Sindrome talassemica: l'anemia come fattore prognostico

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Disclosures of Name Surname

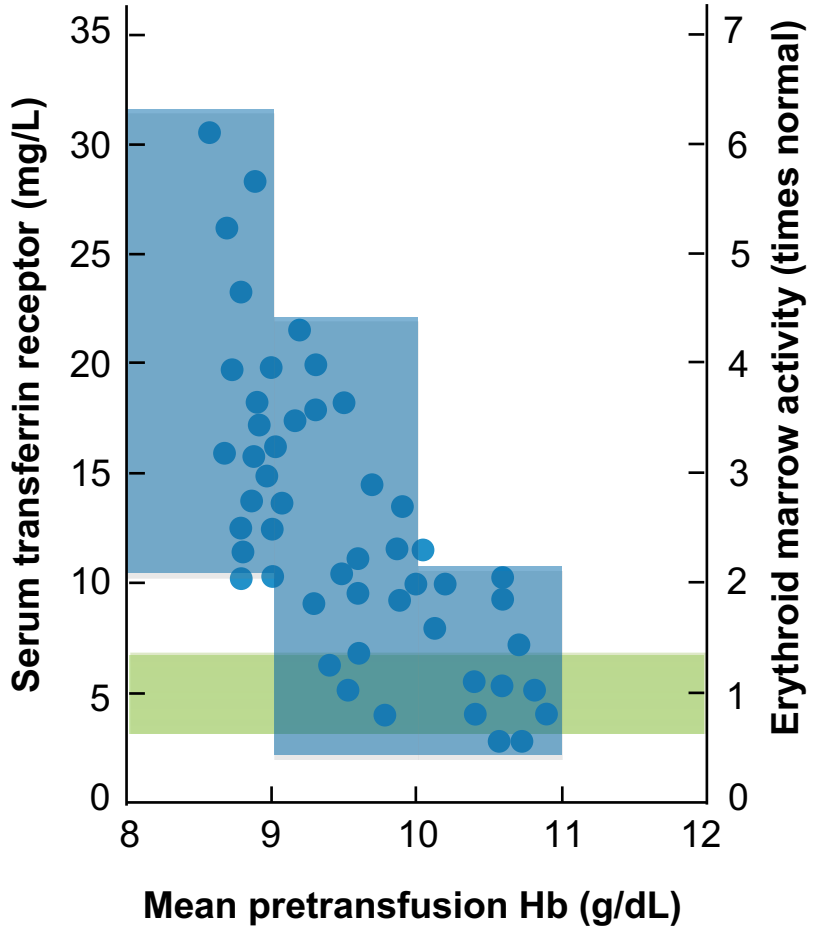
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
VERTEX					X	X	

Regimi trasfusionali utilizzati nel trattamento delle talassemia major

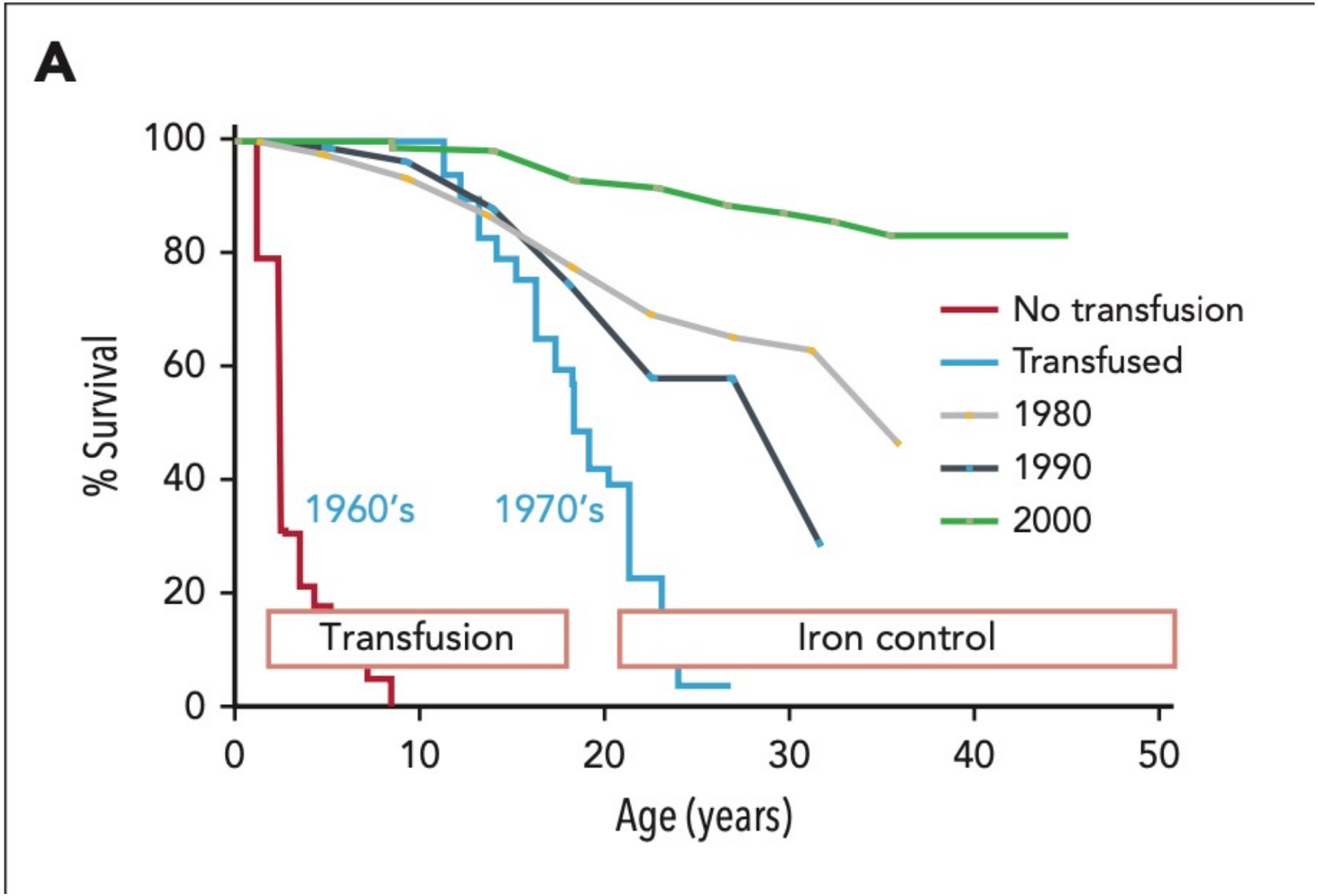
anni	Hb pre-trasfusionale
1955-1960	<6 g/dl
1961 (Orsini)	>6 g/dl
1969 (Wolman e Ortolani)	9.5-10 g/dl
1980 (Propper)	11.5-12 g/dl
1995-1999	9.5 ±0.4 g/dl

Relation between transfusion regimen and suppression of erythropoiesis

- Relation between pre-transfusion Hb level and erythroid activity in thalassemia major patients
  - pre-transfusion Hb 10–11g/dL: 1–2 x normal erythroid activity
  - pre-transfusion Hb 9–10 g/dL: 1–4 x normal erythroid activity
  - pre-transfusion Hb 8–9 g/dL: 2–6 x normal erythroid activity
- A transfusion programme with baseline hemoglobin 9–10 g/dL may provide enough suppression of erythropoiesis



Cazzola M *et al. Br J Haematol* 1995;89:473-478.


A
100
80
60
40
20
0
% Survival
No transfusion
Transfused
1980
1990
2000
1960's
1970's
Transfusion
Iron control
0
10
20
30
40
50
Age (years)

TO THE EDITOR:

Pretransfusion hemoglobin level and mortality in adults with transfusion-dependent β-thalassemia

Khaled M. Musallam,[1] Susanna Barella,[2] Raffaella Origa,[3] Giovanni Battista Ferrero,[4] Roberto Lisi,[5] Annamaria Pasanisi,[6] Filomena Longo,[7] Barbara Gianesin,[8] and Gian Luca Forni,[8,9] on behalf of the Webthal project

- In this landmark study, the 10-year survival of a group of 779 patients with TDT of median age 33.1 years (range 18.1-61 years) increased monotonically from 91% to 100% in 5 categories marked by median pretransfusion hemoglobin levels that increased from <9.0 to ≥10.5 g/dL in 0.5-g/dL increments.
- Of note, 88% of the thalassemia-related deaths were in groups with a median hemoglobin <10 g/dL and 70% were from cardiovascular disease.
- When the data were stratified by ferritin, the association with hemoglobin level groups was only significant for ferritin <1000 ng/mL, consistent with an effect of anemia on survival separate from that of iron overload.

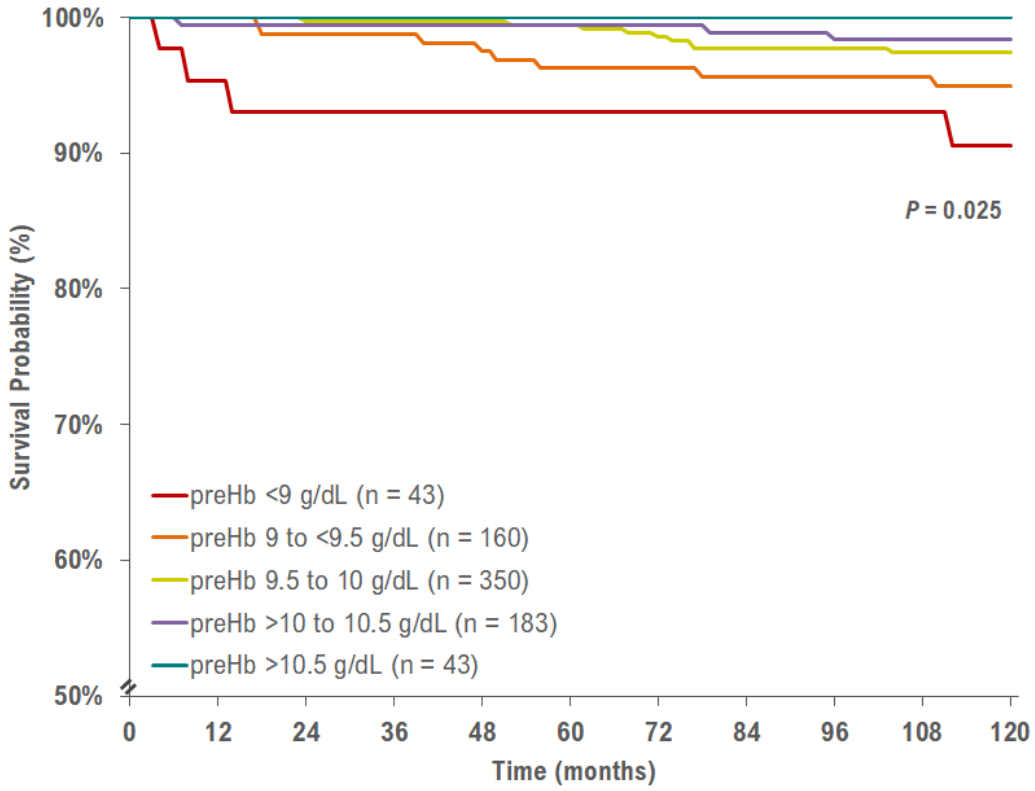
***Blood* 2024;143:930-932**

Pretransfusion hemoglobin level vs mortality in TDT

Pretransfusion hemoglobin[a]	Deaths n (%)	Pearson's Chi-square (P-value)	5-year survival	10-year survival	Log-rank Chi-square (*P*-value)
<9 g/dL (n = 43)	4 (9.3)	10.492 (0.033)	93%	91%	11.370 (0.025)
9 to <9.5 g/dL (n = 160)	8 (5.0)		96%	95%	
9.5 to 10 g/dL (n = 350)	9 (2.6)		99%	97%	
>10 to 10.5 g/dL (n = 183)	3 (1.6)		99%	98%	
≥10.5 g/dL (n = 43)	0 (0.0)		100%	100%	

Pretransfusion hemoglobin[a]	Unadjusted HR	95% CI (P-value)	Adjusted HR[b]	95% CI (*P*-value)
<9 g/dL (n = 43)	1.00 (referent)	-	1.00 (referent)	-
9 to <9.5 g/dL (n = 160)	0.506	0.162-1.681 (0.266)	0.563	0.165-1.919 (0.358)
9.5 to 10 g/dL (n = 350)	0.256	0.079-0.830 (0.023)	0.248	0.074-0.832 (0.024)
>10 to 10.5 g/dL (n = 183)	0.162	0.036-0.724 (0.017)	0.125	0.027-0.574 (0.008)
≥10.5 g/dL (n = 43)	NC	NC	NC	NC

[a]10-year observation period average.
[b]Adjusted for age at study start, center, sex, presence of active morbidity at baseline in a multivariate forward stepwise Cox regression model. HR, hazard ratio; CI, confidence interval; NC, non-calculable.



Musallam KM *et al. Blood* 2024;143:930-932.

Relationship Between Pretransfusion Hemoglobin Level and Mortality in Adult Patients with Transfusion-Dependent β-Thalassemia

Context of research

- A pretransfusion Hb of 9-10 g/dL has been previously shown to adequately suppress the expanded erythropoiesis in β-thalassemia
- The impact of different pretransfusion Hb levels on thalassemia-related mortality is yet unclear

Patients and Methods

- 779 patients
- Multivariate Cox regression model with the outcome of thalassemia-related mortality as the dependent variable

$$h(t)$$

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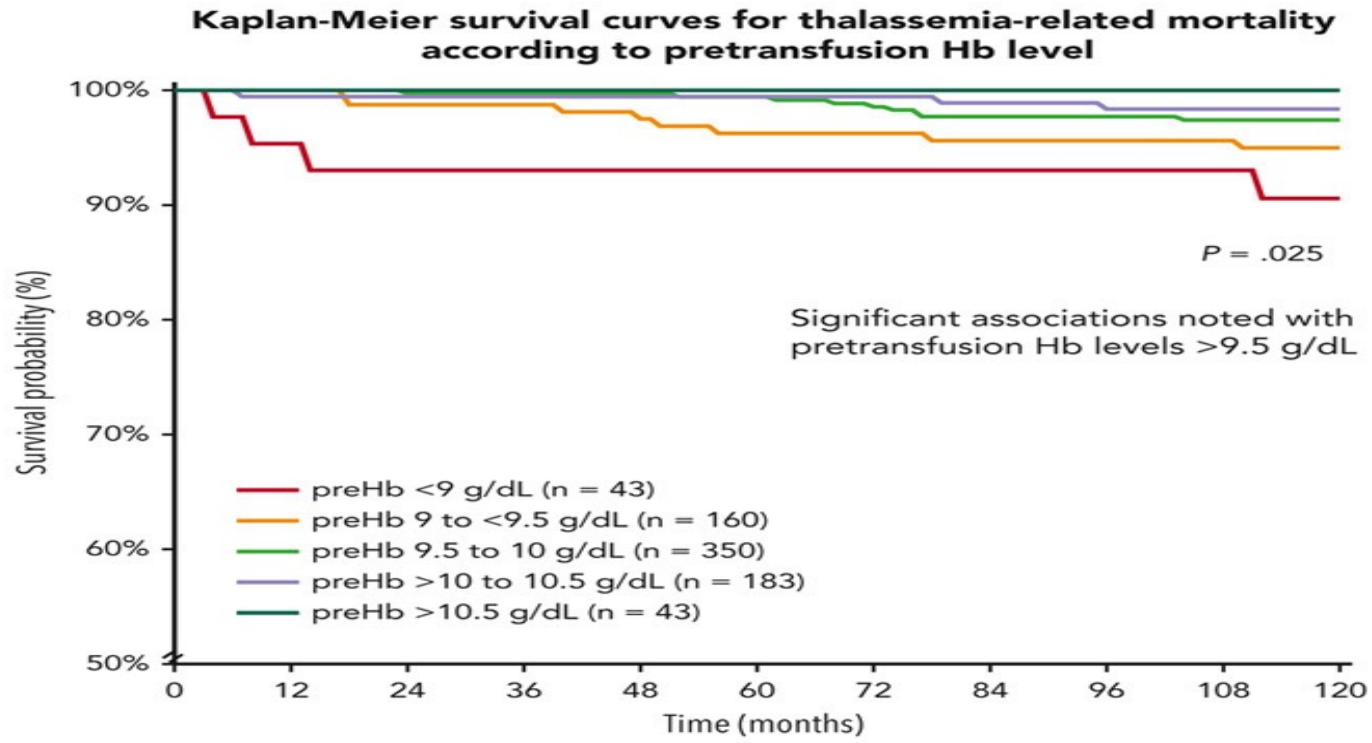
Main findings



Conclusion: In adult patients with transfusion-dependent β-thalassemia, higher pretransfusion Hb levels (starting at 9.5 g/dL) were associated with lower thalassemia-related mortality.

*Musallam et al. DOI: 10.1182/**blood**.2023022460*

blood Visual Abstract

Interpretazioni

- - Incremento del 9% della sopravvivenza significativa su 10 anni
- - Differenze di Hb (9,0 vs 10,5 g/dL) hanno impatto clinico
- - L’anemia cronica danneggia soprattutto tessuti ad alta richiesta di ossigeno (es. cuore)

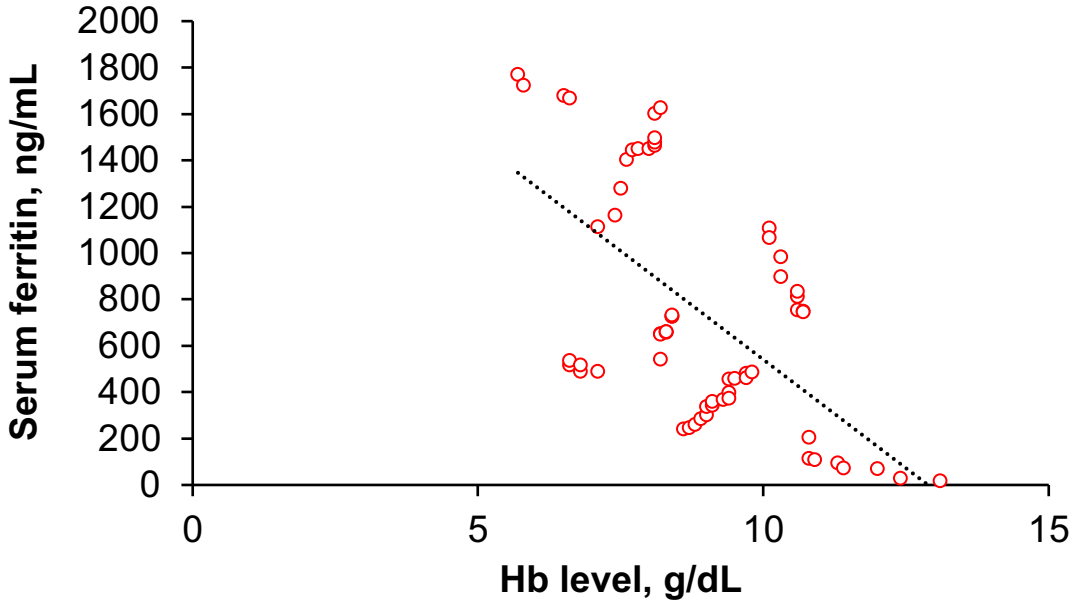
Implicazioni cliniche

- - Target Hb: ≥9,5–10,5 g/dL, idealmente >10,5 g/dL
- - Effetti dell’anemia dipendono da:
- • Causa (eritropoiesi inefficace)
- • Durata (anemia cronica)

Hemoglobin level as a biomarker of morbidity and mortality in NTDT

Chronic anemia is independently associated with clinical morbidity in NTDT

A Hb level of <7 g/dL was the level below which all patients developed a morbidity, while Hb >10 g/dL was the level after which none of the patients had a morbidity (area under the curve = 0.84, 95% CI: 0.70–0.97, p <0.001)



Pearson's r = −0.5951; p <0.001

63 patients

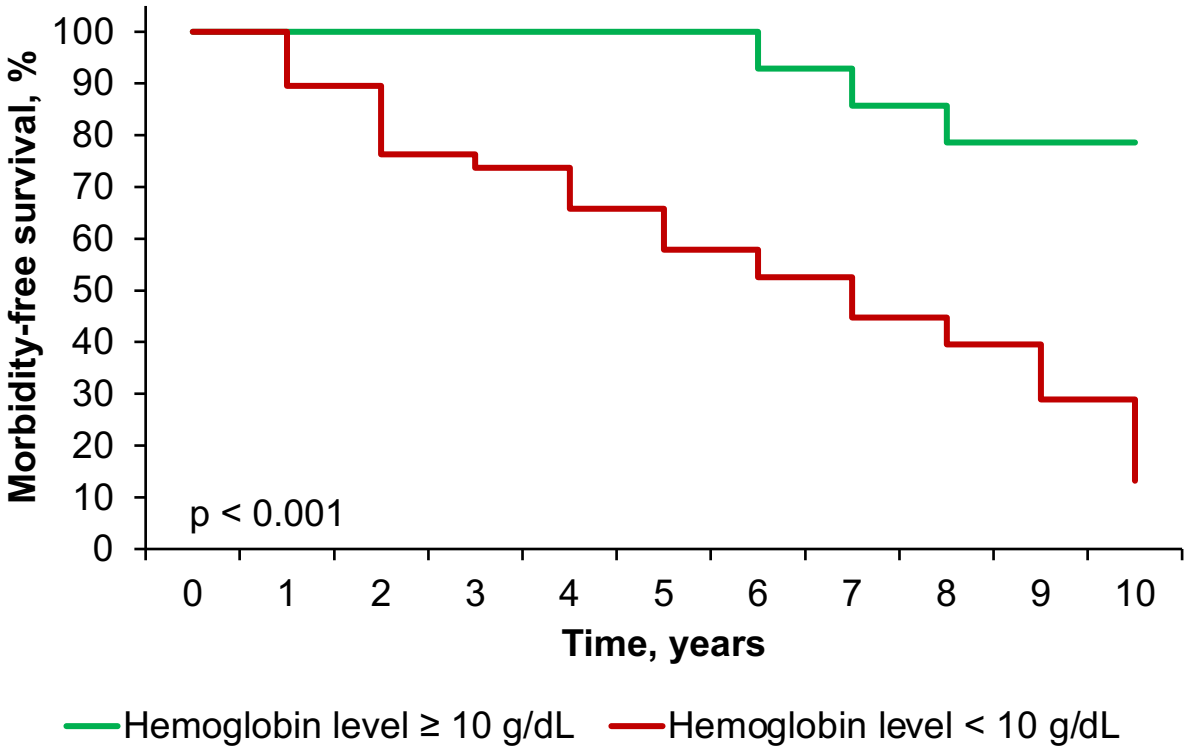
Taher AT, Musallam KM *et al. Blood Cell Mol Dis* 2015;55:108–109.

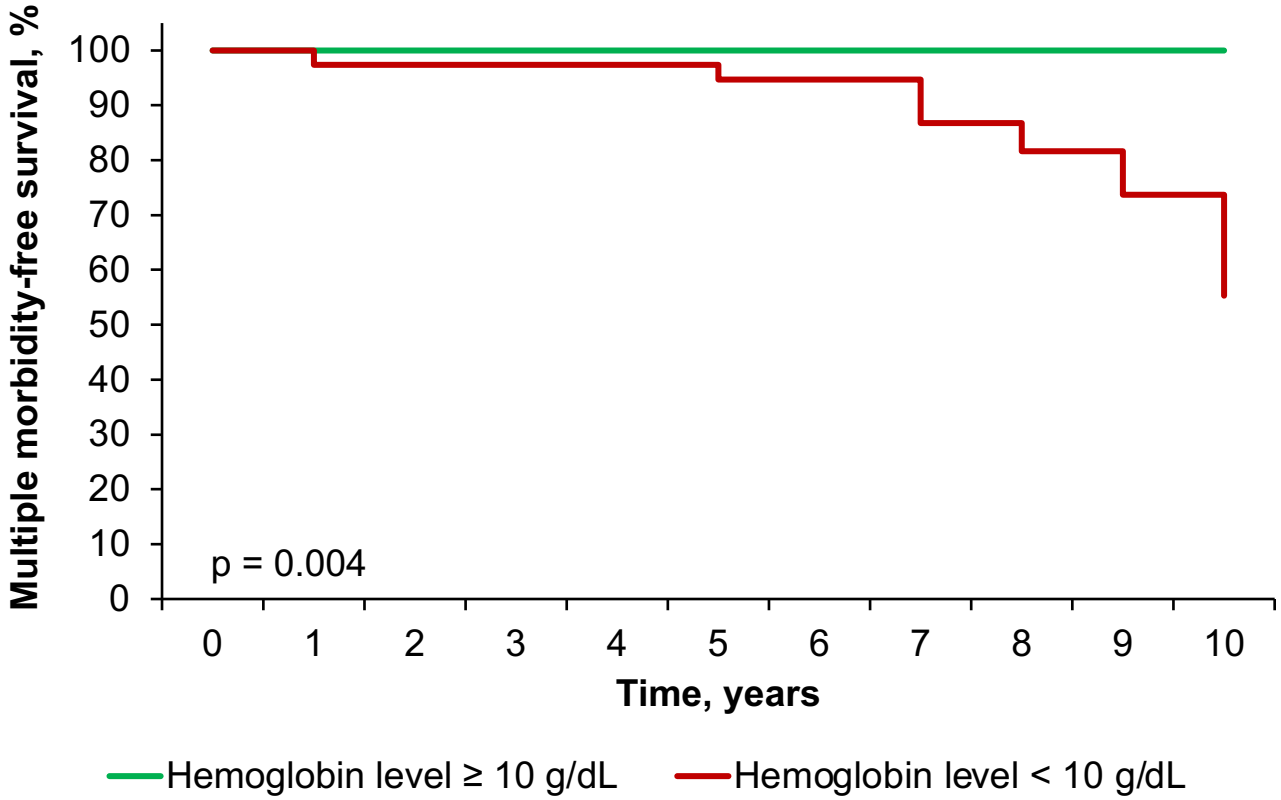
Talassemia intermedia (NTDT)

- Studio su 2033 pazienti: sopravvivenza mediana 46,3 anni
- Se Trasfusi: 95% vivi a 75 anni vs 62,2% se non trasfusi
- Se Trasfusi → −80% mortalità totale e cardiaca
- Hb <10 g/dL Triplica il rischio di morbidità multiple da anemia in 10 anni
- - Sopravvivenza libera da complicanze significativamente migliore con Hb >10 g/dL
- Complicanze: ipertensione polmonare, osteoporosi, deformità ossee, ematopoiesi extramidollare, splenomegalia, ictus, morte prematura

Musallam KM *et al. Ann Hematol* 2022;101:203-204

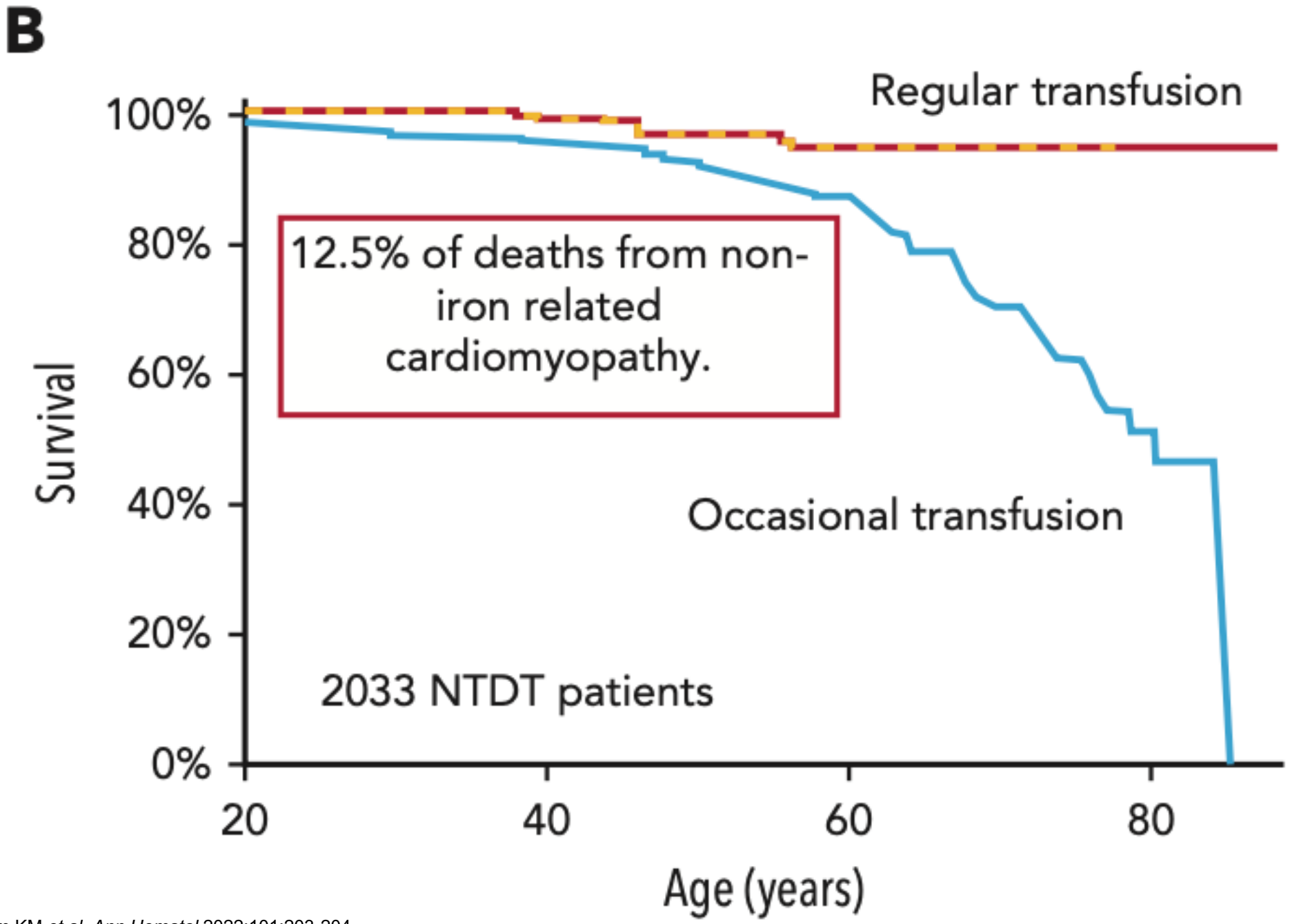
Morbidity free-survival vs hemoglobin level in NTDT



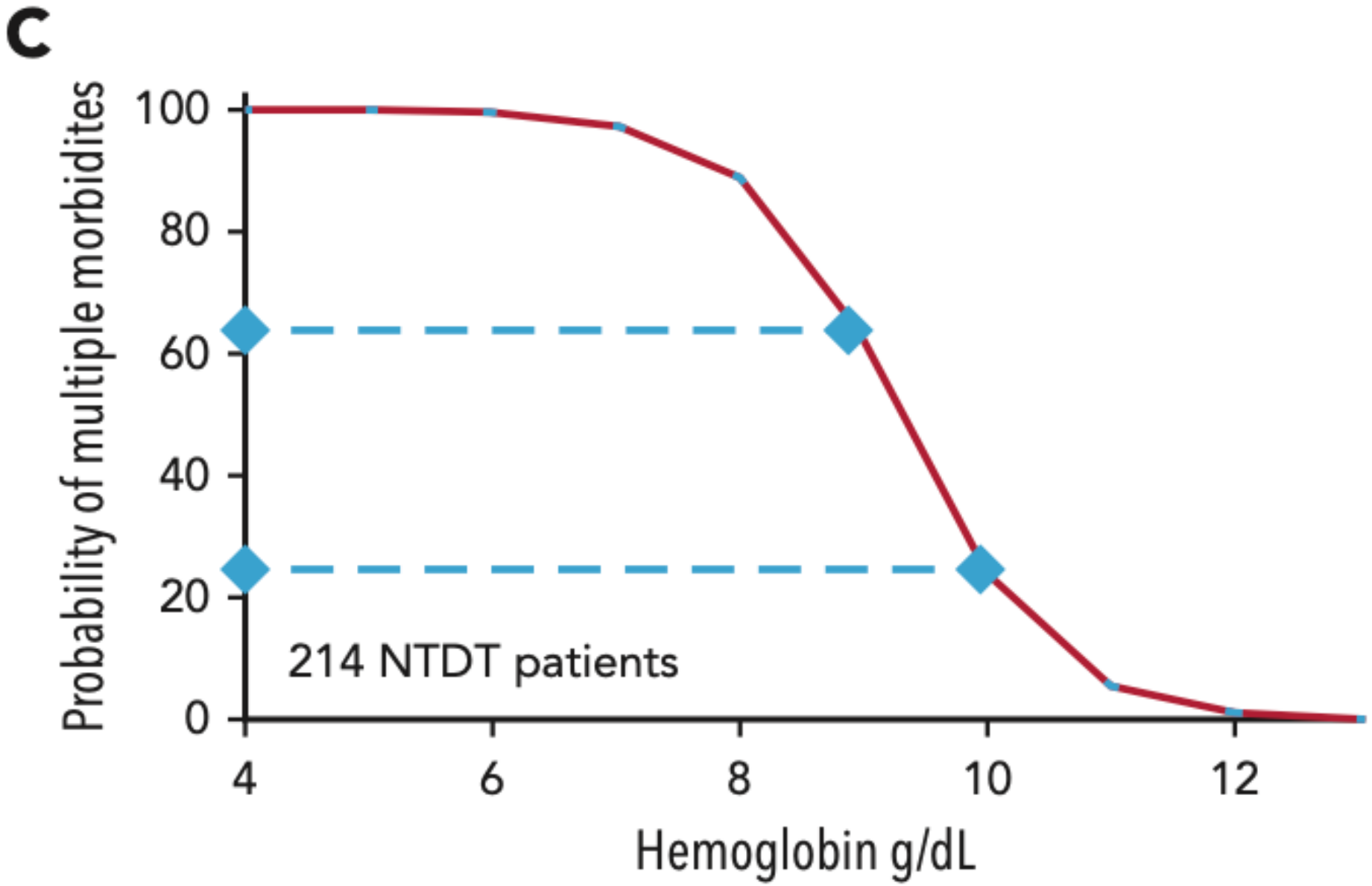


53 patients

Musallam KM *et al. Ann Hematol* 2022;101:203-204.



Musallam KM *et al. Ann Hematol* 2022;101:203-204



Musallam KM *et al. Ann Hematol* 2022;101:203-204

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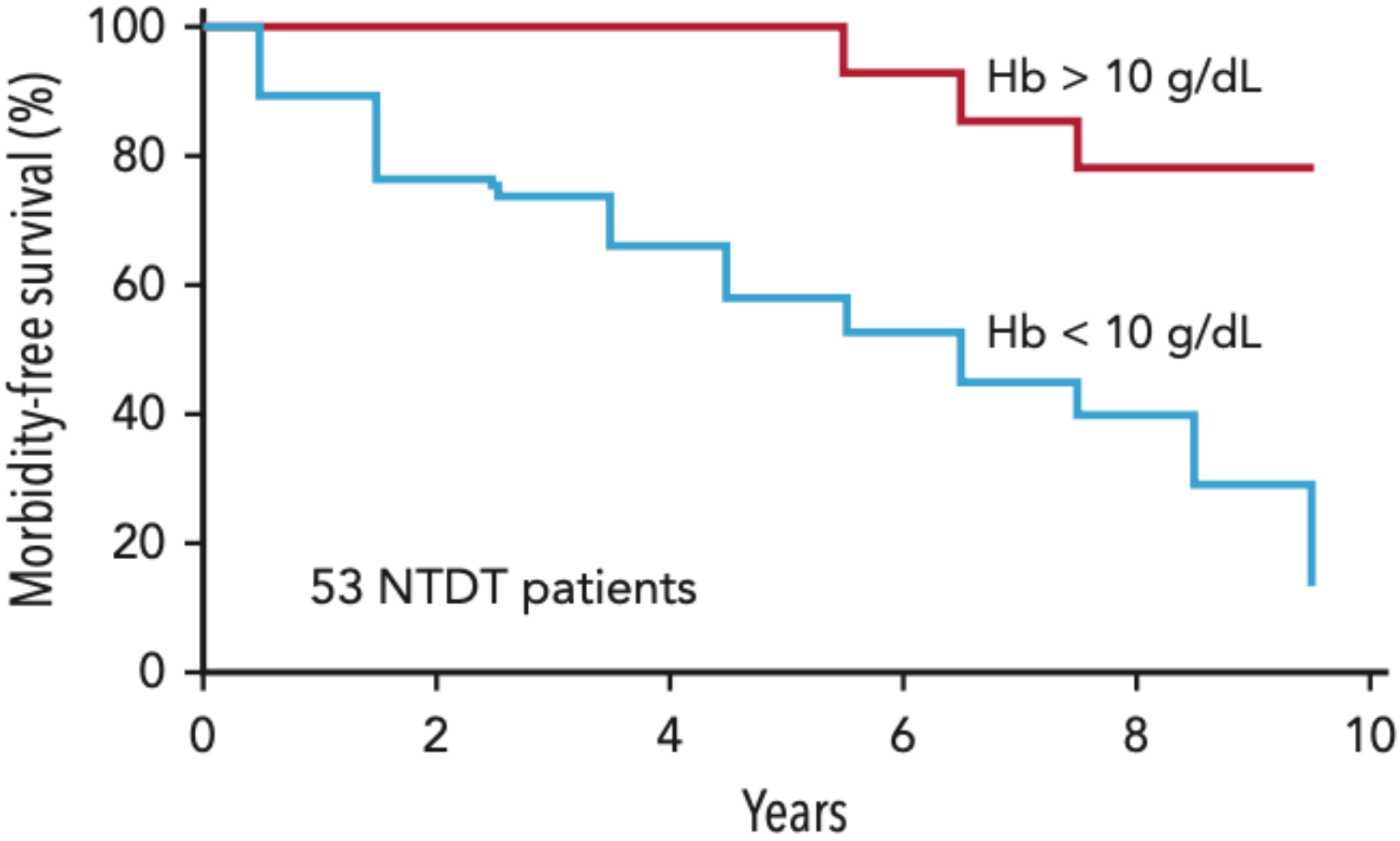
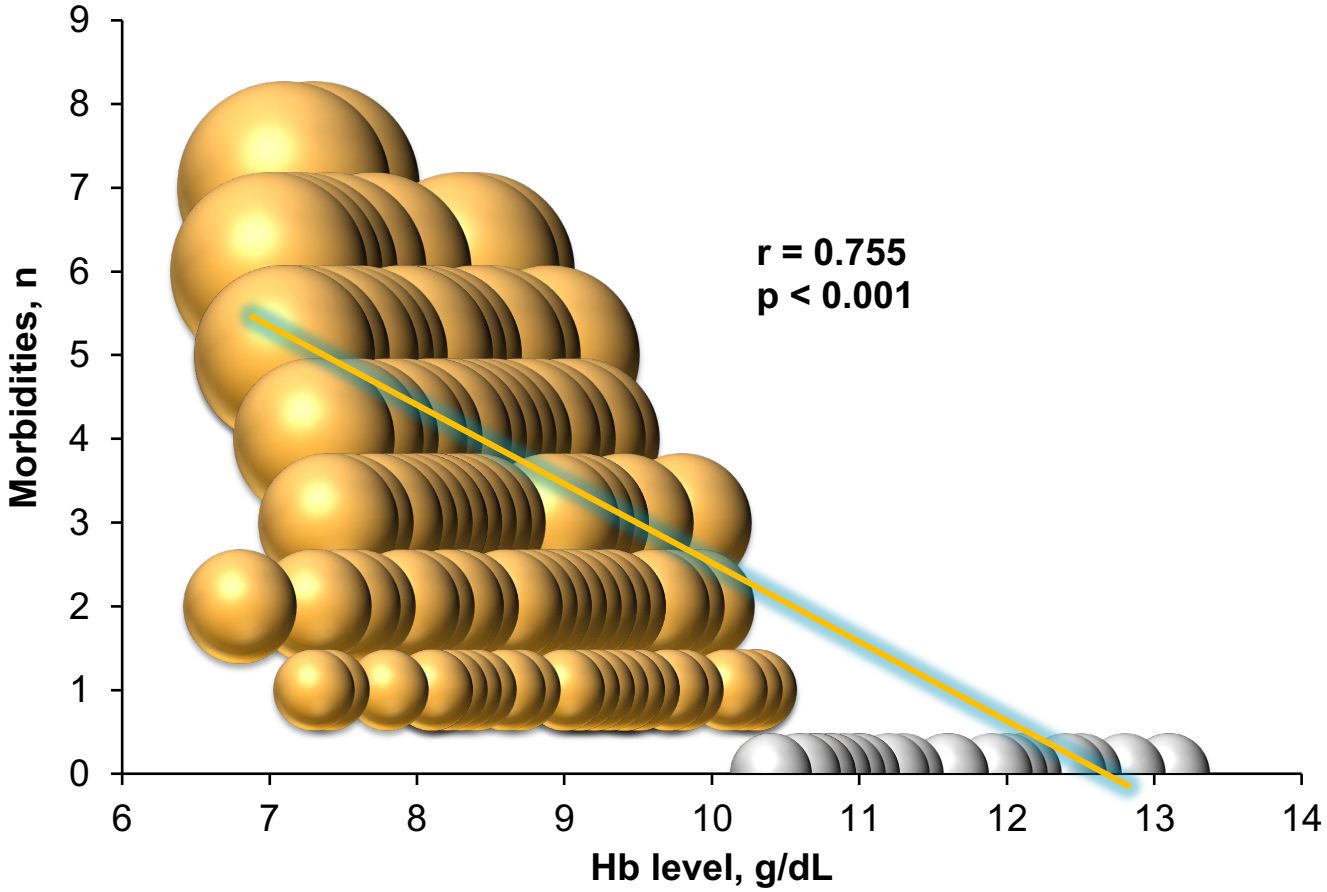
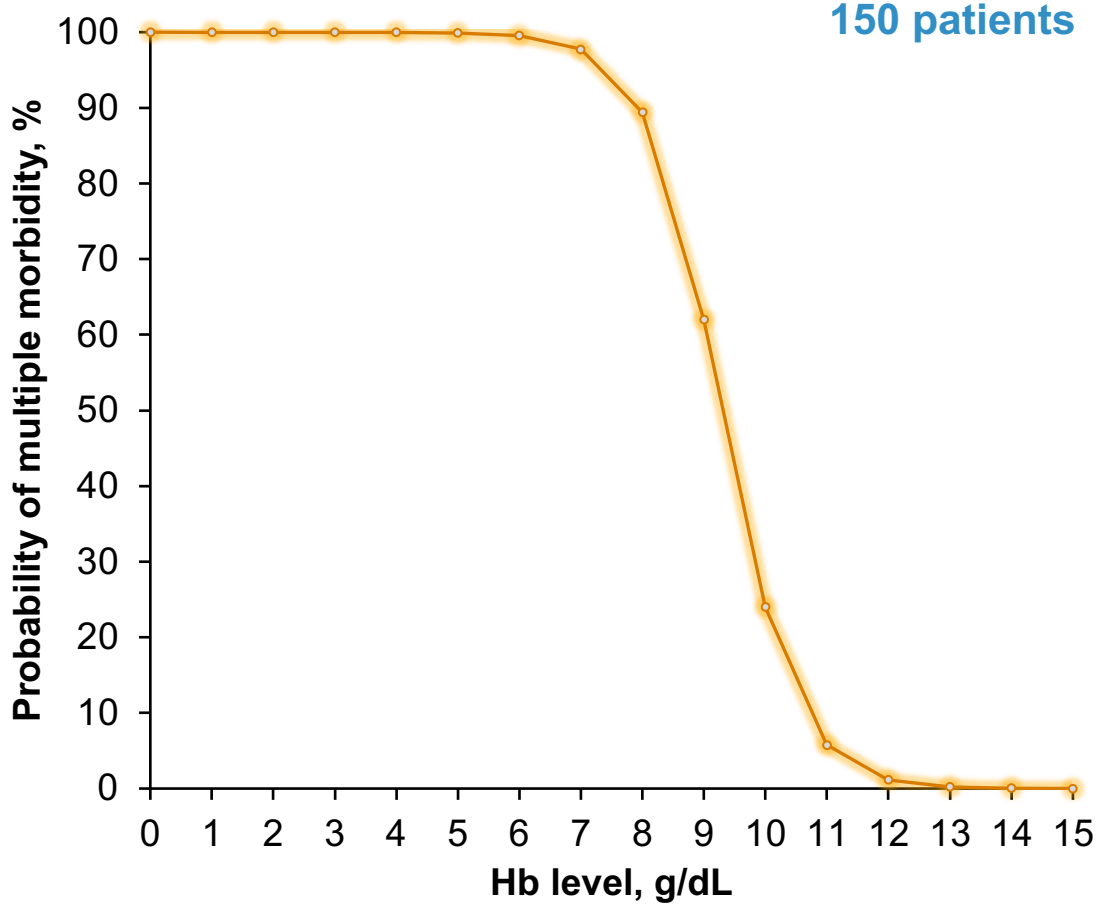


Musallam KM *et al. Ann Hematol* 2022;101:203-204

Variations of 1 g/dL in Hb level vs morbidity development in NTDT

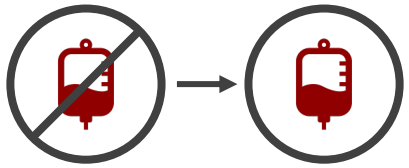




Musallam KM *et al. Ann Hematol* 2021;100:1903-1905.

‘Phenoconversion’ from NTDT to TDT

- Retrospective cohort study of 305 adult patients with non-transfusion-dependent β-thalassemia (NTDT) attending treatment centers across Italy.
- Patients were followed for up to 10 years to evaluate for the rate and risk factors for ‘phenoconversion’ to transfusion-dependent dependent β-thalassemia (TDT) when their annual number of red blood cell (RBC) units received was >10 in any individual year.



13.8%

had phenoconversion

“Annual amount of RBC units received in patients who had phenoconversion”

Pt.	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10
1		7	23	20	21	16	22	22	21	22
2		23	9	24	34	32	33	28	30	29
3			16	68	65	69	70	57	56	57
4	8	9	10	11	12	11	13	13	13	11
5	8	11	9	12	9	11	12	16	12	13
6	2	7	6	22	16	12	29	30	16	16
7	2	6	16	9	25	26	32	24	26	24
8			7	29	26	27	33	30	26	25
9		1	5	10	26	26	25	26	26	26
10			9	8	18	28	22	23	26	26
11				8	24	19	31	30	27	25
12					11	26	29	30	34	36
13					18	58	27	24	21	24
14					12	44	46	40	40	32
15	1	1	1	1	9	21	11	13	13	14
16				29	4			22	24	28
17						15	29	36	29	25
18						29	51	45	41	46
19		2	13	9	10	6	6	8	16	17
20	4	4	8	26	27	17	12	6	4	8
21			14	15	27	13				

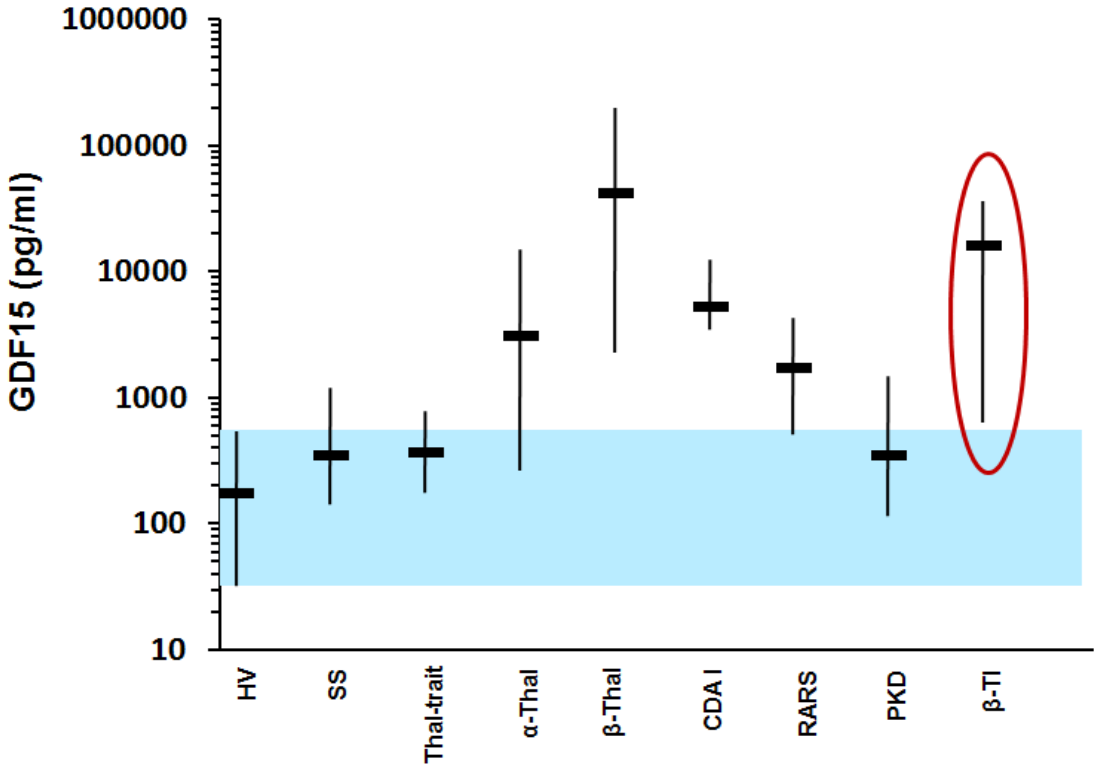
Pt.	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10
22							21	24	26	26
23							14	39	44	37
24								29	40	40
25								30	44	50
26						8	50	44	46	63
27								33	66	39
28						10		1	11	15
29									12	30
30									14	50
31									35	37
32			2			2	8	12	2	4
33						9	6	9	11	10
34									4	20
35										15
36		31		4						
37									10	25
38										18
39										19
40										21
41										26
42		33								

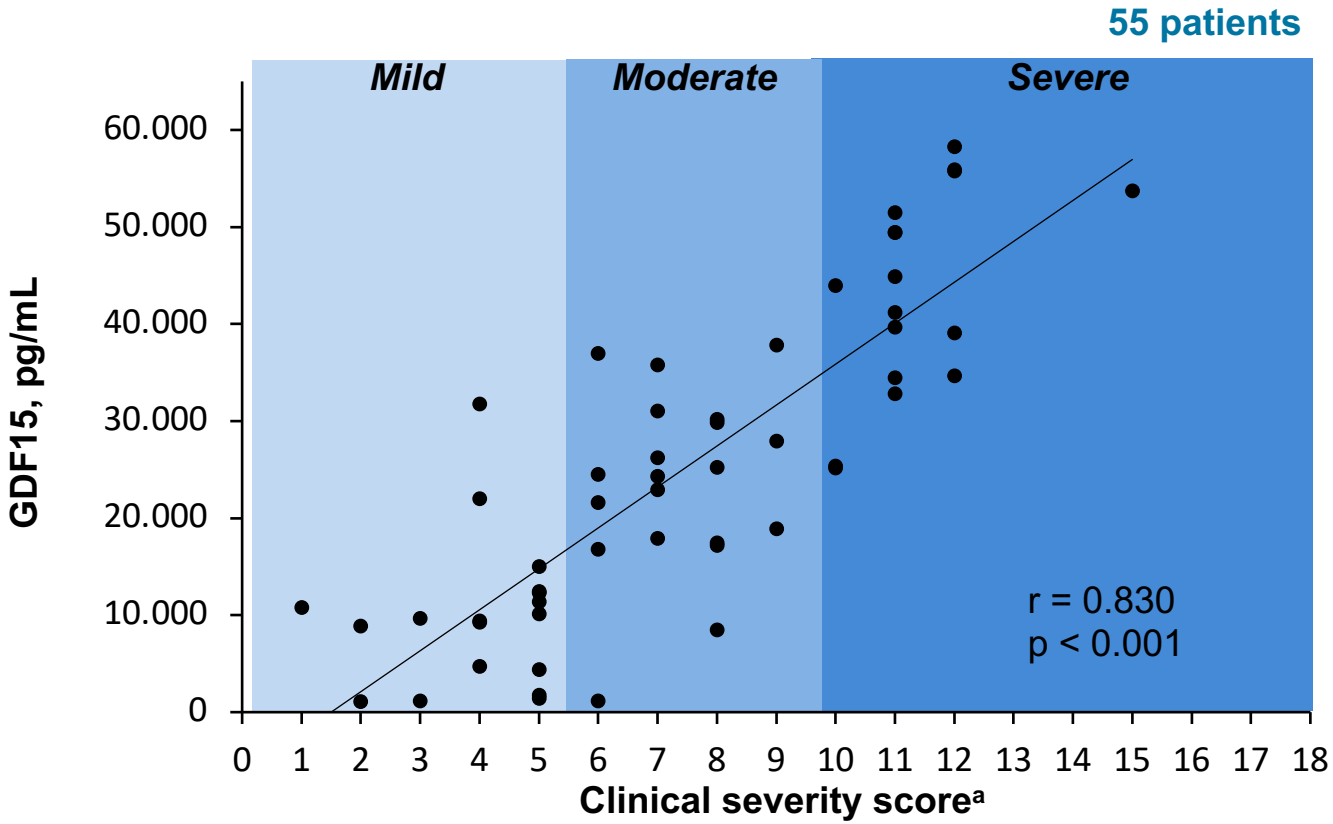
Comorbidity
(hazard ratio [HR]: 4.561, *P* = 0.022)
Hemoglobin level
(HR: 0.492 per 1 g/dL increase, *P* <0.001; <8.5 g/dL best predictor)
Need for iron chelation
(HR: 2.503, *P* = 0.022)

were independent risk factors for phenoconversion

Musallam KM et al. *Am J Hematol* 2024;99:490-493.

Severity of ineffective erythropoiesis correlates with clinical morbidity in NTDT





[a]Severity score is a combination of age, iron overload status, splenectomy, and number of clinical morbidities.

Musallam KM *et al. Blood Cells Mol Dis* 2011;47:232–234.

Mielodisplasia (MDS)

- - Anemia cronica con Eritropoiesi Inefficace simile alla talassemia
- - Sopravvivenza a 10 anni >80% con Hb >11 g/dL
- - Hb <9 g/dL maschi, <8 g/dL femmine → mortalità 3x
- - 63% delle morti non leucemiche per insufficienza cardiaca

Malcovati L, Della Porta MG, Strupp C, et Impact of the degree of anemia on the
outcome of patients with myelodysplastic
syndrome and its integration into the WHO
classi cation-based Prognostic Scoring
System (WPSS). Haematologica. 2011;9

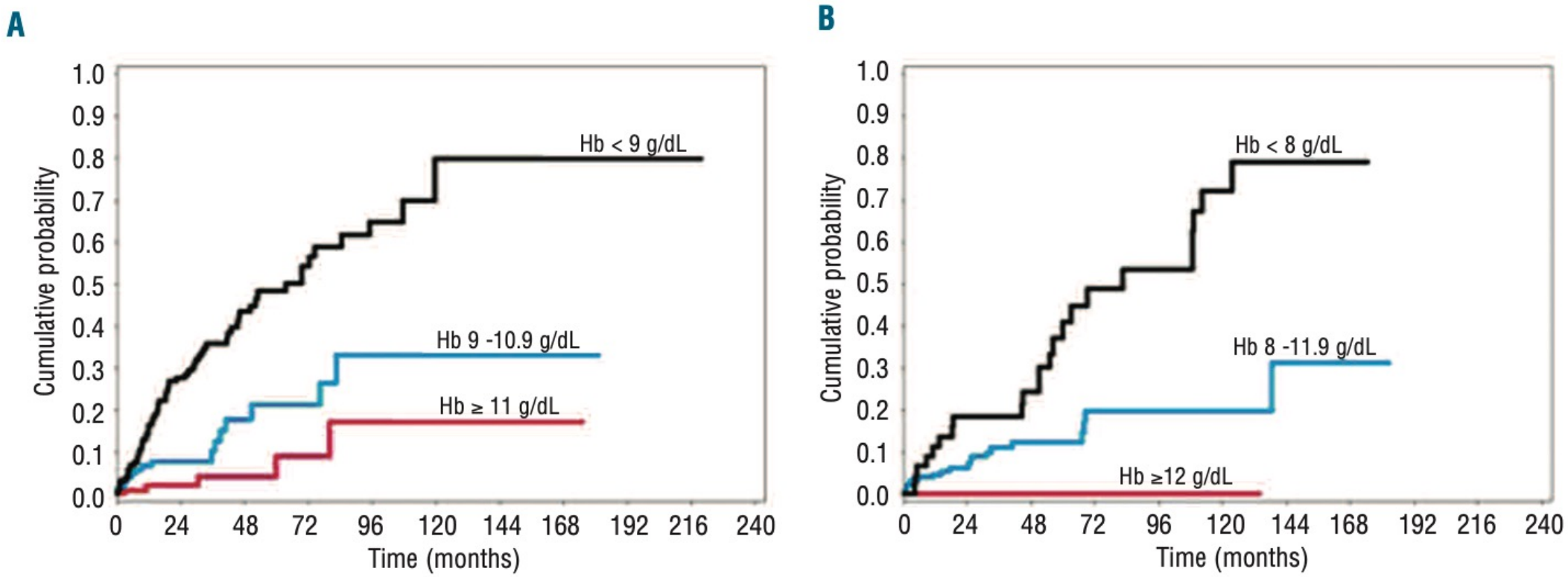


Figure 1. Prognostic relevance of the degree of anemia in patients with MDS. These curves were estimated from Cox's regression analyses with time-dependent covariates in the learning cohort of MDS patients. (A) Probability of non-leukemic death according to the degree of anemia in males (hemoglobin categories that showed no significantly different probabilities of NLD were plotted together). (B) Probability of non-leukemic death according to the degree of anemia in females (hemoglobin categories that showed no significantly different probabilities of NLD were plotted together).

Malcovati L, Della Porta MG, Strupp C, *et Impact of the degree of anemia on the* outcome of patients with myelodysplastic syndrome and its integration into the WHO classi cation-based Prognostic Scoring System (WPSS). Haematologica. 2011;9

Conclusion

CLINICAL TRIALS AND OBSERVATIONS

Comment on Musallam et al, page 930

Higher hemoglobin is better in thalassemia

Thomas D. Coates | Children's Hospital Los Angeles

In this issue of *Blood*, Musallam, Forni, and colleagues show that survival in transfusion dependent β-thalassemia (TDT) is measurably better in patients whose pretransfusion hemoglobin levels are maintained >10.5 g/dL, at the

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eClinicalMedicine. 2024 Jun; 72: 102619.
Published online 2024 May 6. doi: 10.1016/j.eclinm.2024.102619

PMCID: PMC11090906
PMID: 38745964

Journal Article

Global, regional, and national burden of thalassemia, 1990–2021: a systematic analysis for the global burden of disease study 2021

Yuanyuan Tuo,[a,d] Yang Li,[b,d] Yan Li,[a] Jianjuan Ma,[a] Xiaoyan Yang,[a] Shasha Wu,[a] Jiao Jin,[a,**] and Zhixu He[a,c,*]

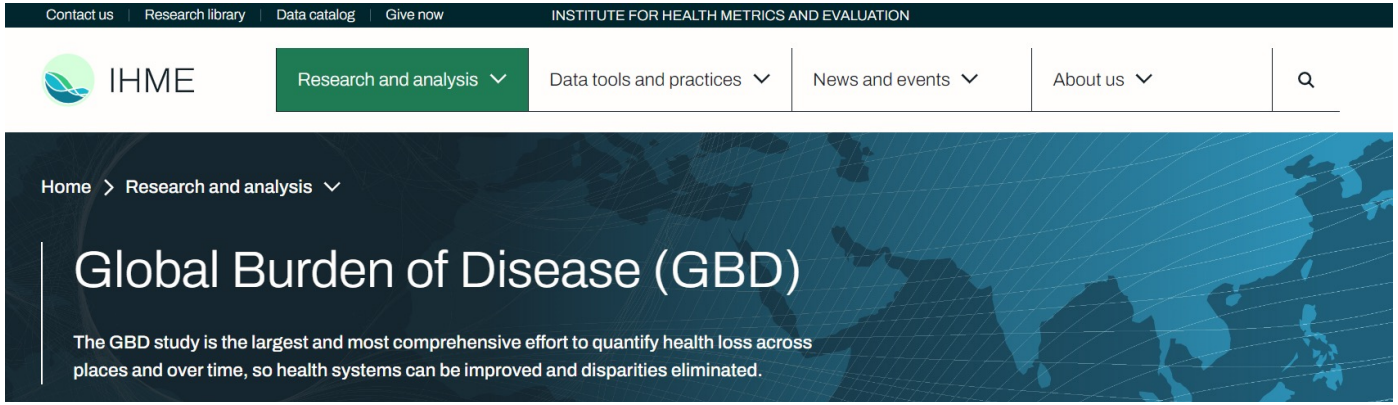
Summary

Background Anemia is a significant contributor to the global disease burden, of which thalassemia is the most common hereditary anaemic disease. Previous estimates were based on data that were geographically limited and lacked comprehensive global analysis. This study provides the prevalence, incidence, mortality and disability-adjusted life years (DALYs) of thalassemia in 204 countries and regions of thalassemia between 1990 and 2021, focusing on the age structure and time trends of the disease burden. To provide effective information for health policy, allocation of medical resources and optimization of patient management programs.

- Lo studio Global Burden of Disease (GBD) è programma di ricerca completo e globale sul carico di malattia che valuta mortalità e disabilità da malattie gravi, infortuni e fattori di rischio.

- GBD è una collaborazione di oltre 3600 ricercatori provenienti da 145 paesi

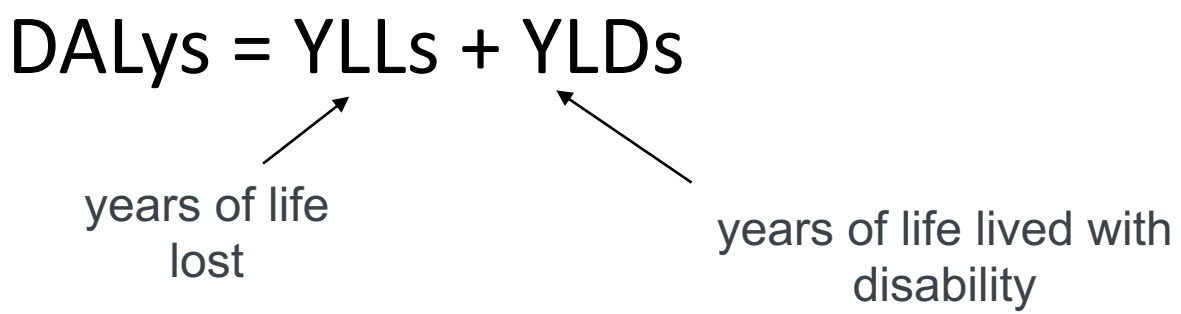
- GBD utilizza molteplici sorgenti dati da tutto il mondo per stimare il carico di malattia



https://www.healthdata.org/research-analysis/gbd

Disability-adjusted life years (DALYs)

DALY is an abbreviation for disability-adjusted life year. It is a universal metric that allows researchers and policymakers to compare very different populations and health conditions across time. DALYs equal the sum of years of life lost (YLLs) and years lived with disability (YLDs). One DALY equals one lost year of healthy life. DALYs allow us to estimate the total number of years lost due to specific causes and risk factors at the country, regional, and global levels.



https://www.healthdata.org/research-analysis/about-gbd

The Lancet Haematology

Global Haematology: In Focus

The importance of national and disease-specific characteristics to estimate disease burden in the GBD: a comparison for haemoglobin disorders in Italy.

Barbara Gianesin[1], Frédéric B. Piel[2], Lucia de Franceschi[3,4] & Gian Luca Forni[1,5] on behalf of the Italian Haemoglobinopathies National Survey Group

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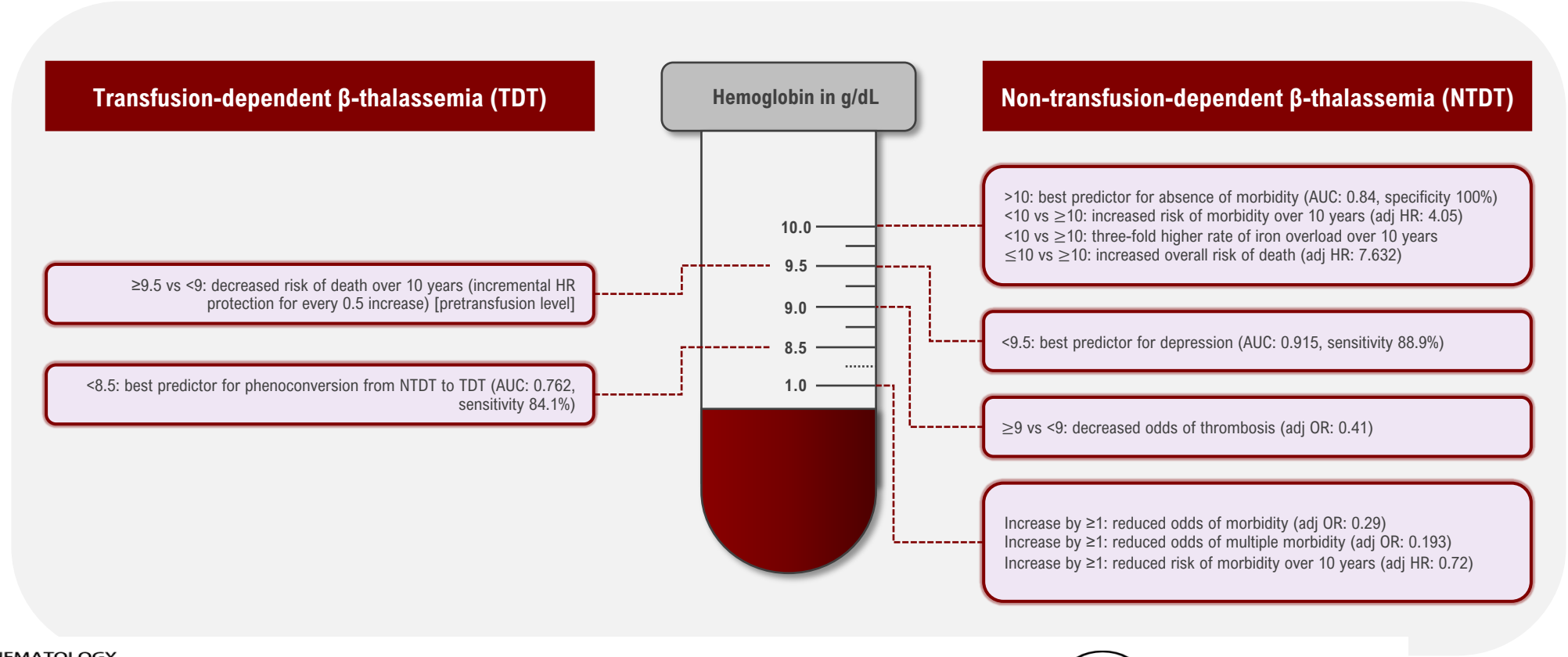
Corresponding Author: Dr Barbara Gianesin, barbara.gianesin@foranemia.org

Region (years)	Pathology	YLDs (10^6 years)
Global (2019)	Thalassemias	0.044 (→0.26)*
Global (2019)	Thalassemias trait	1.98
Global (2019)	Sickle cell disorders	0.57(→1.72)*
Global (2019)	Sickle cell trait	1.69
Global (2019)	G6PD trait	0.015
Global (2019)	G6PD deficiency	0.033
Global (2019)	Chronic kidney disease due to diabetes mellitus type 1	0.28
Global (2019)	Chronic kidney disease due to hypertension	1.36
Global (2019)	Cirrhosis due to alcohol	0.10
Global (2019)	Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms	0.25

YLDs: years lived with disability

*extrapolated value considering that from Italian survey we estimated a possible underestimation of a factor 6 and 3 in the evaluation of YLDs for thalassemias and sickle cell disease respectively

Anemia as a prognostic marker for long-term outcomes in beta-thalassemia



EXPERT REVIEW OF HEMATOLOGY
2024, VOL. 17, NO. 9, 631–642
https://doi.org/10.1080/17474086.2024.2383420

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REVIEW

Check for updates

Anemia and iron overload as prognostic markers of outcomes in β-thalassemia

Khaled M Musallam [a,b], Sujit Sheth [b], Maria Domenica Cappellini [c], Gian Luca Forni [d], Aurelio Maggio [e] and Ali T Taher [f]

In sintesi

- Hb >10 g/dL → migliori outcome in anemie croniche da Eritropoiesi Inefficace
- Regime Trasfusionale >10 g/dL riduce morbidità e mortalità
- Benefici su qualità di vita, complicanze e sopravvivenza a lungo termine
- L'anemia cronica danneggia soprattutto tessuti ad alta richiesta di ossigeno ed Il cuore è l'organo più vulnerabile

Grazie