbidity (mainly TDT: 98.3%, $p < 0.001$), osteoporosis (both NTDT: 32.2%, $p = 0.030$ and TDT: 168.6%, $p < 0.001$), renal morbidity (mainly TDT: 71.8%, $p = 0.001$), sepsis (mainly TDT: 113.9%, $p = 0.039$), leg ulcers (both NTDT: 113.3%, $p = 0.016$ and TDT: 146.2%, $p = 0.027$), EMH masses (NTDT: 105%, $p = 0.015$ and TDT: 113.6%, $p < 0.001$), and cancer (mainly NTDT: 104.4%, $p = 0.044$) (**Table 1**).

We also constructed Kaplan-Meier survival curves and lifetable analyses to capture incidence rates over time, and 18-, 35-, 50-, and 65-year morbidity-free survivals were estimated for a follow-up from birth (**Figure 2**). Data illustrated that endocrine disease

and to a lesser extent osteoporosis emerge early in life, whereas cardiac, vascular, hepatic, and renal complications accumulate progressively with age, with the steepest declines in morbidity-free survival generally occurring after age 35-50 years. Leg ulcers and EMH masses tend to arise later in adulthood, while sepsis and cancer remain primarily diseases of the elderly.

These findings are biologically plausible and consistent with previous evidence linking chronic anemia and iron overload, two major yet often incompletely controlled drivers of disease burden, to the development of long-term complications in both NTDT and TDT.⁹

¹⁰ Even in high-resource settings, complete control of anemia and iron burden remains difficult to achieve, particularly over decades of follow-up, and therefore complications continue to emerge as patients age.⁸ Importantly, age remained an independent predictor of morbidity even after adjustment for other risk factors. This likely reflects not only cumulative exposure to disease-related insults but also the multifactorial nature of thalassemia, whereby older patients may carry legacy risks related to historical treatment practices, as well as age-related biological processes that interact with the underlying disease. Although not specifically evaluated in this study, it should be noted that as individuals with thalassemia live longer, they also face an increasing social and psychological burden related to lifelong disease management, cumulative complications, and evolving challenges in education, employment, relationships, and independence.

The present study demonstrates that β -thalassemia is associated with a progressive accumulation of multisystem morbidity across the lifespan. Age-specific estimates of

morbidity burden may help tailor screening strategies, reinforce vigilance for complications that become more prevalent at specific life stages, and facilitate earlier intervention and multidisciplinary care. More broadly, our results emphasize that optimizing conventional therapies throughout life remains essential and further strengthen the rationale for developing and implementing disease-modifying therapies at younger ages, before irreversible complications develop. The retrospective nature of the study and the relatively small number of patients at the youngest and oldest age strata are important limitations that may have overestimated prevalence rates in children and underestimated them in adults. Moreover, advances in standards of care over the several decades of patient follow-up, including morbidity monitoring, transfusion practices, iron chelation, and complication-specific treatments, may have influenced age-specific morbidity patterns independently of, or in addition to, the effects of chronological ageing. Nevertheless, the longitudinal design, the availability of follow-up data across adulthood, and the inclusion of morbidity incidence during early life provide a comprehensive view of how disease burden evolves across the lifespan in contemporary patients with β -thalassemia. Our findings from two European countries should be confirmed in other geographic regions.

REFERENCES

1. Giancesin B, Piel FB, Musallam KM, et al. Prevalence and mortality trends of hemoglobinopathies in Italy: a nationwide study. *Haematologica*. 2025;110(5):1211-1216.
2. Forni GL, Giancesin B, Musallam KM, et al. Overall and complication-free survival in a large cohort of patients with beta-thalassemia major followed over 50 years. *Am J Hematol*. 2023;98(3):381-387.
3. Pinto VM, Poggi M, Russo R, Giusti A, Forni GL. Management of the aging beta-thalassemia transfusion-dependent population - the Italian experience. *Blood Rev*. 2019;38:100594.
4. Delicou S, Aggeli C, Mani I, et al. Aging with thalassemia and sickle cell disease: a gerontological model of accelerated multimorbidity and function-centered care beyond midlife. *Mediterr J Hematol Infect Dis*. 2026;18(1):e2026039.
5. Taher AT, Musallam KM, El-Beshlawy A, et al. Age-related complications in treatment-naive patients with thalassaemia intermedia. *Br J Haematol*. 2010;150(4):486-489.
6. Delicou S, Xydaki A, Kamposou V, et al. Epidemiological and comorbidity burden in transfusion-dependent patients with thalassemia and sickle cell disease in Greece. *Ann Hematol*. 2026;105(3):95.
7. Teawtrakul N, Jetsrisuparb A, Pongudom S, et al. Epidemiologic study of major complications in adolescent and adult patients with thalassemia in Northeastern Thailand: the E-SAAN study phase I. *Hematology*. 2018;23(1):55-60.
8. Musallam KM, Vitrano A, Inzerillo A, et al. Impact of lifetime anaemia and iron control on outcomes in beta-thalassaemia: Data from the longitudinal de-LIGHT study. *Br J Haematol*. 2025;207(4):1578-1588.
9. Taher A, Musallam K, Cappellini MD. Guidelines for the management of non-transfusion-dependent β -thalassaemia. 3rd ed ed. Nicosia, Cyprus: Thalassaemia International Federation, 2023.
10. Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Guidelines for the management of transfusion-dependent β -thalassaemia. 5th ed ed. Nicosia, Cyprus: Thalassaemia International Federation 2025.

Table 1. Odds of morbidities with each 10-year increase in age.

Morbidity	OR for morbidity with each 10-year increase in age (95% CI)					
	All patients (n = 557)		NTDT (n = 150)		TDT (n = 407)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Cardiac	1.901 (1.593-2.269) p <0.001	1.782 (1.468-2.163) p <0.001	1.509 (1.172-1.944) p = 0.001	1.349 (1.022-1.779) p = 0.034	2.088 (1.585-2.751) p <0.001	2.321 (1.704-3.161) p <0.001
Vascular	2.346 (1.898-2.900) p <0.001	1.976 (1.582-2.468) p <0.001	1.776 (1.351-2.333) p <0.001	1.583 (1.179-2.126) p = 0.002	2.344 (1.654-3.321) p <0.001	2.248 (1.556-3.248) p <0.001
Hepatic	1.866 (1.582-2.201) p <0.001	1.666 (1.344-2.065) p <0.001	1.436 (1.101-1.873) p = 0.008	1.465 (1.041-2.060) p = 0.028	2.992 (2.242-3.993) p <0.001	2.984 (2.182-4.079) p <0.001
Endocrine	1.408 (1.240-1.599) p <0.001	1.492 (1.289-1.728) p <0.001	1.091 (0.874-1.362) p = 0.442	1.041 (0.818-1.327) p = 0.742	1.821 (1.511-2.196) p <0.001	1.983 (1.430-2.749) p <0.001
Osteoporosis	1.799 (1.554-2.802) p <0.001	1.833 (1.562-2.151) p <0.001	1.395 (1.103-1.766) p = 0.003	1.322 (1.028-1.700) p = 0.030	2.547 (2.031-3.193) p <0.001	2.686 (2.103-3.420) p <0.001
Renal	1.360 (1.126-1.642) p = 0.001	1.221 (1.005-1.484) p = 0.045	1.070 (0.806-1.419) p = 0.639	0.914 (0.664-1.258) p = 0.582	1.481 (1.106-1.985) p = 0.008	1.718 (1.253-2.355) p = 0.001
Sepsis	1.509 (1.002-2.274) p = 0.049	1.951 (1.175-3.240) p = 0.010	1.457 (0.823-2.580) p = 0.196	2.093 (0.815-5.375) p = 0.125	2.132 (0.903-5.034) p = 0.084	2.139 (1.039-4.404) p = 0.039
Leg ulcers	2.255 (1.649-3.084) p <0.001	2.540 (1.567-4.116) p <0.001	1.703 (1.155-2.510) p = 0.007	2.133 (1.155-3.939) p = 0.016	2.406 (1.303-4.442) p = 0.005	2.462 (1.111-5.475) p = 0.027
EMH masses	1.643 (1.314-2.054) p <0.001	1.837 (1.391-2.426) p <0.001	1.619 (1.055-2.485) p = 0.027	2.050 (1.151-3.650) p = 0.015	2.006 (1.434-2.808) p <0.001	2.136 (1.449-3.150) p <0.001
Cancer	1.438 (1.092-1.894) p = 0.010	1.598 (1.119-2.282) p = 0.010	1.418 (0.837-2.403) p = 0.194	2.044 (1.019-4.098) p = 0.044	1.627 (1.102-2.402) p = 0.014	1.554 (0.981-2.463) p = 0.061

*Adjusted for gender, center, splenectomy, lifetime hemoglobin level, and lifetime serum ferritin level for all morbidities, and additionally for hepatitis C virus infection for hepatic morbidity.

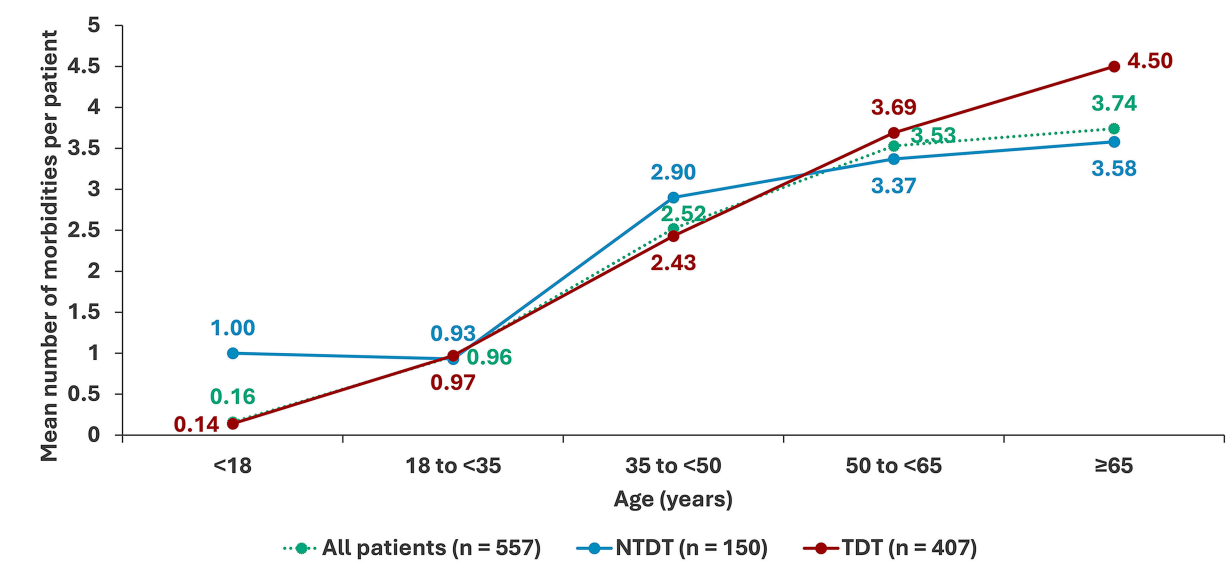
Abbreviations: EMH, extramedullary hematopoiesis; OR, odds ratio; CI, confidence interval.

FIGURE LEGENDS

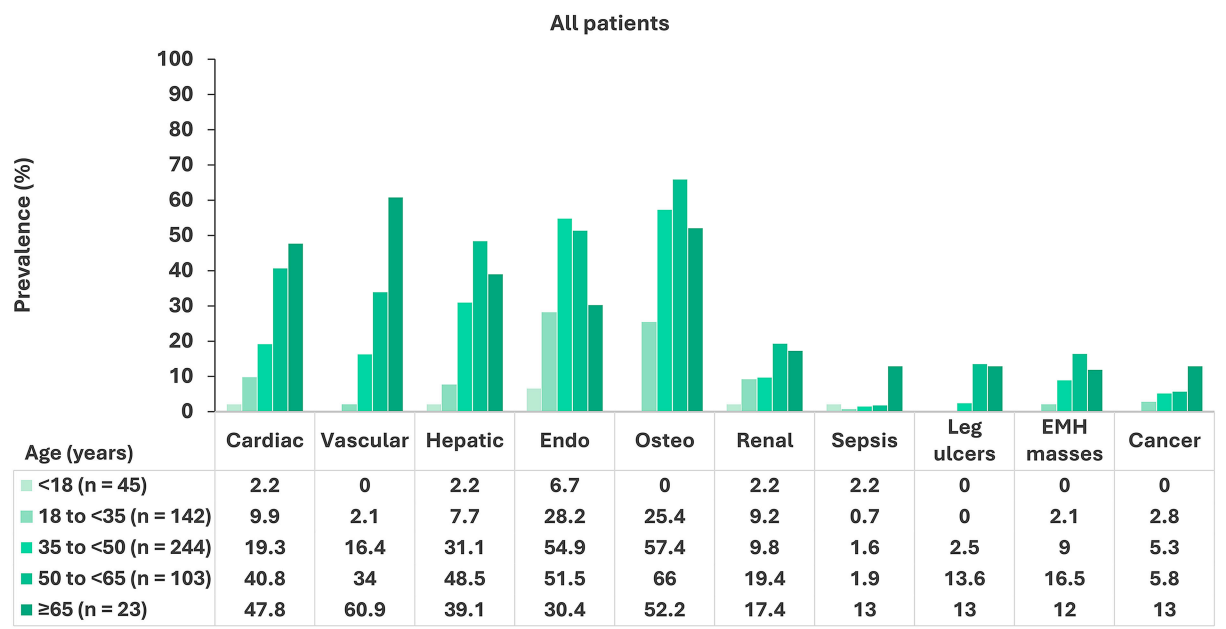
Figure 1. Prevalence of morbidities in β -thalassemia. Figures illustrate (A) the mean number of morbidities by age group for the overall population, NTDT, and TDT patients; and the prevalence of morbidities by age group in (B) the overall population (n = 557), (C) NTDT (n = 115), and (D) TDT (n = 407). Abbreviations: NTDT, non-transfusion-dependent β -thalassemia; TDT, transfusion-dependent β -thalassemia; Endo, endocrine; Osteo, osteoporosis; EMH, extramedullary hematopoiesis.

Figure 2. Cumulative morbidity-free survival from birth by achieved age for the overall population, NTDT, and TDT patients. Data extracted from Kaplan-Meier curves and life tables. Abbreviations: NTDT, non-transfusion-dependent β -thalassemia; TDT, transfusion-dependent β -thalassemia; EMH, extramedullary hematopoiesis.

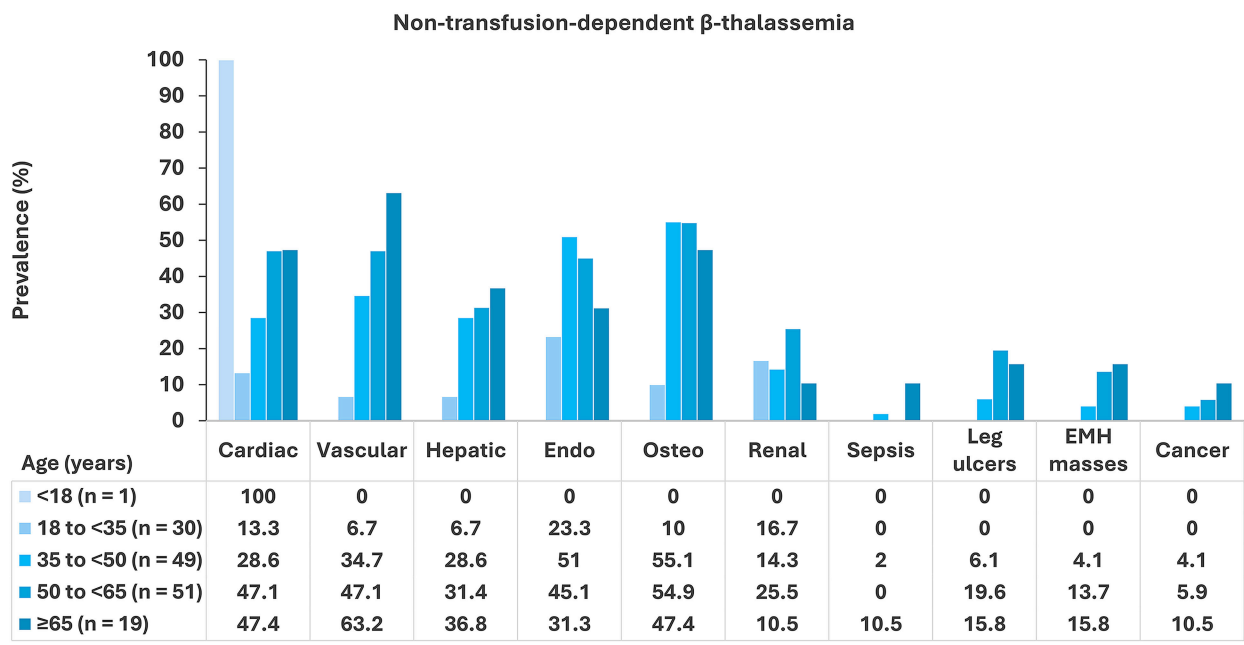
(A)



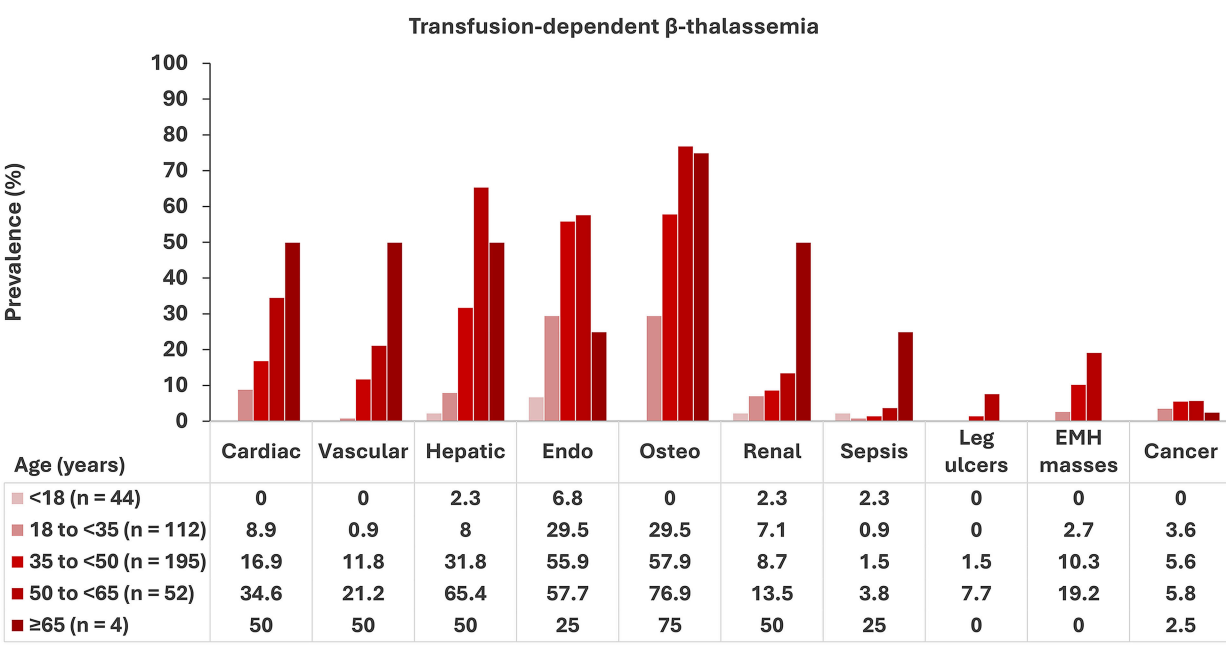
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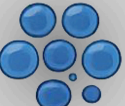


(C)



(D)



	Morbidity	Cumulative morbidity-free survival by achieved age (years)											
		All patients (n = 557)				NTDT (n = 150)				TDT (n = 407)			
		18	35	50	65	18	35	50	65	18	35	50	65
	Cardiac	97%	87%	68%	40%	97%	86%	64%	35%	97%	87%	70%	53%
	Vascular	99%	89%	74%	50%	99%	80%	60%	42%	99%	93%	84%	53%
	Hepatic	94%	82%	61%	43%	99%	87%	75%	55%	92%	80%	49%	33%
	Endocrine	78%	58%	48%	40%	87%	70%	58%	48%	74%	53%	41%	39%
	Osteoporosis	96%	64%	39%	23%	98%	74%	56%	38%	96%	60%	30%	16%
	Renal	99%	92%	84%	72%	99%	88%	79%	71%	98%	94%	87%	63%
	Sepsis	99%	98%	98%	90%	99%	99%	99%	94%	99%	98%	98%	64%
	Leg ulcers	100%	98%	93%	86%	100%	96%	88%	80%	100%	99%	95%	95%
	EMH masses	100%	97%	86%	79%	100%	99%	92%	87%	100%	96%	82%	70%
	Cancer	100%	98%	93%	86%	100%	98%	97%	92%	100%	98%	91%	69%

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SUPPLEMENTAL TABLES**Table S1.** Prevalence of risk factors and morbidities by age group in the overall population (n = 557).

Variable	Age (years)				
	<18 (n = 45)	18 to <35 (n = 142)	35 to <50 (n = 244)	50 to <65 (n = 103)	≥65 (n = 23)
Female, n (%)	21 (46.7)	78 (54.9)	124 (50.8)	63 (61.2)	12 (52.2)
Splenectomy, n (%)	1 (2.2)	64 (45.1)	139 (57.0)	87 (84.5)	10 (43.5)
HCV infection, n (%)	0 (0.0)	10 (7.0)	121 (49.6)	72 (69.9)	7 (30.4)
Hb in g/dL, median	9.8	9.6	9.7	9.3	8.8
SF in ng/mL, median	1392.7	1486.7	1369.6	973.0	1022.4
Morbidity, n (%)					
Cardiac	1 (2.2)	14 (9.9)	47 (19.3)	42 (40.8)	11 (47.8)
Left-sided heart failure	1 (2.2)	11 (7.7)	23 (9.4)	22 (21.4)	7 (30.4)
Right-sided heart failure	0 (0.0)	3 (2.1)	9 (3.7)	9 (8.7)	4 (17.4)
Arrhythmia	0 (0.0)	2 (1.4)	32 (13.1)	25 (24.3)	7 (30.4)
Vascular	0 (0.0)	3 (2.1)	4 (16.4)	35 (34.0)	14 (60.9)
Myocardial infarction	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.0)	1 (4.3)
Pulmonary hypertension	0 (0.0)	1 (0.7)	14 (5.7)	11 (10.7)	7 (30.4)
Peripheral vascular disease	0 (0.0)	0 (0.0)	4 (1.6)	6 (5.8)	4 (17.4)
Venous thrombosis	0 (0.0)	1 (0.7)	8 (3.3)	8 (7.8)	2 (8.7)
Arterial thrombosis	0 (0.0)	1 (0.7)	6 (2.5)	9 (8.7)	2 (8.7)
Stroke	0 (0.0)	0 (0.0)	8 (3.3)	4 (3.9)	2 (8.7)
Hepatic	1 (2.2)	11 (7.7)	76 (31.1)	50 (48.5)	9 (39.1)
Liver fibrosis or cirrhosis	1 (2.2)	6 (4.2)	74 (30.3)	48 (46.6)	7 (30.4)
HCC	0 (0.0)	2 (1.4)	3 (1.2)	5 (4.9)	3 (13.0)
Other liver disease	0 (0.0)	3 (2.1)	2 (0.8)	2 (1.9)	3 (13.0)
Endocrine	3 (6.7)	40 (28.2)	134 (54.9)	53 (51.5)	7 (30.4)
Diabetes	1 (2.2)	7 (4.9)	27 (11.1)	25 (24.3)	5 (21.7)
Hypothyroidism	2 (4.4)	16 (11.3)	71 (29.1)	21 (20.4)	2 (8.7)
Hypoparathyroidism	0 (0.0)	2 (1.4)	19 (7.8)	8 (7.8)	0 (0.0)
Hypogonadism	0 (0.0)	24 (16.9)	105 (43.0)	33 (32.0)	2 (8.7)
Osteoporosis	0 (0.0)	36 (25.4)	140 (57.4)	68 (66.0)	12 (52.2)
Renal	1 (2.2)	13 (9.2)	24 (9.8)	20 (19.4)	4 (17.4)
Nephropathy	1 (2.2)	12 (8.5)	23 (9.4)	17 (16.5)	4 (17.4)
ESRD on dialysis	0 (0.0)	1 (0.7)	2 (0.8)	3 (2.9)	0 (0.0)
Sepsis	1 (2.2)	1 (0.7)	4 (1.6)	2 (1.9)	3 (13.0)
Leg ulcers	0 (0.0)	0 (0.0)	6 (2.5)	14 (13.6)	3 (13.0)
EMH masses	0 (0.0)	3 (2.1)	22 (9.0)	17 (16.5)	3 (13.0)
Cancer	0 (0.0)	4 (2.8)	13 (5.3)	6 (5.8)	3 (13.0)

Abbreviations: HCV, hepatitis C virus; Hb, hemoglobin (lifetime); SF, serum ferritin (lifetime); HCC, hepatocellular carcinoma; ESRD, end-stage renal disease; EMH, extramedullary hematopoiesis.

Table S2. Prevalence of risk factors and morbidities by age group in non-transfusion-dependent β -thalassemia patients (n = 150).

Variable	Age (years)				
	<18 (n = 1)	18 to <35 (n = 30)	35 to <50 (n = 49)	50 to <65 (n = 51)	≥ 65 (n = 19)
Female, n (%)	0 (0.0)	12 (40.0)	24 (49.0)	34 (66.7)	9 (47.4)
Splenectomy, n (%)	0 (0.0)	11 (36.7)	31 (63.3)	44 (86.3)	9 (47.4)
HCV infection, n (%)	0 (0.0)	1 (3.3)	25 (51.0)	28 (54.9)	6 (31.6)
Hb in g/dL, median	9.5	9.2	9.4	9.2	8.8
SF in ng/mL, median	1661.0	726.9	692.4	723.0	964.2
Morbidity, n (%)					
Cardiac	1 (100.0)	4 (13.3)	14 (28.6)	24 (47.1)	9 (47.4)
Left-sided heart failure	1 (100.0)	3 (10.0)	10 (20.4)	16 (31.4)	7 (36.8)
Right-sided heart failure	0 (0.0)	2 (6.7)	5 (10.2)	7 (13.7)	4 (21.1)
Arrhythmia	0 (0.0)	0 (0.0)	9 (18.4)	10 (19.6)	5 (26.3)
Vascular	0 (0.0)	2 (6.7)	17 (34.7)	24 (47.1)	12 (63.2)
Myocardial infarction	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	1 (5.3)
Pulmonary hypertension	0 (0.0)	0 (0.0)	5 (10.2)	8 (15.7)	6 (31.6)
Peripheral vascular disease	0 (0.0)	0 (0.0)	1 (2.0)	3 (5.9)	4 (21.1)
Venous thrombosis	0 (0.0)	1 (3.3)	3 (6.1)	4 (7.8)	1 (5.3)
Arterial thrombosis	0 (0.0)	1 (3.3)	3 (6.1)	8 (15.7)	1 (5.3)
Stroke	0 (0.0)	0 (0.0)	6 (12.2)	3 (5.9)	1 (5.3)
Hepatic	0 (0.0)	2 (6.7)	14 (28.6)	61 (31.4)	7 (36.8)
Liver fibrosis or cirrhosis	0 (0.0)	1 (3.3)	13 (26.5)	14 (27.5)	5 (26.3)
HCC	0 (0.0)	0 (0.0)	1 (2.0)	2 (3.9)	2 (10.5)
Other liver disease	0 (0.0)	1 (3.3)	0 (0.0)	2 (3.9)	2 (10.5)
Endocrine	0 (0.0)	7 (23.3)	25 (51.0)	23 (45.1)	6 (31.3)
Diabetes	0 (0.0)	1 (3.3)	5 (10.2)	12 (23.5)	4 (21.1)
Hypothyroidism	0 (0.0)	3 (10.0)	14 (28.6)	9 (17.6)	2 (10.5)
Hypoparathyroidism	0 (0.0)	1 (3.3)	5 (10.2)	3 (5.9)	0 (0.0)
Hypogonadism	0 (0.0)	5 (16.7)	20 (40.8)	10 (19.6)	2 (10.5)
Osteoporosis	0 (0.0)	3 (10.0)	27 (55.1)	28 (54.9)	9 (47.4)
Renal	0 (0.0)	5 (16.7)	7 (14.3)	13 (25.5)	2 (10.5)
Nephropathy	0 (0.0)	5 (16.7)	6 (12.2)	11 (21.6)	2 (10.5)
ESRD on dialysis	0 (0.0)	0 (0.0)	1 (2.0)	2 (3.9)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	2 (10.5)
Leg ulcers	0 (0.0)	0 (0.0)	3 (6.1)	10 (19.6)	3 (15.8)
EMH masses	0 (0.0)	0 (0.0)	2 (4.1)	7 (13.7)	3 (15.8)
Cancer	0 (0.0)	0 (0.0)	2 (4.1)	3 (5.9)	2 (10.5)

Abbreviations: HCV, hepatitis C virus; Hb, hemoglobin (lifetime); SF, serum ferritin (lifetime); HCC, hepatocellular carcinoma; ESRD, end-stage renal disease; EMH, extramedullary hematopoiesis.

Table S3. Prevalence of risk factors and morbidities by age group in transfusion-dependent β -thalassemia patients (n = 407).

Variable	Age (years)				
	<18 (n = 44)	18 to <35 (n = 112)	35 to <50 (n = 195)	50 to <65 (n = 52)	≥ 65 (n = 4)
Female, n (%)	23 (52.3)	52 (46.4)	95 (48.7)	29 (55.8)	3 (75.0)
Splenectomy, n (%)	1 (2.3)	53 (47.3)	108 (55.4)	43 (82.7)	1 (25.0)
HCV infection, n (%)	0 (0.0)	9 (8.0)	96 (49.2)	44 (84.6)	1 (25.0)
Hb in g/dL, median	9.8	9.7	9.7	9.5	8.8
SF in ng/mL, median	1387.3	1595.1	1491.7	1128.0	1142.7
Morbidity, n (%)					
Cardiac	0 (0.0)	10 (8.9)	33 (16.9)	18 (34.6)	2 (50.0)
Left-sided heart failure	0 (0.0)	8 (7.1)	13 (6.7)	6 (11.5)	0 (0.0)
Right-sided heart failure	0 (0.0)	1 (0.9)	4 (2.1)	2 (3.8)	0 (0.0)
Arrhythmia	0 (0.0)	2 (1.8)	23 (11.8)	15 (28.8)	2 (50.0)
Vascular	0 (0.0)	1 (0.9)	23 (11.8)	11 (21.2)	2 (50.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Pulmonary hypertension	0 (0.0)	1 (0.9)	9 (4.6)	3 (5.8)	1 (25.0)
Peripheral vascular disease	0 (0.0)	0 (0.0)	3 (1.5)	3 (5.8)	0 (0.0)
Venous thrombosis	0 (0.0)	0 (0.0)	5 (2.6)	4 (7.7)	1 (25.0)
Arterial thrombosis	0 (0.0)	0 (0.0)	3 (1.5)	1 (1.9)	1 (25.0)
Stroke	0 (0.0)	0 (0.0)	2 (1.0)	1 (1.9)	1 (25.0)
Hepatic	1 (2.3)	9 (8.0)	62 (31.8)	34 (65.4)	2 (50.0)
Liver fibrosis or cirrhosis	1 (2.3)	5 (4.5)	61 (31.3)	34 (65.4)	2 (50.0)
HCC	0 (0.0)	2 (1.8)	2 (1.0)	3 (5.8)	1 (25.0)
Other liver disease	0 (0.0)	2 (1.8)	2 (1.0)	0 (0.0)	1 (25.0)
Endocrine	3 (6.8)	33 (29.5)	109 (55.9)	30 (57.7)	1 (25.0)
Diabetes	1 (2.3)	6 (5.4)	22 (11.3)	13 (25.0)	1 (25.0)
Hypothyroidism	2 (4.5)	13 (11.6)	57 (29.9)	12 (23.1)	0 (0.0)
Hypoparathyroidism	0 (0.0)	1 (0.9)	14 (7.2)	5 (9.6)	0 (0.0)
Hypogonadism	0 (0.0)	19 (17.0)	85 (43.6)	23 (44.2)	0 (0.0)
Osteoporosis	0 (0.0)	33 (29.5)	113 (57.9)	40 (76.9)	3 (75.0)
Renal	1 (2.3)	8 (7.1)	17 (8.7)	7 (13.5)	2 (50.0)
Nephropathy	1 (2.3)	7 (6.2)	17 (8.7)	6 (11.5)	2 (50.0)
ESRD on dialysis	0 (0.0)	1 (0.9)	1 (0.5)	1 (1.9)	0 (0.0)
Sepsis	1 (2.3)	1 (0.9)	3 (1.5)	2 (3.8)	1 (25.0)
Leg ulcers	0 (0.0)	0 (0.0)	3 (1.5)	4 (7.7)	0 (0.0)
EMH masses	0 (0.0)	3 (2.7)	20 (10.3)	10 (19.2)	0 (0.0)
Cancer	0 (0.0)	4 (3.6)	11 (5.6)	3 (5.8)	1 (25.0)

Abbreviations: HCV, hepatitis C virus; Hb, hemoglobin (lifetime); SF, serum ferritin (lifetime); HCC, hepatocellular carcinoma; ESRD, end-stage renal disease; EMH, extramedullary hematopoiesis.