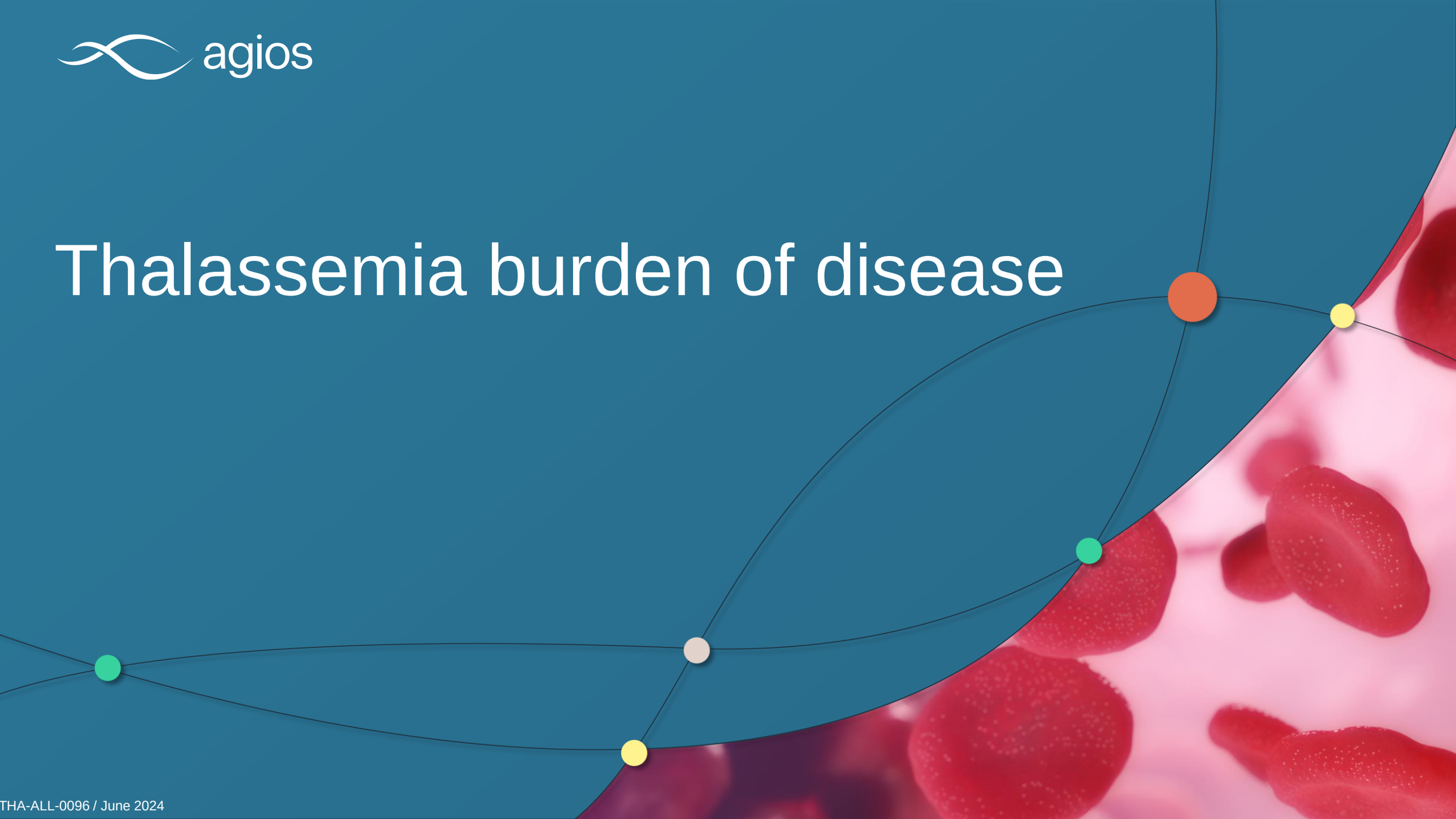
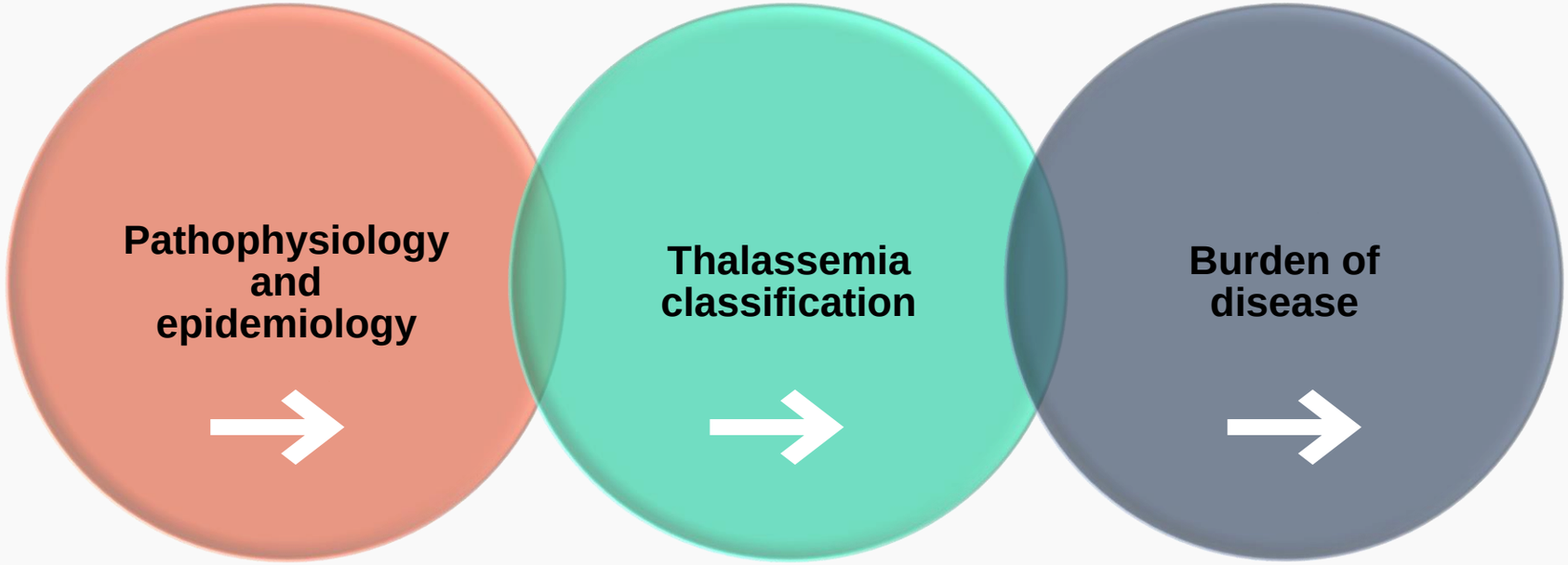
Thalassemia burden of disease

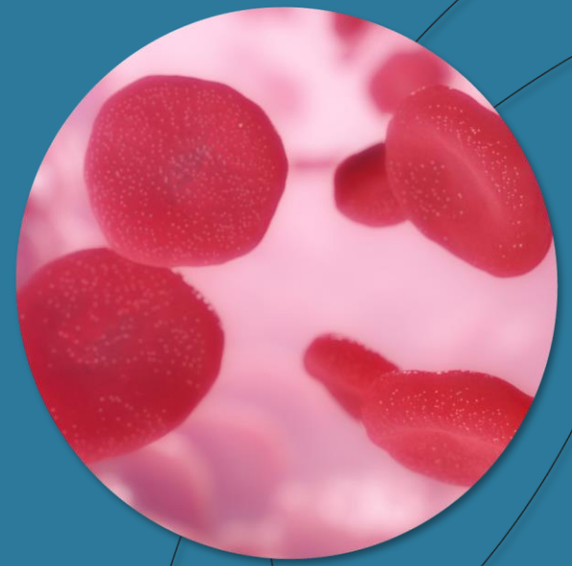


Thalassemias are…

…a group of recessively inherited disorders caused by an imbalance of globin chains; excess globin chains aggregate and damage red blood cells, leading to ineffective erythropoiesis, hemolysis, and chronic anemia



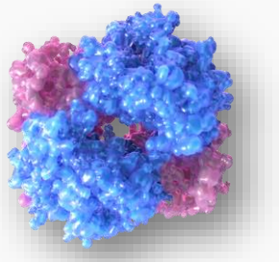
Pathophysiology and epidemiology



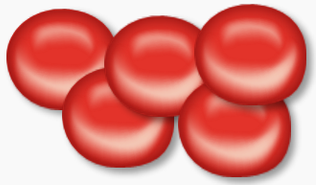
Structure and function of hemoglobin: Overview

- **Hemoglobin** (Hb) is a tetramer, consisting of 4 protein sub-units or globin chains[1]
- 95% of adult Hb (hemoglobin A [HbA]) contains **2 α- and 2 β-globin chains** that are similar in structure and size[1,2]
- Hb's main function is to bind and release oxygen in a cooperative interaction, thereby transporting oxygen from the lung to the tissues[2]
- **Iron** and **bilirubin** are metabolites of hemoglobin[3]
  - The breakdown of heme and recycling of iron are critically important to erythropoiesis[1–3]

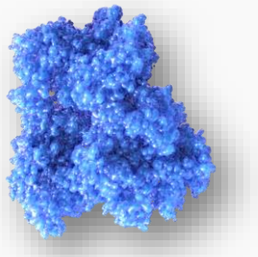
HbA

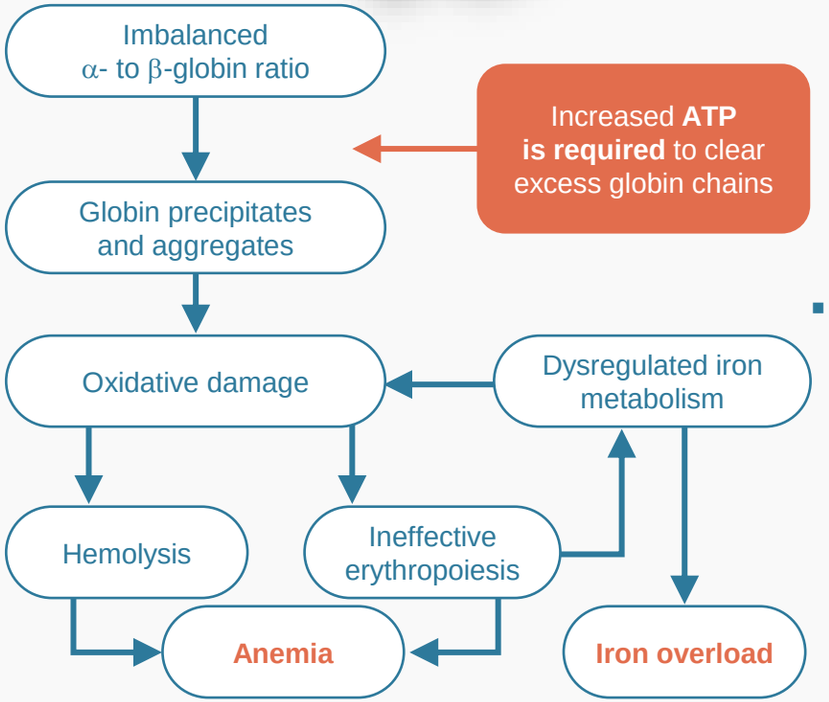


Healthy RBCs



Abnormal Hb in thalassemia





- Abnormal Hb compromises the health of red blood cell (RBC) precursors and RBCs[4]
- Imbalanced **α- and β-globin chains** form insoluble aggregates that cause[4–6]:
  - **Disruption of cell membrane**
  - **Formation of reactive oxygen species (ROS)**
  - **Oxidative stress and cell damage**
- This leads to[4–5]:
  - **Hemolysis**
  - **Ineffective erythropoiesis (IE)**

Hb, hemoglobin; HbA, hemoglobin A; IE, ineffective erythropoiesis; RBC, red blood cell, ROS, reactive oxygen species

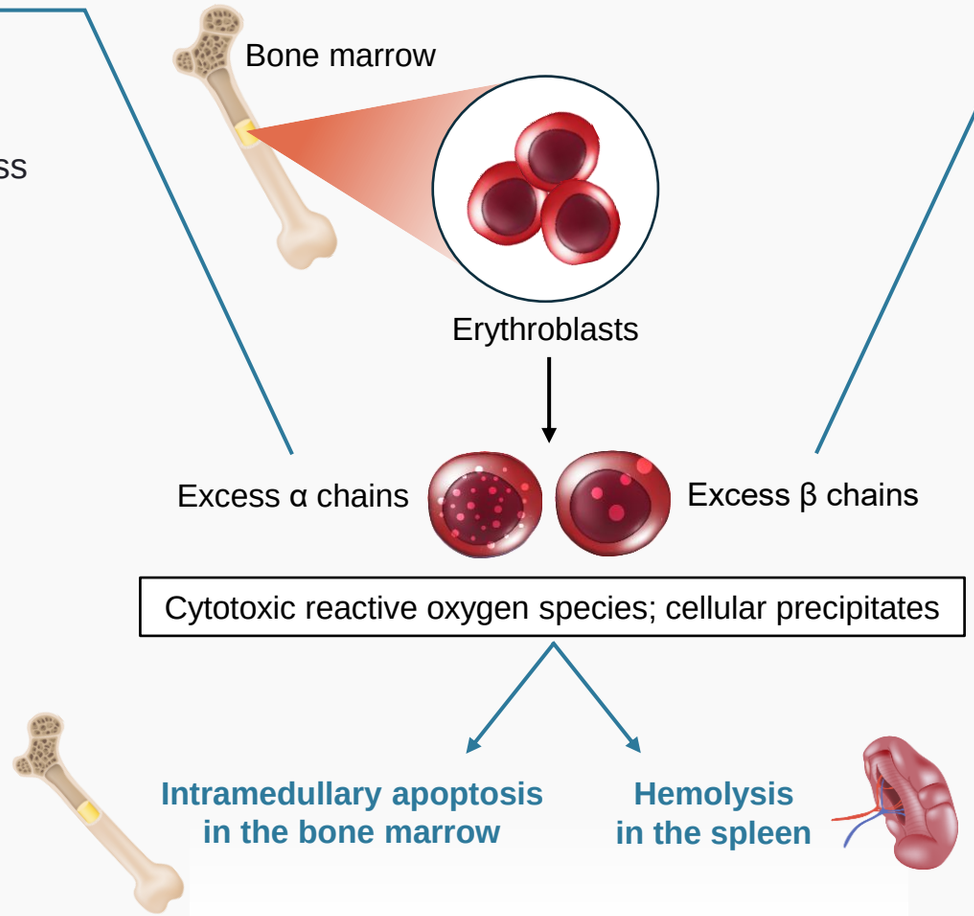
1. Farid Y, et al. Biochemistry, Hemoglobin Synthesis, StatPearls 2022; 2. Ahmed MH. *Subcell Biochem* 2020;94:345–82; 3. Kalakonda A, et al. Physiology, Bilirubin, StatPearls 2021; 4. Cappellini MD, et al. *Blood Rev* 2018;32:300–11; 5. Harewood J, Azevedo AM. 2022. In: StatPearls [Internet]. Treasure Island (FL); 6. Nienhus AW, Nathan DG. *Cold Spring Harb Perspect Med* 2012;2:a011726.

IE and chronic hemolysis are pathologic drivers of anemia in thalassemia

Mechanism of IE and hemolysis in thalassemia[1–3]

β-thalassemia[1–5]

- Decrease or loss of β-globin chain production[1]
- Excessive unstable α-globin chains, less soluble than β-tetramers seen in α-thalassemia
- α-globin chains precipitate in erythroid precursors as well as mature RBCs, leading to IE and the generation of defective RBC precursors, seen in:
  - Intramedullary apoptosis of late-stage erythroblasts
  - Extramedullary hemolysis due to the presence of insoluble α-globin chains in circulating cells



α-thalassemia[6–9*]

- Decrease or loss of α-globin chain production or impaired function
- Excess unbound β-globin chains and accumulation of unstable β-tetramers (also called hemoglobin H [HbH] tetramers)
- Apoptosis of maturing nucleated erythroid cells and IE
- **Non-deletional**
  - Inheritance of 2 deleted genes and 1 gene carrying a non-deletional abnormality (ie, point mutation) that disrupts normal α-globin chain formation
  - Results in unstable hemoglobin that precipitates in RBCs, forming insoluble inclusion bodies that damage and/or destroy the cell membrane
  - In non-deletional HbH disease, intramedullary death of erythroblasts leads to IE
- **Deletional**
  - HbH tetramers are soluble and do not aggregate during erythropoiesis, but are present in mature RBCs, leading to hemolysis

*γ-globin tetramers, called Hb Bart's, are mostly found *in utero* and in neonates[9]

IE leads to cell death either within the marrow (apoptosis) or cell death outside the marrow (hemolysis)[10,11]

HbH, hemoglobin H; IE, ineffective erythropoiesis; RBC, red blood cell

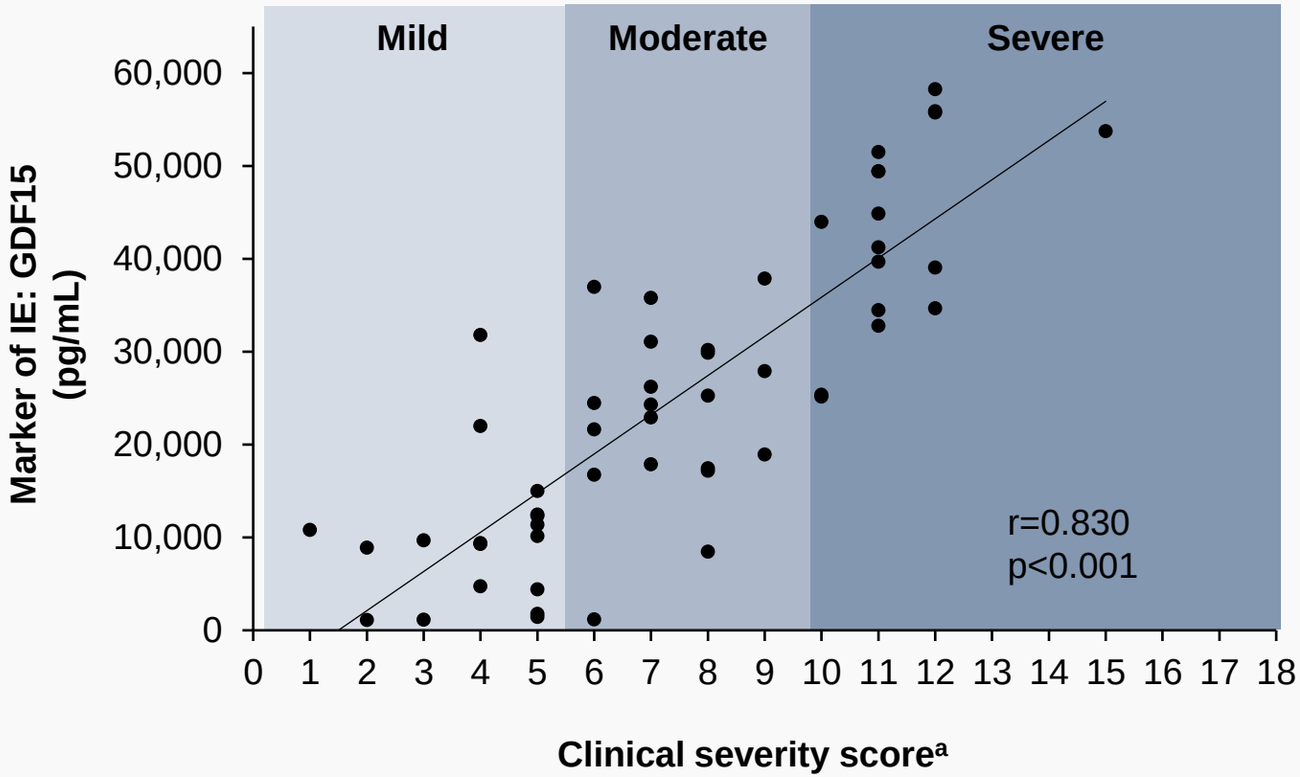
1. Rachmilewitz EA, et al. *Blood* 2011;118(13):3479–88; 2. Taher A, et al. *N Engl J Med* 2021;384(8):727–43; 3. Bajwa H, et al. StatPearls [Internet]. StatPearls Publishing. 2023; 4. Khandros E, et al. *Blood* 2012;119(22):5265–75; 5. Sorenson S, et al. *Blood* 1990;75(6):1333–36; 6. Harewood J, et al. StatPearls [Internet]. StatPearls Publishing. 2023; 7. Kalle Kwaifa I, et al. *Orphanet J Rare Dis* 2020;15:166; 8. Taher A, et al. *Lancet*. 2018;391(10116):155–67; 9. Vichinsky EP, et al. *Cold Spring Harb Perspect Med* 2013;3(5):a011742; 10. Rivella S. *Curr Opin Hematol* 2009;16(3):187–94; 11. Centis F, et al. *Blood* 2000;96(10):3624–29.

NTD β-thal

Severity of IE correlates with clinical morbidity in NTDT

- Morbidity in patients with **NTD β-thalassemia** is directly proportional to the severity of IE and peripheral hemolysis[1,2]
- Strong positive correlation was reported between a marker of IE (GDF15 levels) and the severity score in patients with **β-thalassemia intermedia**[1]
  - GDF15 in patients with **β-thalassemia intermedia** was considerably higher than those reported in patients with other congenital and acquired anemias[1]

Correlation between a marker of IE and clinical severity score in β-thalassemia intermedia[1]



Levels of a marker of IE (GDF15) correlated with anemia, markers of iron overload, and a pre-defined clinical severity score[1]

[a]Severity score is a combination of age, iron overload status, splenectomy, and number of clinical morbidities
GDF15, growth differentiation factor15; IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia
1. Musallam KM, et al. *Blood Cells Mol Dis* 2011;47:232–34; 2. Musallam KM, et al. *Haematologica* 2013;98(6):833–44. Figure reprinted from Musallam KM et al. *Blood Cells Mol Dis* 2011, Copyright (2024), with permission from Elsevier.

Global prevalence of thalassemia

- A global systematic literature review on the prevalence of clinically significant forms of **α-thalassemia** and **β-thalassemia** found that:
  - The estimated prevalence of thalassemia was higher in the **Middle East**, **Asia**, and **Mediterranean** than in **Europe** or **North America**
  - Population-based prevalence estimates were **not available** for many countries, and there was **heterogeneity** in case definitions, **diagnostic methodology**, **type of thalassemia** reported, and details on **transfusion requirements**

To fully understand the global prevalence of thalassemia, up-to-date, population-based epidemiologic data are needed for many countries

Musallam KM, et al. *Am J Hematol* 2023;98(9):1436–51.

Pathophysiology and epidemiology: Key takeaways

Thalassemias are a recessively inherited group of disorders of Hb production with a wide range of clinical severity, and they are classified into α-thalassemia or β-thalassemia depending on the affected globin gene[1–4]

In β-thalassemia, impaired production of β-globin leads to accumulation of unstable α-globin chain tetramers in RBCs, which causes the formation of ROS and results in oxidative stress; this damages RBC membranes, resulting in ineffective erythropoiesis and hemolysis[4–6]

In α-thalassemia, underproduction of α-globin chains gives rise to excess β-globin chains, which form β4 tetramers, or HbH[2,4]

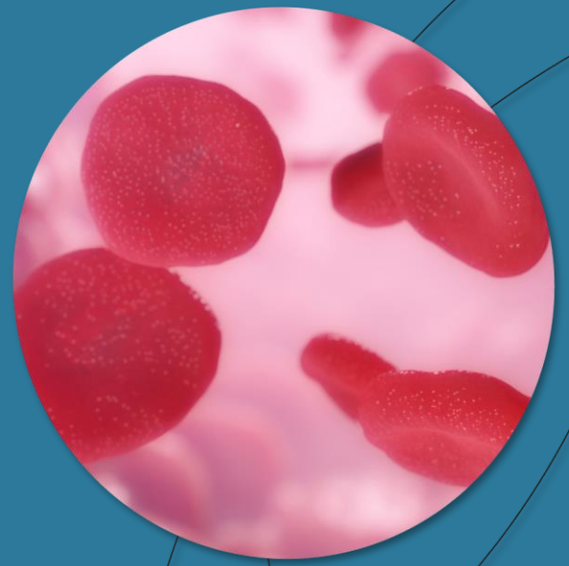
IE and chronic hemolysis are the primary direct consequences of thalassemia, which result in anemia[2,4]

Thalassemia is a rare, under-recognized disease, with geographic variation in its prevalence[7]

Hb, hemoglobin; HbH, hemoglobin H; IE, ineffective erythropoiesis; RBC, red blood cell; ROS, reactive oxygen species

1. Cappellini MD, et al. *Blood Rev* 2018;32:300–11; 2. Harewood J, Azevedo AM. 2022. In: StatPearls [Internet]. Treasure Island (FL); 3. Nienhus AW, Nathan DG. *Cold Spring Harb Perspect Med* 2012;2:a011726;
4. Taher A, et al. *Lancet*.2018;391(10116):155–67; 5. Taher A, et al. *N Engl J Med* 2021;384(8):727–43; 6. Kattamis A, et al. *Lancet* 2022;399(10343):2310–24; 7. Musallam KM, et al. *Am J Hematol* 2023;98(9):1436–51.

Thalassemia classification



Classification and transfusion requirements

- Thalassemia is now often classified phenotypically into 2 main groups[1–3]:
  - **Non–transfusion-dependent thalassemia (NTDT)**
  - **Transfusion-dependent thalassemia (TDT)**
- This classification moves away from the terms **thalassemia trait/minor**, **thalassemia intermedia** (TI), or **thalassemia major** (TM) used traditionally[1,2]
- However, the distinction between **NTDT** and **TDT** is fluid; **transfusion frequency is not always a measure of underlying disease severity**[2]

NTDT[2]

Patients do not require regular transfusion therapy for survival

TDT[1]

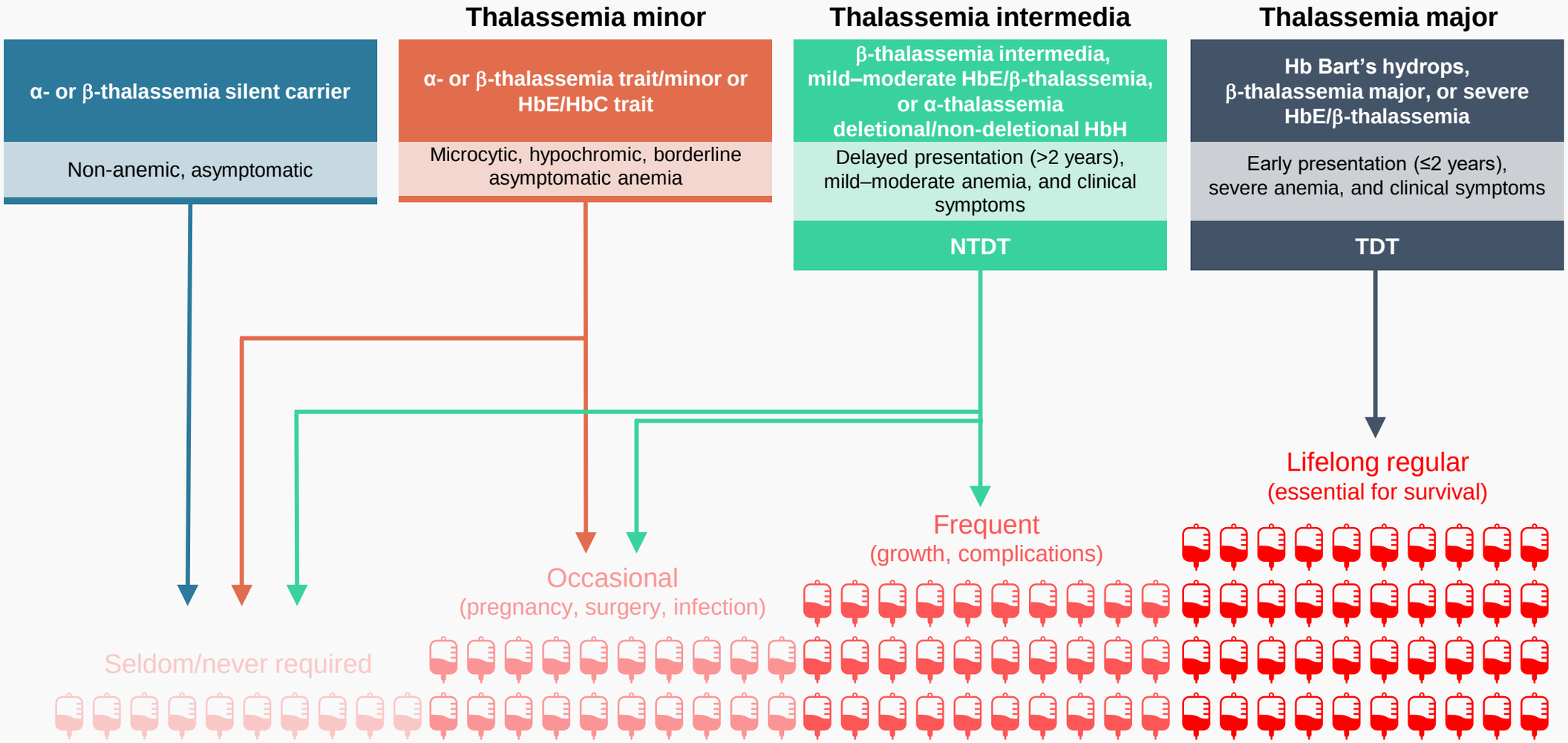
Patients are not capable of producing sufficient Hb to survive without regular RBC transfusions

- **Transfusion requirements and frequency** may change over time due to age-specific factors and the changing biology of the patient[2–4]
- **Non-biologic factors** can also impact the decision to transfuse and the frequency of transfusions[2,3]
  - Patient preferences
  - Variations across regions, practices, and healthcare professionals (eg, access to and cost of healthcare resources, management approaches, disease education)
  - Changes in management approaches over time

Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia; RBC, red blood cell; TDT, transfusion-dependent thalassemia; TI, thalassemia intermedia; TM, thalassemia major

1. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023; 2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023; 3. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023; 4. Musallam KM, et al. *Am J Hematol* 2021;96(2):E56–58.

Transfusion burden across thalassemias[1–4]



Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia

1. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023. Accessed Dec 2023. Modified with permission from the Thalassemia International Federation; 2. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/ Accessed Dec 2023; 3. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/ Accessed Dec 2023; 4. Viprakasit V, Ekwattanakit S. *Hematol Oncol Clin North Am* 2018;32:193–211.

Thalassemia classification: Key takeaways

Traditionally both α- or β-thalassemia have been categorized as minor, intermedia, or major[1,2]

Thalassemia is now commonly categorized as NTDT or TDT, as transfusion requirements typically reflect the underlying pathophysiology[1–3]

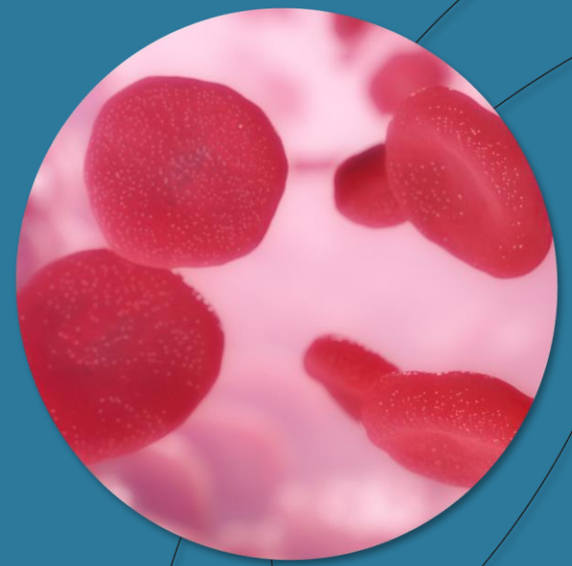
Transfusion requirements and frequency may change over time depending on the disease progression and availability of treatment options[1–4]

Strict classifications may deny the underlying biology of the disease[2]

NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia

1. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023; 2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce% Accessed Dec 2023; 3. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/ Accessed Dec 2023; 4. Musallam KM, et al. *Am J Hematol* 2021;96(2):E54–56.

Burden of disease



Thalassemia complications: Overview

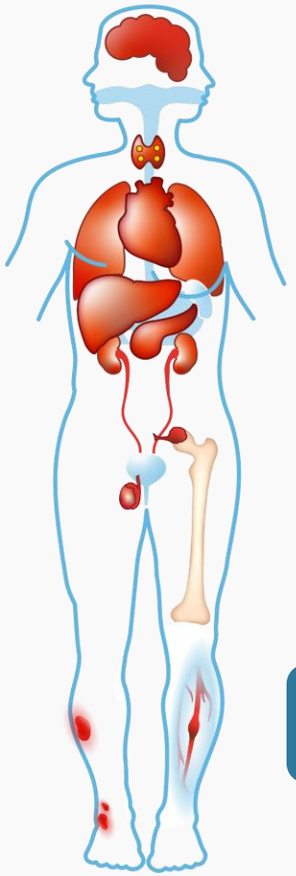
Build slide

α- and β-thalassemia risk factors

- Hemolysis
- Anemia
- Hypercoagulability
- 1° Iron overload
- 2° Iron overload

Treatments

- Splenectomy
- Transfusions
- Iron chelation



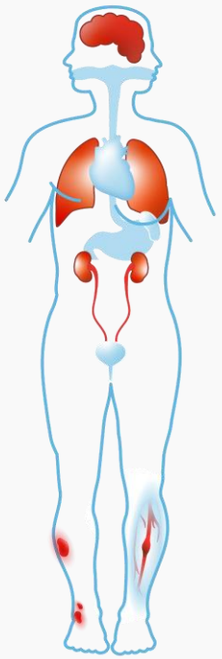
- Infections
- Facial & bone deformities
- Extramedullary hematopoietic pseudotumors
- Endocrinopathy
- Thrombosis & vascular events
- Growth & pubertal delay
- PHT & right heart failure
- Cardiac failure & arrhythmia
- Hepatosplenomegaly
- Liver fibrosis, cirrhosis, & HCC
- Hyperbilirubinemia & gallstones
- Renal complications
- Leg ulcers
- Iron chelator side effects
- Cancers
- Osteoporosis & bone disease
- Viral hepatitis

HCC, hepatocellular carcinoma; PHT, pulmonary hypertension

Modified from Taher A, et al. *N Engl J Med* 2021;384:727–43; Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/ Accessed Dec 2023;Viprakasit V, et al. *Orphanet J Rare Dis* 2014;9:131; Viprakasit V, Ekwattanakit S. *Hematol Oncol Clin N Am* 2018;32:193–211.

Complications of HbH disease are associated with the severity of chronic anemia[1,2]

Characteristic and complications	α-thalassemia syndromes (deletional HbH and non-deletional HbH)
Presenting age (years)	Usually >2
Presenting Hb level (g/dL)	8–11
HbF (%)	Not raised, but HbH (β_4) and Hb Bart's (Y_4) present
HbA2/HbE (%)	<2
Jaundice	■■■■
Growth retardation	■
Bone and skeletal abnormalities	■■■■
Splenomegaly	■■
Leg ulcers	■
Cholelithiasis	■■
Acute hemolytic episodes	■■■
Thrombotic events	■
Extramedullary hematopoiesis	■
Pulmonary hypertension	■



No. of ■ represents frequency of occurrence (%)

■ 0–10
■■ 10–30
■■■ 30–60
■■■■ 60–100

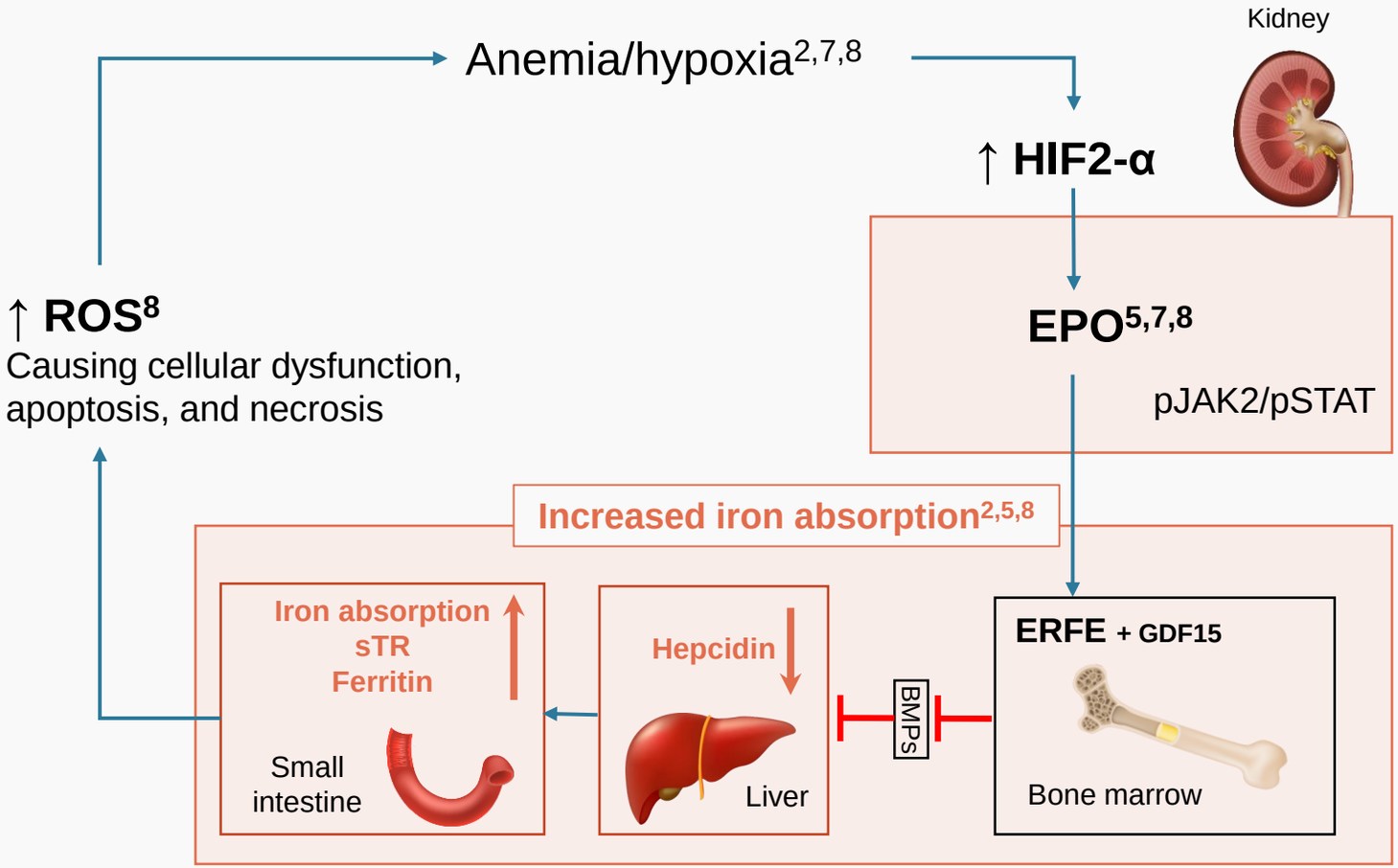
Hb, hemoglobin; HbA, hemoglobin A; HbE, hemoglobin E; HbF, fetal hemoglobin; HbH, hemoglobin H

1. Viprakasit V, et al. *Orphanet J Rare Dis* 2014;9:131. Table used with permission, DOI: 10.1186/s13023-014-0131-7; 2. Taher A, et al. *Vox Sang* 2014;108:1–10.

Iron loading anemia is triggered by IE

- In response to **hypoxia** and **HIF2-α**, increased **EPO** released from the kidney suppresses hepcidin via **ERFE** secretion from erythroblasts in the marrow[1–4]
  - **GDF15** is another stress erythropoiesis factor that is being investigated in regulating production of hepcidin[5]
  - Excessive iron can also cause the generation of **ROS**, which may further damage cellular components and contribute to hypoxia[6]

Iron loading and erythropoiesis[2,5,7,8]

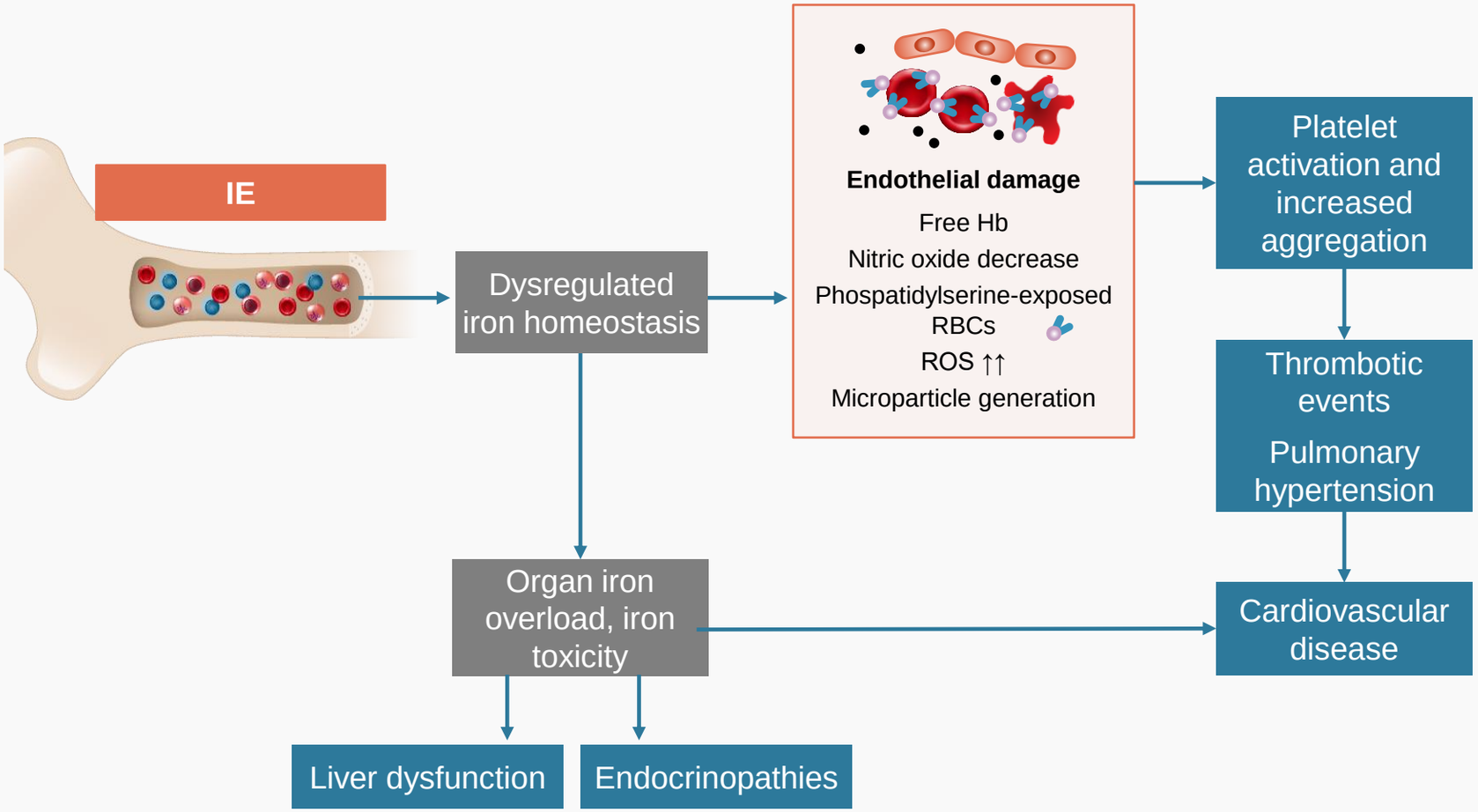


EPO, erythropoietin; ERFE, erythroferrone; GDF15, growth differentiation factor 15; HIF2α, hypoxia inducible factor 2α; IE, ineffective erythropoiesis; pJAK2, phosphorylated Janus activating kinase 2; pSTAT, phosphorylated signal transducer and activator of transcription; ROS, reactive oxygen species; sTR, soluble transferrin

1. Scortegagna M, et al. *Blood* 2005;105(8):3133–40; 2. Kautz L, et al. *Nat Genet* 2014;46(7):678–84; 3. Nicolas G, et al. *J Clin Invest* 2002;110(7):1037–44; 4. Pak M, et al. *Blood* 2006;108(12):3730–35; 5. Tanno T, et al. *Nat Med* 2007;13(9):1096–101; 6. Jin X, et al. *Haematologica* 2018;103(10):1627–34; 7. Gupta R, et al. *Hematol Oncol Clin North Am* 2018;32(2):213–21; 8. Saad HKM, et al. *Biomedicines* 2022;10(1):189.

IE contributes to iron overload, which drives multiple downstream complications in thalassemia

IE and iron overload in thalassemia[1]



- Iron overload can lead to cardiac dysfunction, liver dysfunction, including fibrosis, cirrhosis, or endocrinopathies[1,2]
- Excessive iron deposits in organs are one of the leading causes of morbidity and mortality in thalassemia[3,4]

Hb, hemoglobin; IE, ineffective erythropoiesis; RBC, red blood cell; ROS, reactive oxygen species

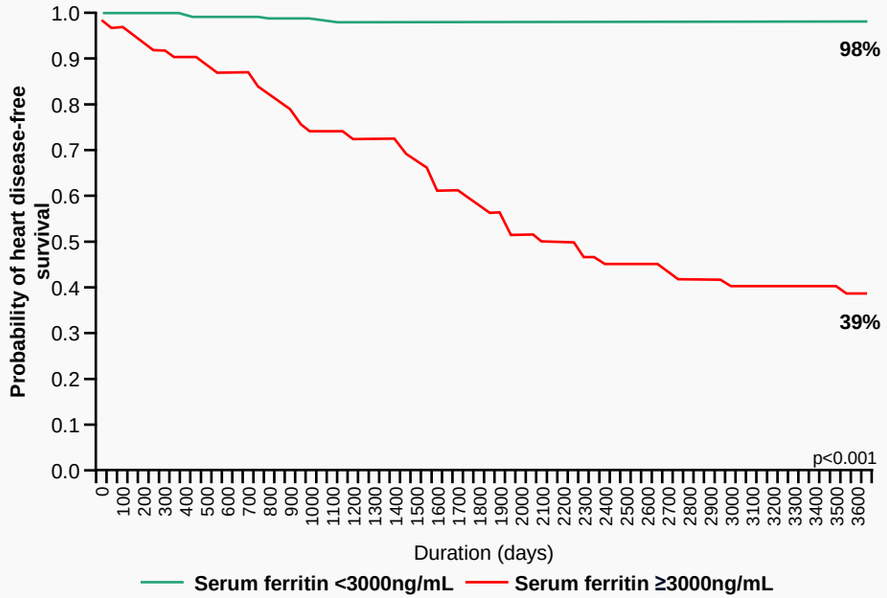
1. Kattamis A, et al. *Lancet* 2022;399(10343):2310–24; 2. Thalassemia: Complications and Treatment. Centers for Disease Control and Prevention. Updated April 27, 2023. https://www.cdc.gov/ncbddd/thalassemia/treatment.html. Accessed Nov 16, 2023; 3. Taher A, et al. *Hematology Am Soc Hematol Educ Program* 2017;2017(1):265–71; 4. Musallam KM, et al. *Haematologica* 2021;106(9):2489–91.

Iron overload is a common clinical complication in patients with thalassemia, irrespective of their transfusion status, and is associated with multiple comorbitidies[1–6]

TDT

- Patients primarily have **secondary iron overload**[1,2]
- Iron accumulates in target organs like the **heart**, **liver**, and **endocrine glands**, leading to high rates of morbidity, mortality, and healthcare resource utilization[1,2]

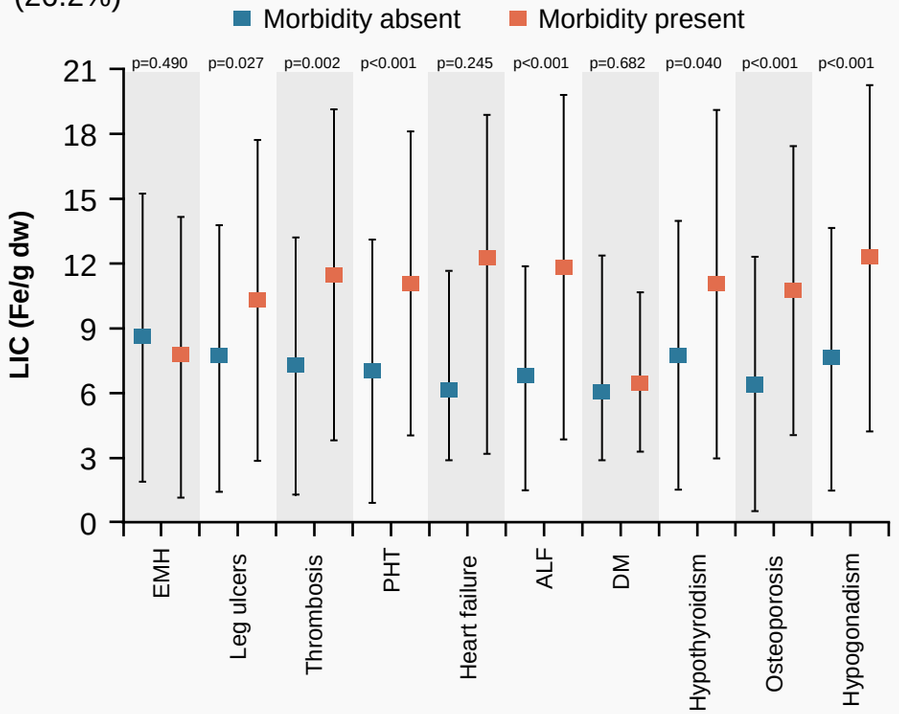
Heart disease-free survival in TDT[3]



Serum ferritin ≥3000 ng/mL
58% heart disease-free survival for 5 years
39% heart disease-free survival for 10 years

NTDT

- Patients primarily have **primary iron overload**[1,2]
- Higher levels of **liver iron concentration** (LIC) are associated with an increased prevalence of complications in patients with NTDT[4]
  - Population consists of patients with β-thalassemia intermedia with a transfusion history of none (26.2%), occasional (47.6%), and regular (26.2%)[4]



Regardless of the cause, iron overload puts patients with thalassemia at risk for multi-organ complications due to organ iron accumulation

ALF, abnormal liver function; DM, diabetes mellitus; dw, dry weight; EMH, extramedullary hematopoiesis; LIC, liver iron concentration; NTDT, non–transfusion-dependent thalassemia; PHT, pulmonary hypertension; TDT, transfusion-dependent thalassemia; 1. Taher A, et al. *N Engl J Med* 2021;384(8):727–43; 2. Tang CH, et al. *Transfusion* 2021;61(10):2906–17; 3. Derchi G, et al. *Intern Emerg Med* 2019;14(3):365–370; 4. Musallam KM, et al. *Haematologica* 2011;96(11):1605–12; 5. Chan LKL, et al. *Br J Haematol* 2021;192(1):171–78; 6. Chen FE, et al. *N Engl J Med* 2000;343(8):544–50. Figure (left) reprinted from Derchi G et al. *Intern Emerg Med* 2019, Copyright (2024), with permission from Springer Nature. Figure (right) reprinted from Musallam KM et al. *Haematologica* 2011, Copyright (2024), with permission from Ferrata Storti Foundation.

Iron overload-associated complications in α-thalassemia

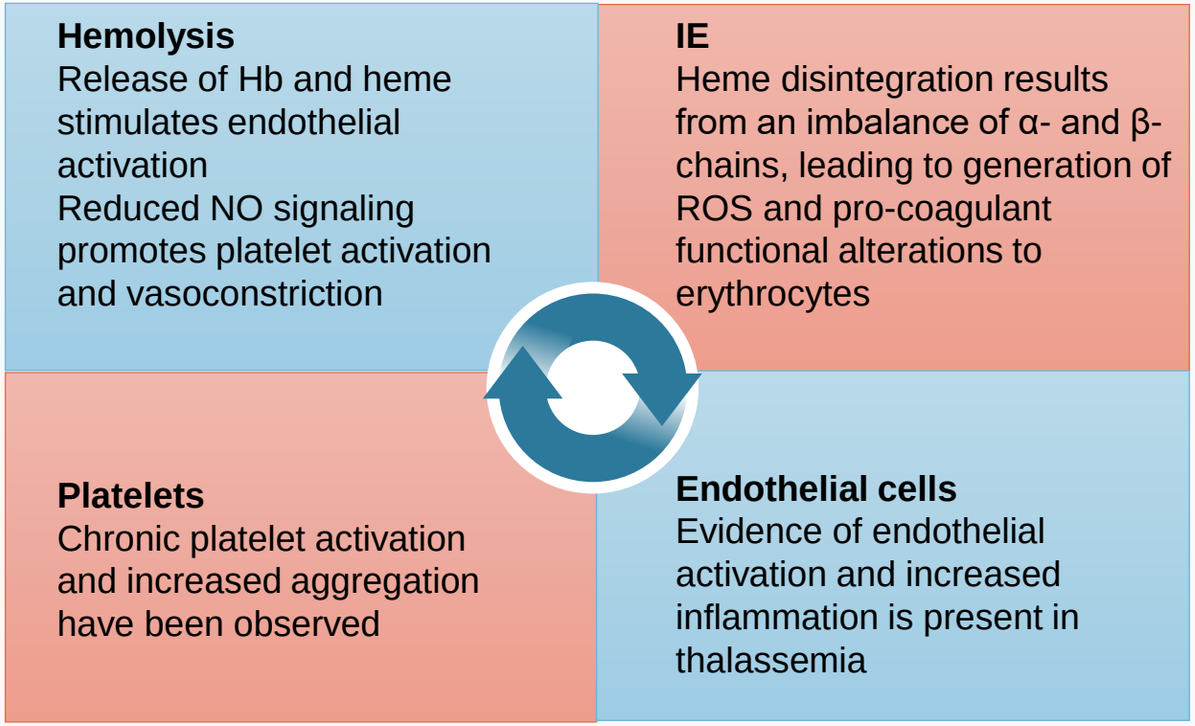
- In patients with **α-thalassemia**, iron overload has been significantly associated with **fibrosis** and **cirrhosis** of the liver, as well as **heart failure**[1]
  - **Ferritin** level increased significantly with age ($p<0.001$), regardless of transfusion history[1]
  - **LIC** also increased with higher ferritin levels[1]
- Patients with **HbH disease** and those aged >45 years are susceptible to **iron overload** even if they do not receive regular blood transfusions[2]

Iron overload-associated complications are a common cause of morbidity in patients with α-thalassemia and increase with advancing age[1,2]

IE, ineffective erythropoiesis; HbH, hemoglobin H; LIC, liver iron concentrationTaher A et al. *Am J Hematol* 2013;88(6):503–6.
1. Chen FE, et al. *N Engl J Med* 2000;343(8):544–50; 2. Viprakasit V, et al. *Orphanet J Rare Dis* 2014;9:131.

IE contributes to hypercoagulation in patients with thalassemia via several mechanisms

Several mechanisms have been implicated in the pathogenesis of hypercoagulation in thalassemia[1–8]



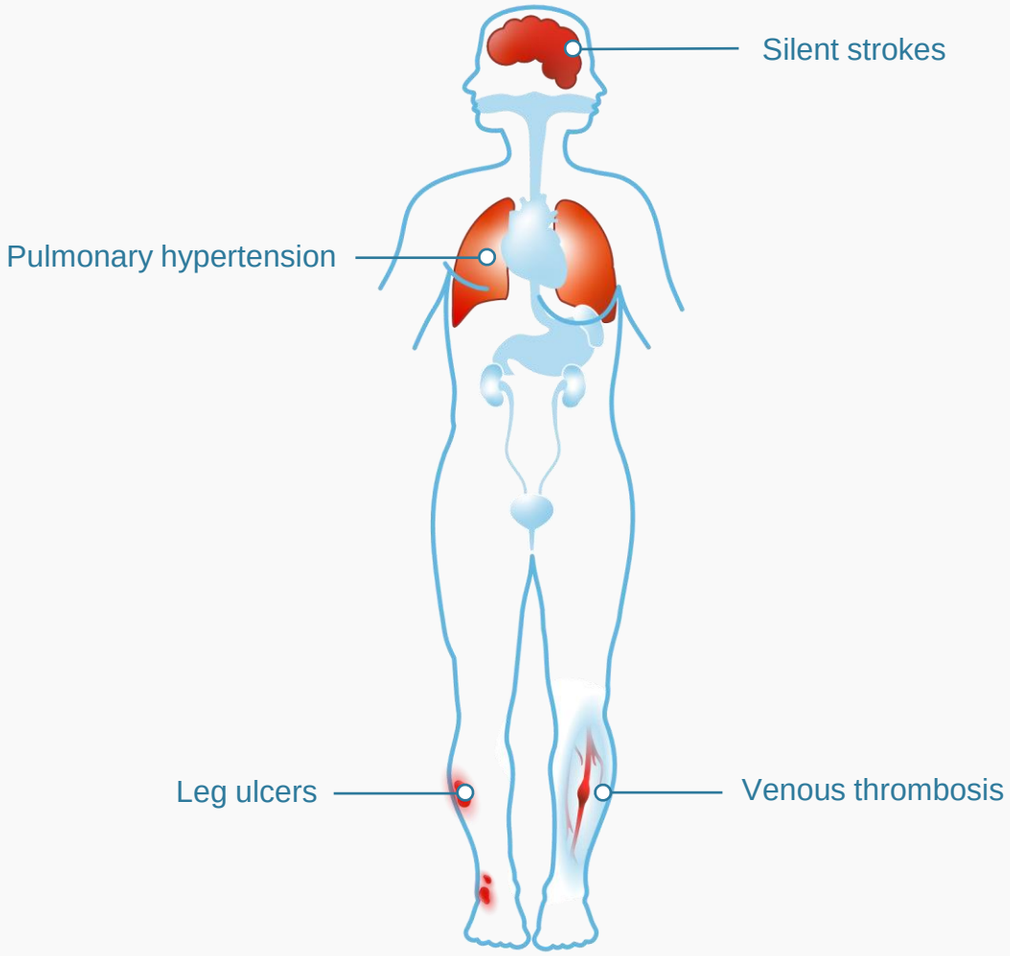
- An elevated (>4-fold) risk of **thromboembolic events** was found with **NTDT**, supported by an analysis of patients (n=8860) with **β-thalassemia major** vs **β-thalassemia intermedia**[9,10]
- Although less common in **TDT**, potentially due to the beneficial impact of transfusions on RBC health, studies show **thromboembolic events** can still occur in 4% of these patients[11,12]

Hb, hemoglobin; IE, ineffective erythropoiesis; NO, nitric oxide; NTDT, non–transfusion-dependent thalassemia; RBC, red blood cell; ROS, reactive oxygen species; TDT, transfusion-dependent thalassemia

1. Musallam KM, et al. *Haematologica.* 2013;98(6):833–44; 2. Rivella S. *Curr Opin Hematol* 2009;16(3):187–94; 3. Rivella S. *Blood Rev* 2012;26(1)(Suppl 1):S12–S15; 4. Cappellini MD. *Hematology Am Soc Hematol Educ Program*. 2007;74–78; 5. Rkiouak A, et al. *Clin Med Rev Case Rep* 2020;7(11):329; 6. Mahdi ZN, et al. *Hematol Oncol Stem Cell Ther* 2019;12(1):15–18; 7. Stoyanova E, et al. *PLoS One* 2012;7(6):e38089; 8. Abd A, et al. *J Blood Disord Transfus* 2015;6:3; 9. Taher A, et al. *Thromb Haemostasis* 2006;96(4):488–91; 10. Taher A, et al. NTDT Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-clinical-management-of-non-transfusion-dependent-thalassaemias-updated-version/. Accessed Dec 2023; 11. Borgna-Pignatti C, et al. *Acta Haematol* 1998;99(2):76–79; 12. Cappellini MD, et al. *Expert Rev Hematol* 2012;5(5):505–11.

Hypercoagulability in NTDT may lead to downstream vascular anomalies and mortality[1,2]

Impact of hypercoagulability in NTDT[1,2]



- In a retrospective study of patients with **NTDT** (N=2,033) thrombosis was among the most common causes of death in this patient population[2,3]
- In a retrospective study of patients (N=584) with **β-thalassemia intermedia**, the prevalence of vascular comorbidities and complications was reported as[4]:
  - **Thrombosis:** 14.0%
  - **Pulmonary hypertension:** 11.0%
  - **Leg ulcers:** 7.9%

IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia

1. Derchi G, et al. *Circulation* 2014;129(3):338–45; 2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023; 3. Musallam KM, et al. *Haematologica* 2021;106(9):2489–92; 4. Taher A, et al. *Blood* 2010;115(10):1886–92.

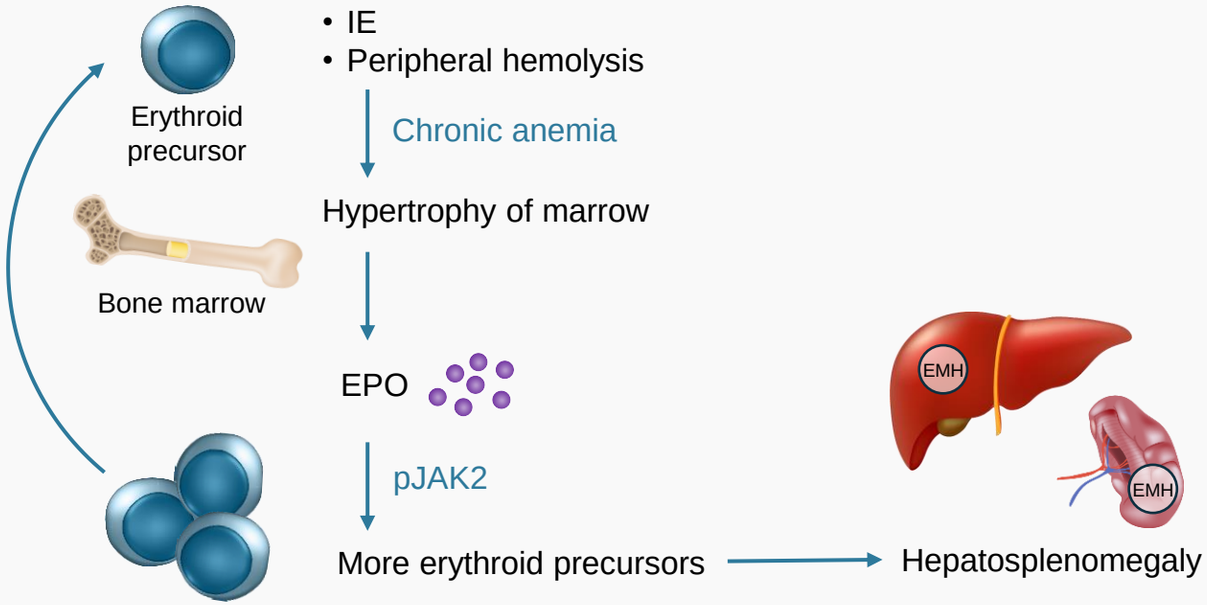
Extramedullary hematopoiesis is a complication of IE[1,2]

- Erythroid expansion caused by IE is associated with extramedullary hematopoiesis (EMH), the homing and proliferation of erythroid precursors in the **spleen**, **liver**, **and other organs**[1,2]
  - EMH pseudotumors are more common in patients with more severe IE, and occur more frequently in **NTDT** (20%) vs **TDT** (<1%)

Localization of EMH in thalassemia[1,3–8]	
▪ Lymph nodes ▪ Thymus ▪ Heart ▪ Breast ▪ Prostate ▪ Ligaments ▪ Kidneys ▪ Adrenal glands	▪ Pleura ▪ Retroperitoneum ▪ Skin ▪ Peripheral/cranial nerves ▪ Brain ▪ Spinal canal

- In thalassemia, **anemia** and **hypoxia** increase levels of EPO, thus activating JAK2, which acts on erythroid precursors to drive pathologic EMH[2,9,10]

Pathogenesis of EMH in thalassemia[11–13]



~15% of patients with EMH may face paraspinal involvement, leading to severe clinical problems including neurologic issues and varied consequences such as pain, deformities, and hematopoietic pseudotumors, depending on the location of EMH[1]

EMH, extramedullary hematopoiesis; EPO, erythropoietin; IE, ineffective erythropoiesis; JAK2, Janus kinase 2; NTDT, non–transfusion-dependent thalassemia; pJAK2, phosphorylated Janus activating kinase 2; TDT, transfusion-dependent thalassemia

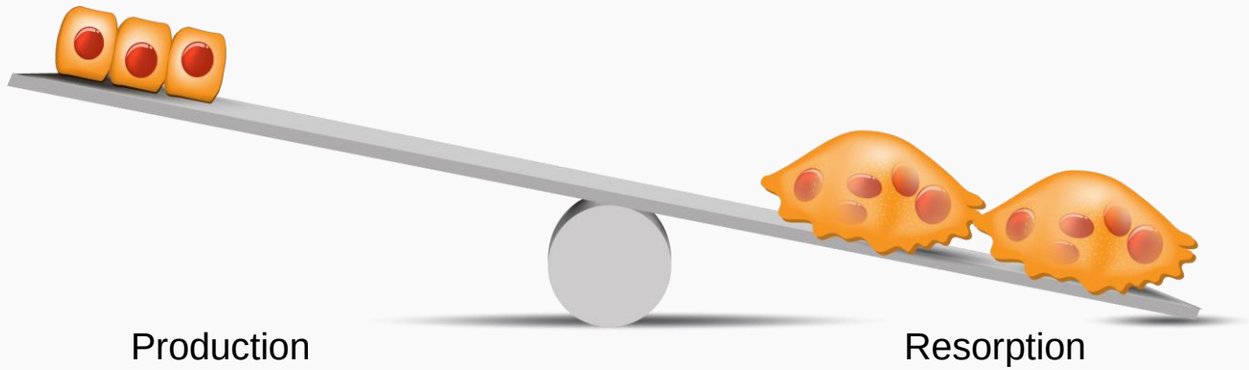
1. Taher A, et al. Extramedullary Hematopoiesis. Weatherall D, ed. In: Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT). Thalassaemia International Federation; 2013; 2. Rivella S, et al. *Blood Rev* 2012;26(1)(Suppl 1):S12–15; 3. Intragumtornchai T, et al. *Postgrad Med J* 1993;69(807):75–77; 4. Fucharoen S, et al. *E Arch Intern Med* 1985;145(4):739–42; 5. Karimi M, et al. *Lancet* 2008;372(9647):1436; 6. Tan TC, et al. *J Clin Neurosci* 2002;9(6):721–25; 7. Porcaro AB, et al. *Int Urol Nephrol* 2001;33(4):601–03; 8. Fan N, et al. *Blood Cancer J* 2018;8(12):119; 9. Bhoopalan SV, et al. *F1000Res* 2020;9:F1000 Faculty Rev–1153; 10. Tusi BK, et al. *Nature* 2018;555(7694):54–60; 11. Yang X, et al. *Cell Mol Life Sci* 2020;77(14):2723–38; 12. Galanello R, Origa R. *Orphanet J Rare Dis* 2010;5:11; 13. Gardenghi S, et al. *Hematol Oncol Clin North Am* 2010;24(6):1089–107.

Erythroid expansion caused by IE drives pathologic changes in bone composition, structure, and morphology[1–6]

Bone disease in thalassemia

- Erythroid expansion and IE are directly implicated as pathogenic drivers of osteoporosis[1]
- Bone loss occurs due to an imbalance in osteoclast production and resorption, although the exact cause of bone loss with IE is unclear[2–4]
- Expansion of the bone marrow space causes thinning of the bone cortex, particularly in the skull and hands[4,5]
  - Expansion of the osseous structures of the face

Pathogenesis of bone remodeling[6]



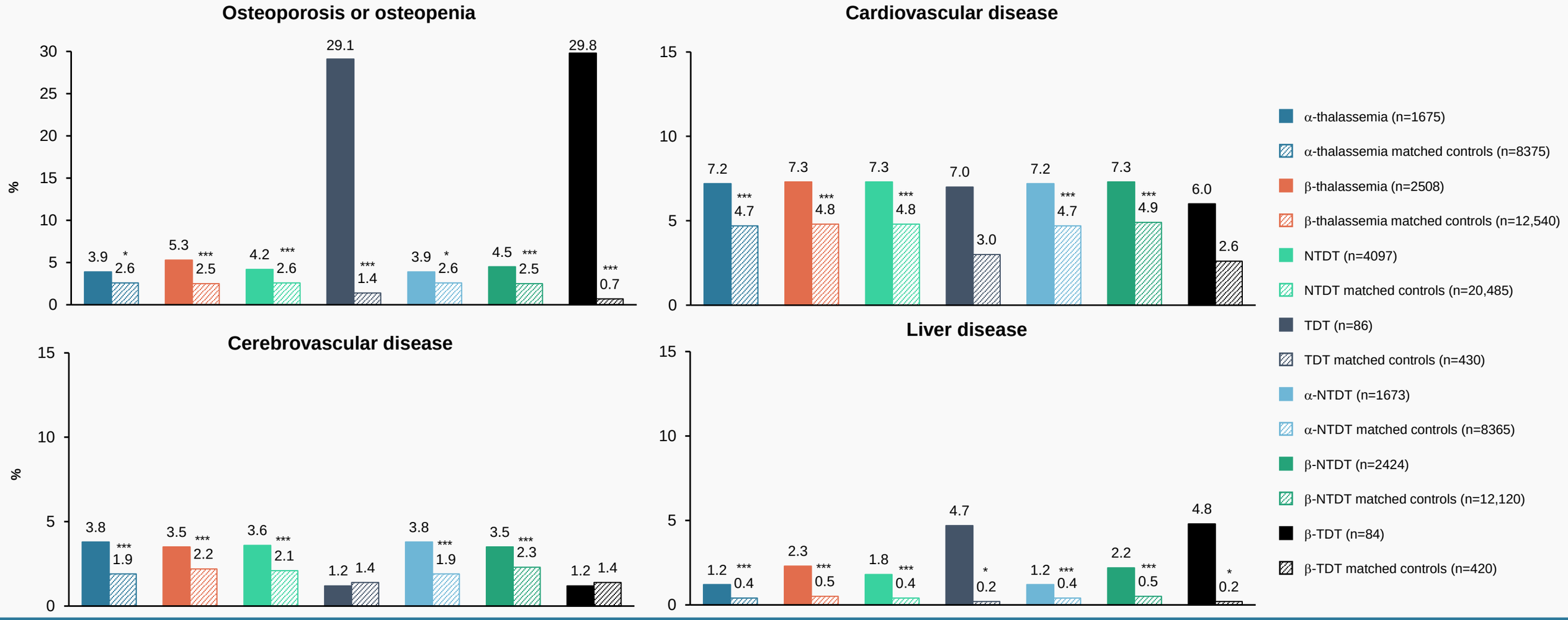
Osteoporosis and bone deformities are a distinct feature of under-transfused thalassemia[a,4]

[a]Regular use of transfusion support is implicated in reducing the prevalence of bone deformities and osteoporosis in TDT[4]

IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia

1. Rivella S. *Blood Rev* 2012;26(1)(Suppl 1):S12–15; 2. Morabito N, et al. *J Bone Miner Res* 2004;19(5):722–27; 3. Wong P, et al. *Endocrine Reviews* 2016;37(4):320–46; 4. De Sanctis V, et al. *Metabolism* 2018;80:66–79; 5. Bedair EM, et al. *Pediatr Endocrinol Rev* 2008;6(Suppl 1):123–26; 6. Rao S, et al. *Trends Cell Bio* 2018;28(3):213–23.

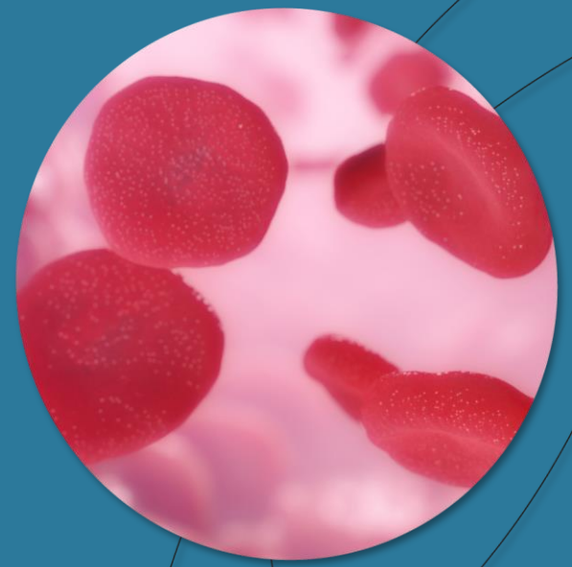
Patients with thalassemia have higher rates of complications/comorbidities compared with their matched controls: **Commercial/Medicare population**



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

*p<0.05; ***p<0.001
NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia
Langer AL, et al. *Blood* 2022;140(Suppl 1):5362–64.

Burden of disease: Health-related quality of life (HRQoL) burden



Patient with thalassemia have worse HRQoL than matched controls[1–4]

NTD vs TD β-thalassemia

- **Adult patients with NTDT may have similar or worse HRQoL compared with patients with TDT**
  - In a systematic literature review of studies in patients with **NTDT** or **TDT**[1]
    - Adult patients' HRQoL total scores were significantly poorer in patients with **NTDT** (**β-thalassemia intermedia**) vs **TDT** (**β-thalassemia major**)
  - In a sample of 48 patients with thalassemia who completed the HRQoL assessment[2–4]
    - A higher percentage of patients with NTDT reported worse physical health and functioning, mental health, general health, and vitality than patients with TDT

NTDT

- **HRQoL impairment and significant burden are also present in patients with NTDT**
  - In a systematic literature review of studies in patients with **NTDT,** 3 studies in pediatric patients with **NTD β-thalassemia** identified significantly worse Pediatric Quality of Life Inventory scores across nearly all domains for patients compared with healthy controls[1]

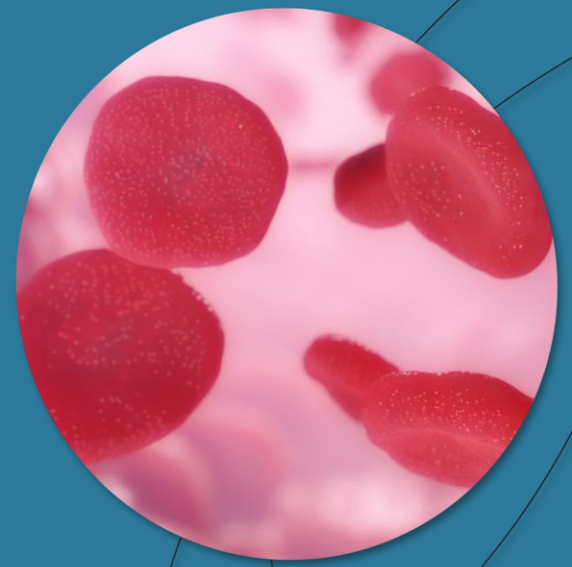
TDT

- **Patients with TDT experience significantly worse HRQoL compared with the healthy population**
  - In a systematic literature review of studies in patients with **TDT**, most studies (16/22; 72.7%) found significantly poorer HRQoL total scores in adults and adult/pediatric patients compared with healthy controls[1]
    - The burden associated with pediatric patients with **TD β-thalassemia** also impacted caregivers, with 1 study reporting significantly reduced HRQoL as measured by the Short Form 36 Health Survey (SF-36) compared with caregivers of healthy controls ($p<0.001$)
    - A median of 38% adults with **TD β-thalassemia** (n=44) and 30% of caregivers (n=13) reported work productivity loss, and 50% of adults (n=88) and 30% of caregivers (n=29) reported activity impairment

HRQoL, health-related quality of life; NDT, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; SF-36, Short Form 36 Health Survey; TD, transfusion-dependent; TDT, transfusion-dependent thalassemia

1. Musallam KM, et al. *Hemasphere* 2022;6:2103–04; 2. 2. Shah R, Badawy SM. *Ann N Y Acad Sci* 2024 Jan 25. doi: 10.1111/nyas.15100. Epub ahead of print; 3. Musallam KM, et al. *Eur J Haematol* 2011 Jul;87(1):73–79; 4. Pakbaz Z, et al. *Ann N Y Acad Sci* 2005;1054:457–61.

Burden of disease: Association of Hb with outcomes

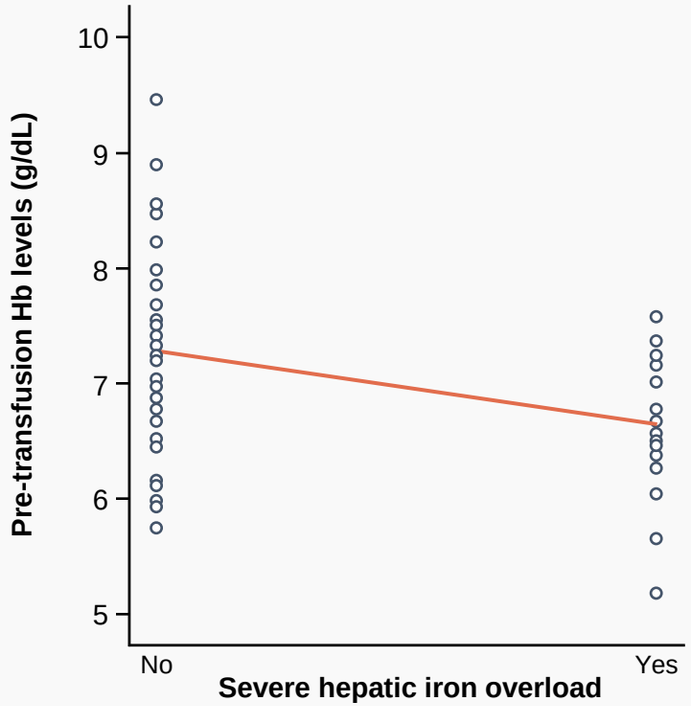


In patients with TDT and NTDT, lower Hb levels are associated with an increased risk of iron overload and other complications

TDT

Low Hb values were significantly associated with:

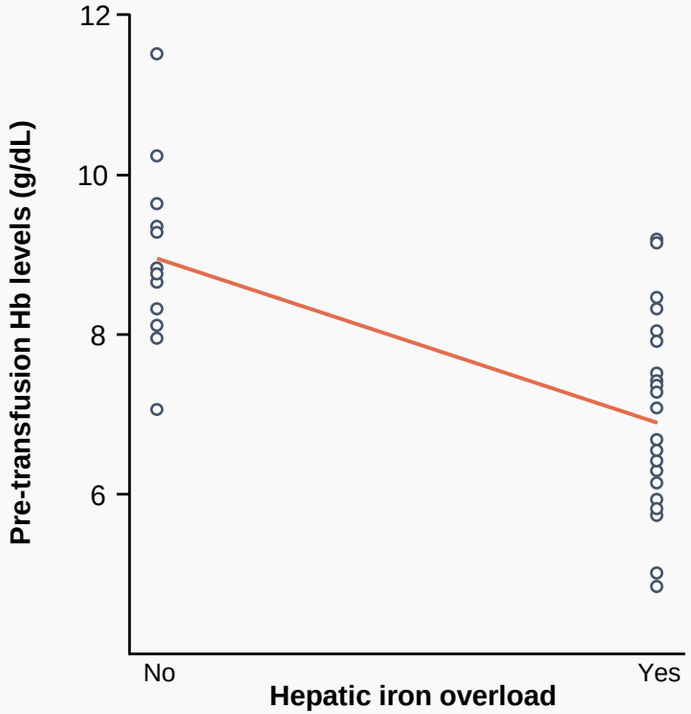
- **Severe hepatic iron overload** (odds ratio [OR] [95% confidence interval (CI)]: 0.358 [0.148, 0.864])
- **Hypogonadism** (OR [95% CI]: 0.380 [0.145, 0.994])



NTDT

Low Hb levels were significantly associated with:

- **Hepatic iron overload** (OR [95% CI]: 0.120 [0.21, 0.701])
- **Osteoporosis** (OR [95% CI]: 0.146 [0.31, 0.688])
- **Pulmonary hypertension** (OR [95% CI]: 0.157 [0.031, 0.809])



CI, confidence interval; Hb, hemoglobin; NTDT, non-transfusion-dependent thalassemia; OR, odds ratio; TDT, transfusion-dependent thalassemia

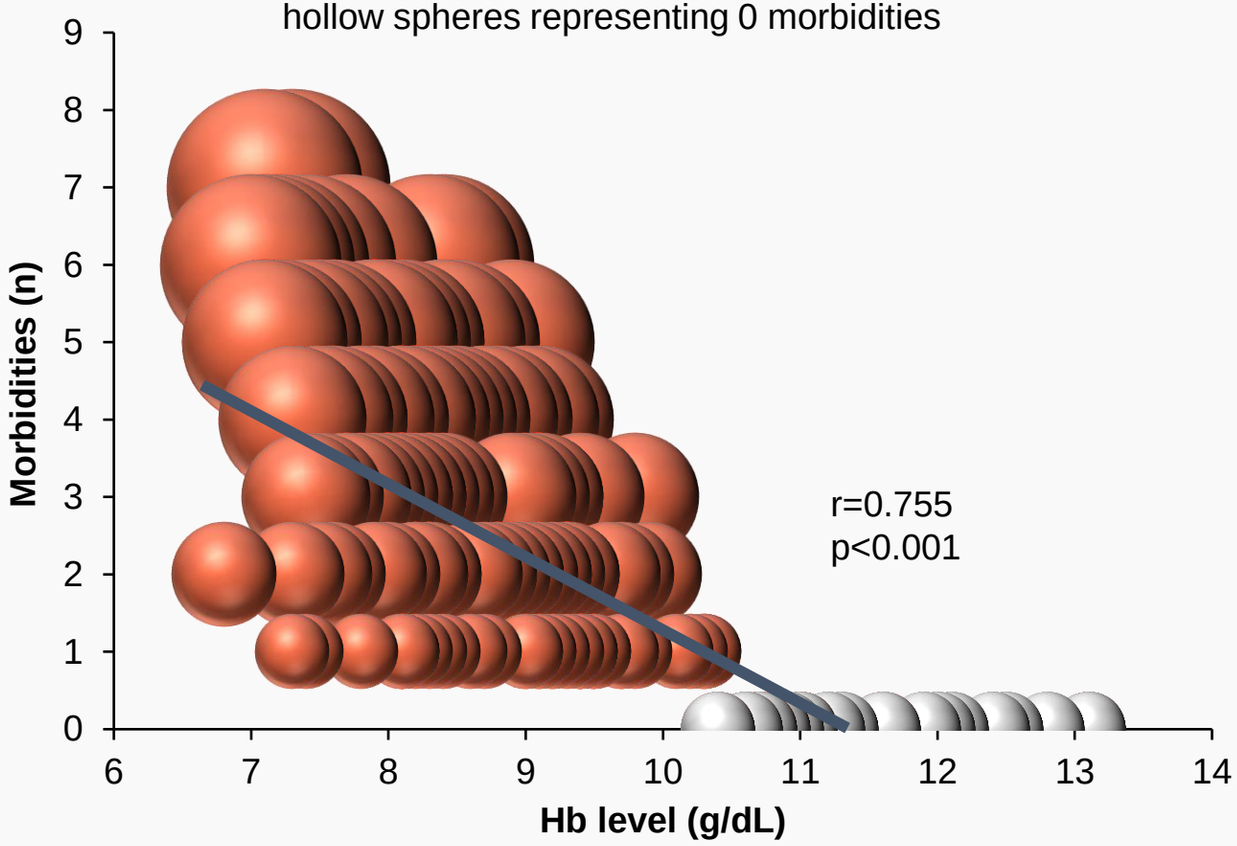
Wanchaitanawong W, et al. *Hematology* 2021;26(1):1–8. Figures used with permission, DOI: 10.1080/16078454.2020.1856513.

NTD β-thal

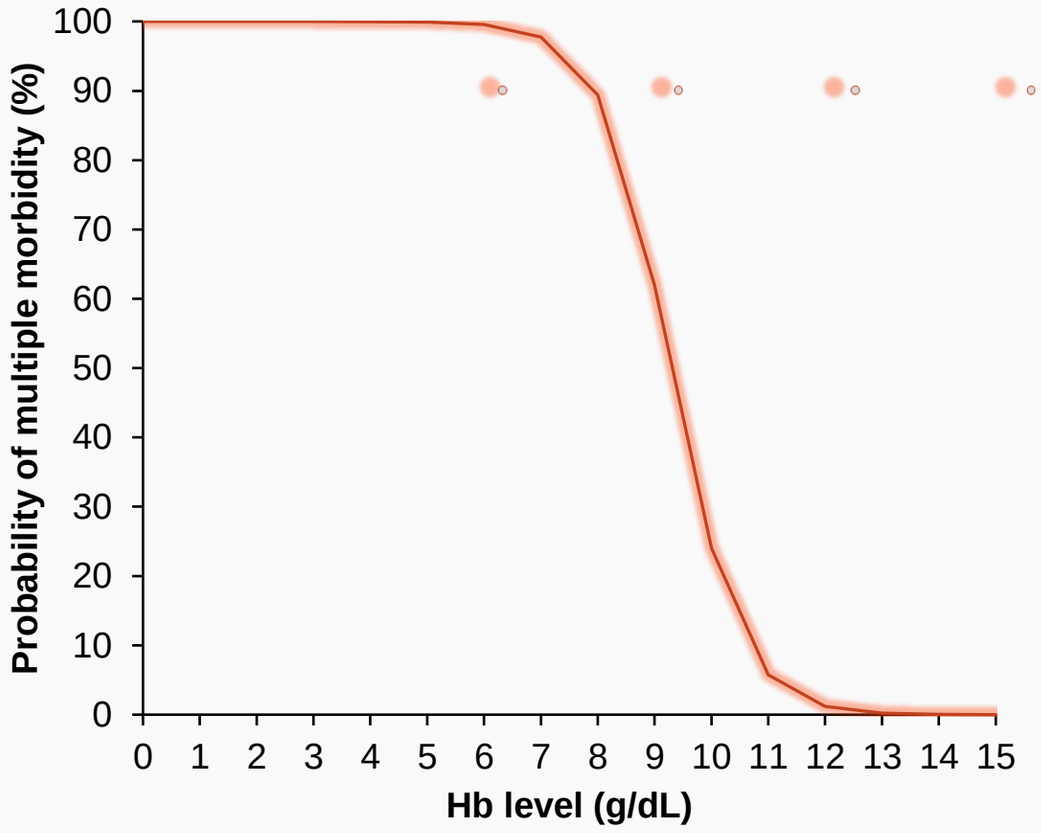
Variations of 1 g/dL in Hb level are independently associated with the number of morbidities in NTDT (n=150)

Correlation between Hb level and number of morbidities

Sphere sizes represent increments in number of morbidities, with hollow spheres representing 0 morbidities



Probability of multiple morbidity development at various Hb levels



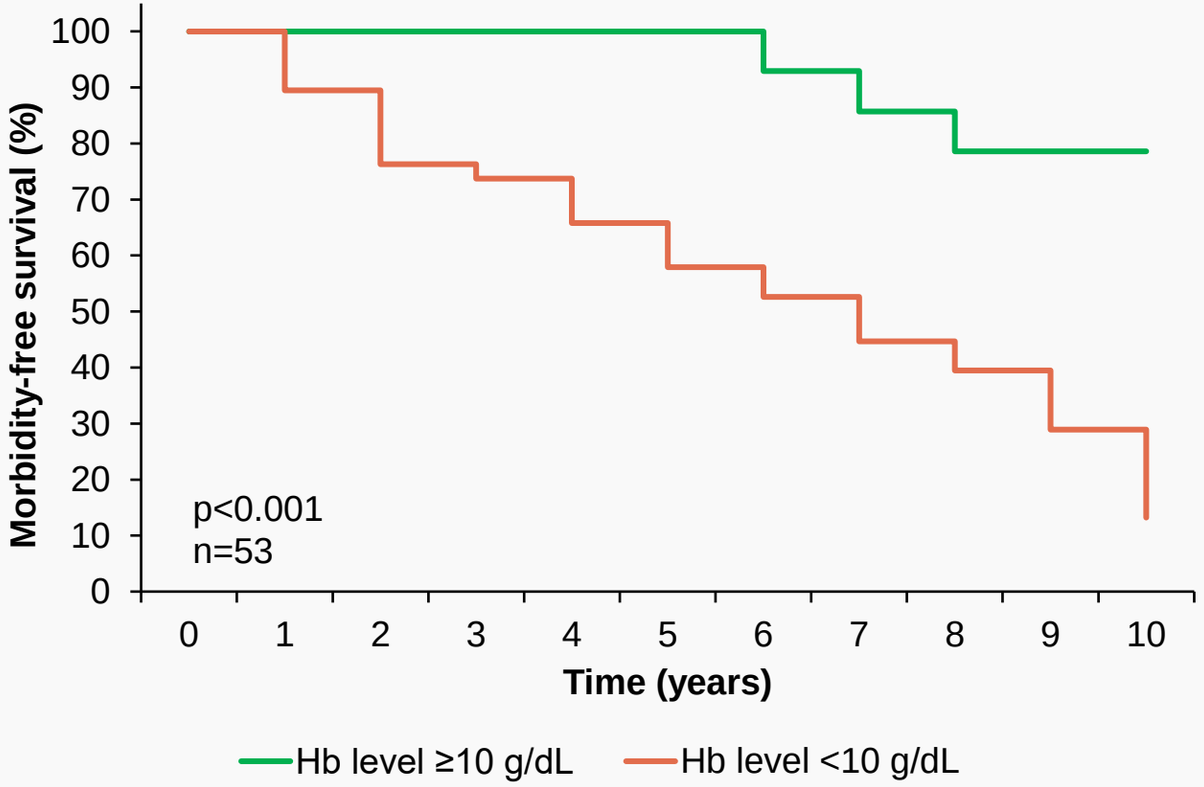
Each 1 g/dL increase in Hb level is independently associated with a 0.75 decrease in the number of morbidities (ie, +1.5 g/dL is associated with a decrease in 1 morbidity) and vice versa

Hb, hemoglobin; NDT, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia

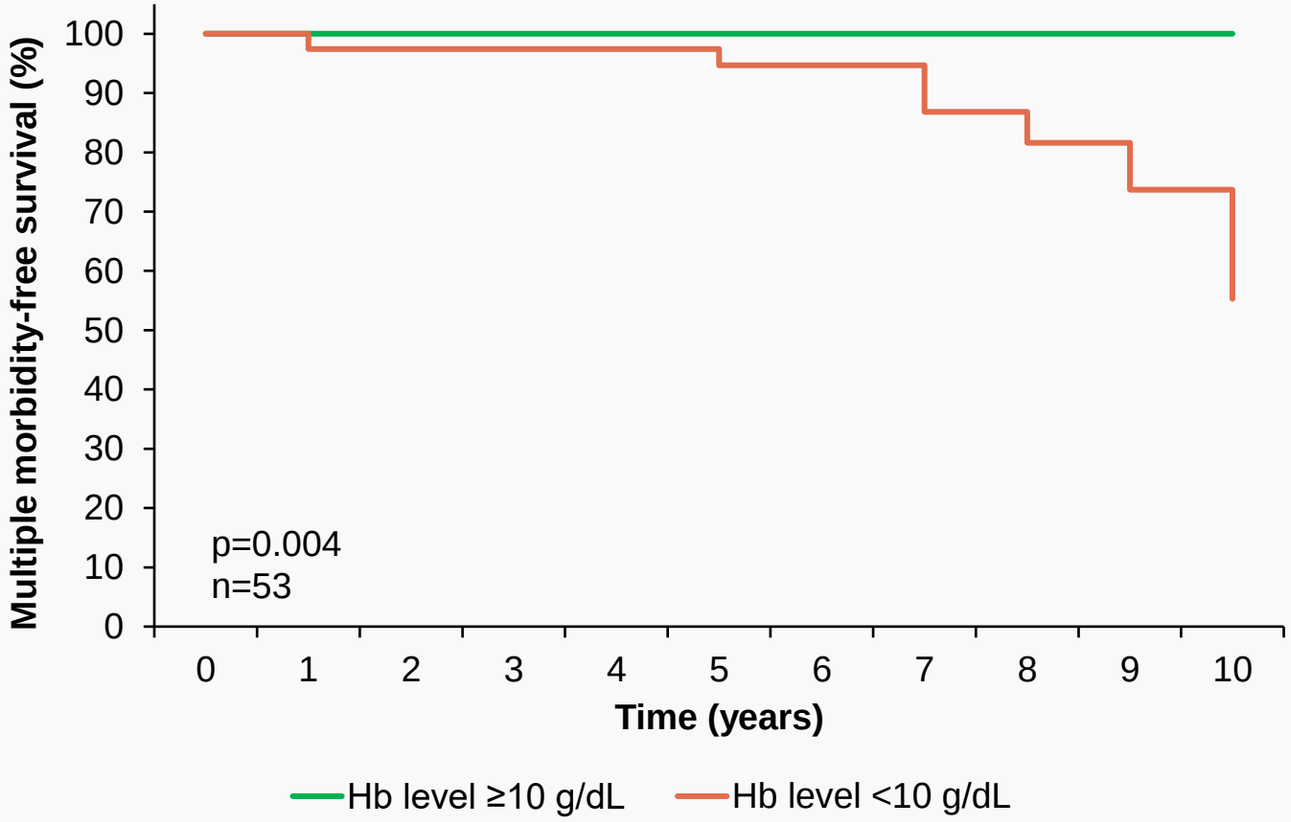
NTD β-thal

Morbidity-free survival vs Hb level in NTDT

The 5-year and 10-year cumulative morbidity-free survival:
- Patients with Hb level <10 g/dL were 57.9% and 13.2%, respectively
- Patients with Hb level ≥10 g/dL were 100% and 78.6%, respectively



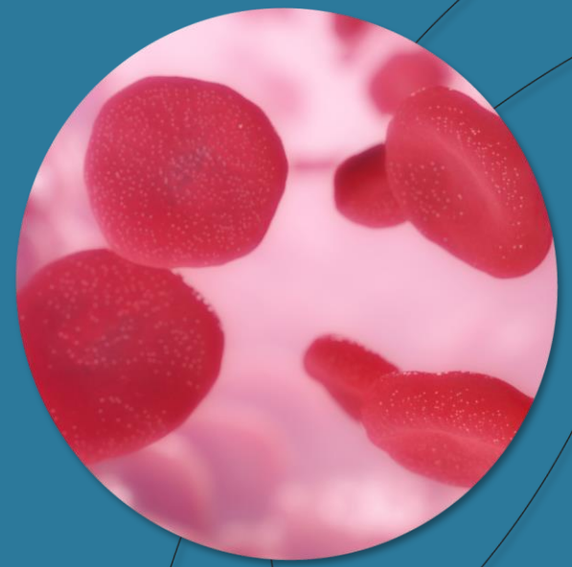
The 5-year and 10-year cumulative multiple morbidity-free survival:
- Patients with Hb level <10 g/dL were 94.7% and 55.3%, respectively
- Patients with Hb level ≥10 g/dL were 100% and 100%, respectively



Each 1 g/dL increase in baseline Hb level was associated with a 28% reduction in morbidity risk (hazard ratio [95% CI]: 0.72 [0.55, 0.96]; p=0.024)

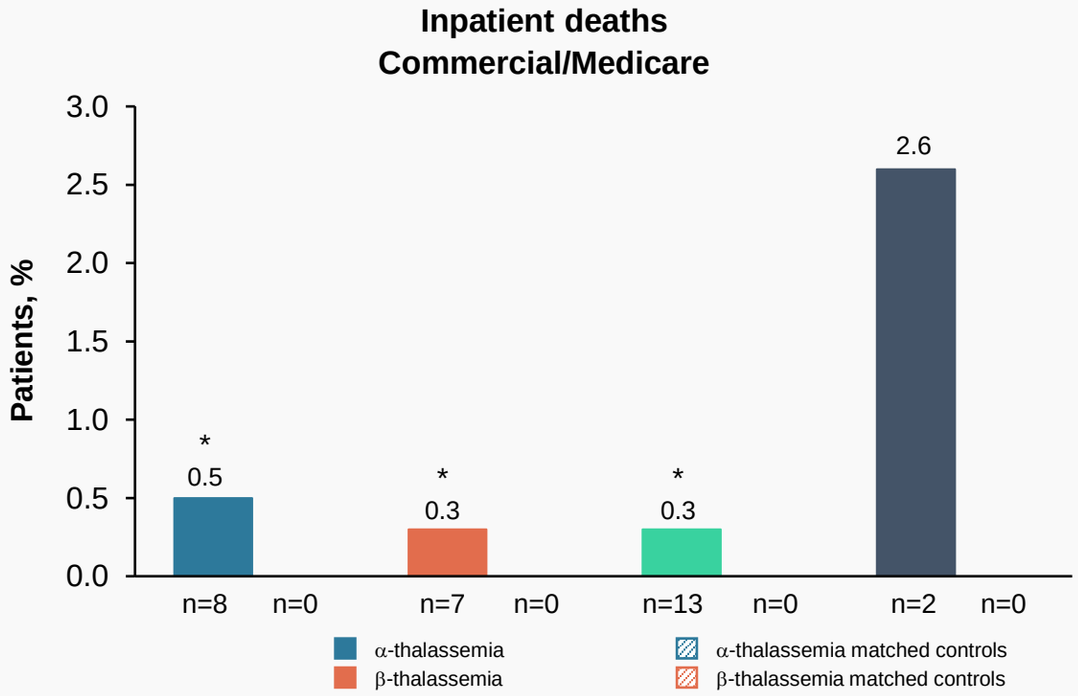
Hb, hemoglobin; NDT, non–transfusion-dependent; NTD, non–transfusion-dependent thalassemia

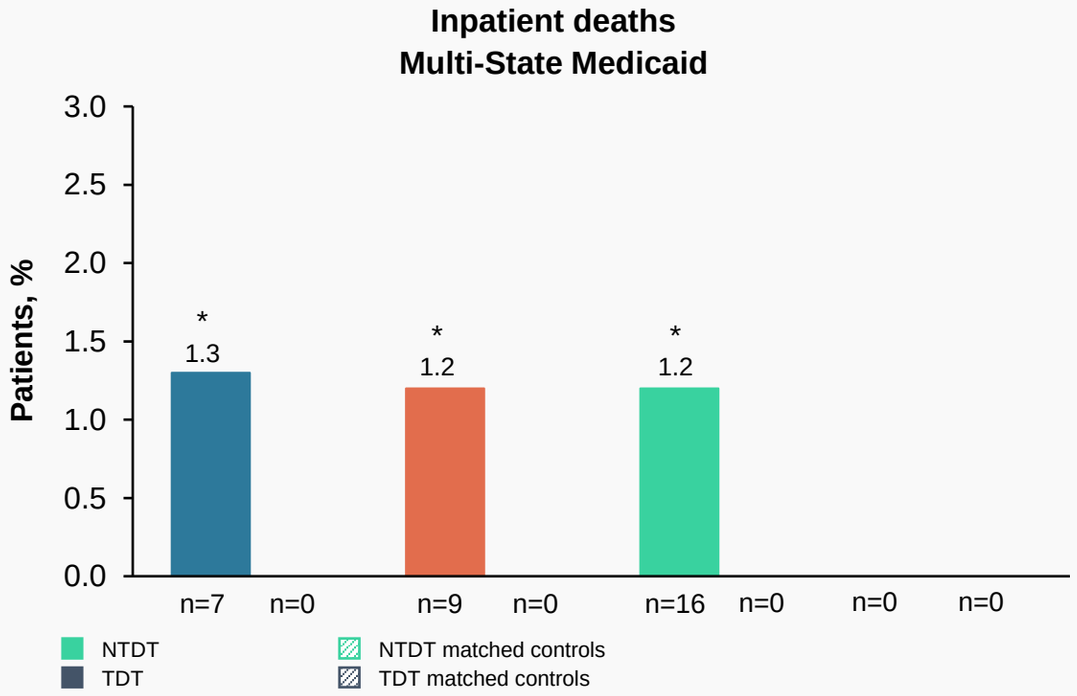
Burden of disease: Survival/mortality



Inpatient survival of patients with thalassemia

- In a study of the **US MarketScan® Commercial and Medicare claims data**, the authors found that during the variable-length follow-up:
  - Significantly more **inpatient deaths** occurred in **all cohorts of patients with thalassemia** compared with matched control groups (all p<0.05) in the **Commercial/Medicare** population
  - Significantly more **inpatient deaths** occurred in patients with **α-thalassemia**, **β-thalassemia**, and **NTDT** cohorts compared with matched control groups (all p<0.05) in the **Medicaid** population. No deaths occurred in the **TDT** patient group

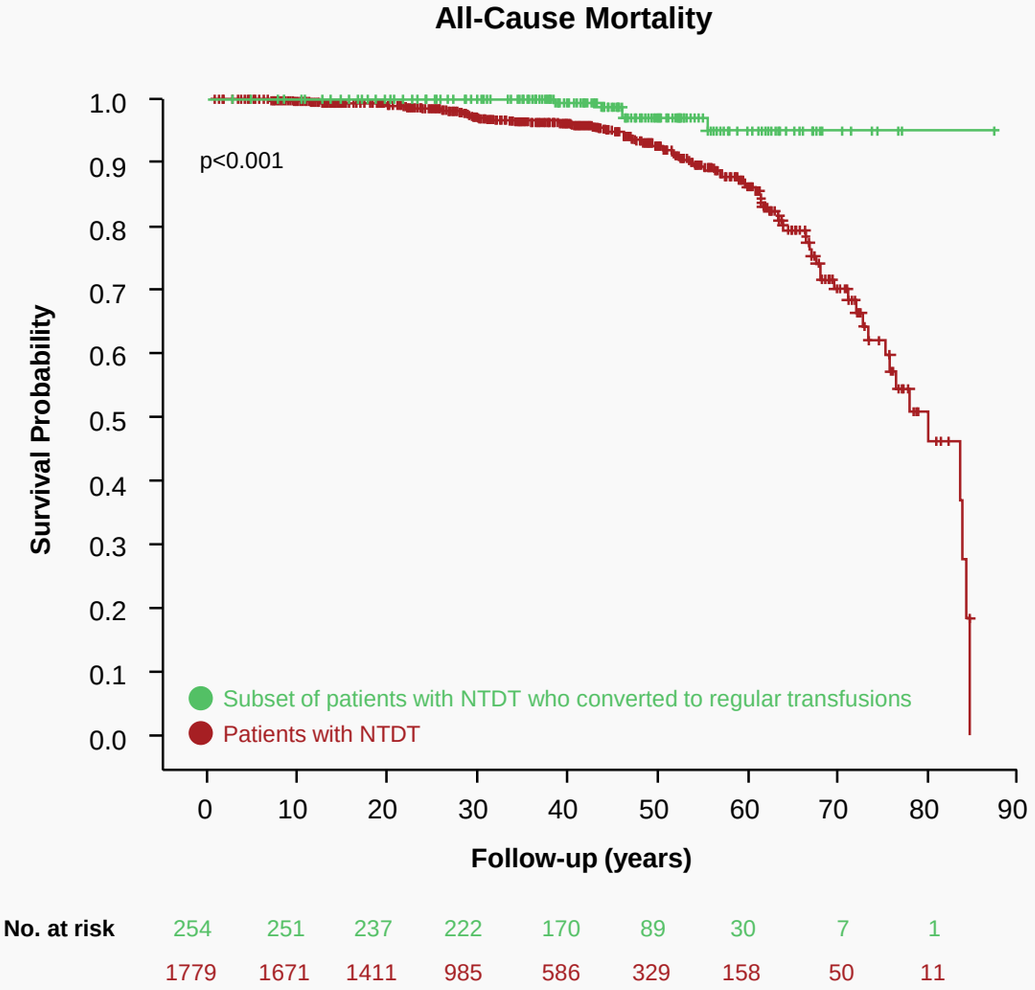




*p<0.05
NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia
Langer AL, et al. *Hemasphere* 2023;7(Suppl):e333151f.

NTD β-thal

Survival in 2033 patients with NTDT: A global registry



Cause	n	% among deaths (n=113)	% among population (n=2033)	Median age at death (min–max), years
Cardiovascular disease (cardiomyopathy, myocardial infarction, valvular disease, pulmonary hypertension, thrombosis or peripheral vascular disease)	41	36.3	2.0	34.2 (19–85)
Hepatic disease (fibrosis, cirrhosis, or HCC)	23	20.4	1.1	55.4 (26–76)
Cancer (solid or hematologic malignancy excluding HCC)	14	12.4	0.7	54.0 (12–85)
Infection	13	11.5	0.6	44.1 (12–68)
Unclassified thalassemia-related complications	17	15.0	0.8	19.8 (7–64)
Non–thalassemia-related causes	5	4.4	0.2	62.0 (27–73)

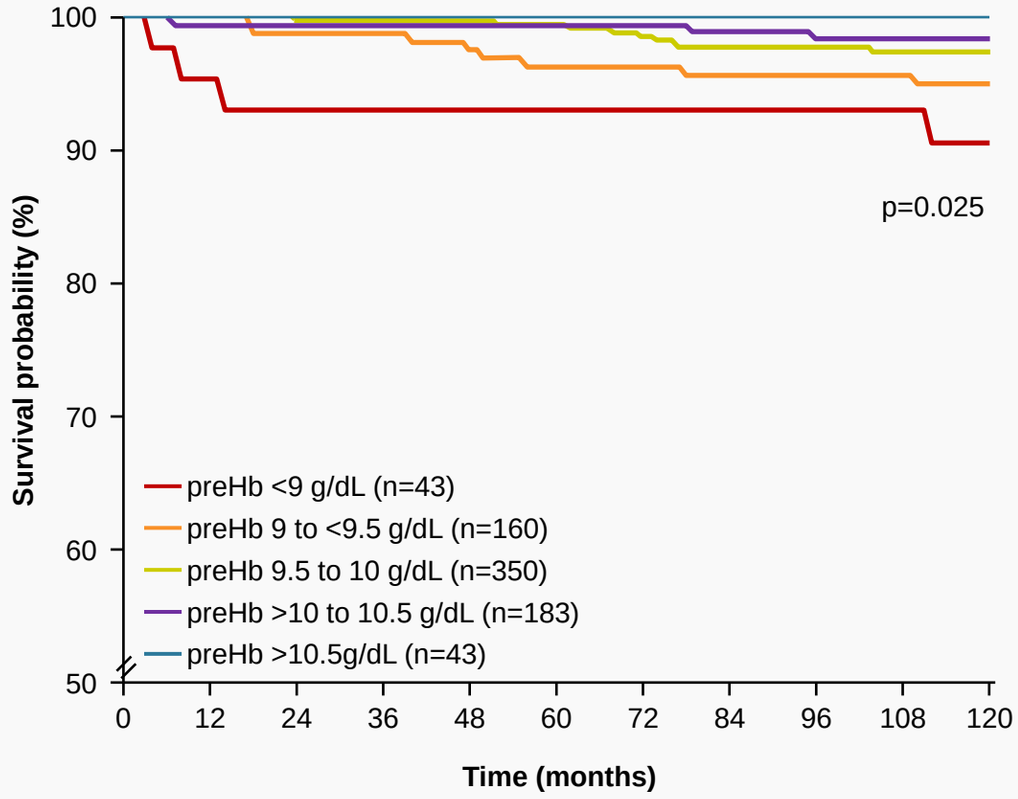
Survival was significantly worse in NTDT patients compared to the subset of NTDT patients who converted to regular transfusions, for all-cause mortality. Cumulative survival estimates were 99.3% vs 100% (18 years), 92.6% vs 97.1% (50 years), 79.5% vs 95.0% (65 years), 62.2% vs 95.0% (75 years), and 18.5% vs 95.0% (85 years), respectively

HCC, hepatocellular carcinoma; NDT, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia

Association of pretransfusion Hb levels with mortality in TD β-thalassemia

- A retrospective study of patients (N=779) with **TD β-thalassemia** found that ascending pretransfusion Hb levels were associated with a **decrease** in the **thalassemia-related mortality rate** and **prolonged survival**[1]
  - **Mortality rate:** 9.3% (Hb <9 g/dL) to 0% (Hb ≥10.5 g/dL), p=0.033
  - **5-year survival:** 93% (Hb <9 g/dL) to 100% (Hb ≥10.5 g/dL), p=0.025
  - **10-year survival:** 91% (Hb <9 g/dL) to 100% (Hb ≥10.5 g/dL), p=0.025
  - Protective effects were incremental with higher Hb pretransfusion levels and significant associations between pretransfusion Hb and mortality were established with Hb levels ≥9.5 g/dL
- These data support the pretransfusion Hb target of >9.5–10.5 g/dL in patients with TDT[2]

β-thalassemia-related mortality according to pretransfusion Hb levels[1]



Pretransfusion Hb levels ≥9.5 g/dL were associated with a reduced mortality risk in adults with TD β-thalassemia[1]

Hb, hemoglobin; preHb, pretransfusion hemoglobin; TD, transfusion-dependent; TDT, transfusion-dependent thalassemia

1. Musallam KM, et al. *Blood* 2023 Nov 17:blood.20230224602. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/ Accessed January 2024. Figure reprinted from Musallam KM et al. *Blood* 2023, Copyright (2024), with permission from Elsevier.

Disease burden: Key takeaways

The signs, symptoms, complications, and comorbidities of thalassemia are heterogeneous, varying widely depending on a multitude of factors[1–5]

The disease burden for TD β-thalassemia is well-established, while the disease burden for NTD β-thalassemia is less well-recognized[3,5]

The disease burden for α-thalassemia is underappreciated; there are relatively few studies with data on complications of α-thalassemia and no data are available for mortality[2]

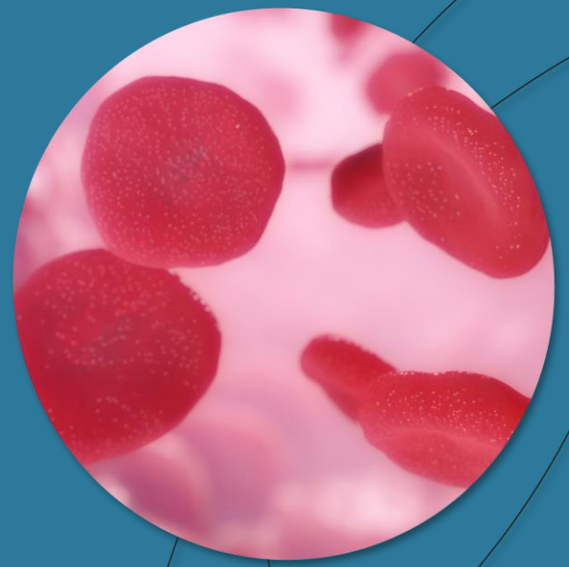
Patients with both α- and β-thalassemia, regardless of transfusion status, report that the disease negatively affects their HRQoL, including daily activities, physical functioning, and emotional state[4]

Patients with TDT tend to have complications and comorbidities compounded by their regular transfusion treatment[6]

HRQoL, health-related quality of life; NTD, non–transfusion-dependent; TD, transfusion-dependent; TDT, transfusion-dependent thalassemia

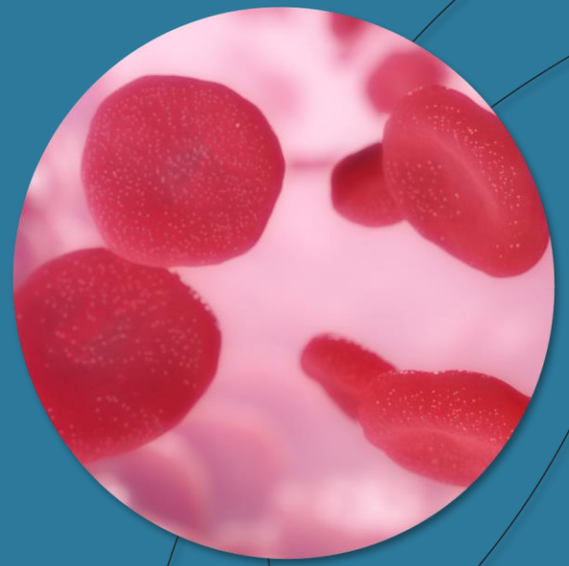
1. Taher A, et al. *N Engl J Med* 2021;384:727–43; 2. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/ Accessed Dec 23; 3.Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce% Accessed Dec 23; 4. Musallam KM, et al. *Hemasphere* 2022;6:2103–04; 5. Viprakasit V, et al. *Orphanet J Rare Dis* 2014;9:131; 6. Vichinsky E, et al. *Transfusion* 2014 Apr;54(4):972–81.

Back up slides

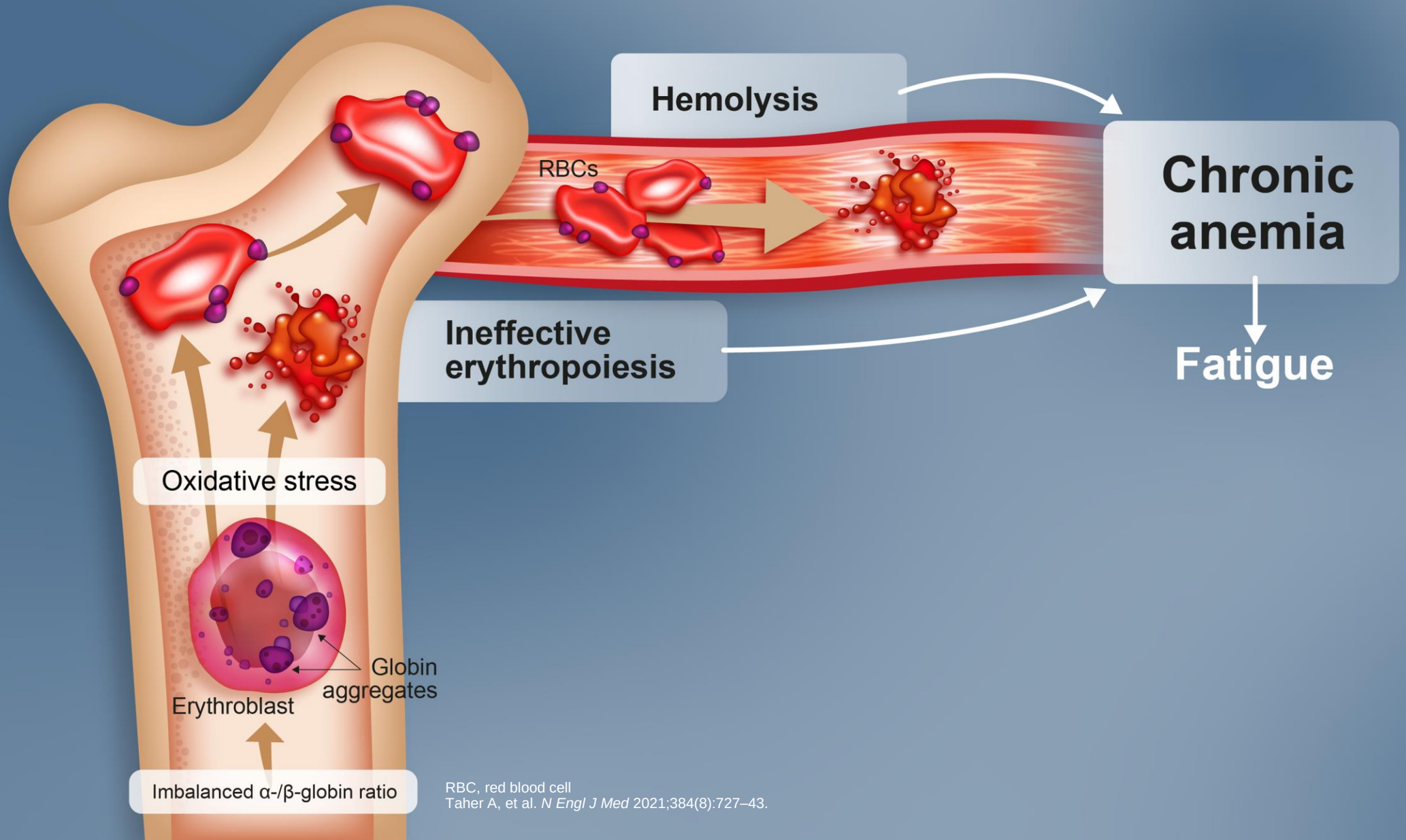


Pathophysiology

Taher A, et al. European Hematology Association (EHA) Hybrid Congress, June 13–16, 2024, Madrid, Spain, and Virtual: Plenary Presentation S104.



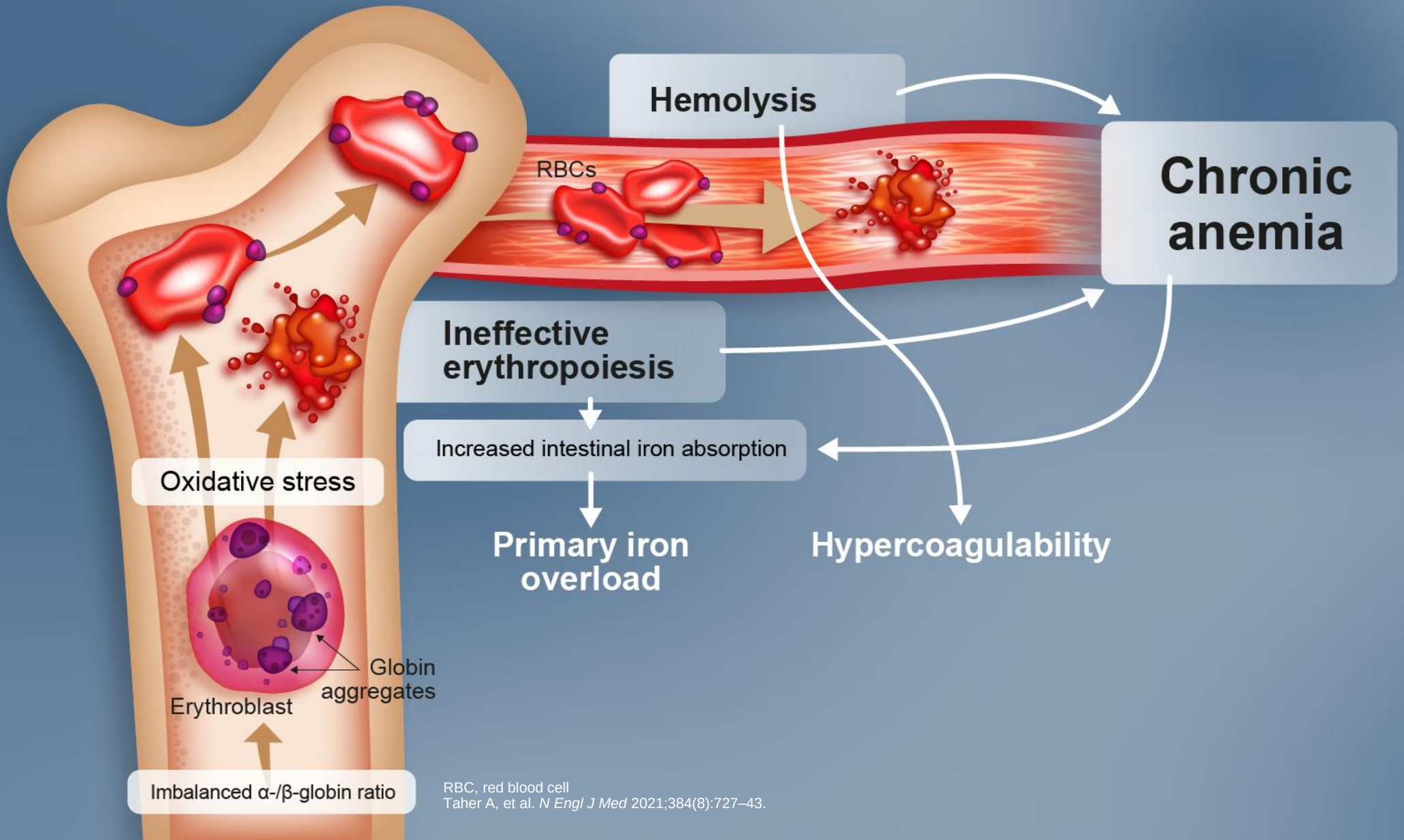
Pathophysiology of thalassemia



RBC, red blood cell

Taher A, et al. *N Engl J Med* 2021;384(8):727–43.

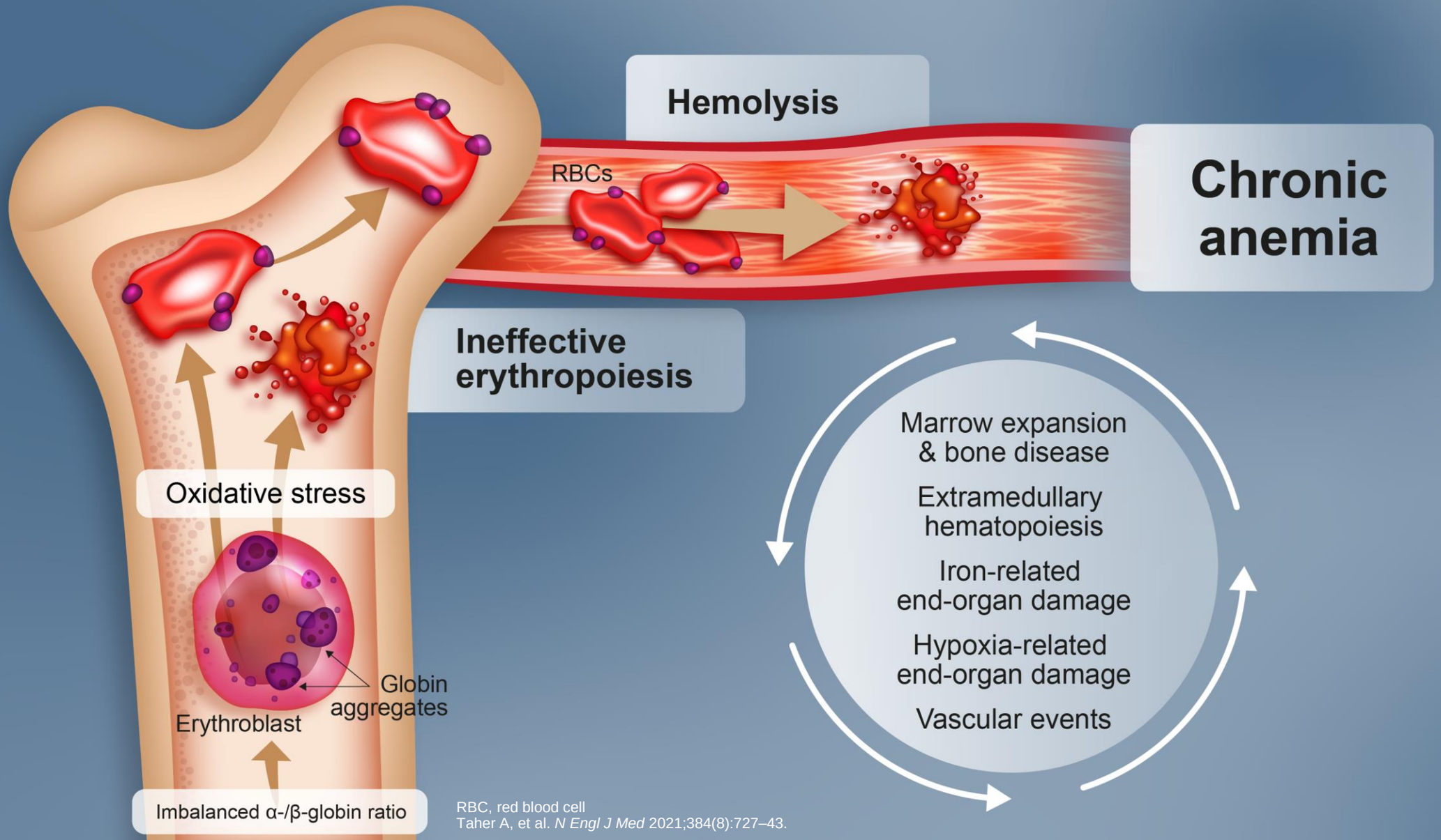
Pathophysiology of thalassemia



RBC, red blood cell

Taher A, et al. *N Engl J Med* 2021;384(8):727–43.

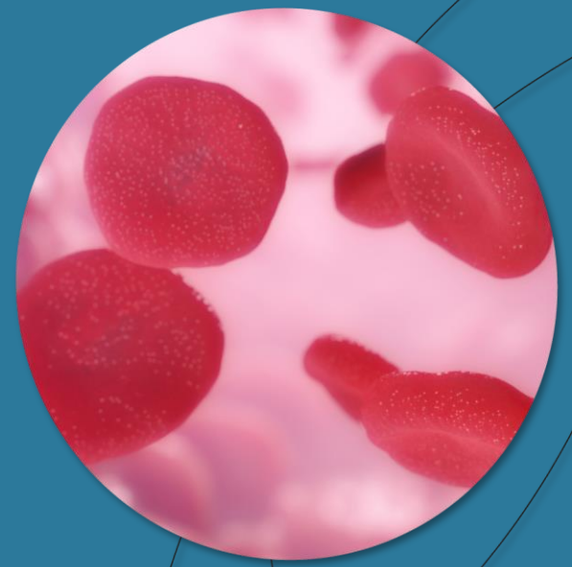
Pathophysiology of thalassemia



RBC, red blood cell

Taher A, et al. *N Engl J Med* 2021;384(8):727–43.

Management guidelines



α-thal

TIF management guidelines: Overview and assessments

Deletional HbH	
Domain	**Management**
Frequency of clinic visits	Every 3 months for the first 2 years, then annually for life
Iron overload assessments	Check ferritin annually Check liver magnetic resonance imaging (MRI) for LIC if ferritin >200 ng/mL Mild-to-moderate iron overload is observed in the fourth to fifth decades of life, and is earlier in males than females
Endocrinology evaluation	If onset of puberty is delayed >2 years or if concern of slow growth Obtain family history and consider X-ray for bone age
Dual-energy X-ray absorptiometry (DXA) scan	Every 3 years starting at 12 years
Echocardiogram (ECHO)	Check at 10–12 years to assess for pulmonary artery pressure If normal, repeat every 3–5 years

Non-deletional HbH	
Domain	**Management**
Recommended follow-up intervals for NTD patients	Baseline Hb >8 g/dL: every 6 months Baseline Hb ≤8 g/dL: every 3–6 months
Assessment of growth, bone changes, spleen size, and pubertal development	Assessments essential at every clinic visit during childhood and adolescents
Complete blood count with reticulocyte count, hemolytic markers, serum ferritin, transferrin saturation, and liver enzymes	Assessments essential at every clinic visit
Note: Monitoring and management of TD patients with non-deletional HbH should be performed similar to patients with TD β-thalassemia	

DXA, dual-energy X-ray absorptiometry; ECHO, echocardiogram; Hb, hemoglobin; HbH, hemoglobin H; LIC, liver iron concentration; MRI, magnetic resonance imaging; NTD, non-transfusion–dependent; TD, transfusion-dependent; TIF, Thalassemia International Federation

Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023.

α-thal

TIF management guidelines: Anemia (1/3)

Deletional HbH	
Transfusions	▪ Regular transfusions are not required ▪ Episodic transfusions are not needed during most febrile illnesses, unless the Hb level drops below 6 g/dL in young children or 6.5 g/dL in adolescents and adults ▪ Transfusion may be needed for surgery or other specific indications

Non-deletional HbH	

Transfusions	▪ A pre-transfusion Hb target of 8–9 g/dL is acceptable in most patients; those with a high proportion of circulating HbH and those with IE may require higher pre-transfusion Hb targets
	▪ Red blood cell transfusion at a volume of 10–15 mL/kg should be considered 1 or more times to manage acute hemolytic episodes in patients of all ages when Hb <7 g/dL, with an aim to restore Hb to 8–9 g/dL
	▪ Regular blood transfusions are considered for prevention of significant growth failure, facial bone changes, failure of secondary sexual development, and massive splenomegaly in pediatric patients. They should also be considered for patients with the following:
	  ▪ Hb at steady-state <7 g/dL
	  ▪ Hb at steady-state 7–8 g/dL with the presentation of symptoms at <2 years of age and/or spleen size ≥3 cm below costal margin
	▪ Frequent transfusions may be considered in more severely affected adult patients for primary prevention of disease-related complications and for improvement of their quality of life
	▪ Regular blood transfusions should be considered for managing complications such as thrombotic diseases, cerebrovascular complications, and pulmonary hypertension
	▪ Periodic reassessment of TD pediatric and young adult patients is critical for tapering off or withdrawing blood transfusion when a sustained clinical benefit is achieved

Hb, hemoglobin; HbH, hemoglobin H; IE, ineffective erythropoiesis; TD, transfusion-dependent; TIF, Thalassemia International Federation

Taher A et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023.

NTD β-thal

TIF management guidelines: Anemia (2/3)

Hb level	IE/anemia-related symptoms or morbidities	IE/anemia-related intervention considerations and treatment objectives[a]
<10 g/dL	No	Long-term intervention to raise Hb level by ≥1 g/dL and prevent symptoms or morbidities
	Yes	▪ Short/limited-term intervention to reverse/alleviate symptoms or morbidities per physician's judgment, and ▪ Long-term intervention to raise Hb level by ≥1 g/dL and prevent progression or recurrence of symptoms or morbidities
≥10 g/dL	No	None
	Yes	▪ Short/limited-term intervention to reverse/alleviate symptoms or morbidities per physician's judgment, and ▪ Long-term intervention to prevent progression or recurrence of symptoms or morbidities per physician's judgment
Guide		
IE/anemia-related interventions	▪ Luspatercept (in patients aged ≥18 years) ▪ Blood transfusion (careful consideration of secondary iron overload [especially in patients with iron-related morbidity such as hepatic and endocrine disease] with long-term intervention and risk of alloimmunization) ▪ Hydroxyurea (in patients with *XmnI* polymorphism or Lepore or δβ-thalassemia, careful consideration of adverse events and loss of response with long-term intervention) ▪ Clinical trials	

[a]In conjunction with other management and prevention strategies indicated for specific symptoms or morbidities

Hb, hemoglobin; IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia; TIF, Thalassemia International Federation

Taher A, et al. NTDT Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-clinical-management-of-non-transfusion-dependent-thalassaemias-updated-version/. Accessed Dec 2023.

TDT

TIF management guidelines: Anemia (3/3)

	TDT

Criteria for initiating transfusion therapy	▪ Confirmed diagnosis of thalassemia
	▪ Laboratory criteria:
	  ▪ Hb <7 g/dL on 2 occasions, >2 weeks apart (excluding all other contributory causes such as infections)
	AND/OR
	▪ Clinical criteria irrespective of Hb level:
	  ▪ Hb >7 g/dL with any of the following:
	  ▪ Significant symptoms of anemia
	  ▪ Poor growth/failure to thrive
	  ▪ Complications from excessive intramedullary hematopoiesis such as pathologic fractures and facial changes
	  ▪ Clinically significant extramedullary hematopoiesis

Hb, hemoglobin; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation

Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023.

α-thal

TIF management guidelines: Iron overload (1/2)

	Deletional HbH	Non-deletional HbH
Iron overload assessment	▪ Check ferritin annually ▪ Check liver MRI for LIC if ferritin >200 ng/mL ▪ Mild-to-moderate iron overload is observed in the fourth to fifth decades of life, and is earlier in males than females	▪ Patients with NTDT: Monitor serum ferritin levels with every clinical visit and measure LIC with MRI if ferritin is >300 ng/mL
Iron chelation	▪ Start if LIC >5 mg/g dw or ferritin >500 ng/mL ▪ Treat until LIC <3 mg/g dw and ferritin <300 ng/mL, then stop ▪ Treat at lower level of LIC in presence for specific indications	▪ Patients with NTDT: Iron chelation should be started if LIC >5 mg/g dw or ferritin >500 ng/mL

dw, dry weight; Hb, hemoglobin; HbH, hemoglobin H; LIC, liver iron concentration; MRI, magnetic resonance imaging; NTDT, non–transfusion-dependent thalassemia; TIF, Thalassemia International Federation

Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023.

TIF management guidelines: Iron overload (2/2)

	NTD β-thalassemia[1]	TDT[2]
Iron overload assessment	All patients with NTDT aged ≥10 years should be frequently assessed for iron overload status	▪ Serum ferritin concentration is measured at least every 3 months (1–3 months) ▪ Target value is currently between 500–1000 µg/L ▪ Measuring the trends in serum ferritin over a period of at least 3 months is a more reliable indicator for adjusting therapy than the use of single values ▪ LIC and myocardial iron should be monitored regularly in patients from age <9 years if they are able to tolerate MRI scanning without sedation
Iron chelation	Deferasirox should be initiated in patients with NTDT aged ≥10 years if any of the below are evident: ▪ Liver iron concentration ≥5 mg Fe/g dw ▪ Serum ferritin level ≥800 ng/mL ▪ Serum ferritin level >300 to <800 ng/mL (LIC measurement is not possible) and other clinical/laboratory measures indicative of iron overload	In children aged >6 years and adults ▪ Deferoxamine: First-line TM ▪ Deferiprone: Under European licensing, deferiprone is approved if other chelators or deferoxamine are inadequate ▪ Deferasirox: First-line TM and NTDT

dw, dry weight; Hb, hemoglobin; LIC, liver iron concentration; MRI, magnetic resonance imaging; NTD, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation; TM, thalassemia major

1. Taher A, et al. NTDT Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-clinical-management-of-non-transfusion-dependent-thalassaemias-updated-version/. Accessed Dec 2023; 2. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023.

TIF management guidelines: Endocrine and bone disease (1/2)

	Deletional and non-deletional HbH[1]	NTD β-thalassemia[2]
Endocrine disease	If onset of puberty is delayed >2 years or if concerns of slow growth, obtain a family history and consider X-ray for bone age	▪ Hypogonadism (adults): Routine assessment for infertility, secondary hypogonadism, impotence ▪ Hypothyroidism (≥10 years): Annual assessment of free thyroxine and thyroid-stimulating hormone (TSH) ▪ Hypoparathyroidism (≥10 years): Annual assessment of calcium, phosphate, vitamin D, and parathyroid hormone (if indicated) ▪ Diabetes mellitus (≥10 years): Annual assessment of fasting blood sugars and oral glucose tolerance test (if indicated) ▪ Adrenal insufficiency (≥10 years): Annual assessment adrenocorticotropic hormone stimulation test
Bone disease	DXA scan every 3 years (or more frequently if indicated) starting at 12 years	▪ Osteoporosis (≥10 years): bone mineral density (BMD) spine, hip, radius, ulna (DXA) every 24 months/12 months with abnormality ▪ Standards for osteoporosis prevention in patients with NTDT should follow guidelines for patients with TDT ▪ Patients with established endocrine disease or osteoporosis should be referred to an endocrinologist for management according to local standards or international guidelines or as per recommendations in patients with TDT

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HbH, hemoglobin H; NTD, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation; TSH, thyroid-stimulating hormone

1. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023; 2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023.

TDT

TIF management guidelines: Endocrine and bone disease (2/2)

	TDT
Endocrine disease	▪ Periodic evaluation for endocrine complications should be carried out in patients with TDT with iron overload ▪ Sub-clinical hypothyroidism (basal TSH 5–8 mUI/mL) requires regular follow-up and optimizing chelation therapy ▪ Normalization of total body iron load with intensive combined chelation (deferoxamine plus deferiprone) reverses cardiac and endocrine complications of TDT ▪ Monitoring of growth, pubertal development, reproductive ability, and endocrine functions in general are essential to achieve a good quality of life in TDT
Bone disease	▪ Annual checking of BMD, biochemical markers of bone metabolism (NTX, CTX, bALP) ▪ Physical activity encouraged ▪ Smoking discouraged ▪ Adequate calcium intake during skeletal development can increase bone mass in adult life, and in combination with low-dose vitamin D, may prevent bone loss and fractures ▪ Early diagnosis of diabetes mellitus ▪ Adequate iron chelation may prevent iron toxicity in the bone ▪ Hormonal replacement where it is needed ▪ Bisphosphonates should be given concomitantly with calcium and vitamin D, and not for >2 years

bALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CTX, C-terminal cross-linking telopeptide of collagen type-I; NTX, N-terminal cross-linking telopeptide of collagen type-I; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation; TSH, thyroid-stimulating hormone

Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023.

TIF management guidelines: Splenectomy

Deletional and non-deletional HbH[1]	NTD β-thalassemia[2]	TDT[3]

Deletional: Not indicated
 	
Non-deletional HbH:
▪ Splenectomy can increase Hb levels and decrease need for transfusions in patients with HbH-CS
▪ Splenectomy should be avoided in patients aged <5 years
▪ Procedure should be reserved for patients with severe anemia and limited access to blood transfusions, hypersplenism with anemia, leukopenia or thrombocytopenia resulting in infections or bleeding, or massive splenomegaly with left upper quadrant pain that increases the risk of splenic rupture
▪ Prophylactic use of low-dose aspirin recommended for all patients who have undergone splenectomy
	▪ The spleen size should be examined in clinical visits and splenectomy should generally be avoided in patients with NTDT aged <5 years, and otherwise reserved for cases of:
	  ▪ When other interventions to manage anemia are contraindicated
	  ▪ Hypersplenism leading to worsening anemia, leukopenia, or thrombocytopenia and causing clinical problems such as recurrent bacterial infections or bleeding
	  ▪ Splenomegaly accompanied by symptoms such as left upper quadrant pain or early satiety
	  ▪ Massive splenomegaly (largest dimension >20 cm) with concern about possible splenic rupture
		▪ Splenectomy is not currently recommended as a standard procedure due to the large evidence of disease burden and links to complications such as PHT, silent brain infarcts, venous thrombosis, and sepsis
		▪ Current optimal transfusion regimens and iron chelation have considerably reduced the incidence of splenomegaly and iron overload in patients with TDT
		▪ Splenectomy should be considered in 3 clinical scenarios:
		  ▪ Increased blood requirement that prevents adequate control with iron chelation therapy
		  ▪ Hypersplenism
		  ▪ Symptomatic splenomegaly

Hb, hemoglobin; HbH, hemoglobin H; HbH-CS, hemoglobin Constant Spring; NDT, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; PHT, pulmonary hypertension; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation

1. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023;
2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023;
3. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023.

TIF management guidelines: Pulmonary hypertension (PHT)

Deletional and non-deletional HbH[1]	NTD β-thalassemia[2]	TDT[3]

ECHO: Check at 10–12 years to assess for pulmonary arterial pressure; if normal repeat every 3–5 years	▪ Annual ECHO for the assessment of tricuspid-valve regurgitant jet velocity (TRV)
	  ▪ TRV >2.5 m/s and asymptomatic: “possible” to have PHT
	  ▪ TRV >2.5 m/s and symptomatic or with other echocardiographic criteria suggestive of PHT: “likely” to have pulmonary hypertension
	  ▪ TRV >3.2 m/s: “likely” to have PHT
	▪ Patients “likely” to have PHT: Undergo right heart catheterization to confirm diagnosis; ventilation/perfusion lung scan testing also recommended
	▪ Patients confirmed PHT: Refer to cardiologist and managed per local standards/international guidelines for treatment of PHT
	▪ Patients “possible,” “likely,” or confirmed PHT should be closely monitored and managed for IE/anemia, iron overload, and hypercoagulability
		▪ Clinical examination, electrocardiogram, chest radiogram, ECHO
		  ▪ Repeat annual if normal
		  ▪ Every 6–12 months in cardiac iron overload (T2*<20 ms)
		  ▪ Every ≤6 months in heart disease
		  ▪ Repeat if disease development/change of symptoms
		▪ MRI T2*
		  ▪ Every ≥2 years if normal
		  ▪ Every ≤12 months in cardiac iron overload (T2*<20 ms) or heart disease
		  ▪ Repeat if disease development or diagnosis of heart disease

ECHO, echocardiogram; HbH, hemoglobin H; IE, ineffective erythropoiesis, MRI, magnetic resonance imaging; NTD, non–transfusion-dependent; PHT, pulmonary hypertension; TDT, transfusion-dependent thalassemia; TIF, Thalassemia International Federation; TRV, tricuspid-valve regurgitant jet velocity

1. Taher A, et al. Alpha-thalassemia Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed Dec 2023;
2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023;
3. Farmakis D, et al. A short guide for the management of TDT: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed Dec 2023.

NTD β-thal

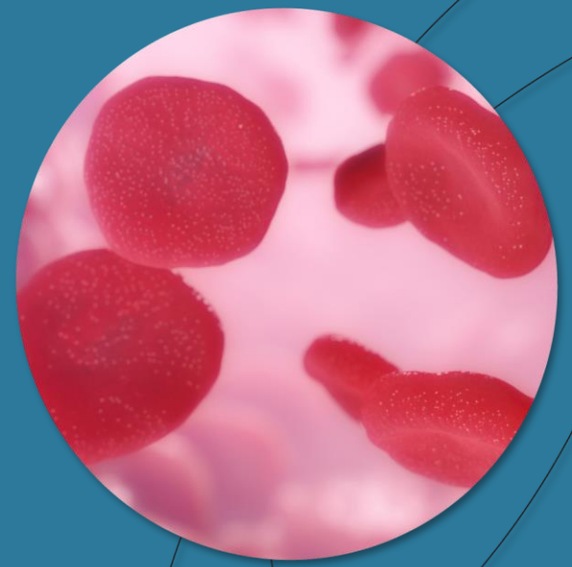
TIF management guidelines: Hypercoagulability and thrombotic disease

	NTD β-thalassemia
Hypercoagulability and thrombotic disease	▪ Patients who present with unprovoked, spontaneous thrombosis at unusual sites should also be worked up for thrombophilia, especially in regions with high prevalence of common mutations ▪ High-risk patients should be closely monitored and managed for IE/anemia and iron overload ▪ Prophylactic intervention with anticoagulant or antiaggregant therapy in high-risk patients should follow local standards or international guidelines: ▪ Enoxaparin or newer oral anticoagulants may be considered, while acknowledging lack of data in thalassemia, especially if long-term prophylaxis is needed ▪ Aspirin therapy should be considered in splenectomized patients with NTDT with elevated platelet counts (≥500 × 10^9/L) ▪ Patients who develop thrombotic or cerebrovascular disease should be treated as per local standards or international guidelines in patients without thalassemia

IE, ineffective erythropoiesis, NTD, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; TIF, Thalassemia International Federation

Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Dec 2023.

Burden of disease: Healthcare resource utilization (HCRU) burden



Patients with thalassemia have higher costs and HCRU than matched controls[1–3]

TD β-thalassemia

- A study comparing adults with **TDT (all β-thalassemia)** vs healthy controls found that the mean annual total, drug, emergency room (ER), inpatient (IP), and outpatient (OP) costs were **significantly higher** (all p<0.05) in patients compared with controls in a 2-year follow-up[1,2]
  - **TD β-thalassemia** was associated with high **annual iron chelation costs** ($59,596 [cost year not reported]) and iron chelation drug administration ($2,690 [cost year not reported])[1]
  - The **mean cost of a transfusion procedure** in **TD β-thalassemia** was $29,461 (cost year not reported) and the cost of blood tests to screen for infectious disease pathogens prior to transfusion was $9,235 (cost year not reported)[1]

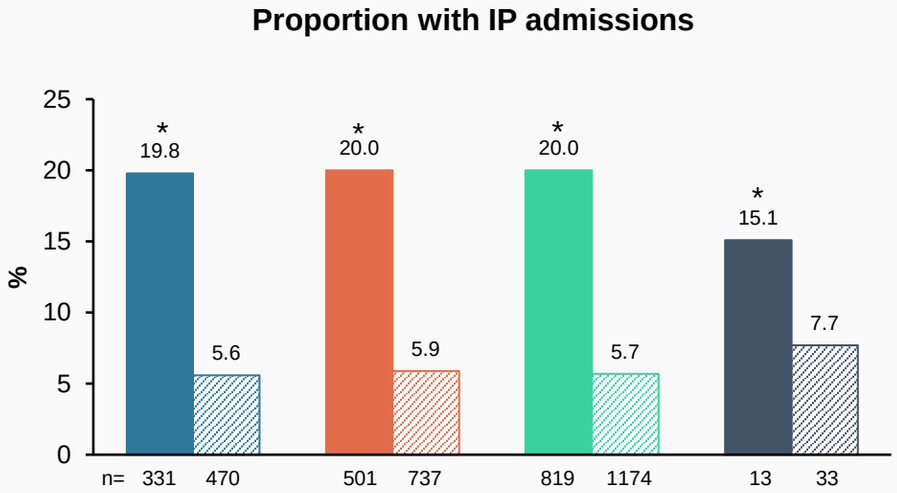
NTD vs TD β-thalassemia

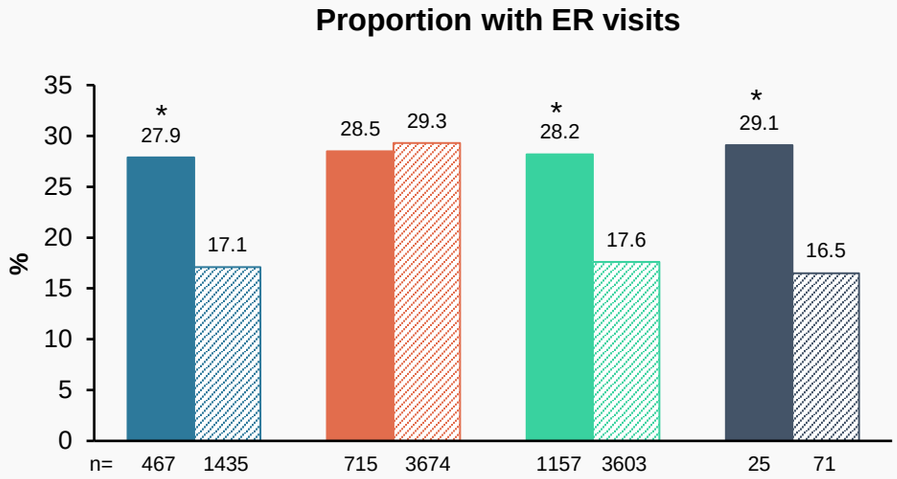
- A cross-sectional Lebanese study in patients with **β-thalassemia** measured out of pocket costs in a mixed adult **TDT** and **NTDT** population with separate outcomes for each subgroup[3]
  - **No significant differences** in the monthly out of pocket expenditures between adults with **TD** and **NTD** **β-thalassemia** were found
    - Median (range) out of pocket costs: $47.50 ($0–500) [cost year not reported] for **TI** vs $150 ($0–500) [cost year not reported] for **TM**, p=0.238

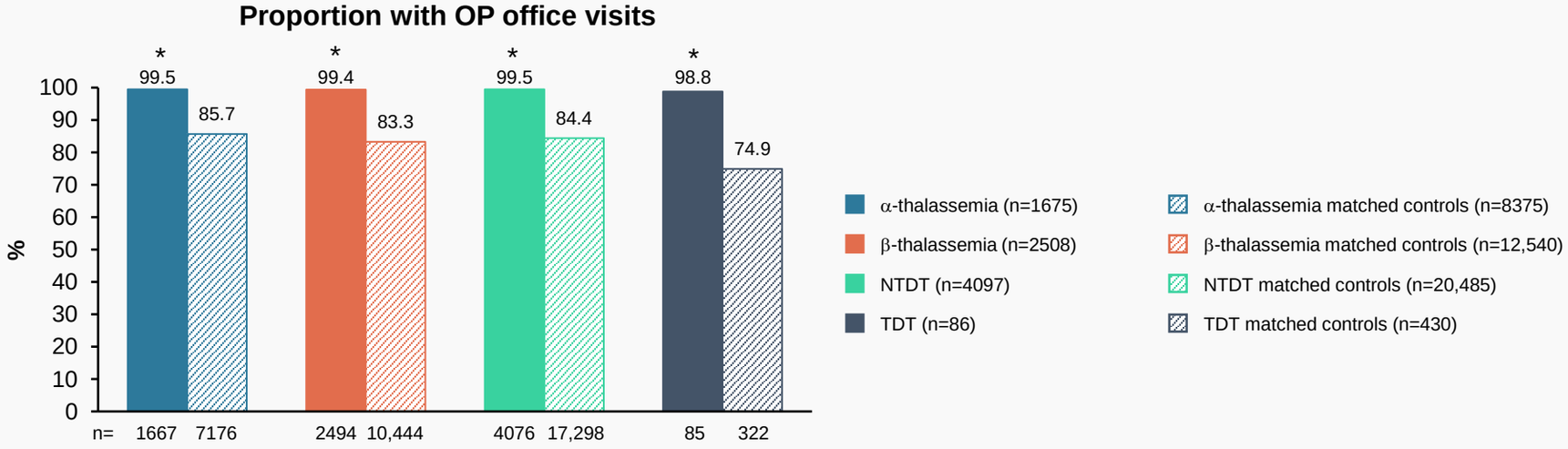
ER, emergency room; HCRU, healthcare resource utilization; IP, inpatient; NTD, non–transfusion-dependent; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; PPPY, costs per patient per year; TD, transfusion-dependent; TDT, transfusion-dependent thalassemia; TI, thalassemia intermedia; TM, thalassemia major

1. Weiss M, et al. *Am J Hematol* 2019;94(5):E129–32; 2. Sheth S, et al. *Blood* 2017;130:2095; 3. Musallam KM, et al. *Eur J Haematol* 2011;87(1):73–79.

Healthcare utilization in the Commercial/Medicare population during 12-month follow-up



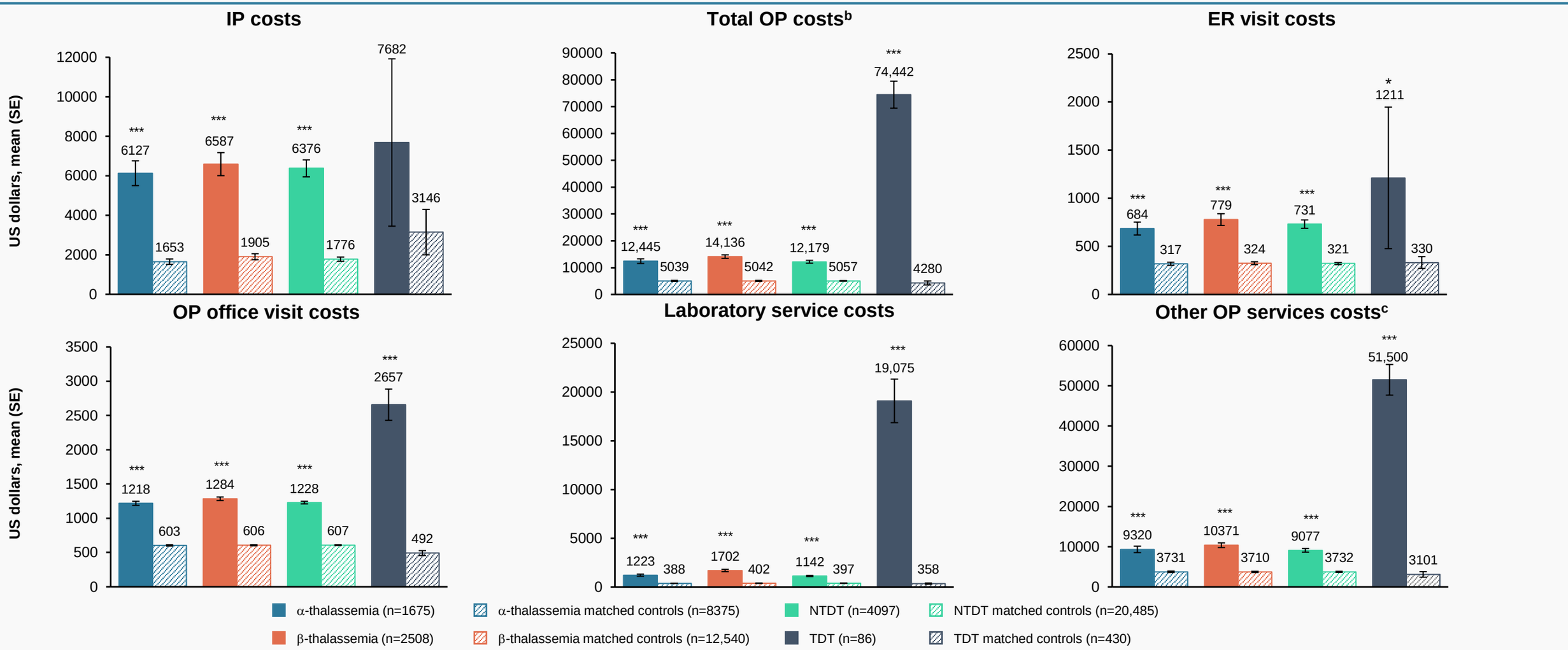




Most of the HCRU outcomes during the 12-month follow-up were significantly higher across all thalassemia cohorts compared with matched controls (p<0.05)

*p<0.05
ER, emergency room; HCRU, healthcare resource utilization; IP, inpatient; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; TDT, transfusion-dependent thalassemia
Langer AL, et al. *Hemasphere* 2023 Aug 8;7(Suppl):e333151f.

Healthcare costs in the **Commercial/Medicare** population during 12-month follow-up[a]



Healthcare costs during the 12-month follow-up were significantly higher across all thalassemia cohorts compared with matched controls (all p<0.05)

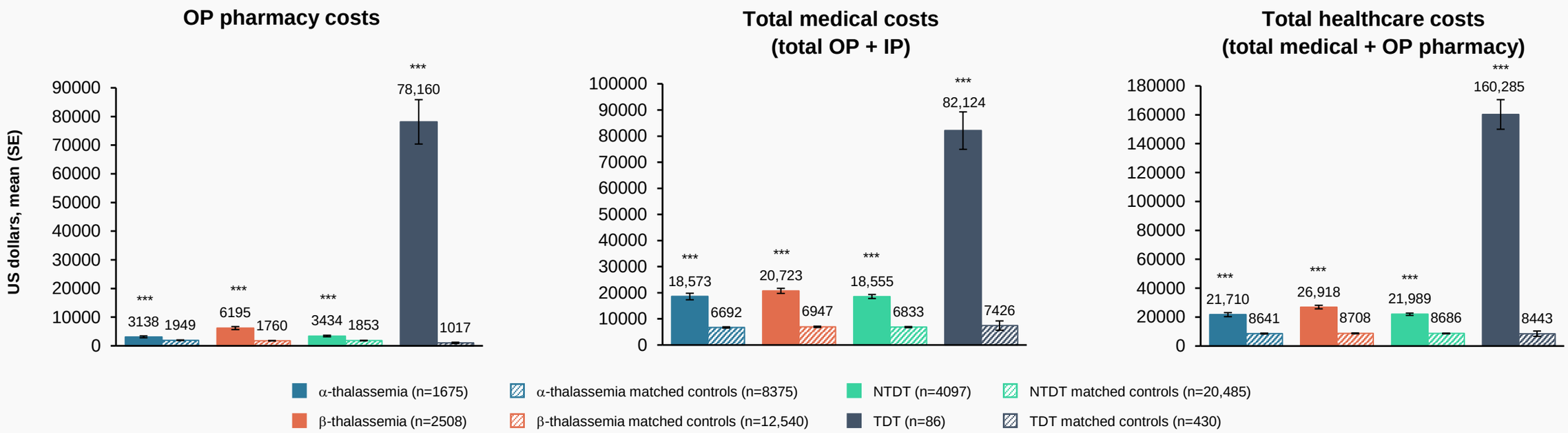
*p<0.05; **p≤0.01; ***p≤0.001

[a]Costs are per patient per year. [b]Total OP costs include those for OP office visits, laboratory services, other OP services, and ER visits. [c]Other OP costs include those for physical therapy, occupational therapy, chiropractic services, transfusions, chelation therapy, MRIs, and bone mineral density scans.

ER, emergency room; IP, inpatient; MRI, magnetic resonance imaging; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; TDT, transfusion-dependent thalassemia

Langer AL, et al. *Hemasphere* 2023;7(Suppl):e333151f.

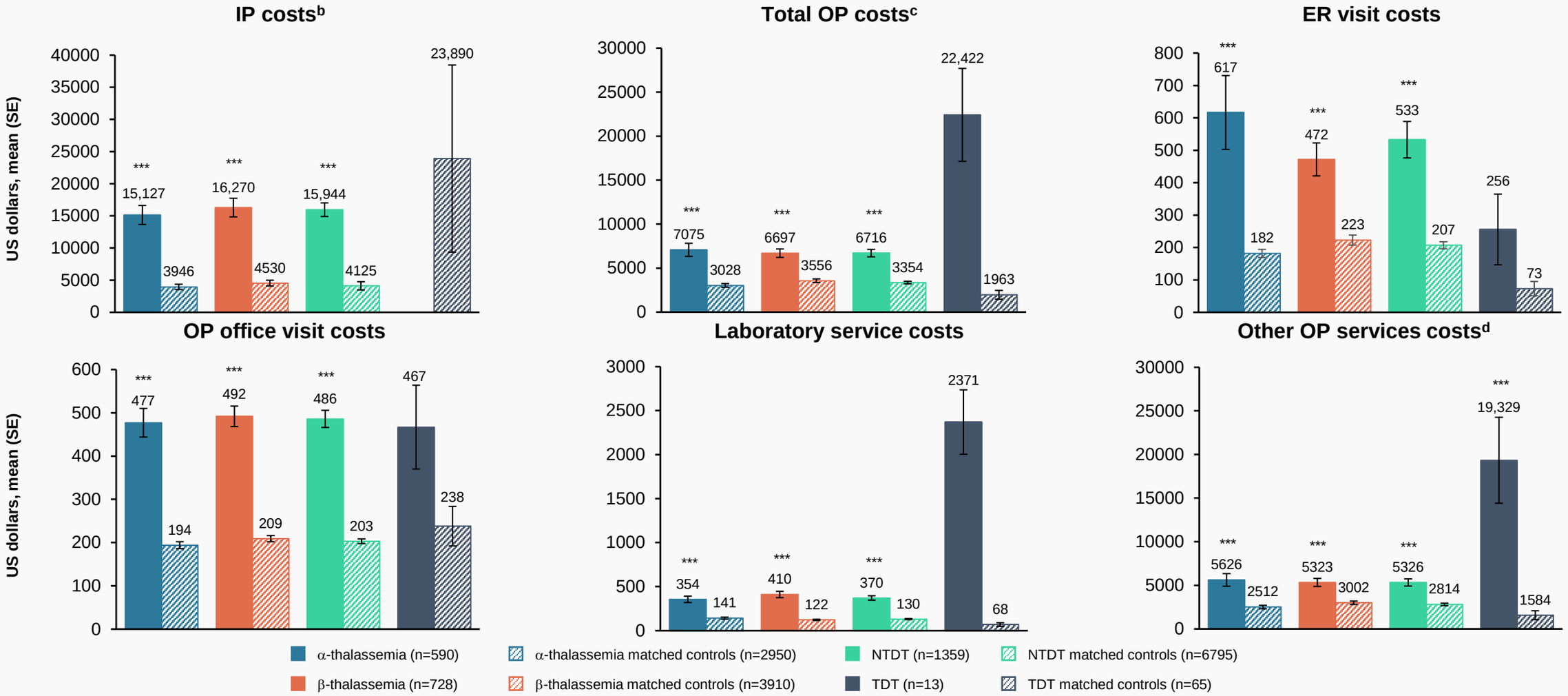
Healthcare costs in the **Commercial/Medicare** population during 12-month follow-up[a]



Healthcare costs during the 12-month follow-up were significantly higher across all thalassemia cohorts compared with matched controls (all p<0.05)

*p<0.05; **p≤0.01; ***p≤0.001
[a]Costs are per patient per year
IP, inpatient; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; TDT, transfusion-dependent thalassemia
Langer AL et al. *Hemasphere* 2023;7(Suppl):e333151f.

Healthcare costs in the **Medicaid** population during 12-month follow-up[a]



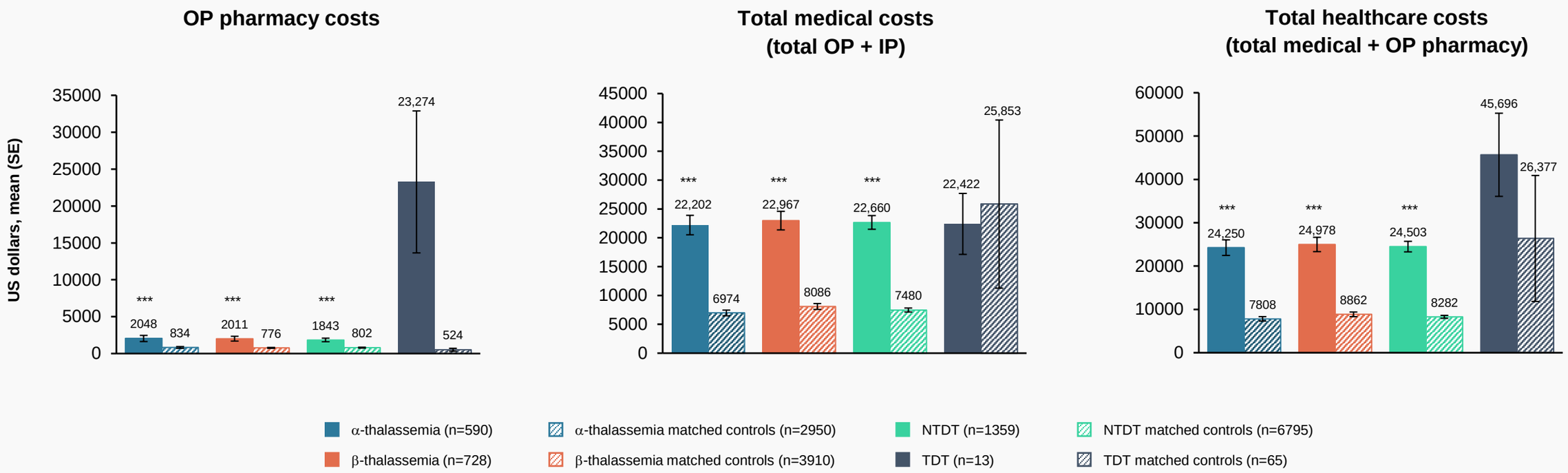
Healthcare costs were significantly higher across the α-thalassemia, β-thalassemia, and NTDT cohorts compared with matched controls (all p<0.05)[e]

[a]Costs are per patient per year. [b]Although 1 Medicaid patient with TDT had 2 IP admissions, the IP per person per year costs were reported as $0.00. [c]Total OP costs include those for OP office visits, laboratory services, other OP services, and ER visits. [d]Other OP costs include those for physical therapy, occupational therapy, chiropractic services, transfusions, chelation therapy, MRIs, and bone mineral density scans. [e]Sample sizes were low in TDT groups, and statistical comparisons were not conducted in TDT groups vs their matched controls.

ER, emergency room; IP, inpatient; MRI, magnetic resonance imaging; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; TDT, transfusion-dependent thalassemia

Langer AL, et al. *Hemasphere* 2023;7(Suppl):e333151f.

Healthcare costs in the **Medicaid** population during 12-month follow-up[a]



Healthcare costs were significantly higher across the α-thalassemia, β-thalassemia, and NTDT cohorts compared with matched controls (all p<0.05)

*p<0.05; **p≤0.01; ***p≤0.001

[a]Costs are per patient per year. [b]Although 1 Medicaid patient with TDT had 2 IP admissions, the IP per person per year costs were reported as $0.00. [b]Total OP costs include those for OP office visits, laboratory services, other OP services, and ER visits. [c]Other OP costs include those for physical therapy, occupational therapy, chiropractic services, transfusions, chelation therapy, MRIs, and bone mineral density scans

ER, emergency room; IP, inpatient; MRI, magnetic resonance imaging; NTDT, non–transfusion-dependent thalassemia; OP, outpatient; TDT, transfusion-dependent thalassemia

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NTDT

In patients with NTDT, lower Hb levels are associated with higher HCRU

- A US retrospective claims analysis study using **Merative MarketScan Commercial**, **Medicare**, and **Lab results** databases, for the 12-month follow-up period found that:

	All NTDT (α or β) n=898	α-NTDT subgroup n=400
HCRU: Incidence rate ratio associated with 1 g/dL decrease in average Hb (mean [95% CI])		
IP admissions	1.17 [1.10, 1.24]***	1.15 [1.05, 1.25]*
OP visits	1.08 [1.05, 1.10]***	1.06 [1.02, 1.10]*
ER visits	1.11 [1.05, 1.18]***	1.16 [1.08, 1.26]*
Cost: Percentage change in cost associated with 1 g/dL decrease in average Hb (mean [95% CI])		
Total healthcare costs	15% [10%, 21%]***	14% [7%, 22%]***
IP costs	56% [35%, 81%]***	47% [19%, 82%]***
OP costs	12% [7%, 17%]***	10% [4%, 17%]***
ER costs	20% [7, 36%]*	30% [9%, 54%]*
Prescription costs	12% [0%, 26%]	9% [–8%, 31%]

Each 1 g/dL decrease in Hb level was associated with significantly higher HCRU and costs in all patients with NTDT, including all patients with α-NTDT

*p<0.01; ***p<0.001

CI, confidence interval; ER, emergency room; Hb, hemoglobin; HCRU, healthcare resource utilization; IP, inpatient; NTDT, non–transfusion-dependent thalassemia; OP, outpatient

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