Talassemie approccio diagnostico e terapeutico

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Il/La sottoscritto/a, in qualità di Relatore
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

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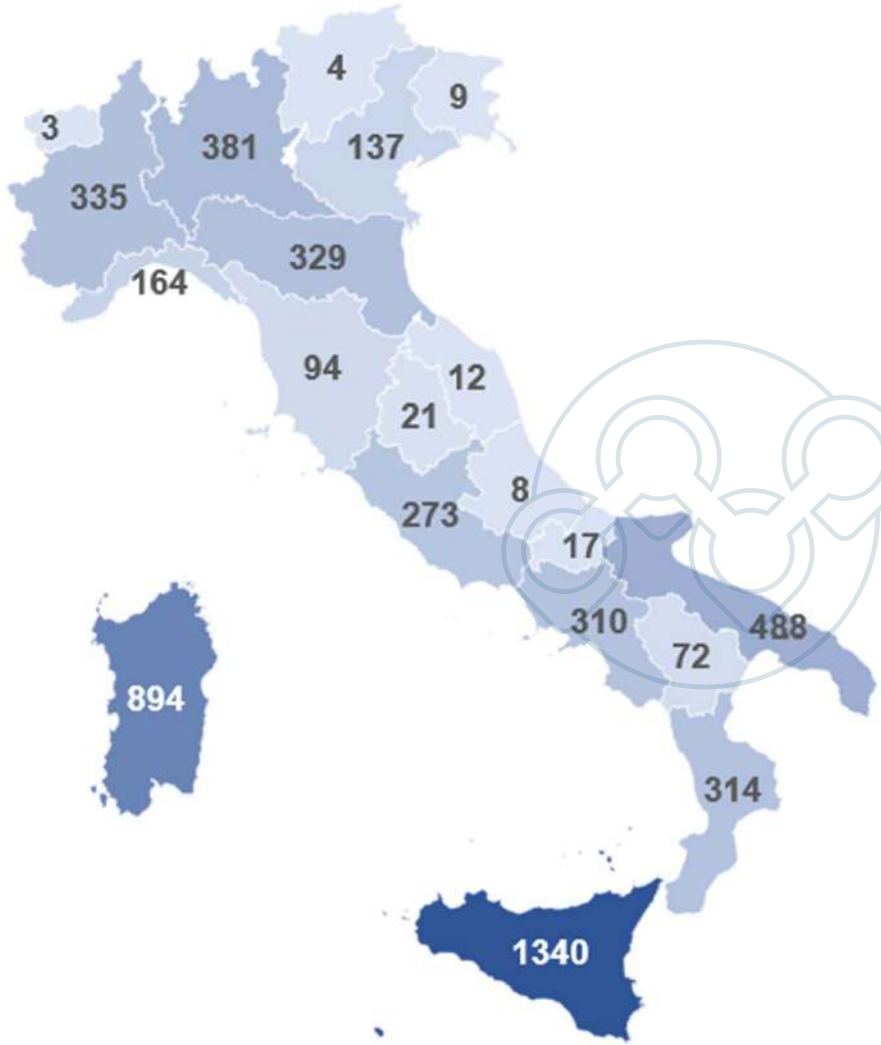
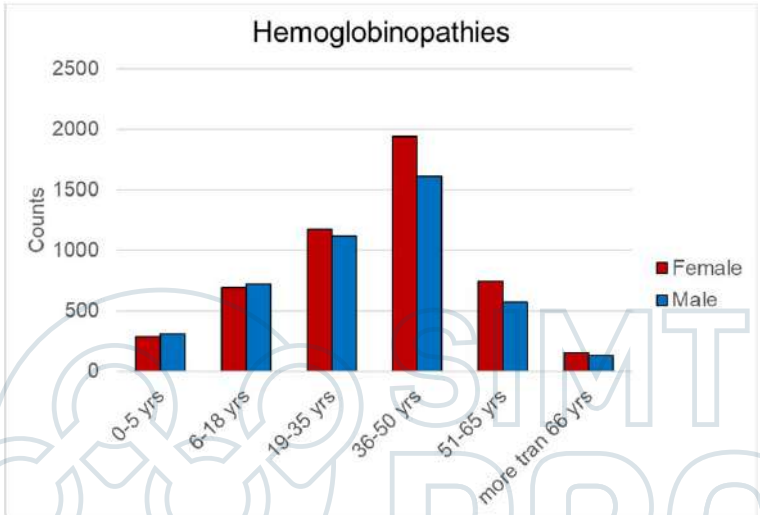
Survey S.I.T.E. – Distribuzione regionale dei pazienti TDT

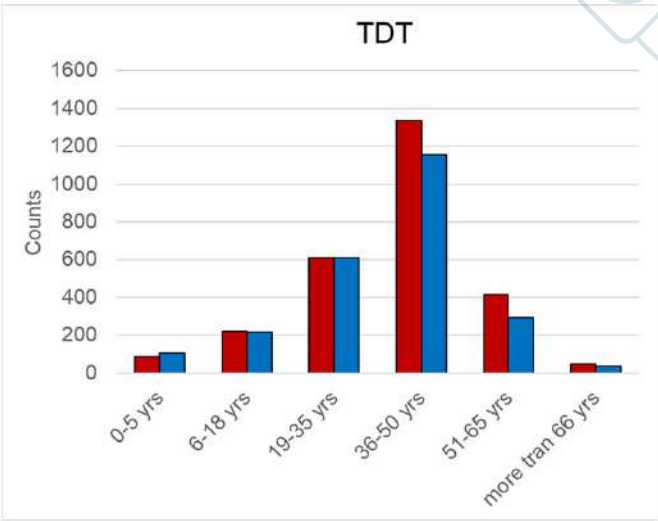


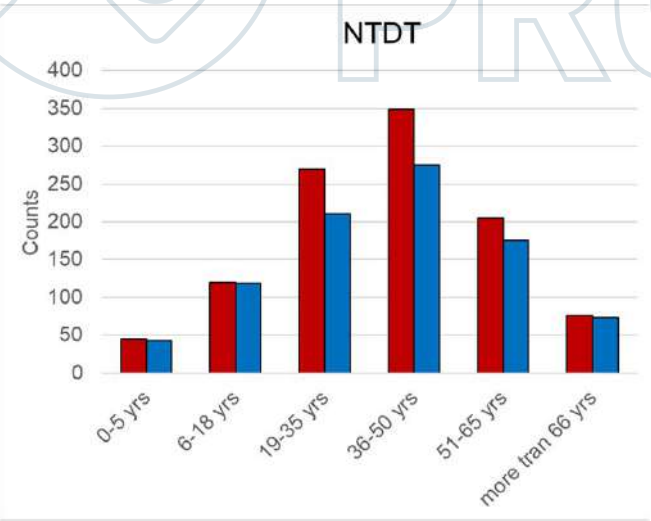
Regions	TDT
Abruzzo	**8**
Basilicata	**72**
Calabria	**314**
Campania	**310**
Emilia-Romagna	**329**
Friuli-Venezia-Giulia	**9**
Lazio	**273**
Liguria	**164**
Lombardia	**381**
Marche	**12**
Molise	**17**
Piemonte	**335**
Puglia	**488**
Sardegna	**894**
Sicilia	**1340**
Toscana	**94**
Trentino Alto Adige	**4**
Umbria	**21**
Valle d'Aosta	**3**
Veneto	**137**
Total	**5205**

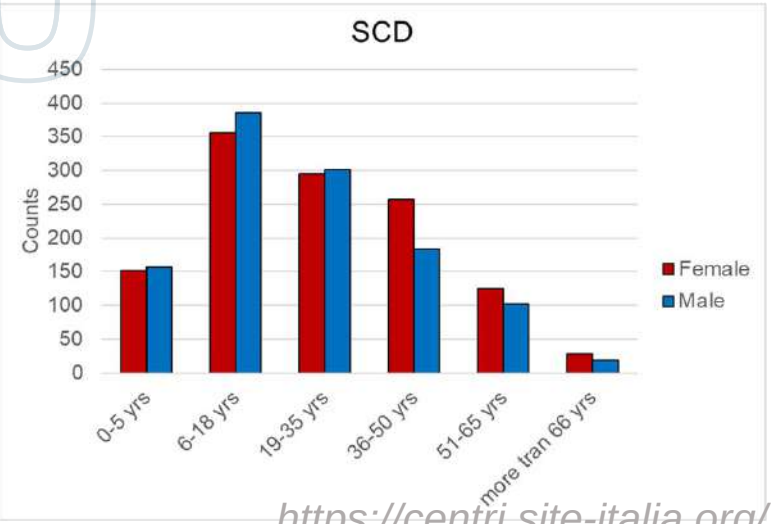
https://centri.site-italia.org/

Survey S.I.T.E. – Distribuzione per sesso/età/patologia

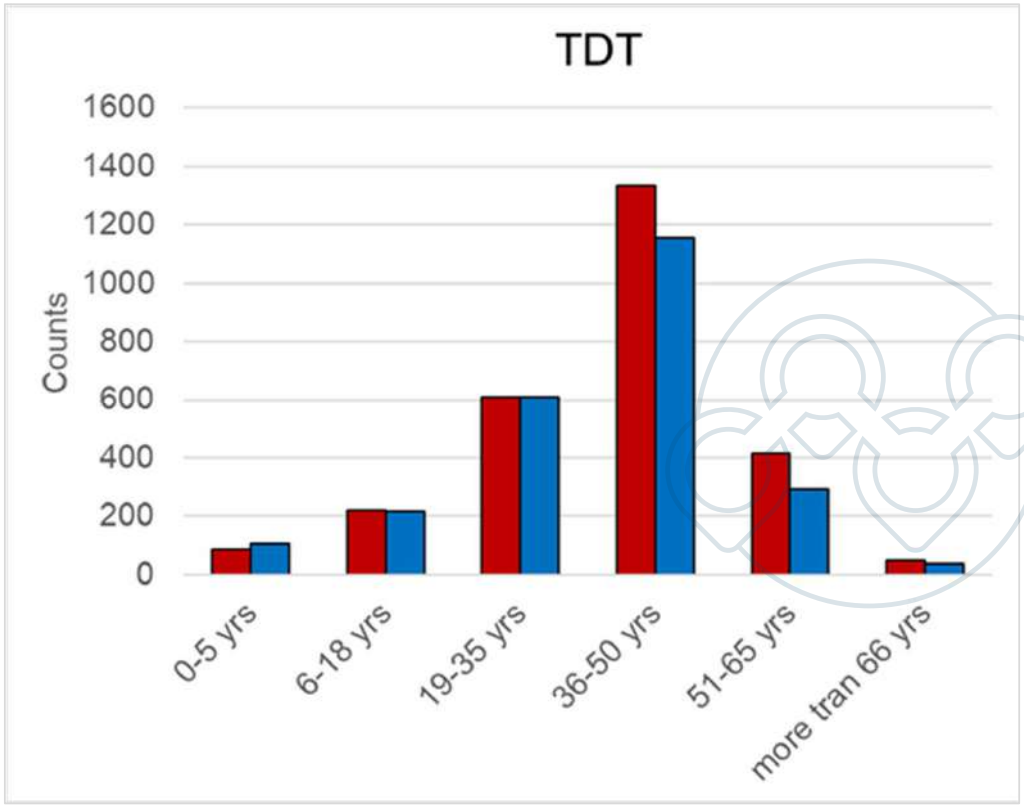


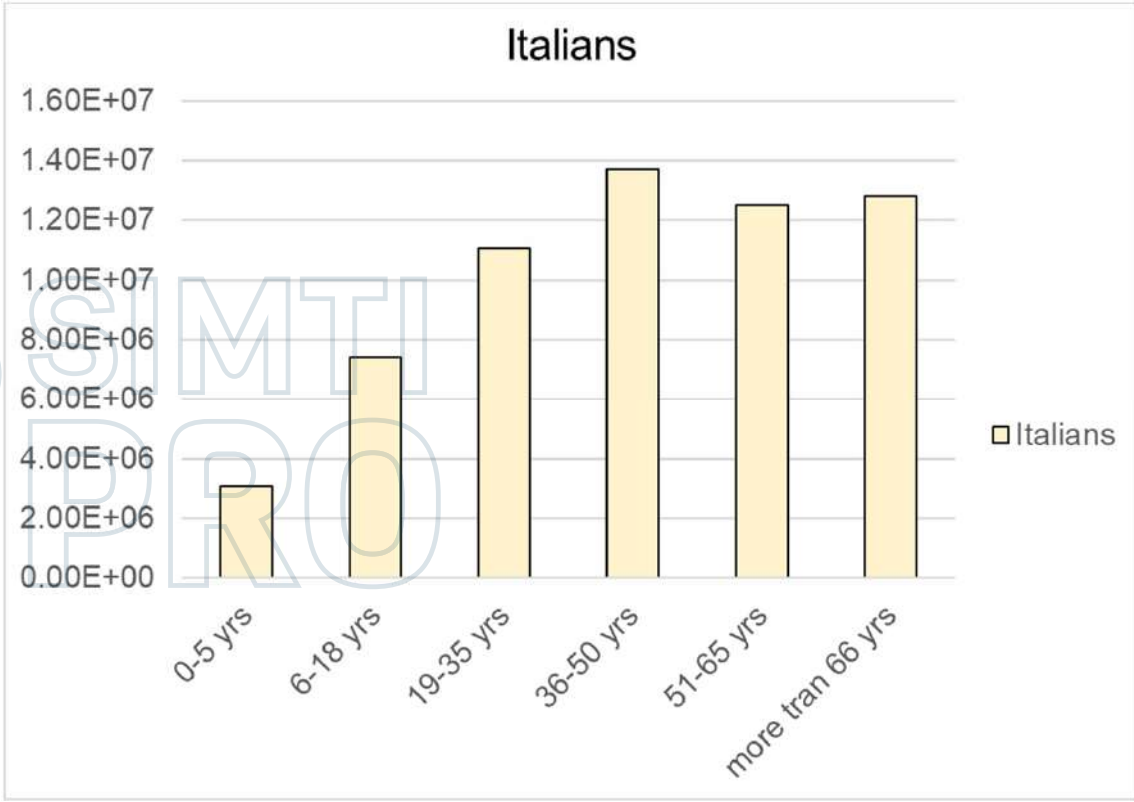






Survey S.I.T.E. – Distribuzione per età: confronto con la popolazione Italiana





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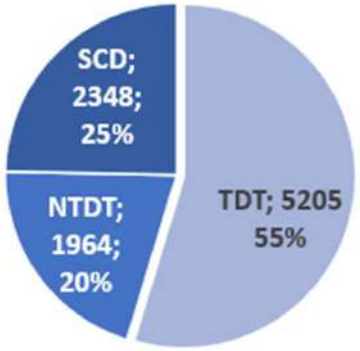
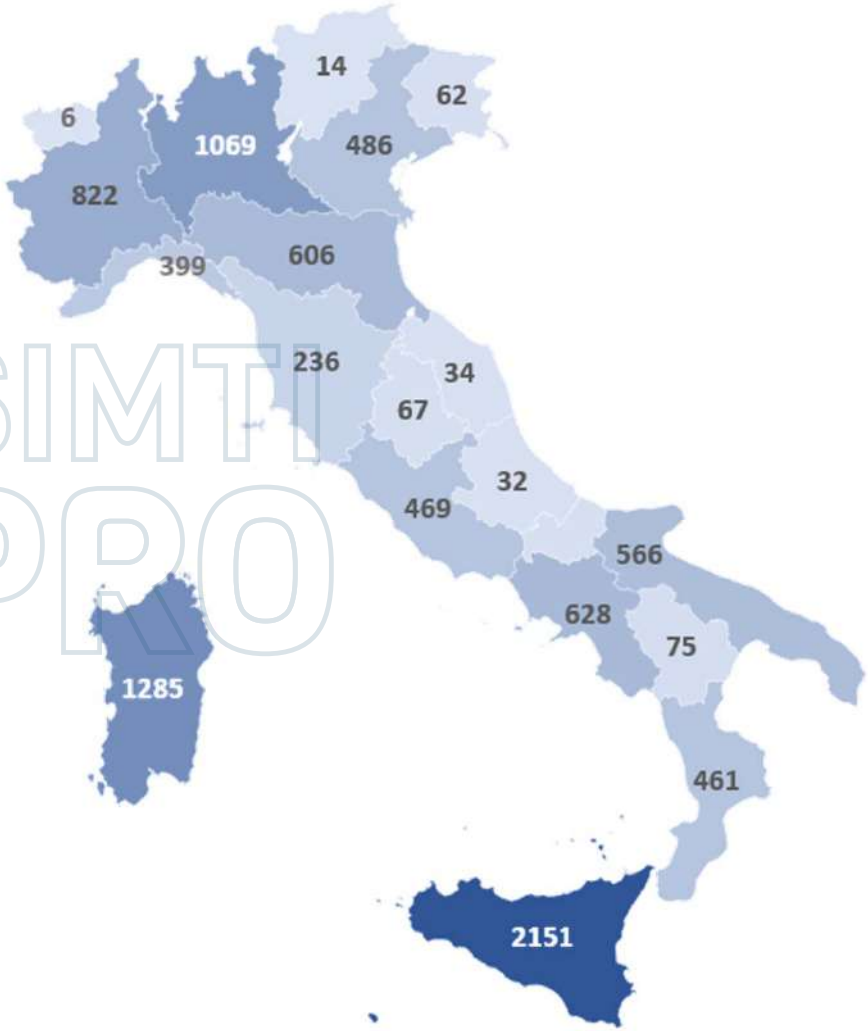
Survey S.I.T.E. – Distribuzione regionale dei pazienti con Emoglobinopatie

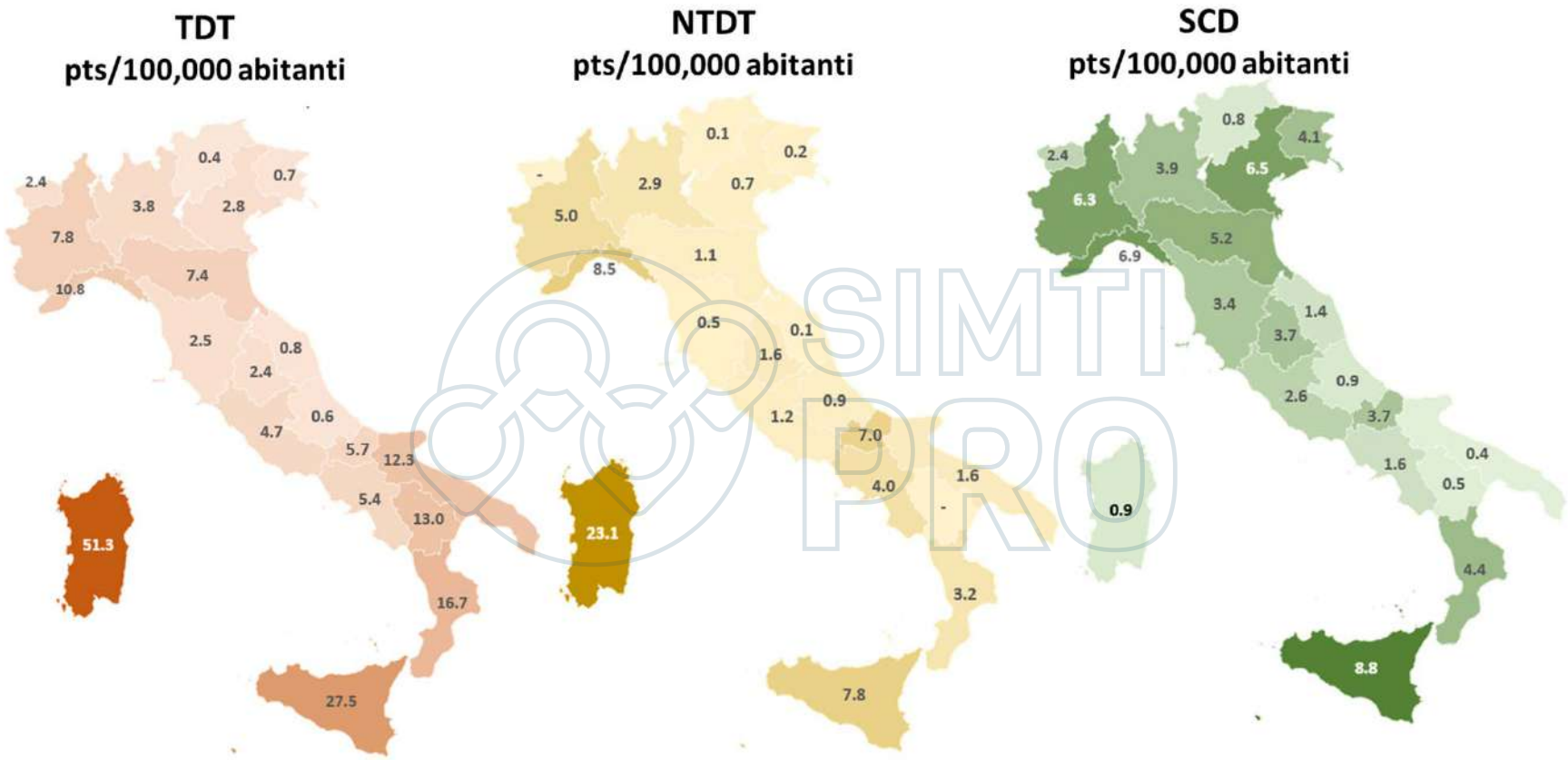


Prevalenza delle Emoglobinopatie in Italia Casi/100,000 abitanti			
Emoglobinopatie	TDT	NTDT	SCD
16,0	8,7	3,3	3,9



https://centri.site-italia.org/

Survey S.I.T.E. – Distribuzione sul territorio



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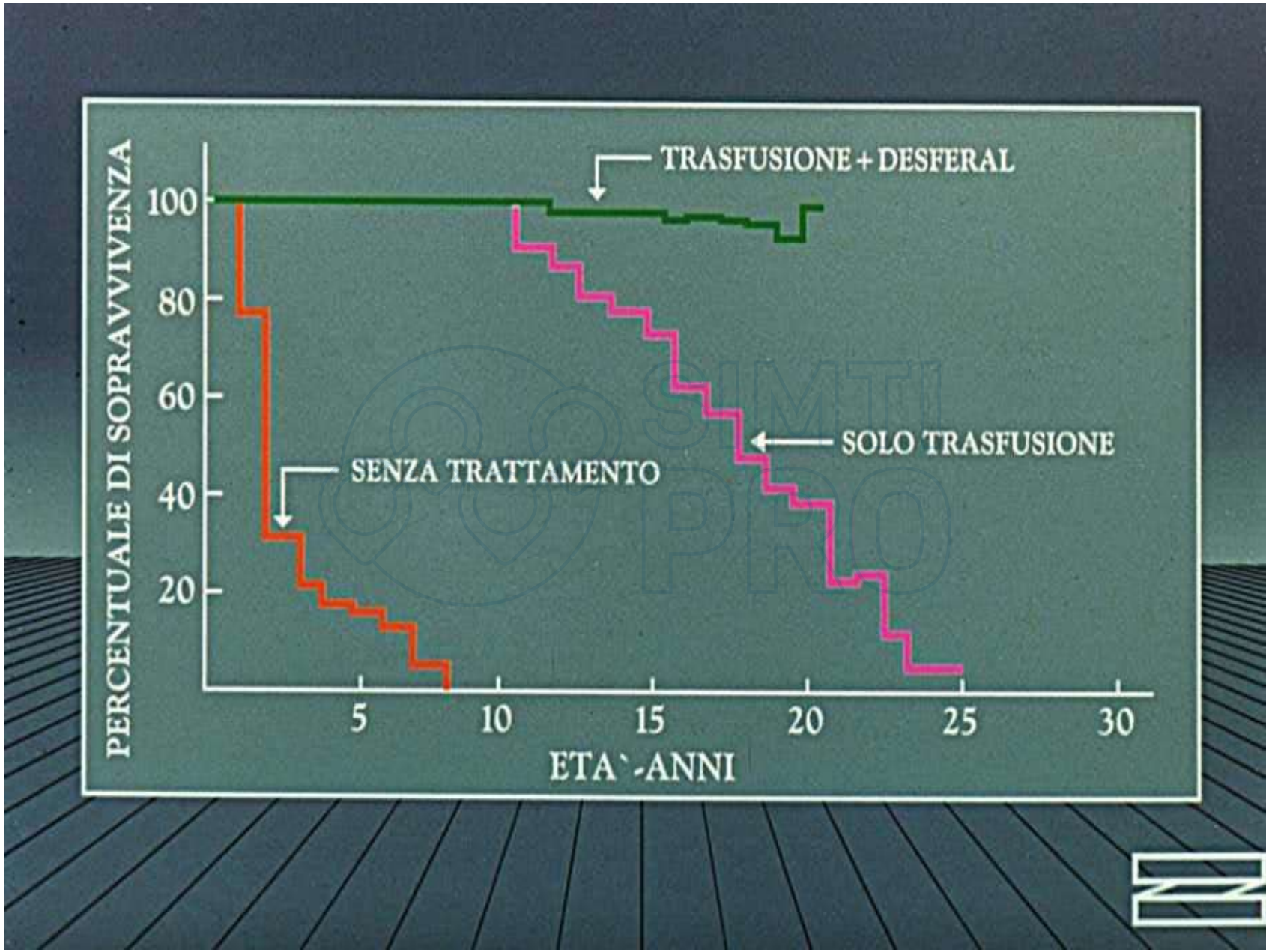
TRASFUSIONE + DESFERAL
SOLO TRASFUSIONE
SENZA TRATTAMENTO
PERCENTUALE DI SOPRAVVIVENZA
100
80
60
40
20
5
10
15
20
25
30
ETA`-ANNI

SURVIVAL AND CAUSES OF DEATH IN THALASSAEMIA MAJOR

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CATERINA MELEVENDI FELICIA DI GREGORIO
MARIA GABRIELLA BURATTINI
SEVERINA TERZOLI

IRCCS "San Matteo", Pavia, Italy; Departments of Paediatrics of the Universities of Milan, Verona, Torino, Catania, and Bari; and Divisions of Paediatrics of Ospedale Galliera, Genova, and Ospedale Sant' Anna, Ferrara

Summary Survival and causes of death were studied in 1087 Italian patients with thalassaemia major who were born on or after Jan 1, 1960. At the age of 15 years, the Kaplan-Meier estimate of survival after the first decade of life was 80·6% for subjects born in 1960–64, 84·2% for those born in 1965–69, and 96·9% for those born in 1970–74. At the age of 20 years, survival from the age of 10 was 59·1% for patients born in 1960–64, and 70·2% for those born in 1965–69; at 25 years, survival from the age of 10 was 40·7% in the 1960-64 cohort. Overall survival from birth for patients born in 1970–74 was 97·4% at 10 years, and 94·4% at 15 years. The most common cause of death was heart disease, followed by infection, liver disease, and malignancy.

TABLE I—STATUS OF POPULATION BY YEAR OF BIRTH

Status	Birth cohort						
	1960–64	1965–69	1970–74	1975–79	1980–84	1985 or later	Total
Alive	37 (39)	148 (66·7)	284 (90·7)	274 (93·2)	127 (95·5)	31 (100)	901 (82·9)
Lost	..	3 (1·4)	1 (0·3)	2 (0·7)	..	..	6 (0·6)
BMT	..	1 (0·4)	3 (1·0)	12 (4·1)	5 (3·8)	..	21 (1·9)
Dead	57 (61)	70 (31·5)	25 (8·0)	6 (2·0)	1 (0·7)	..	159 (14·6)
Total	94	222	313	294	133	31	1087

Number (% of cohort).
BMT = underwent bone marrow transplant.

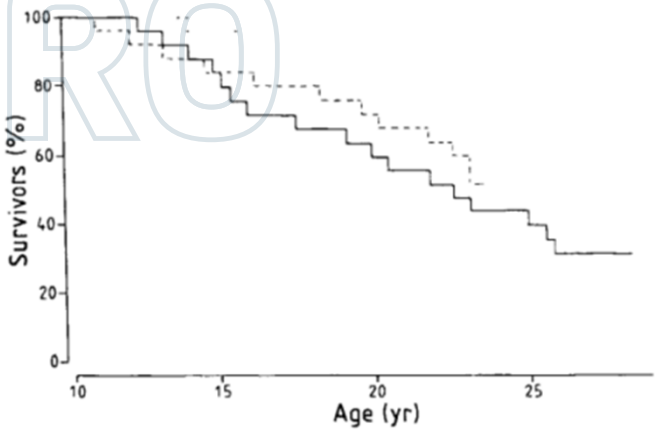


Fig 1—Survival after first decade of life by cohort of birth.

——— = 1960–64 cohort; – – – – = 1965–69 cohort; and ····· = 1970–74 cohort.

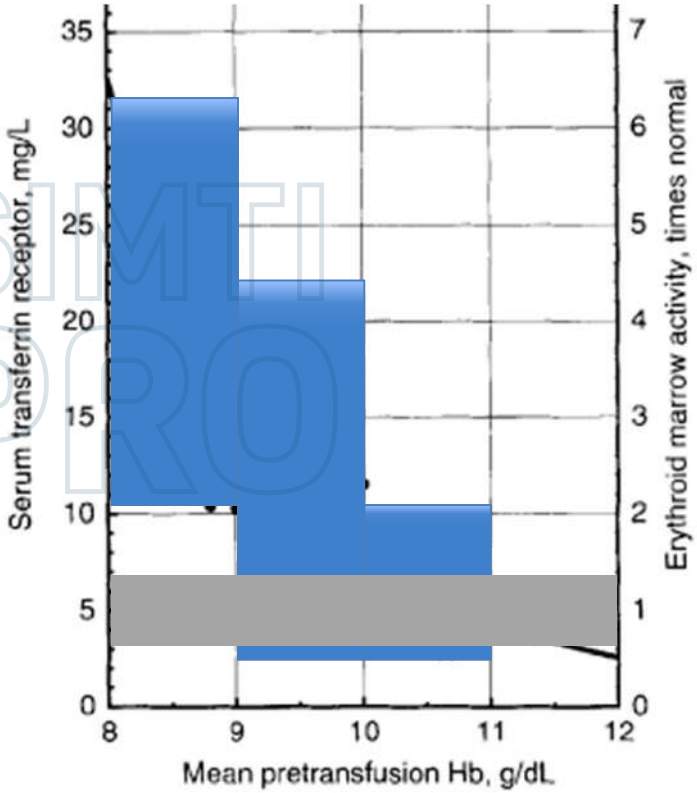
Zurlo et al, 1989, The Lancet

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

Relationship between transfusion regimen and suppression of erythropoiesis

- **52 patients with thalassaemia major whose mean pre-transfusion haemoglobin levels ranged from 8.6 to 10*9g/dl**
- **Multiple regression analysis showed that serum transferrin receptor was the parameter more closely related to mean pretransfusion haemoglobin (r = -0.77, *P < 0.001)***
- **Pretransfusion Hb 10-11g/dl- 1-2x normal**
- **Pretransfusion Hb 9-10 g/dl- 1-4x normal**
- **Pretransfusion Hb 9.6-9 g/dl- 2-6 x norma Cazzola, 1995 #906}**



[haematologica]
2004;89:1187-1193

CATERINA BORGNA-PIGNATTI
SIMONE RUGOLOTTO
PIERO DE STEFANO
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MARIA DOMENICA CAPPELLINI
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MARIA ANTONIETTA ROMEO
GIAN LUCA FORNI
MARIA RITA GAMBERINI
ROBERTA GHILARDI
ANTONIO PIGA
AVITAL CNAAN

Thalassemia • Research Paper

Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine

A B S T R A C T

Background and Objectives. Seven Italian centers reported data on survival, causes of death and appearance of complications in patients with thalassemia major. The interactions between gender, birth cohort, complications, and ferritin on survival and complications were analyzed.

Design and Methods. Survival after the first decade was studied for 977 patients born since 1960 whereas survival since birth and complication appearance was studied for the 720 patients born after 1970. Better survival was demonstrated for patients born in more recent years ($p<0.00005$) and for females ($p=0.0003$); 68% of the patients are alive at the age of 35 years. In the entire population 67% of the deaths were due to heart disease.

Results. There was a significant association between birth cohort and complication-free survival ($p<0.0005$). The prevalence of complications was: heart failure 6.8%, arrhythmia 5.7%, hypogonadism 54.7%, hypothyroidism 10.8%, diabetes 6.4%, HIV infection 1.7%, and thrombosis 1.1%. Lower ferritin levels were associated with a lower probability of heart failure (hazard ratio =3.35, $p<0.005$) and with prolonged survival (hazard ratio = 2.45, $p<0.005$), using a cut-off as low as 1,000 ng/mL.

Interpretation and Conclusions. Survival and complication-free survival of patients with thalassemia major continue to improve, especially for female patients born shortly before or after the availability of iron chelation.

Key words: thalassemia, survival, causes of death, ferritin, hemosiderosis.

Borgna-Pignatti et al, haematologica, 2004

SevenItalianCenters Study

C. Borgna-Pignatti: University of Ferrara

A. Piga: University of Torino

S. Rugolotto: University of Verona

P. De Stefano: University of Pavia

R. Gamberini : Ospedale Ferrara

G.Forni: Ospedale Galliera, Genova

M.A. Romeo: University of Catania

G.C. DelVecchio:University of Bari

M.D. Cappellini: University of Milan

Statistical analysis

Huaqing Zhao, Avital Cnaan:
CHOP Philadelphia

SevenItalianCenters Study

- Study started in 1983
- Treatment included transfusion and DFO
- BMT, DFP censored
- Follow-up performed in 1999

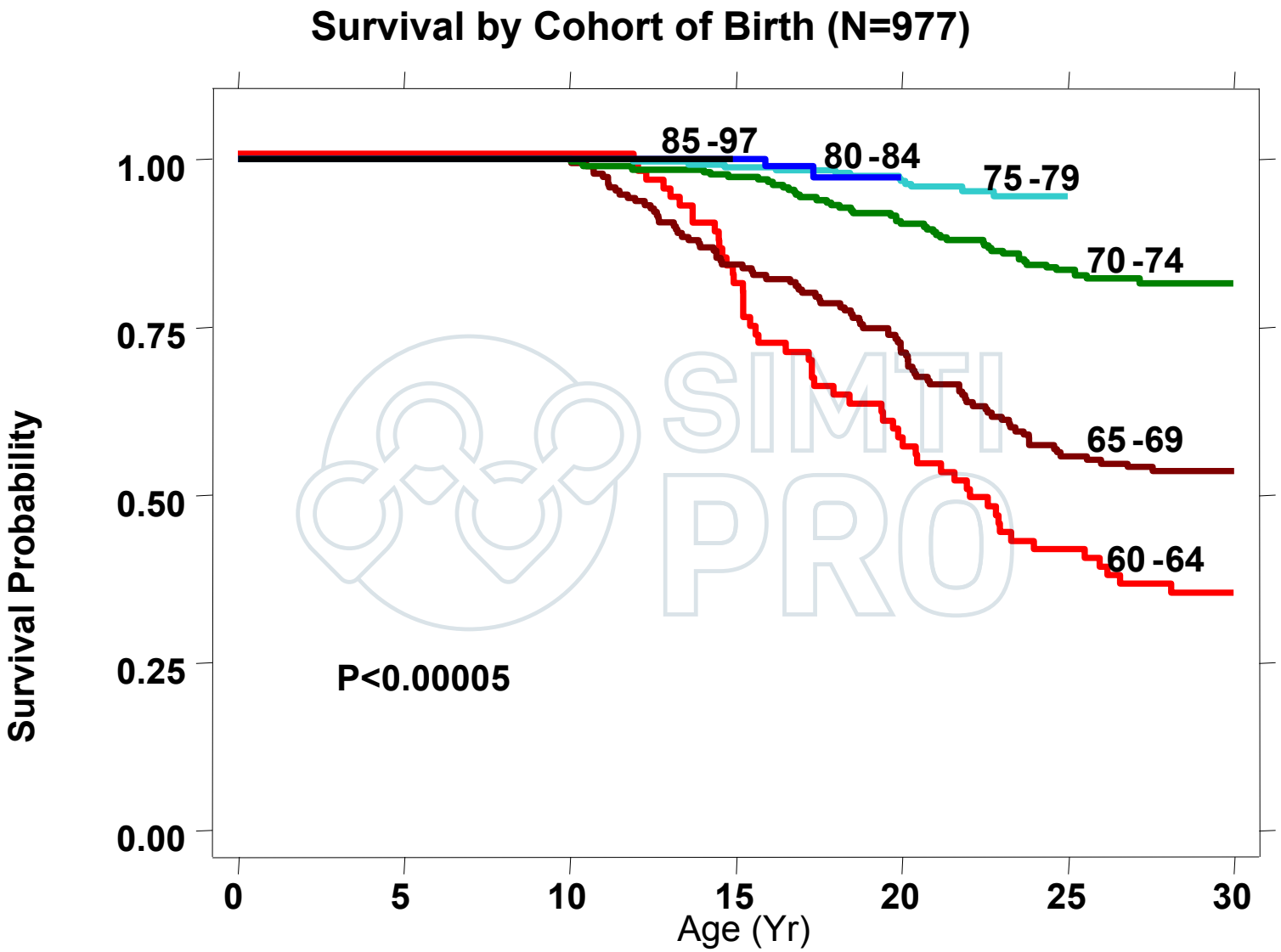
Borgna-Pignatti et al. Haematologica, 2004;89:1187

Borgna-Pignatti et al, haematologica, 2004

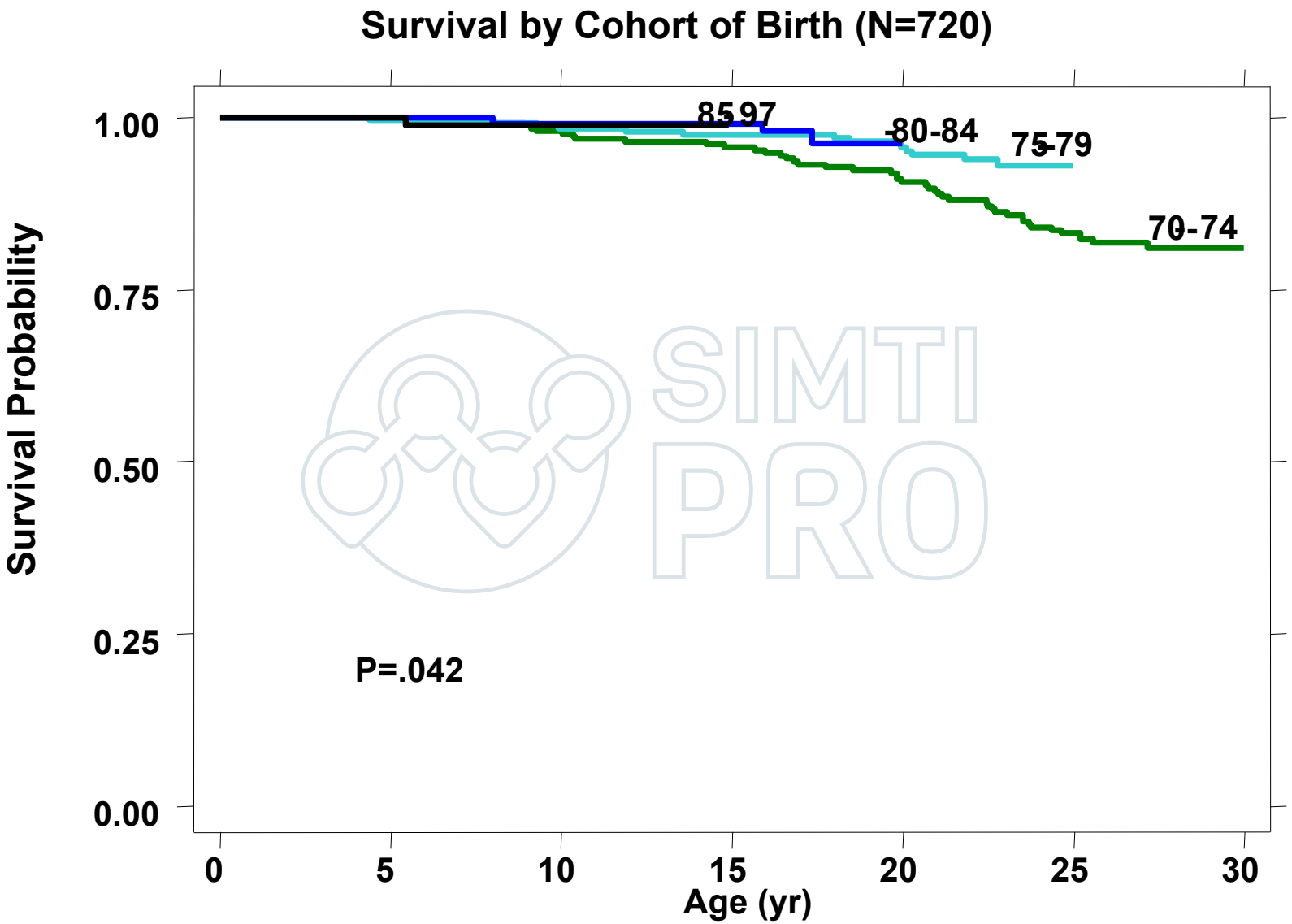
Study population

- 977 pts (47% female) born after 1960
- 720 patients born after 1970

Borgna-Pignatti et al, haematologica, 2004

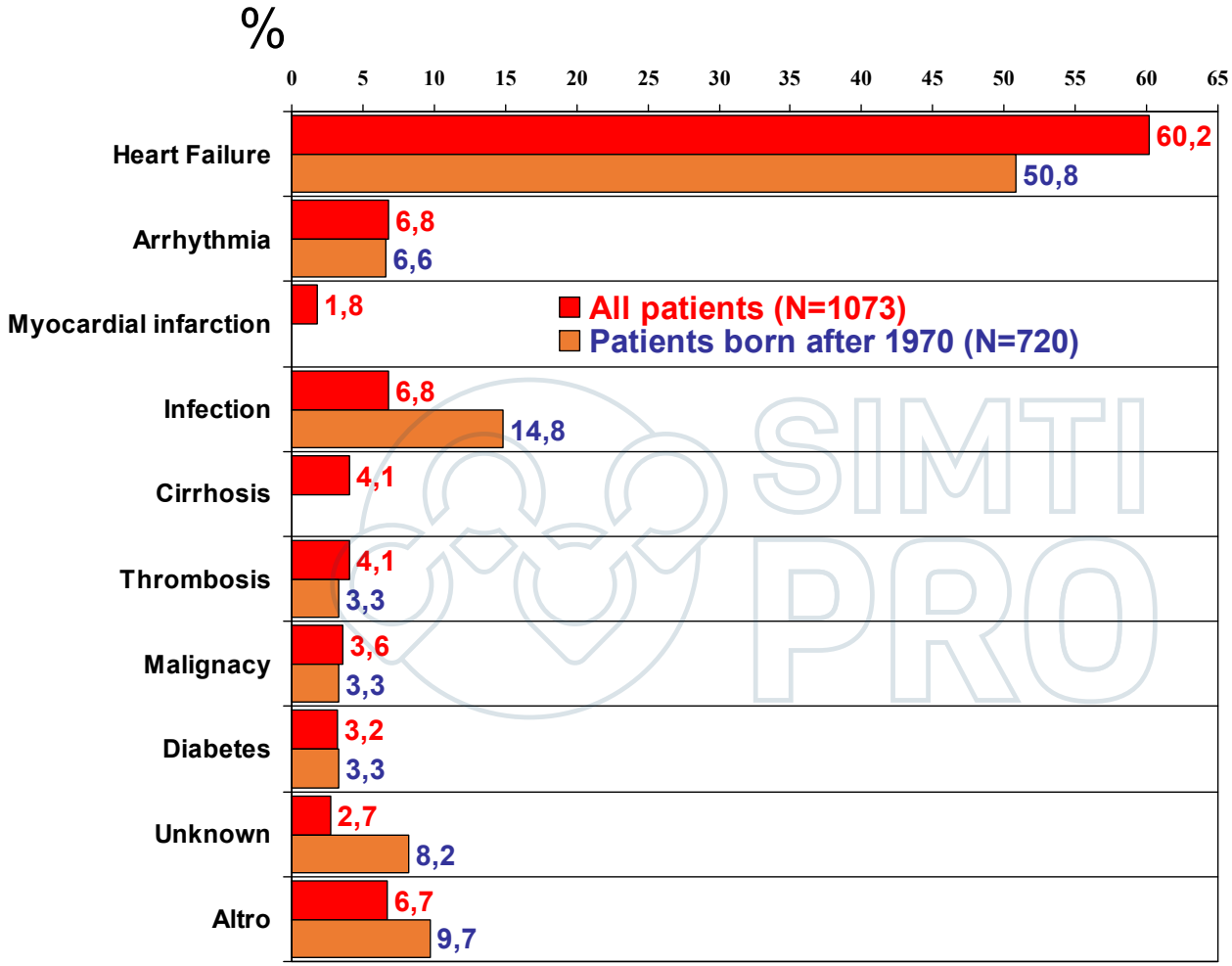


Borgna-Pignatti et al, haematologica, 2004



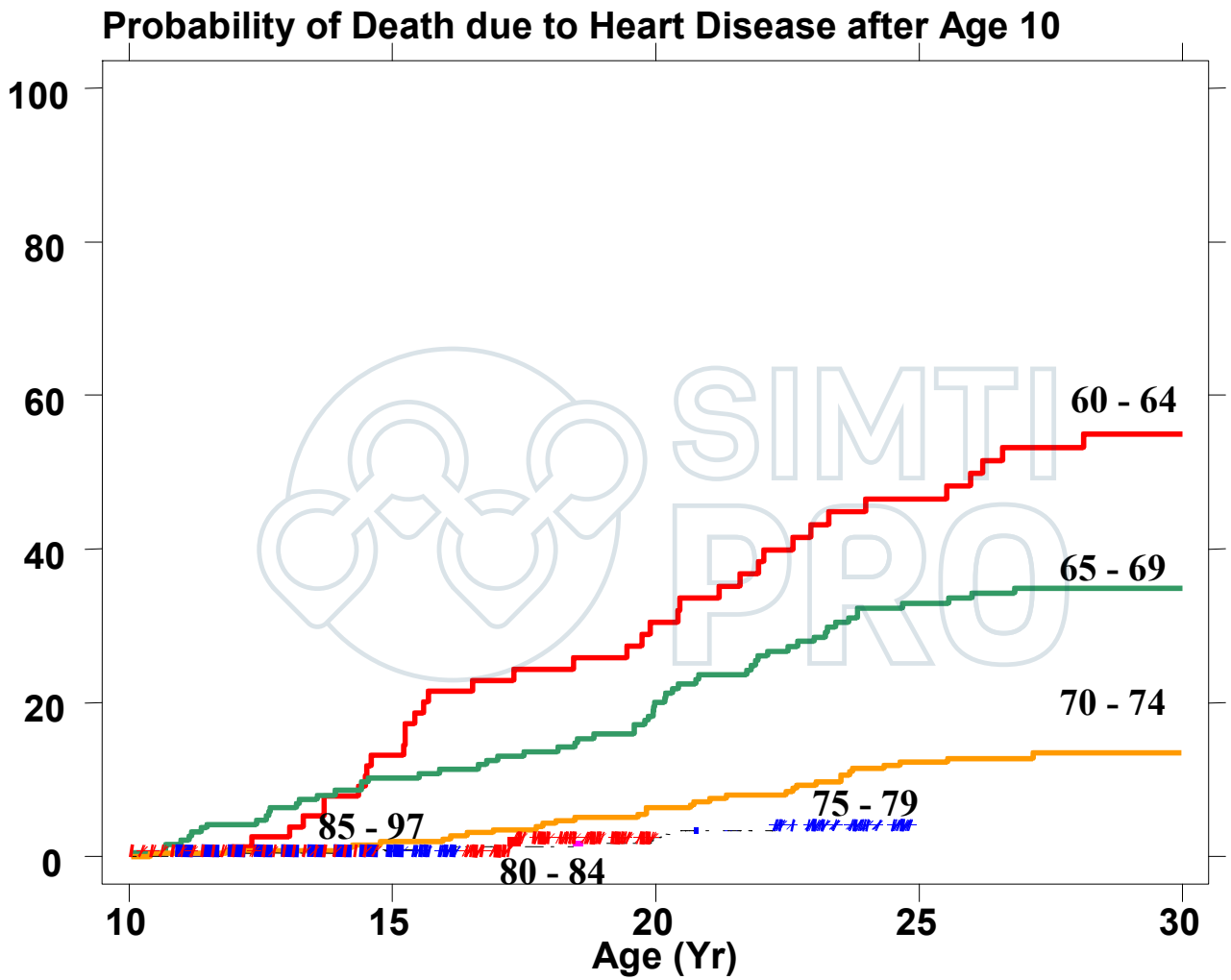
Borgna-Pignatti et al, haematologica, 2004

Causes of death for the entire population of patients and for those born after 1970



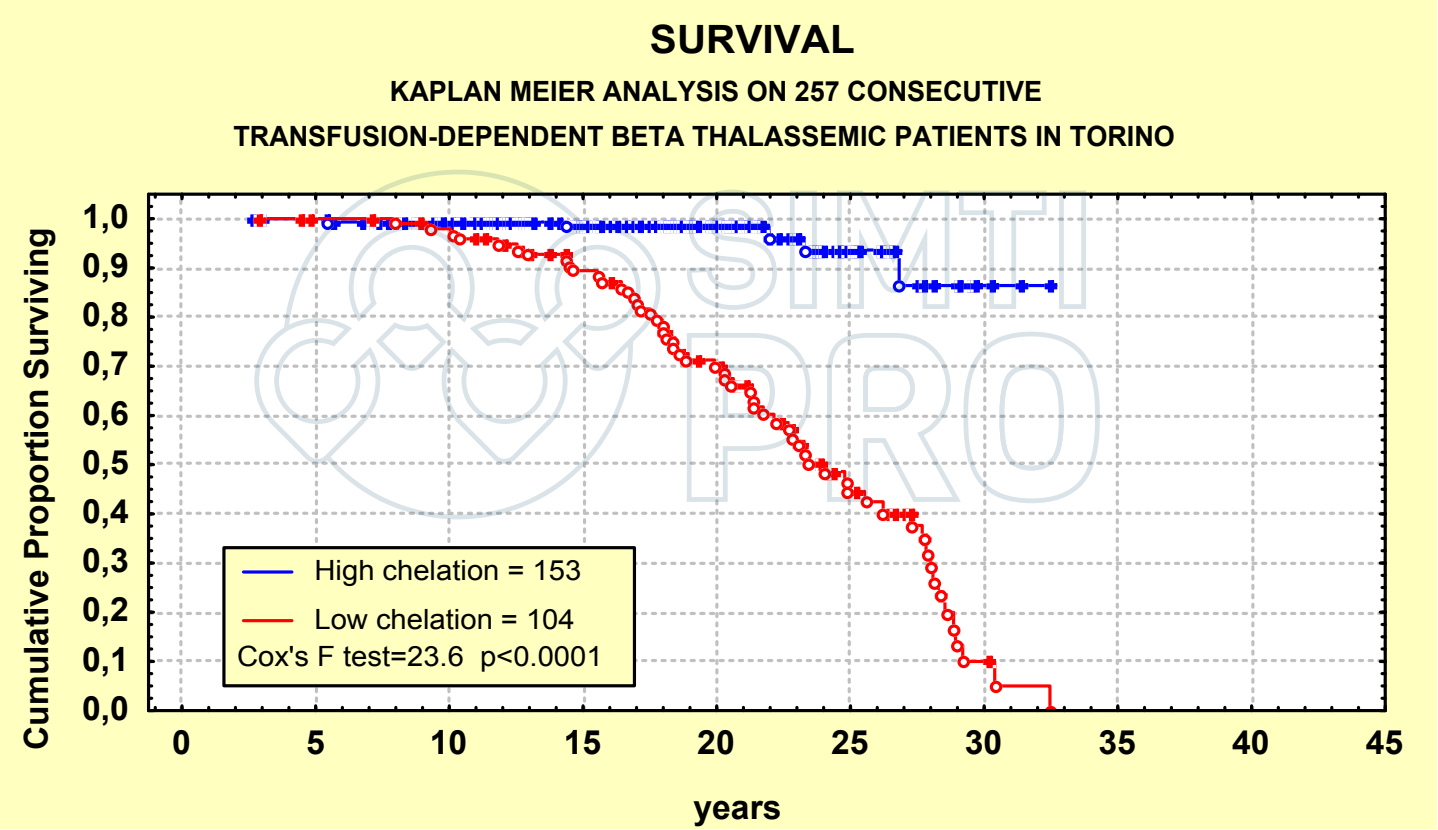
Accident, Renal Failure, HIV/AIDS, Familial autoimmune disorder, Anorexia, Hemolytic Anemia, Thrombocytopenia.

Borgna-Pignatti et al, haematologica, 2004



Borgna-Pignatti et al, haematologica, 2004

La terapia chelante cambia la prognosi della malattia



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RESEARCH ARTICLE

AJH WILEY

Overall and complication-free survival in a large cohort of patients with β-thalassemia major followed over 50 years

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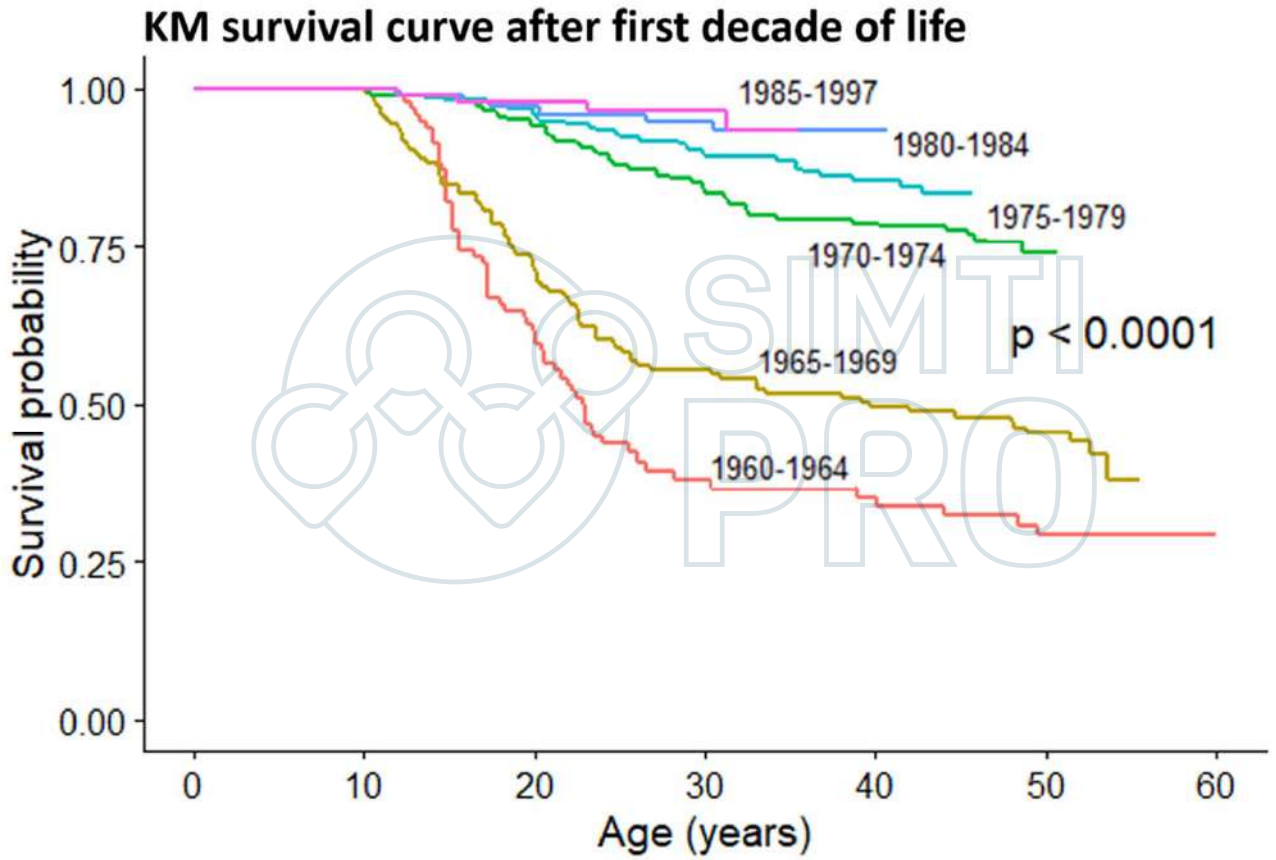
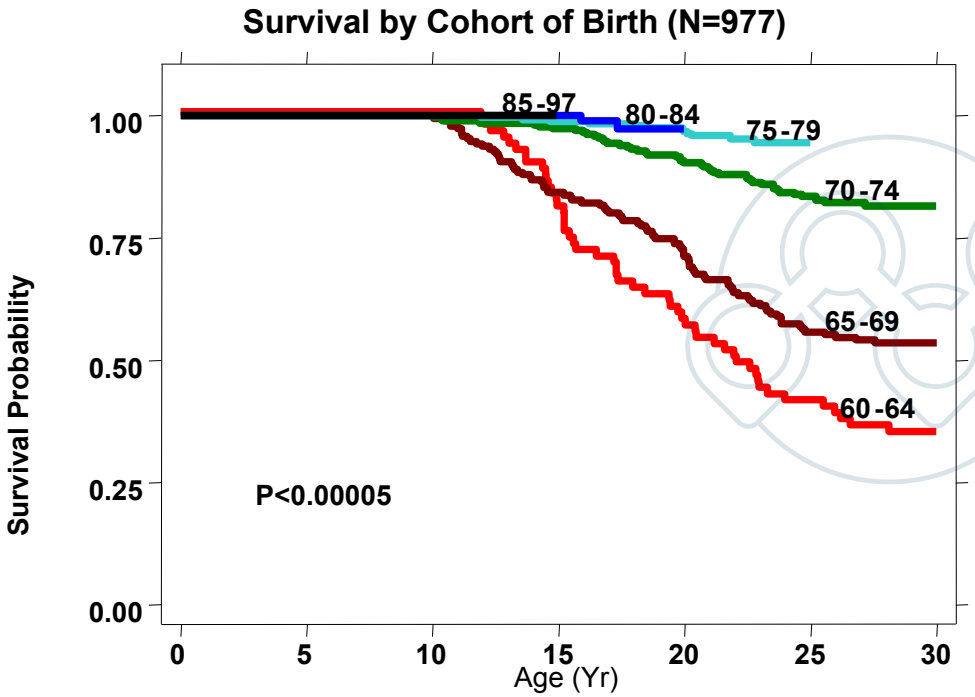
G.L. Forni et al 2022 , AHJ

Parameter	All (N = 709)	Birth cohort			
		1970-1974 (N = 213)	1975-1979 (N = 245)	1980-1984 (N = 125)	1985-1997 (N = 126)
Male, n (%)	362 (51.1)	110 (51.6)	123 (50.2)	67 (53.6)	62 (49.2)
Age in years at last follow-up, median (IQR)	33.5 (21.3-43.3)	45.7 (24.5-48.1)	40.7 (26.2-43.4)	30.1 (19.2-39.4)	24.8 (16.4-31.2)
Patient-years of observation	22,443	7,939	8,217	3,443	2,843
BMT, n (%)	73 (10.3)	15 (7.0)	23 (9.4)	21 (16.8)	14 (11.1)
Age at BMT in years, median (IQR)	10.7 (7.9-15.5)	17.1 (15.6-19.1)	11.7 (10-13.4)	8.2 (6.5-10.4)	3.8 (2.7-10.3)
Splenectomy, n (%)	271 (38.2)	123 (57.7)	89 (36.3)	38 (30.4)	21 (16.7)
Age at splenectomy in years, median (IQR)	10 (8-16)	9 (7-12)	11 (8-17)	15 (10.2-20)	14 (6.8-23)
Deaths, n (%)	93 (13.1)	45 (21.1)	32 (13.1)	8 (6.4)	8 (6.3)
Age of death in years, median (IQR)	23.2 (16.9-30)	24.4 (19.8-31.3)	24.1 (18.3-31)	16.6 (10.9-21.8)	10.8 (8.4-17.3)

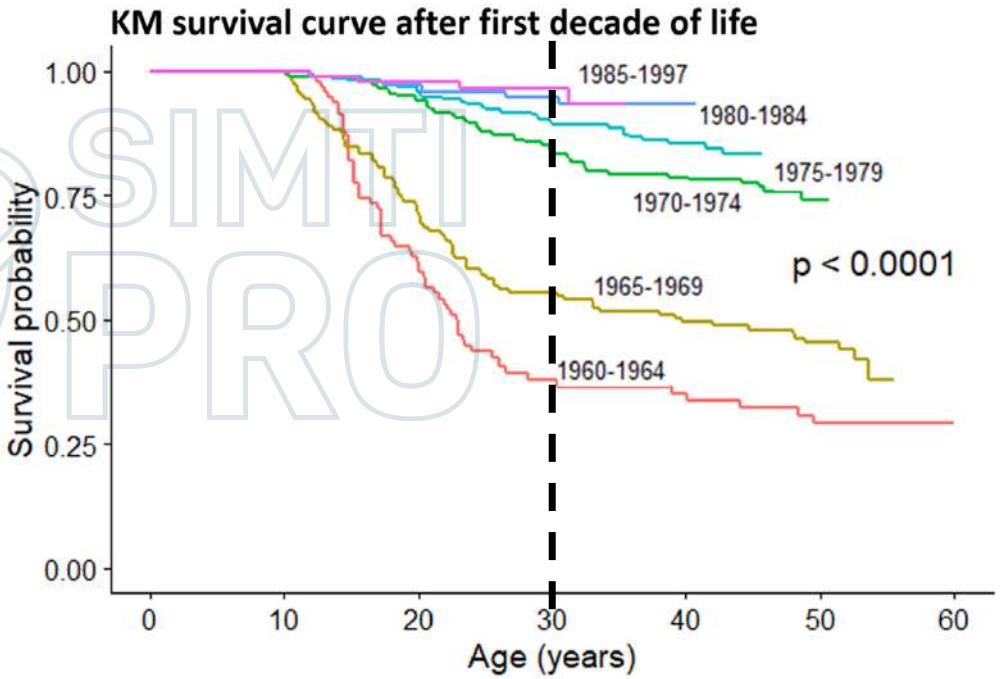
G.L. Forni et al 2022 , AHJ



G.L. Forni et al 2022 , AHJ

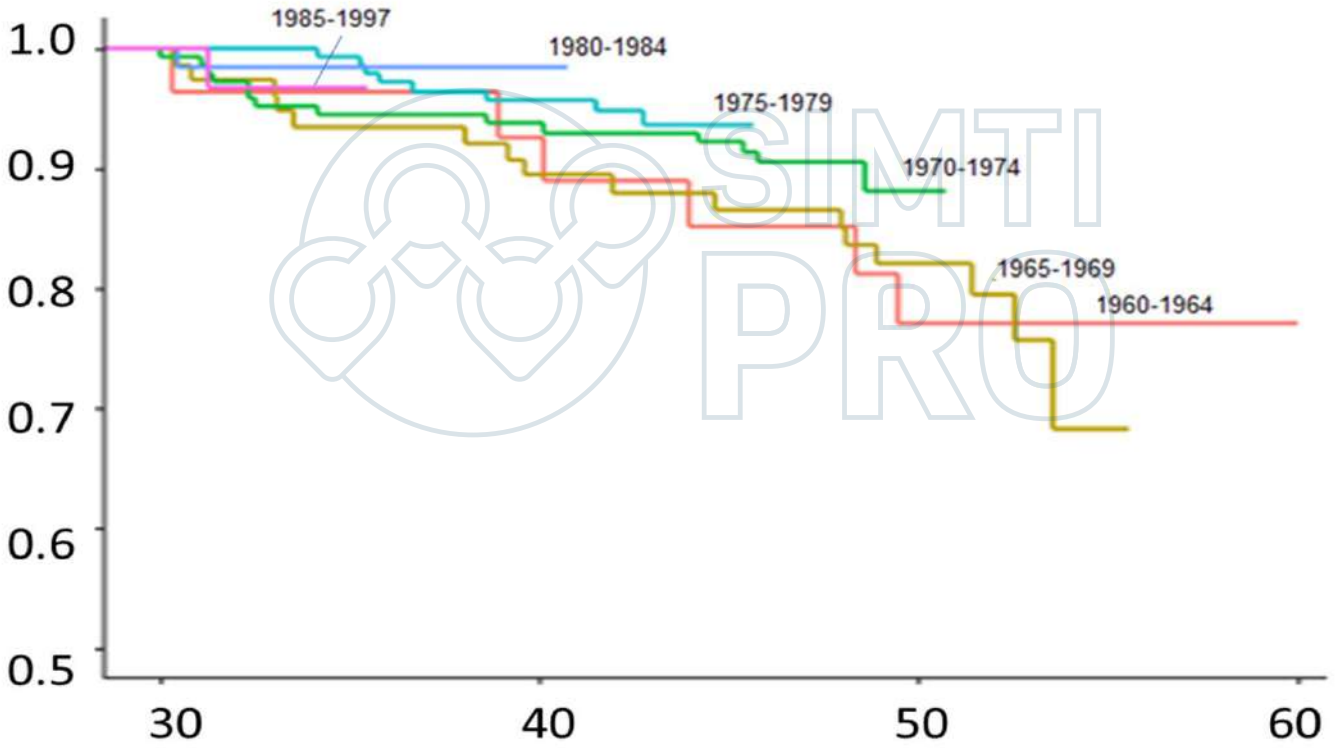


Borgna-Pignatti et al, haematologica, 2004



G.L. Forni et al 2022 , AHJ

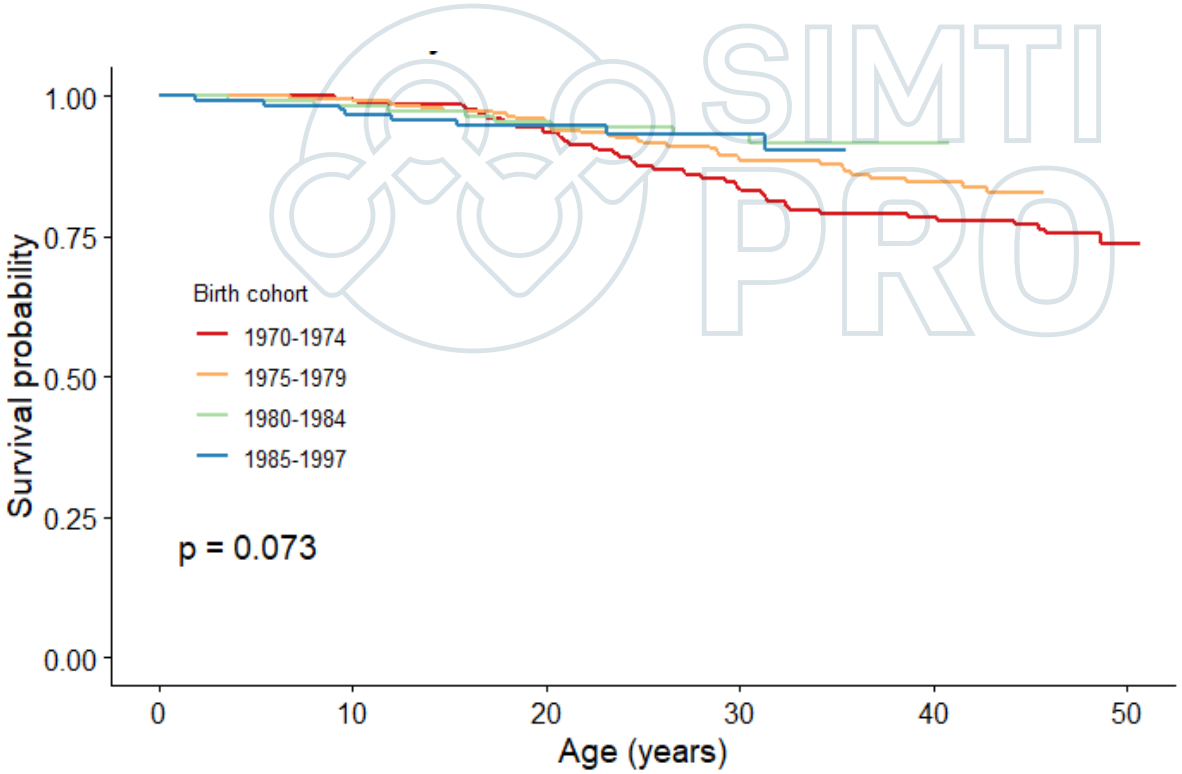
KM survival curve after the third decade of file



G.L. Forni et al 2022 , AHJ

Survival in thalassemia major: aggiornamento dopo un follow-up di 50 anni
Sopravvivenza per coorte di nascita

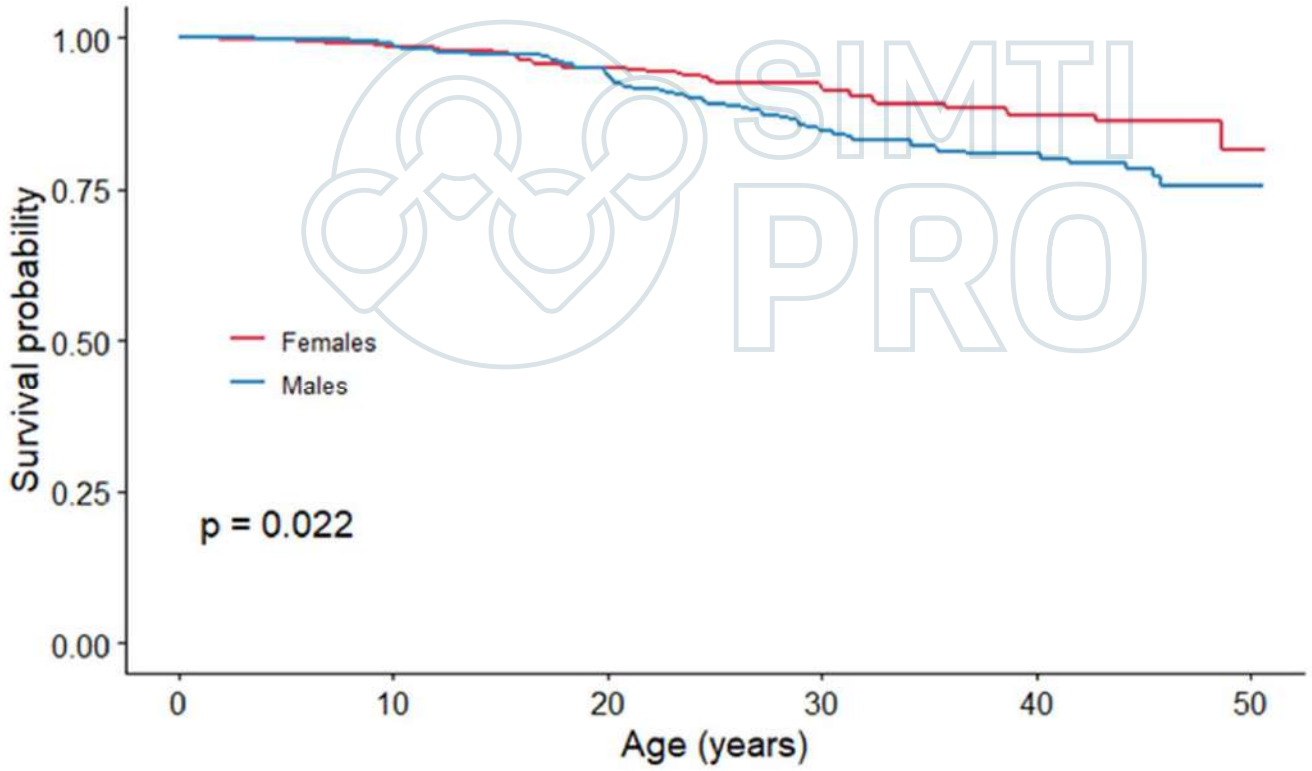
Overall survival probability at 30 years was 83.6% (95%CI: 78.5–89.1) in the oldest birth cohort (1970–1974) compared with 93.3% (95%CI: 88.6–98.3) in the youngest birth cohort (1985–1997) (p = 0.073).



G.L. Forni et al 2022 , AHJ

Survival in thalassemia major: aggiornamento dopo un follow-up di 50 anni
Sopravvivenza per sesso

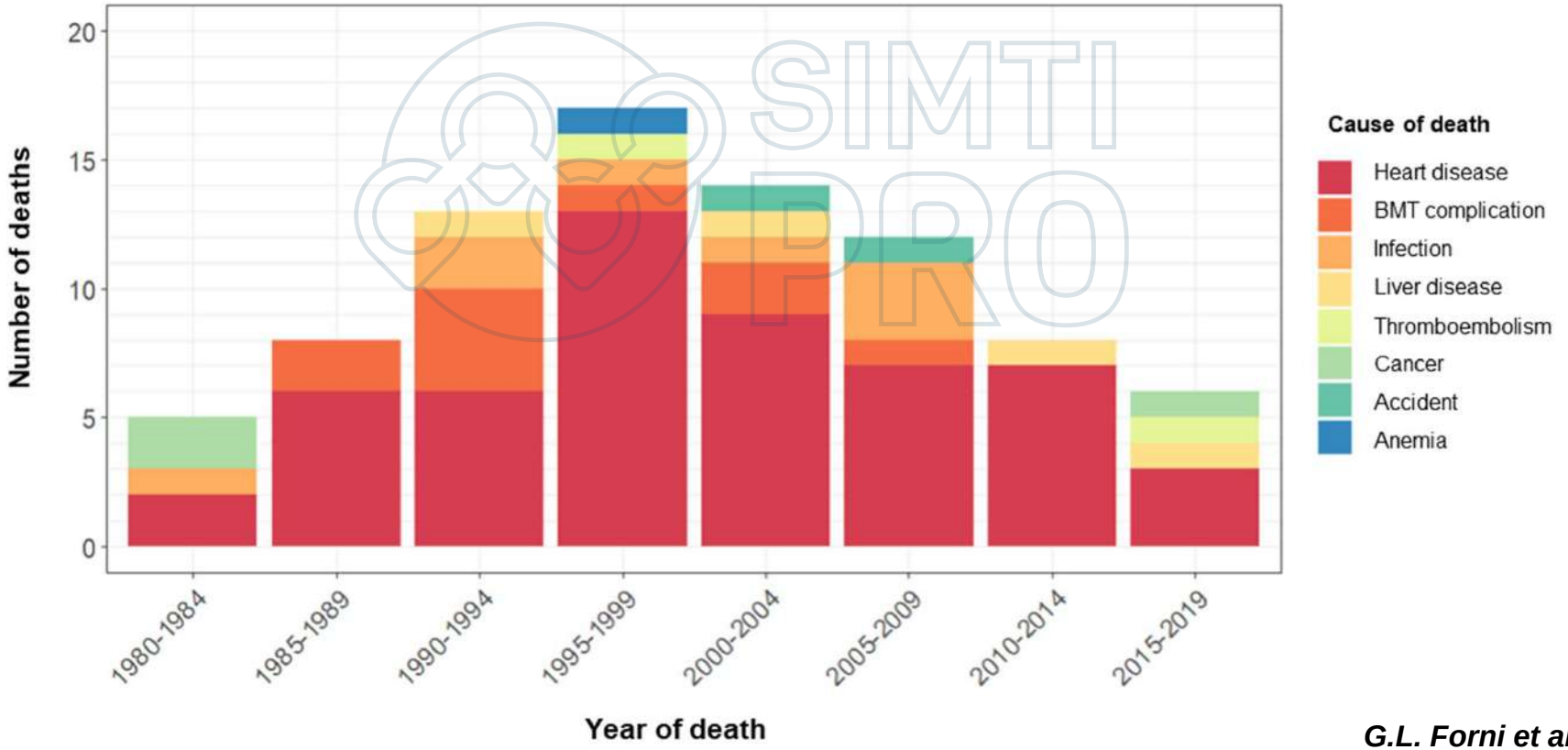
Females had better survival than males (p = 0.022) with a survival probability at 30 years of 91.8% (95%CI: 88.7–95.0) in females compared with 84.6% (95%CI: 80.5–88.8) in males.



G.L. Forni et al 2022 , AHJ

Survival in thalassemia major: aggiornamento dopo un follow-up di 50 anni
Cause di morte per coorte di nascita

- Distribution of causes of death over the years (excluding 10 patients with the cause of death not reported or unknown)
- There were a total of 93 deaths at a median age of 23.2 years (IQR: 16.9–30)



G.L. Forni et al 2022 , AHJ

Causes of death

Parameter	All (N = 709)	Birth cohort			
		1970-1974 (N = 213)	1975-1979 (N = 245)	1980-1984 (N = 125)	1985-1997 (N = 126)
Cause of death, n (% of deaths)					
Heart disease	53 (57.0)	32 (71.1)	16 (50.0)	4 (50.0)	1 (12.5)
BMT complication	10 (10.8)	3 (6.7)	2 (6.3)	2 (25.0)	3 (37.5)
Infection	8 (8.6)	3 (6.7)	3 (9.4)	-	2 (25.0)
Liver disease	4 (4.3)	2 (4.4)	2 (6.3)	-	-
Cancer	3 (3.2)	1 (2.2)	1 (3.1)	1 (12.5)	-
Thromboembolism	2 (2.2)	-	2 (6.3)	-	-
Accident	2 (2.2)	1 (2.2)	1 (3.1)	-	-
Anemia	1 (1.1)	-	-	1 (12.5)	-
Unknown	10 (10.8)	3 (4.4)	5 (15.6)	-	2 (25.0)

G.L. Forni et al 2022 , AHJ

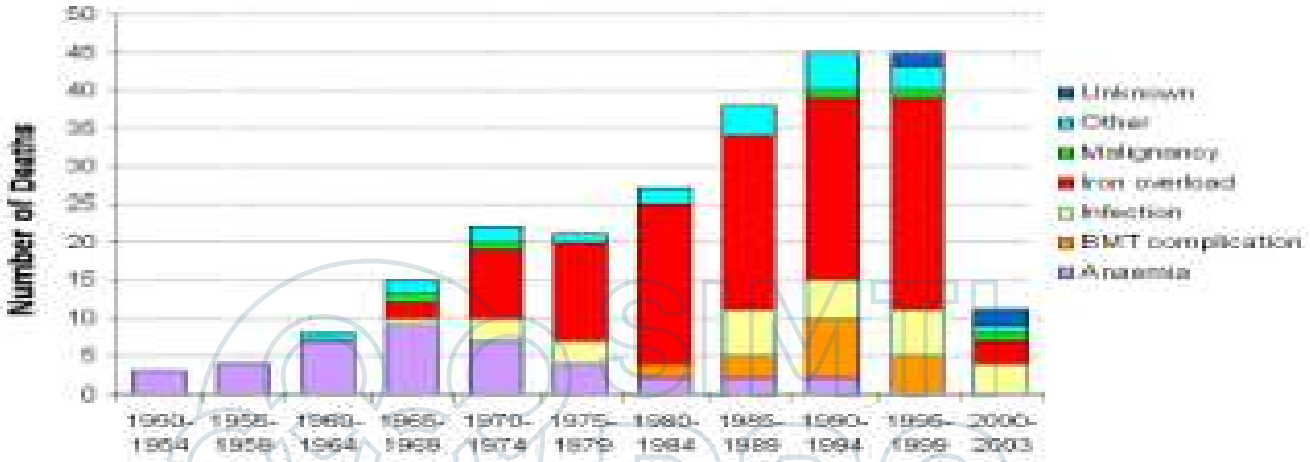


Figure 1
Number of deaths of patients with thalassaemia major in the UK by intervals. The number of deaths in the 2000–2003 interval represents deaths during 4 years, and in all the other groups the number of deaths is over 5 years. Iron overload replaced anaemia as the commonest cause of death after 1970, when adequate transfusion schemes became the norm. Iron chelation therapy by subcutaneous infusion of deferoxamine was standard practice after 1980. In 1999, T2* CMR was introduced in the UK, and doctors caring for thalassemia patients were informed of the high cardiac death rate and new options for iron chelation therapy. There has been a 71% reduction in the annualized death-rate from iron overload since 2000.

Overview of clinical complications

Parameter	Age at presentation in years, median (IQR)	All (N = 709)	Birth cohort			
			1970-1974 (N = 213)	1975-1979 (N = 245)	1980-1984 (N = 125)	1985-1997 (N = 126)
Any complication	-	**480/709 (67.7)**	**178/213 (83.6)**	**185/245 (75.5)**	**70/125 (56.0)**	**47/126 (37.3)**
Hearth failure	22.4 (18.5-28.5)	96/697 (13.8)	47/213 (22.1)	31/244 (12.7)	11/123 (8.9)	7/117 (6.0)
Arrhythmia	26.7 (22.7-34.2)	58/697 (8.3)	32/213 (15.0)	21/244 (8.6)	4/123 (3.3)	1/117 (0.9)
Diabetes	23.3 (16.1-30.9)	78/698 (11.2)	44/213 (20.7)	24/245 (9.8)	8/123 (6.5)	2/117 (1.7)
Hypothyroidism	19.4 (14.8-24.4)	120/698 (17.2)	55/213 (25.8)	52/245 (21.2)	10/123 (8.1)	3/117 (2.6)
Hypogonadism	16 (14.9-17)	335/683 (49.0)	148/213 (69.5)	144/245 (58.8)	33/121 (27.3)	10/104 (9.6)
Osteoporosis	27.6 (23-32.9)	263/402 (65.4)	82/118 (69.5)	100/139 (71.9)	50/71 (70.4)	31/74 (41.9)
Thrombosis	25.8 (19.4-34.7)	22/698 (3.2)	8/213 (3.8)	10/245 (4.1)	1/123 (0.8)	3/117 (2.6)
Cancer	39 (36-41.8)	21/709 (3.0)	15/213 (7.0)	6/245 (2.4)	0/125 (0.0)	0/126 (0.0)
HIV infection	11.2 (8.7-13.6)	10/698 (1.4)	5/213 (2.3)	5/245 (2.0)	0/123 (0.0)	0/117 (0.0)
≥2 complications	-	**301/709 (42.5)**	**132/213 (62.0)**	**129/245 (52.7)**	**31/125 (24.8)**	**9/126 (7.1)**
≥3 complications	-	**137/709 (19.3)**	**69/213 (32.4)**	**54/245 (22.0)**	**13/125 (10.4)**	**1/126 (0.8)**

Data presented as n/N (%) unless otherwise indicated. IQR, interquartile range; HIV, human immunodeficiency virus.

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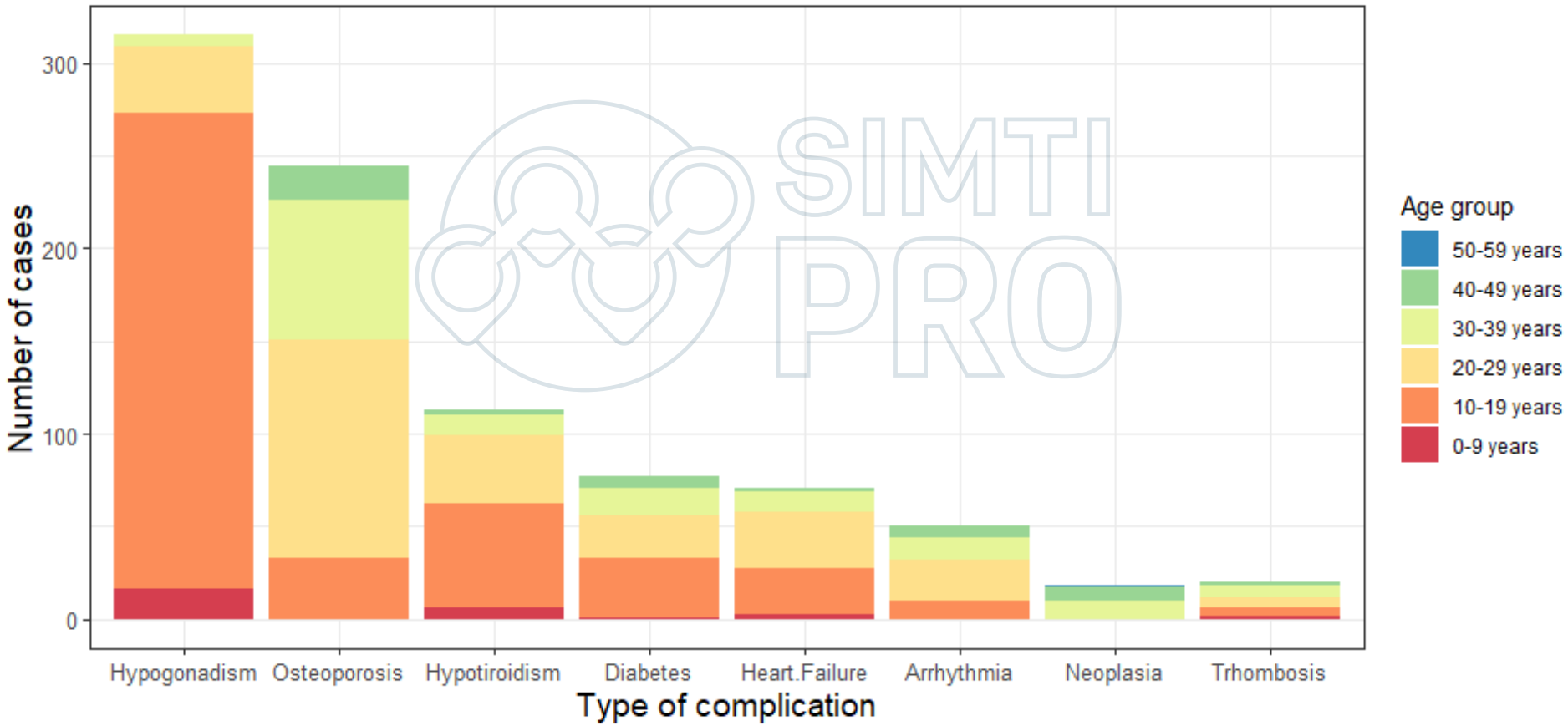
Distribution of age at presentation for different complications (human immunodeficiency virus infection excluded)



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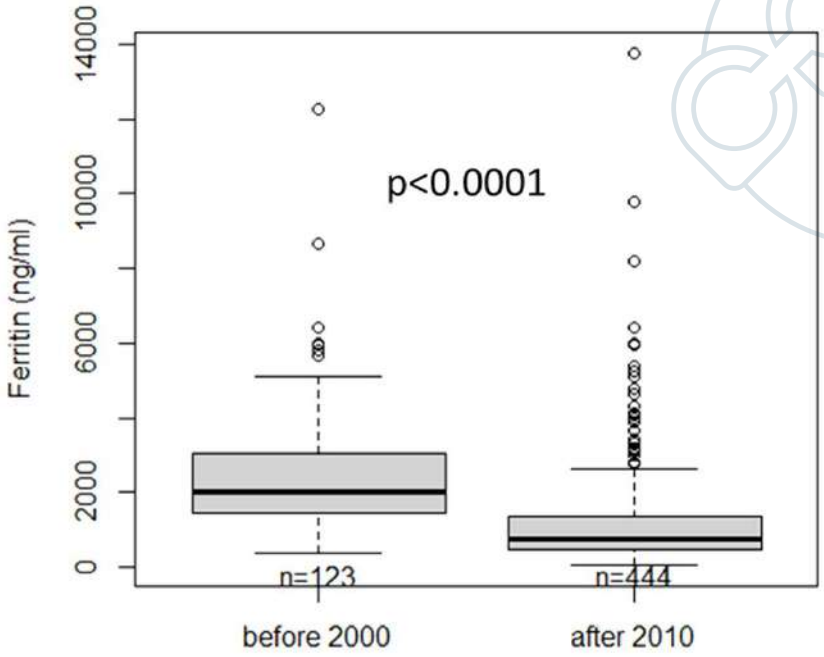
Time comparison of ferritin (before 2000 and after 2010) patients followed by two centres

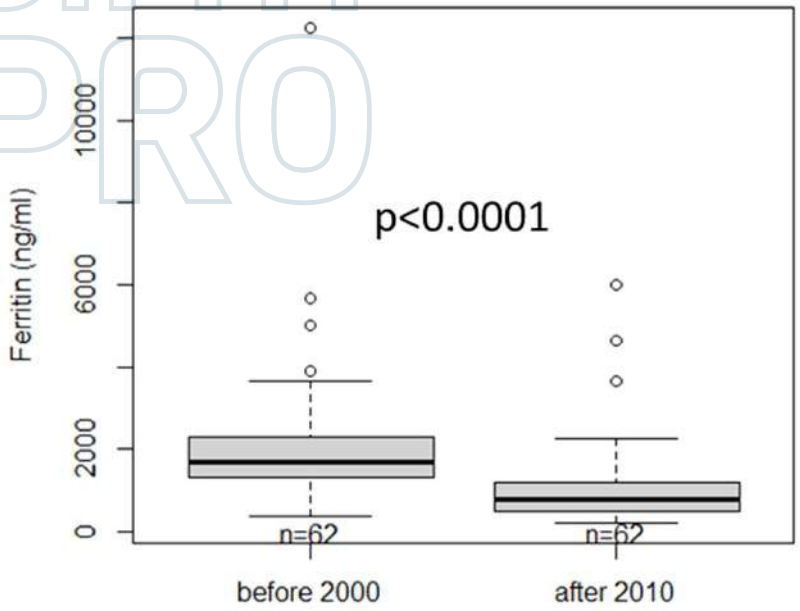
Patients from 2 centers
- 123 patients with ferritin assessment before 2000
- 444 patients after 2010

Before 2000: 2034.2 (1454.2-3036.7)
After 2010: 772.8 (485.3-1353.2))



Patients from 2 centers
- 62 patients with ferritin assessment before 2000 and after 2010

Before 2000: 1685.4 (1307.5-2285.9)
After 2010: 764.3 (486.1-1188.7)



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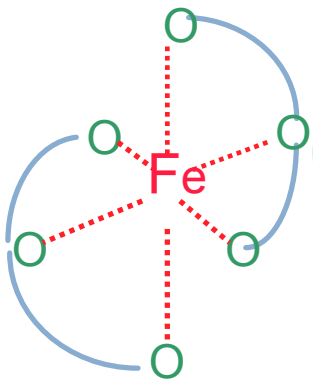
How Chelators Bind Iron

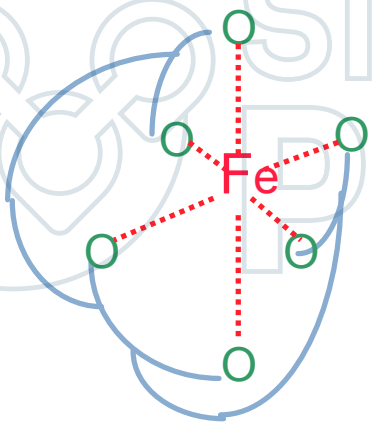
Deferasirox (DFS)

Tridentate



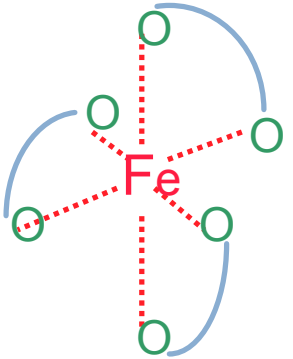
Desferrioxamine (DFO)

Hexadentate



Deferiprone (DFP)

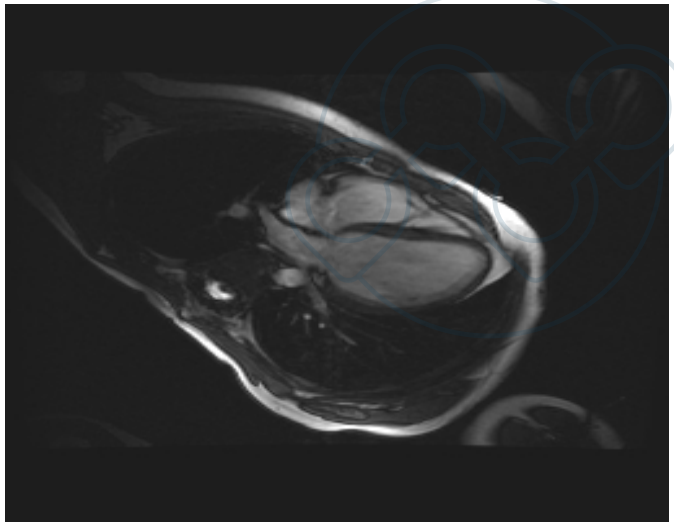
Bidentate



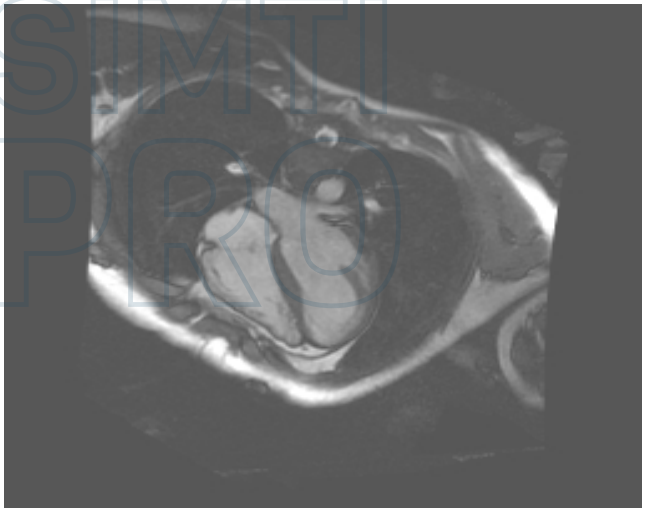
Adapted from Porter JB, et al. *Baillieres Clin Haematol*. 1989;2:257.

Rapido effetto della chelazione intensiva combinata in un caso di grave scompenso cardiaco da accumulo di ferro

FE 30%



FE 50%



Journal of Cardiovascular Magnetic Resonance

BioMed Central

Research

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Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction

Mark A Tanner[1], Renzo Galanello[2], Carlo Dessi[2], Gillian C Smith[1], Mark A Westwood[1], Annalisa Agus[2], Martina Pibiri[2], Sunil V Nair[3], J Malcolm Walker[3] and Dudley J Pennell*[1]

Received: 27 July 2017 | Revised: 12 September 2017 | Accepted: 15 September 2017

DOI: 10.1002/ajh.24911

RESEARCH ARTICLE

WILEY AJH

Treatment of hepatitis C virus infection with direct-acting antiviral drugs is safe and effective in patients with hemoglobinopathies

Raffaella Origa[1] | Maria Laura Ponti[2] | Aldo Filosa[3] | Alfonso Galeota Lanza[3] | Antonio Piga[4] | Giorgio Maria Saracco[4] | Valeria Pinto[5] | Antonino Picciotto[6] | Paolo Rigano[7] | Salvatore Madonia[7] | Rosamaria Rosso[8] | Domenico D'Ascola[9] | Maria Domenica Cappellini[10] | Roberta D'Ambrosio[10] | Immacolata Tartaglione[11] | Lucia De Franceschi[12] | Barbara Gianesin[5] | Vito Di Marco[13] | Gian Luca Forni[5] | Italy for THAlassemia and hepatitis C Advance - Società Italiana Talassemie ed Emoglobinopatie (ITHACA-SITE)

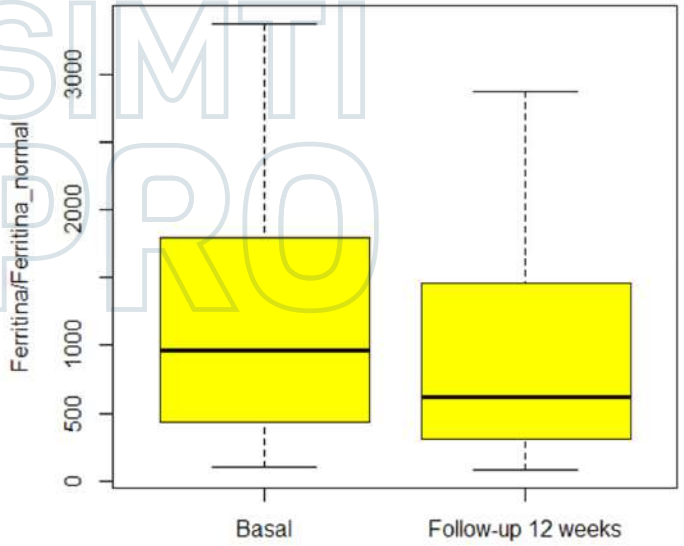
Fondazione Franco e Piera Cutino
Guarire dalla TALASSEMIA

Serum Ferritin

- **Baseline: (1450 ± 1660) mg/mL (range: 103−11,190 mg/mL), n=117**

- **Week 12 of follow up: (1080 ± 1144) mg/mL (range: 88−5696 mg/mL), n=61 HCV-RNA negative**

Mean difference: 433 mg/mL (p<0.001)



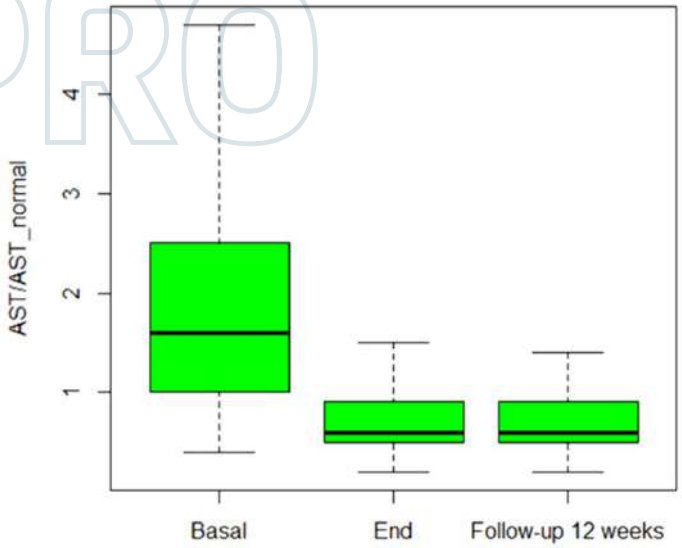
Fondazione FrancoePieraCutino
Guarire dalla TALASSEMIA

AST/AST$_{normal}$ ratio

- Baseline: (2.0 ± 1.4), n=136
- End of the treatment:(0.75 ± 0.45), n=105
- Week 12 of follow up: (0.72 ± 0.42), n=62

Reductions in serum AST levels from baseline were statistically significant both at the end of treatment (p<0.001) and at Week 12 of post-treatment follow up (p<0.001).

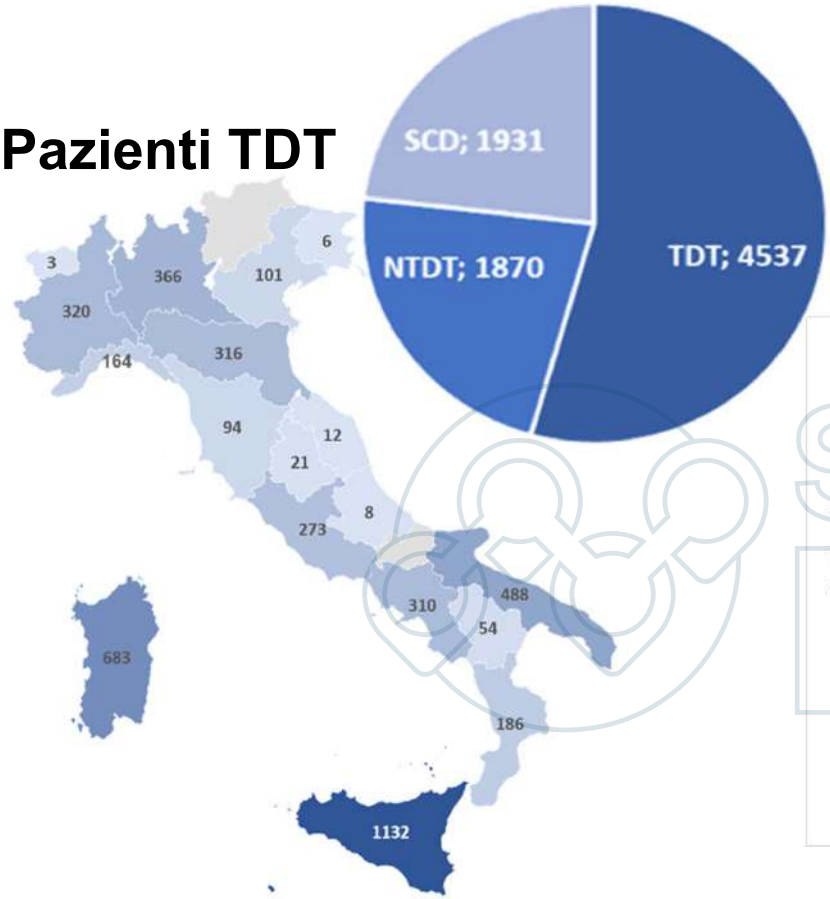
The reduction in AST level between the end of DAA treatment and Week 12 was not statistically significant (p=0.86).

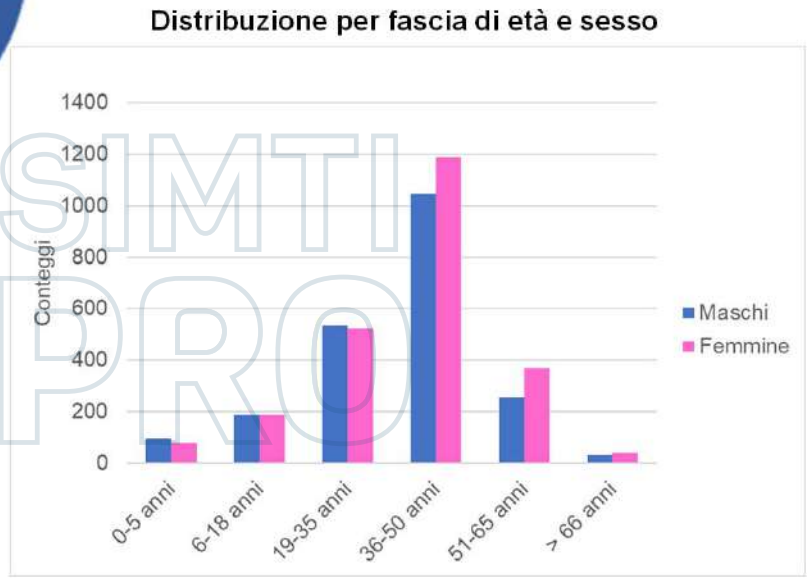


Agenda

L’invecchiamento dei pazienti

Pazienti TDT





Received: 14 July 2022 | Revised: 6 August 2022 | Accepted: 22 August 2022

DOI: 10.1002/cncr.34509

ORIGINAL ARTICLE

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021

Raffaella Origa MD[1] | Barbara Gianesin PhD[2] | Filomena Longo MD[3] | Rosario Di Maggio MD[4] | Elena Cassinerio MD[5] | Maria Rita Gamberini MD[6] | Valeria Maria Pinto MD[7] | Antonella Quarta MD[8] | Maddalena Casale MD[9] | Giorgio La Nasa MD[10] | Giovanni Caocci MD[10] | Antonio Piroddi MD[11] | Andrea Piolatto MSc[3] | Alessandra Di Mauro MD[5] | Claudia Romano MD[8] | Antonia Gigante BA[2] | Susanna Barella MD[12] | Aurelio Maggio MD[4] | Giovanna Graziadei MD[5] | Silverio Perrotta MD[9] | Gian Luca Forni MD[7]

[1]Università di Cagliari, SSD Talassemia, Ospedale Microcitemico 'A. Cao,' ASL8 Cagliari, Cagliari, Italy

Results: A total of 197 diagnoses of cancer were reported (incidence rate, 442 cases per 100,000 person-years). The liver was the most frequent site of tumors in both sexes, with a higher incidence (190 cases per 100,000 person-years) in comparison with the general population found in all types of hemoglobinopathies (except hemoglobin H disease). In recent years, tumors have become the second cause of death in patients with transfusion-dependent thalassemia. A lower risk of breast and prostate cancer was observed in the whole group of patients with hemoglobinopathies. The first cancer diagnoses dated back to the 1980s, and the incidence rate sharply increased after the 2000s. However, although the incidence rate of cancers of all sites but the liver continued to show an increasing trend, the incidence of HCC showed stability.

Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

EightItalianCenters Study

Raffaella Origa	Cagliari
Barbara Gianesin	Genova
Filomena Longo	Torino
Rosario Di Maggio	Palermo
Elena Cassinerio	Milano
Maria Rita Gamberini	Ferrara
Valeria Maria Pinto	Genova
Antonella Quarta	Brindisi
Maddalena Casale	Napoli
Giorgio La Nasa	Cagliari
Giovanni Caocci	Cagliari
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Gian Luca Forni	Genova

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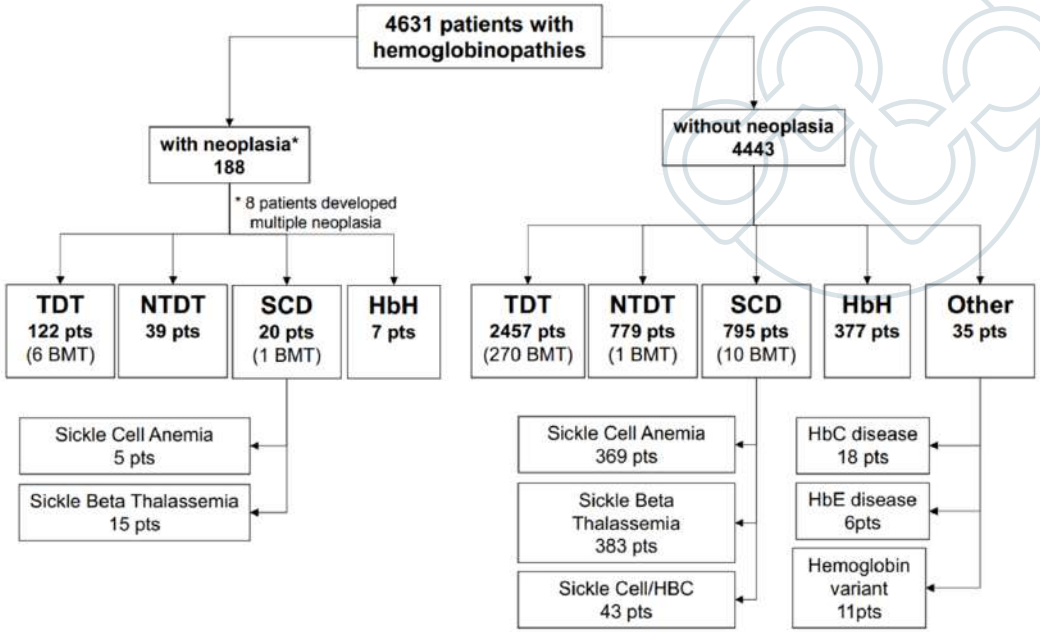
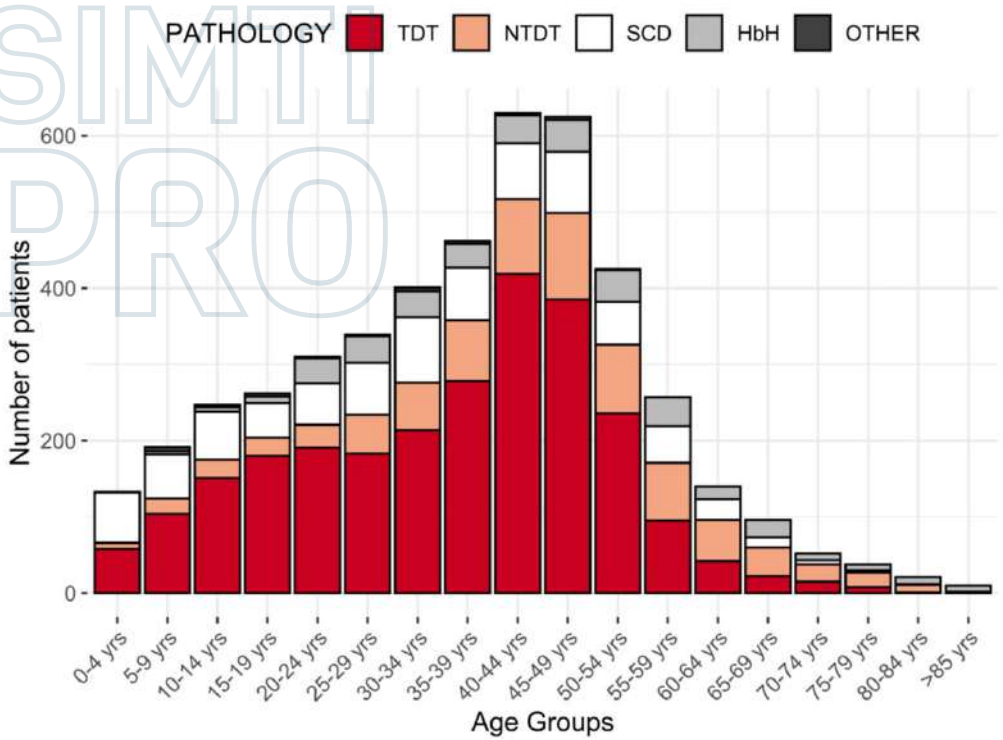
Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

La popolazione in studio comprendeva 4.631 pazienti (48% maschi), seguiti tra il 1970 e il 2021, per un totale di 161.468 anni-persona di osservazione.
Il gruppo di pazienti più rappresentato nella coorte di studio era quello del TDT con 2.579 soggetti (55,6%),





Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 -

Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Caratteristiche della popolazione in studio comprese le cause di morte.

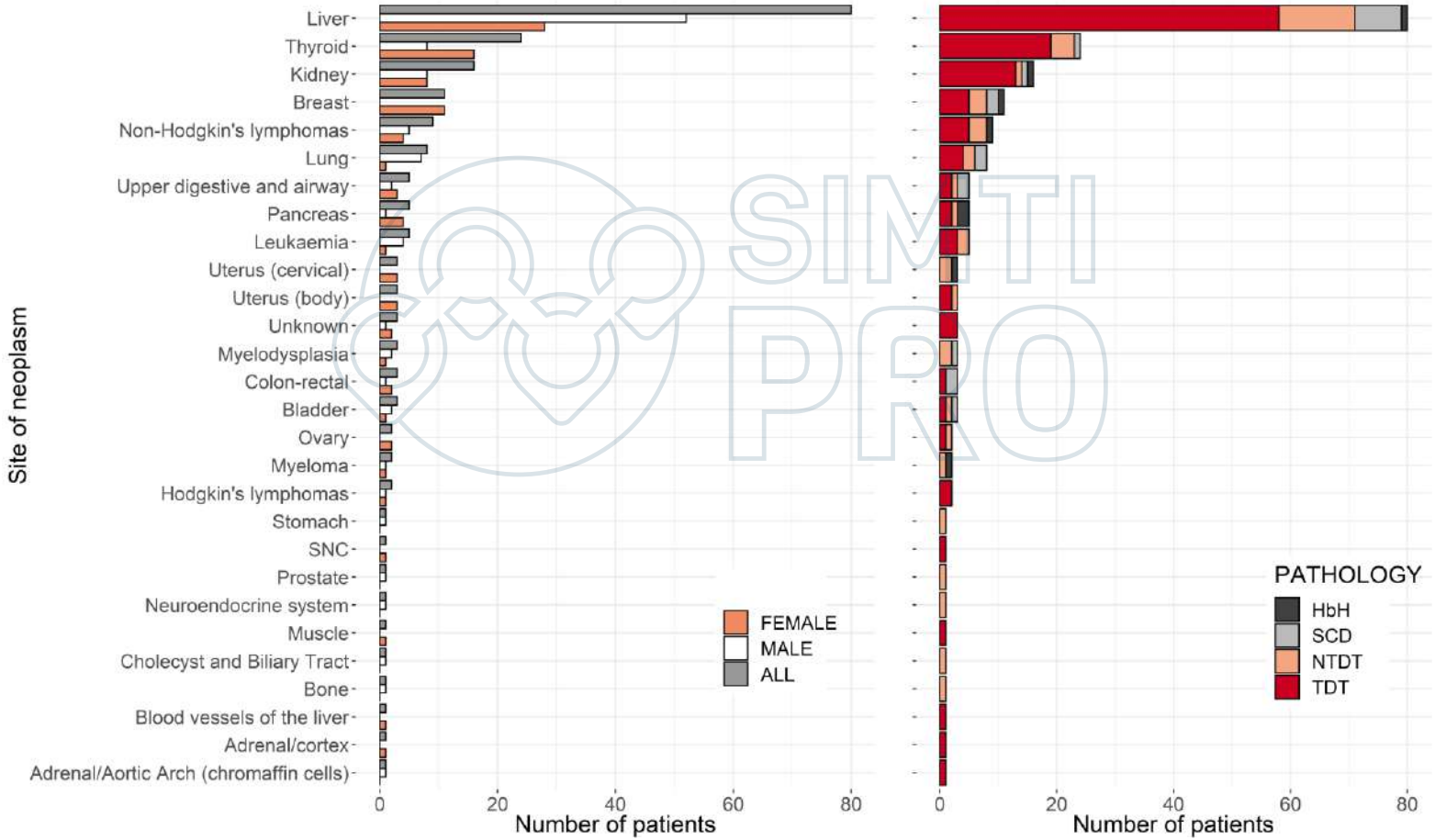
Cause of death	*All**	TDT	NTDT	SCD	HbH
N (% of males)	*4631 (48%)*	2579 (49%)	818 (47%)	815 (49%)	384 (42%)
Age at last follow-up	*39.1;23.7;46.8*	45.5;33.8;55.9	45.5;33.8;55.9	33.3;17.4;46.7	45.4;30.8;57.1
Number of BMT	*288*	276	1	11	
Pts with neoplasia	*188*	122	39	20	7
Pts with HCC	*80*	58	13	8	1
Alive at last follow-up	*4040*	2094	761	781	371
Dead at last follow-up	*591*	485	57	34	13
Causes of death					
- Heart failure	*283*	257	19	4	2
- Neoplasia	*86*	53	18	10	5
- Infection/Sepsis	*74*	61	9	3	
- BMT complications	*31*	31			
- Sudden death	*15*	15			
- Hepatic Failure/Cirrhosis	*22*	14	3	5	
- Accident	*14*	12	1	1	
- Other	*49*	34	4	11	
- Unknown	*17*	8	3		6

TDT: Transfusion-Dependent Beta Thalassemia; NTDT: Non-Transfusion-Dependent Beta Thalassemia; SCD: Sickle Cell Disease HbH: Hemoglobin H Disease; BMT: Bone Marrow Transplantation; HCC: Hepatocellular Carcinoma

*Patients (pts) with hemoglobinopathy different from TDT/NTND/SCD/HbH are included

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Mentre la distribuzione dei tumori era simile nei pazienti con TDT, β-NTDT e SCD, solo un caso di carcinoma epatocellulare è stato riportato in pazienti con malattia da HbH.



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Tassi di incidenza (rispetto alla popolazione generale)

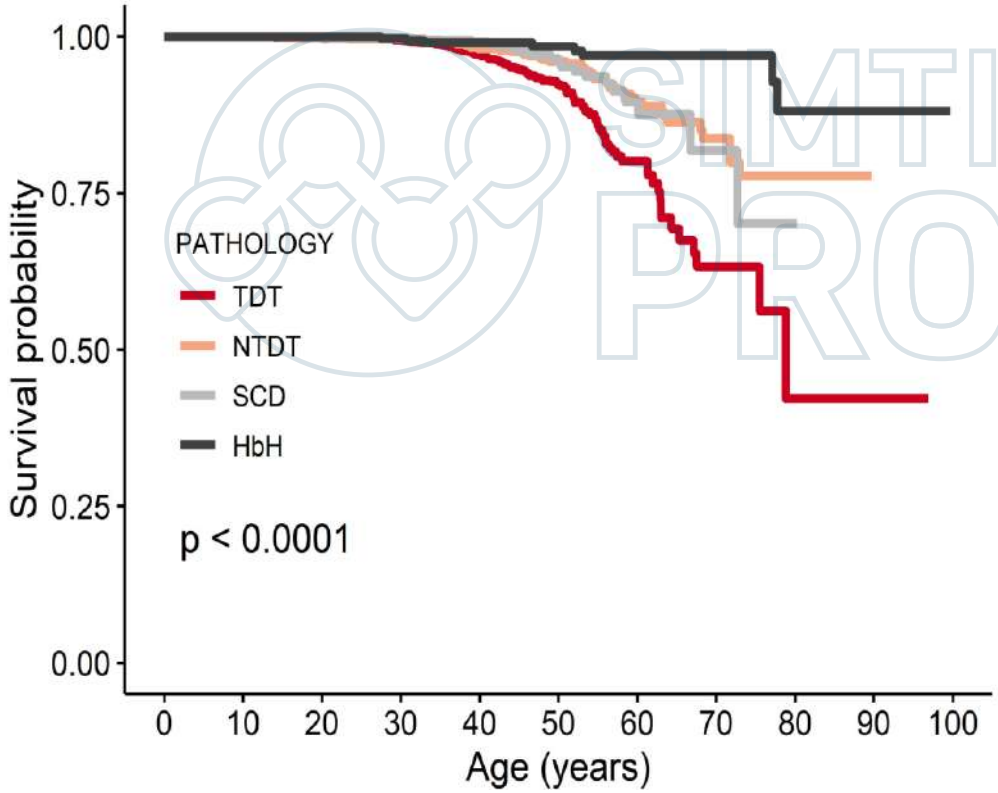
- Non sono state riscontrate differenze significative nell'età della diagnosi di HCC stratificazione per genere [maschi 46,3 anni (42,1-53,7), femmine 51 anni (46,6-54,8)] e tipi di emoglobinopatia [TDT 47,5 anni (42,6-53,3), β- NTDT 51 anni (46,4-56), SCD 50 anni (42-57,3)].

- Il tasso di incidenza globale aggiustato per l'età del cancro nell'emoglobinopatia è stato stimato in 442 casi/100.000 anni persona (IC 95% 340-700) che non era statisticamente diverso da quello della popolazione generale italiana (632 casi/100.000 anni persona), considerando sia l'emoglobinopatia in totale che ogni sottogruppo di pazienti.

- I pazienti con TDT avevano il più alto tasso di incidenza di HCC e quindi la maggiore differenza con la popolazione generale (445 casi/100.000 anni-persona, IC 95% 132-826, p<0,001), seguiti dai pazienti con β-NTDT (102 casi/100.000 persone- anni, 95% CI 39.198, p<0.001).

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

La probabilità di sviluppare una neoplasia è significativamente più alta (p<0,001) nei soggetti con TDT



Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

TABLE 2 Characteristics of HCV RNA–negative patients previously treated with antivirals who achieved a sustained virological response and developed HCC

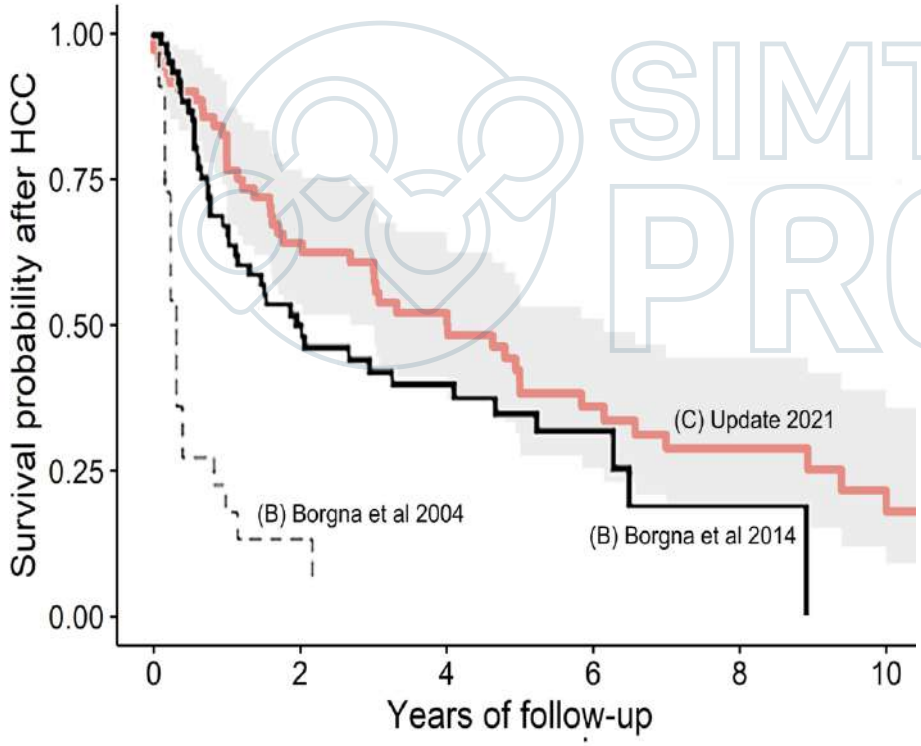
Patient	Gender	Diagnosis	Age at HCC, years	Cirrhosis	Therapy type	HCC after therapy, years	Last ferritin (peak) (ng/ml) before HCC	Last LIC (peak) (mg/g dw) before HCC
1	Female	TDT	50	Yes	DAA	4	653 (773)	4.1 (5)
2	Male	TDT	46	Yes	DAA	4	290 (9100)	5.5 (23.3)
3	Male	TDT	40	Yes	DAA	1	81 (2250)	1.2 (5.5)
4	Male	SCD	43	Yes	DAA	2	727 (2710)	11.89 (11.89)
5	Female	TDT	55	No	DAA	5	351 (3998)	2.4 (6.6)
6	Female	TDT	47	No	IFN + RIBA	3	241 (1850)	2 (3.89)
7	Male	TDT	53	Yes	DAA	5	543 (NA)	3.88 (–)
8	Female	TDT	51	Yes	IFN + RIBA	4	929 (1632)	9.5 (–)
9	Male	TDT	39	–	IFN	6	– (–)	– (–)
10	Male	TDT	39	Yes	DAA	1	395 (3890)	2.9
11	Female	SCD	57	Yes	DAA	4	272 (–)	– (–)
12	Male	SCD	32	No	NA	>3	5686 (7147)	10.4 (20.5)
13	Male	TDT	52	Yes	DAA	2	854 (2098)	5.53 (5.53)
14	Male	TDT	44	Yes	IFN + RIBA	3	483 (2384)	7.44 (18.22)
15	Male	TDT	46	Yes	IFN	18	788 (4851)	6.96 (6.96)
16	Male	TDT	46	Yes	IFN + RIBA	3	357 (9200)	5.28 (21.4)
17	Male	TDT	43	No	DAA	1	204 (–)	1.4 (10.37)
18	Female	TDT	37	Yes	DAA	2	225 (5000)	2.04 (13.2)
19	Female	TDT	51	No	IFN + RIBA	8	643 (1631)	2.73 (13.86)

Abbreviations: DAA, direct antiviral agent; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LIC, liver iron concentration; NA, not available; RIBA, ribavirin; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.

Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Sopravvivenza dopo la diagnosi di HCC: confront con le coorti riportate nei lavori di Borgna et al. (2004) and Borgna et al. (2014)

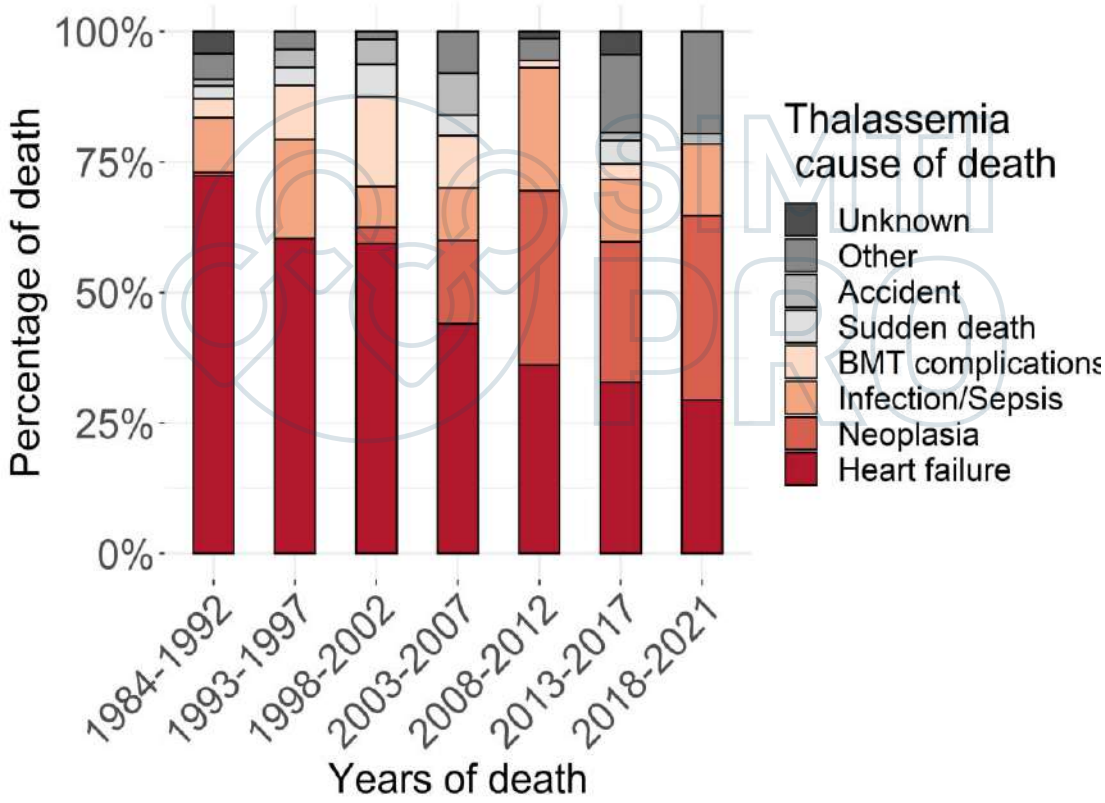


Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Causa di morte in talassemia.

Distribuzione delle cause di morte per periodi di 5 anni nei pazienti con TDT e β-NTDT.



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Incidence of cancer and related deaths in hemoglobinopathies: A follow-up of 4631 patients between 1970 and 2021 - Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

La probabilità di sviluppare qualsiasi tipo di neoplasia o carcinoma epatocellulare era significativamente più alta (p<0,001) nei soggetti con TDT).
Inoltre, il sesso maschile, la positività dell'anticorpo anti-HCV e il rilevamento dell'HCVRNA sono emersi come fattori di rischio significativi per l'HCC dall'analisi univariata. Tutti, esclusa la positività anti-HCV, sono stati confermati come significativi dall'analisi multivariata

Supporting Table S3 Univariate and multivariate Cox-regression analysis for survival to the event HCC in Italian patients with hemoglobinopathies.

		Cox regression model Univariate analisys		Cox regression model Multivariate analisys		
Variabile	***HR***	***95% CI***	***p-value***	***HR***	***95% CI***	***p-value***
Pathology: SCD vs NTDT	1,39	(0.57, 3.36)	p=0.5	*1,98*	*0.75, 5.22*	*0,2*
Pathology: : TDT vs NTDT	3,67	(1.98, 6.79)	p<0,001	2.47	1.17, 5.25	0.018
Gender: males vs female	2,34	(1.47, 3.74)	p<0,001	2.79	1.64, 4.72	<0,001
BMT: YES vs NO	1.71	0.41, 7.03	p=0.5	0,7	0.17, 2.96	0,6
Anti HCV POS vs NEG	6,36	3.46, 11.7	p<0,001	2.27	1.04, 4,96	0.040
HCV-RNA: POS vs NEG	9,12	5.60, 14.8	p<0,001	5.97	3.45, 10.4	p<0,001
HR: hazard ratio; TDT: transfusion dependent thalassemia; NTDT: transfusion dependent thalassemia; SCD: Sickle Cell Disease; BMT: bone marrow transplantation						

Origa et al. Cancer. 2022 Nov 2. doi: 10.1002/cncr.34509. Epub ahead of print. PMID: 36321594.

Agenda

L’invecchiamento dei pazienti

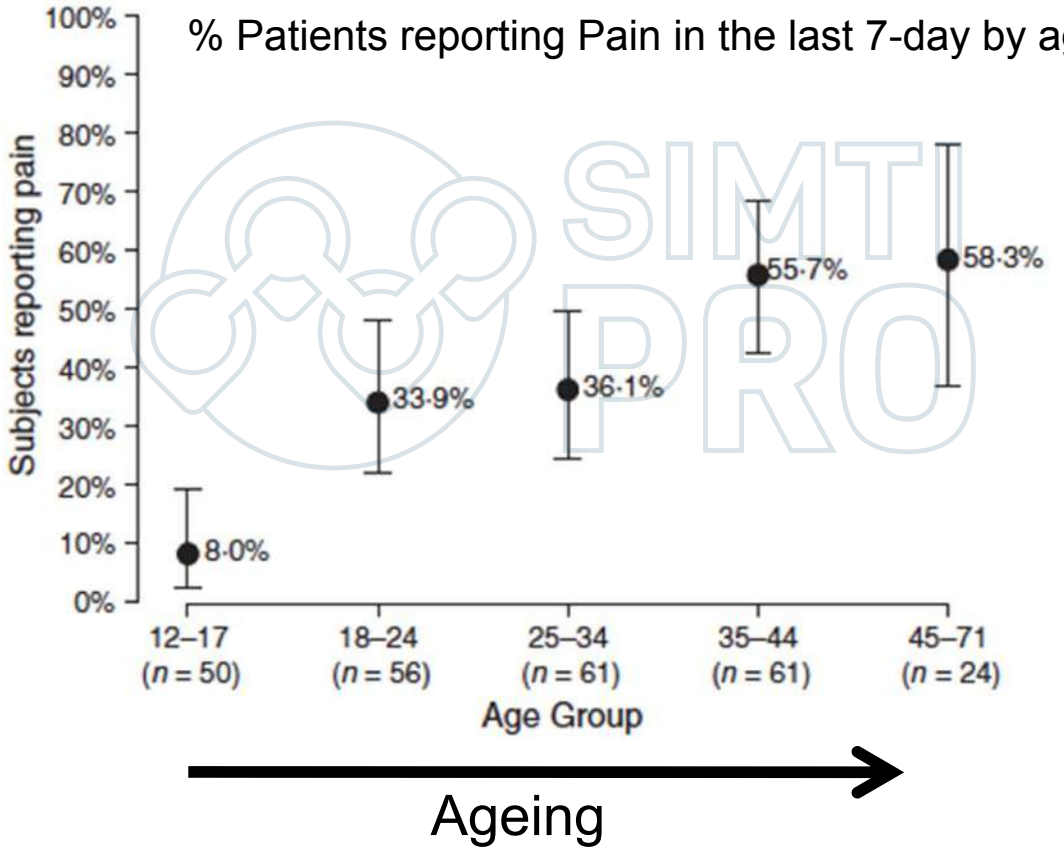
SITE UNITED ISTUD: Il valore per la persona con Beta Talassemia Major, 2015 –
Le testimonianze

"per i dolori alle caviglie e per l'artrosi ho dovuto rinunciare ad andare ai concerti, ora sto spesso a casa, se devo uscire valuto con chi e dove, altrimenti non posso"

"dopo i 30 anni i dolori articolari e soprattutto alla schiena sono diventati abbastanza invalidanti"

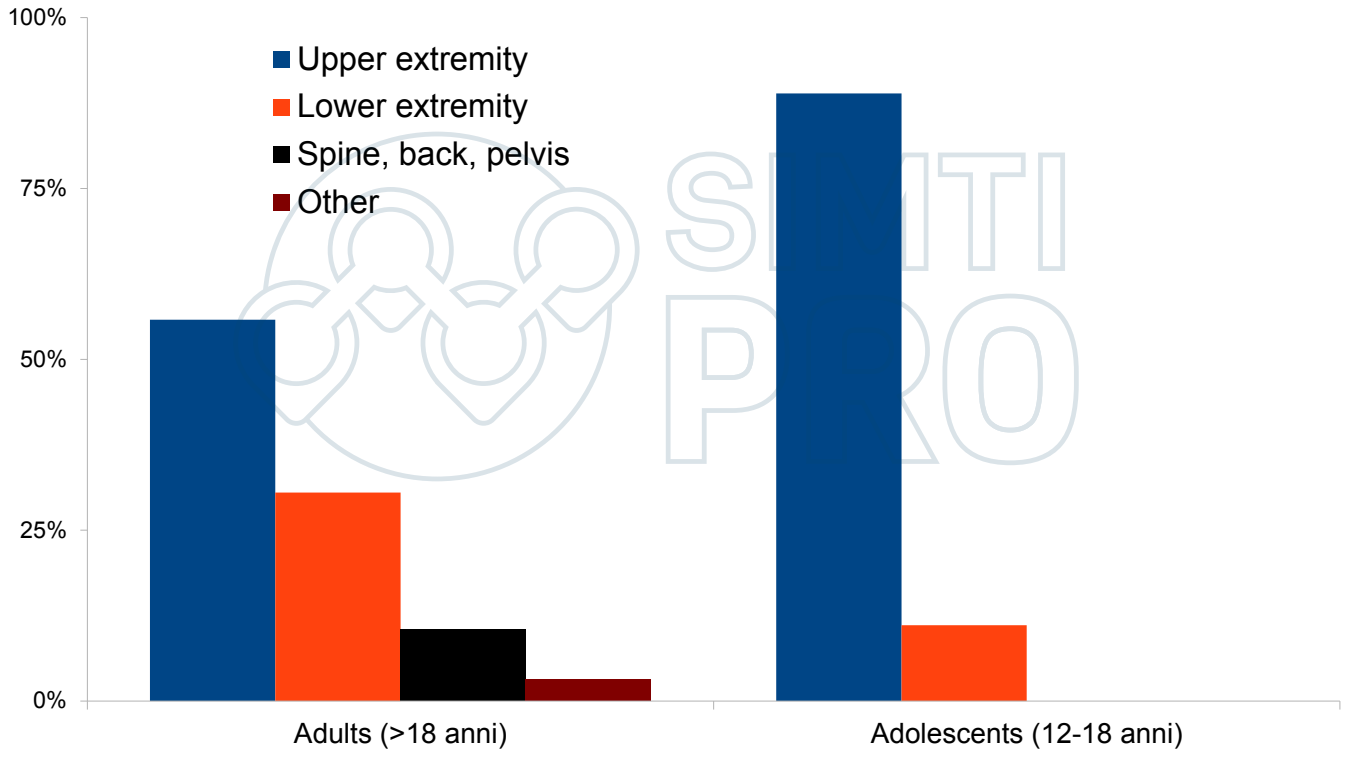
"l'insorgenza dei problemi di deambulazione (per osteoporosi, fratture, artropatia, dismetria degli arti inferiori) mi ha portato a chiudere l'attività nel 2011".

The Burden of Musculoskeletal in the Ageing Thalassemic: Pain



Haines D et al., Br J Haematology 2013

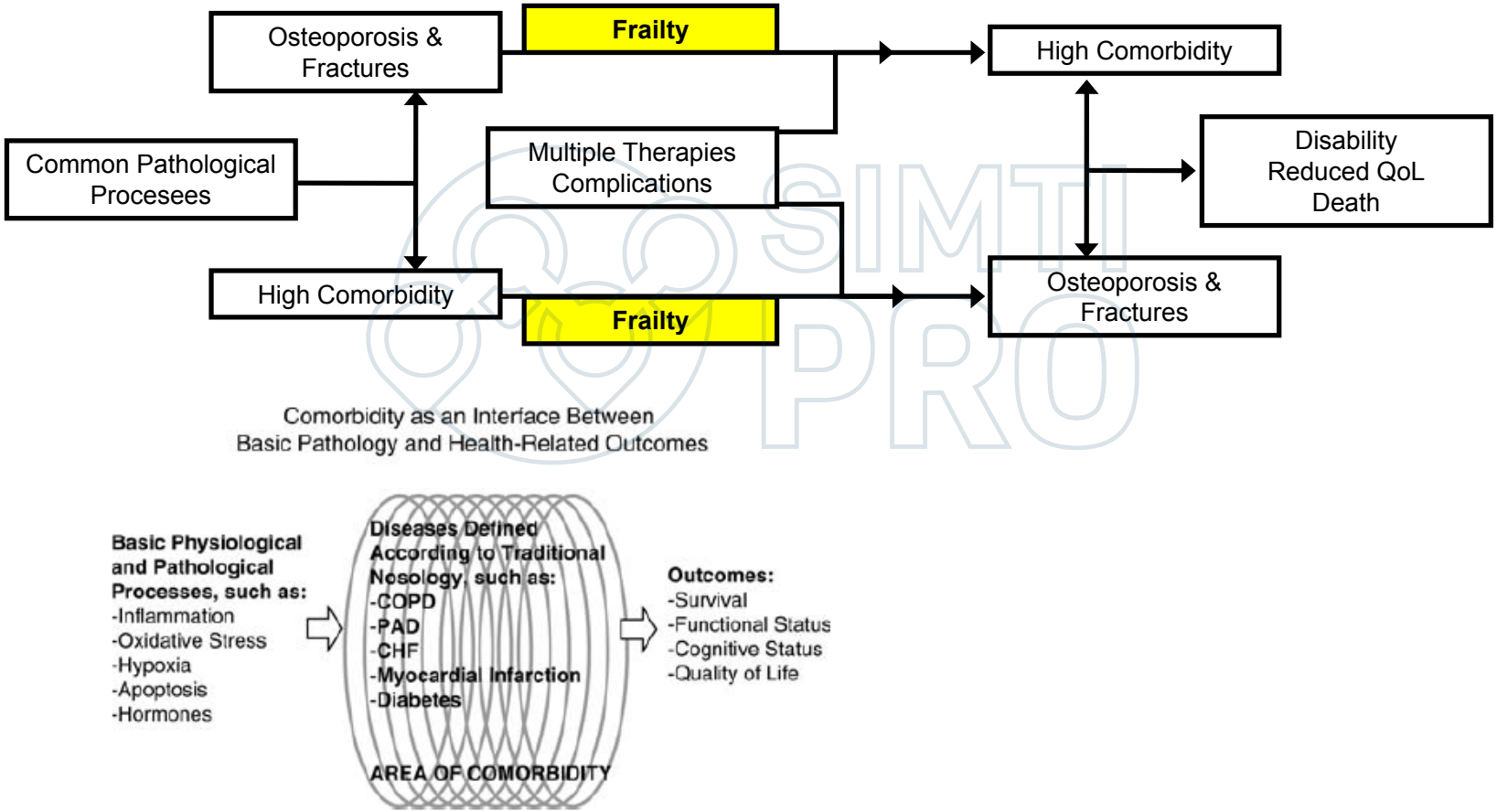
The Burden of Musculoskeletal in the Ageing Thalassemic: Fractures



Aging

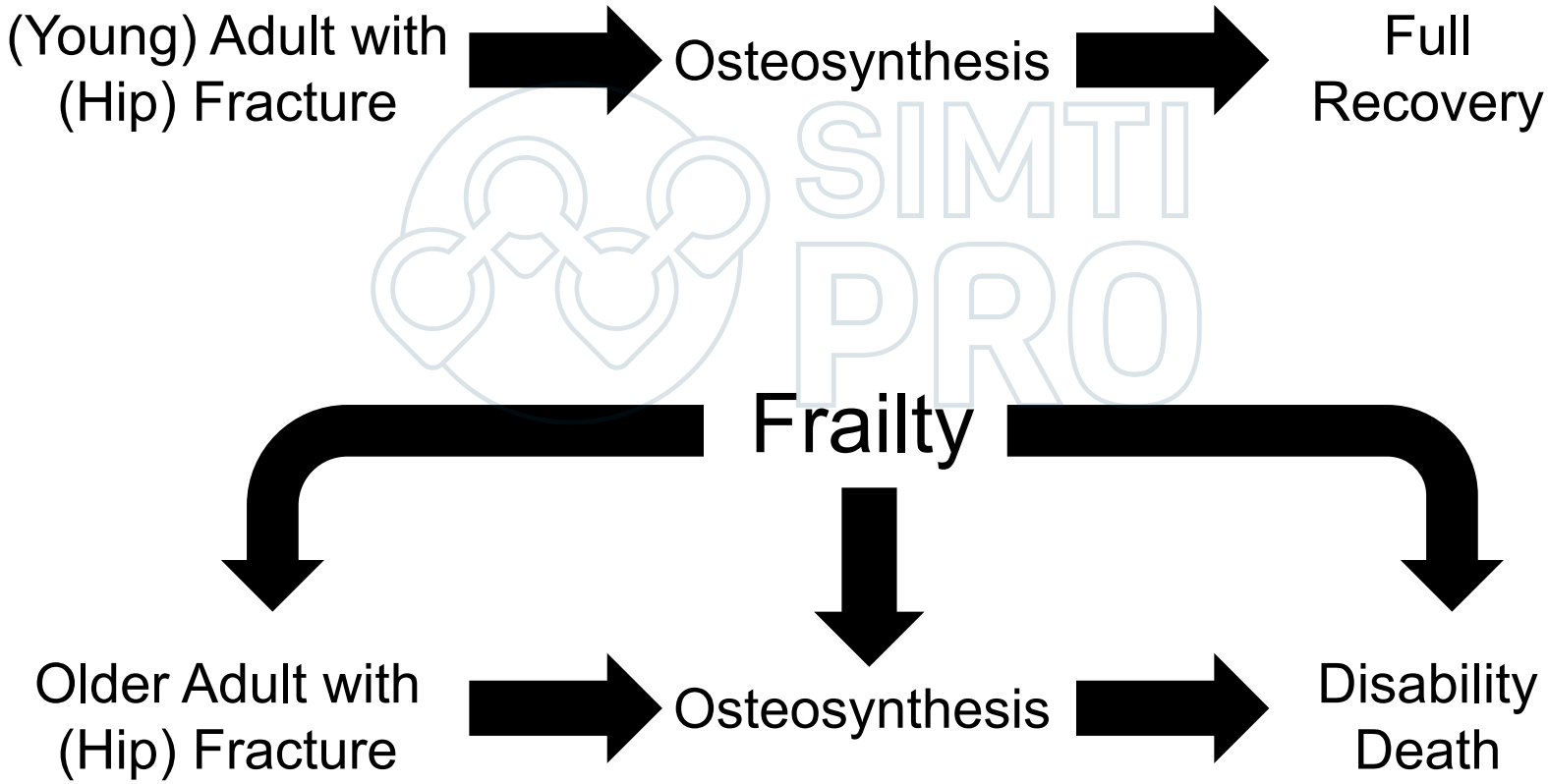
Fung EB et al., Bone 2008

Interactions Between Frailty, Comorbidity & Fractures

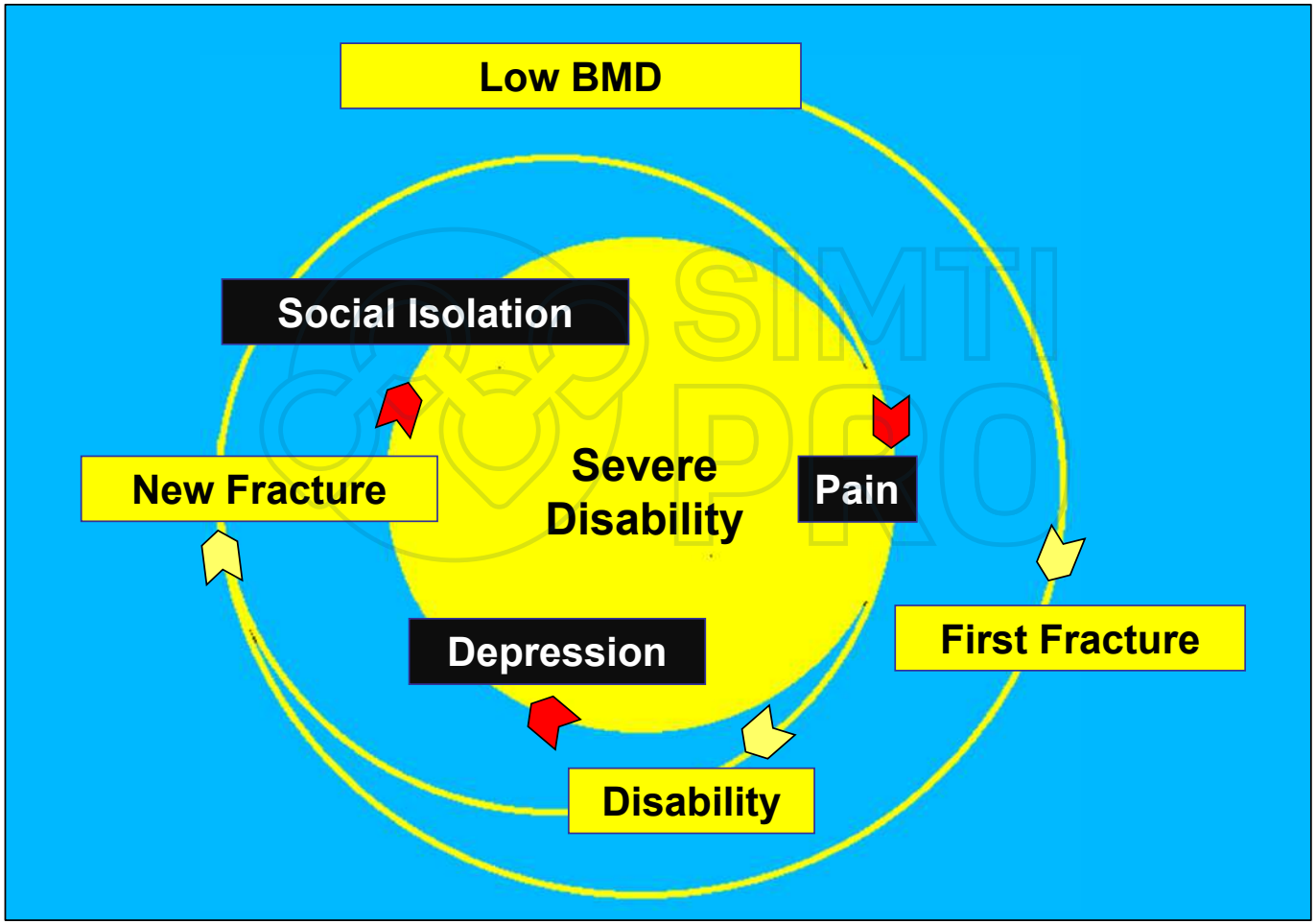


Yancik R et al., J Gerontol 2007

The Fracture “Pathway”: Adult versus Older Adults



Osteoporotic Fractures: A Vicious Circle



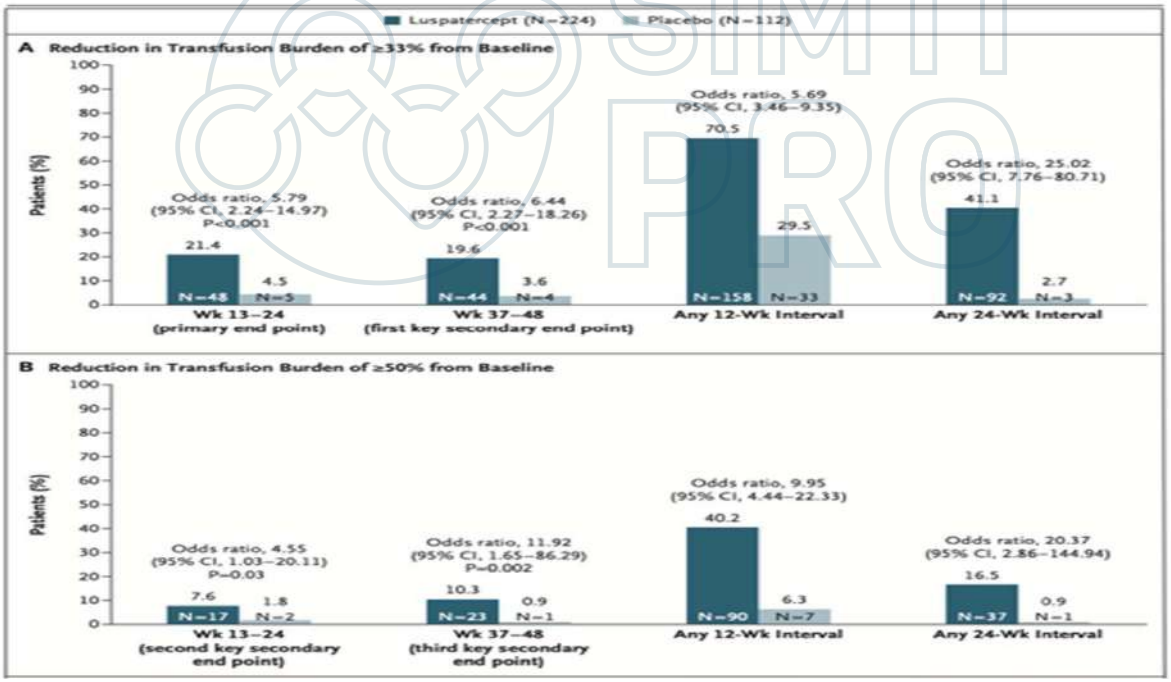
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia

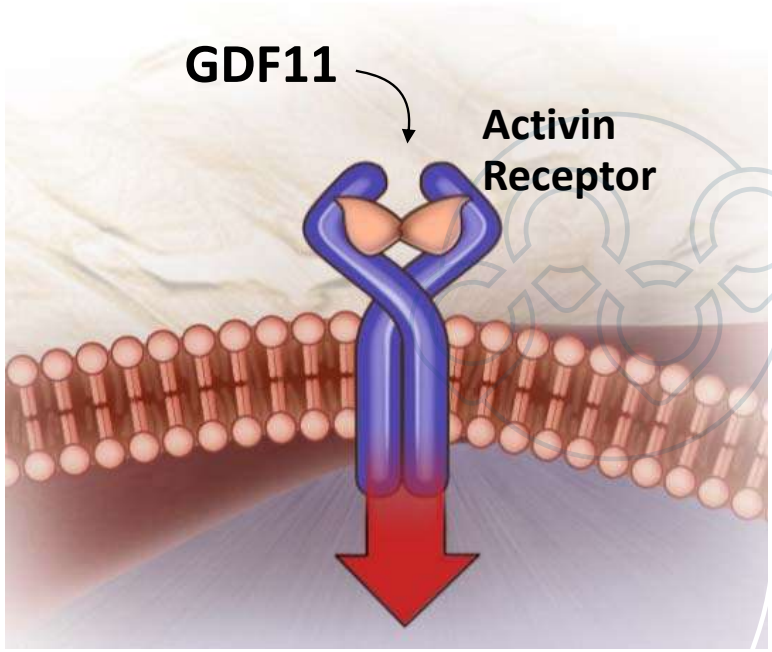
M.D. Cappellini, V. Viprakasit, A.T. Taher, P. Georgiev, K.H.M. Kuo, T. Coates, E. Voskaridou, H.-K. Liew, I. Pazgal-Kobrowski, G.L. Forni, S. Perrotta, A. Khelif, A. Lal, A. Kattamis, E. Vlachaki, R. Origa, Y. Aydinok, M. Bejaoui, P.J. Ho, L.-P. Chew, P.-C. Bee, S.-M. Lim, M.-Y. Lu, A. Tantiworawit, P. Ganeva, L. Gercheva, F. Shah, E.J. Neufeld, A. Thompson, A. Laadem, J.K. Shetty, J. Zou, J. Zhang, D. Miteva, T. Zinger, P.G. Linde, M.L. Sherman, O. Hermine, J. Porter, and A. Piga, for the BELIEVE Investigators*

N ENGL J MED 382;13 NEJM.ORG MARCH 26, 2020

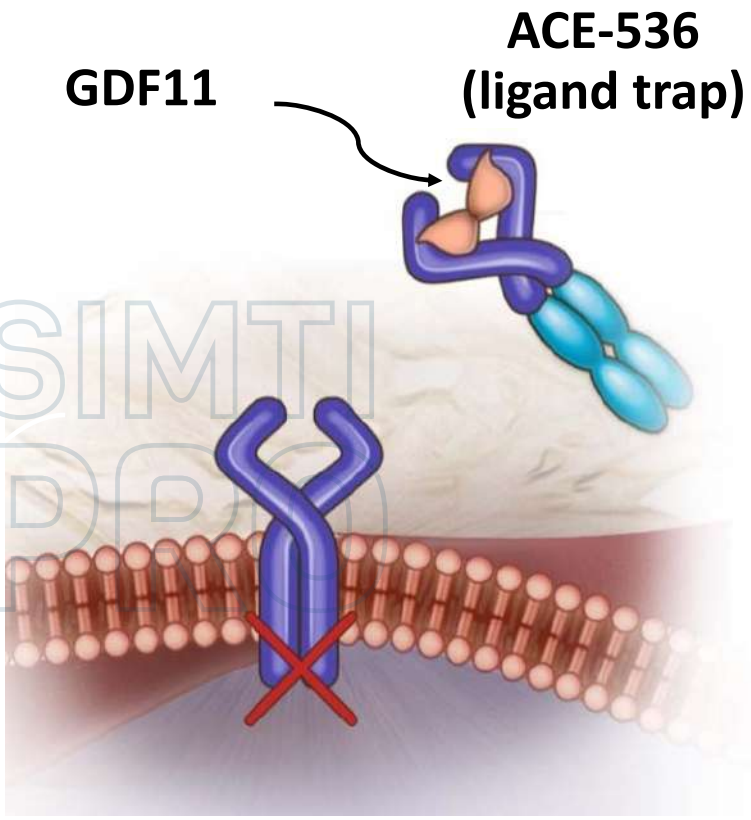


Luspatercept approval

Luspatercept has been approved by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020 and by the AIFA in 2021 to treat anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions

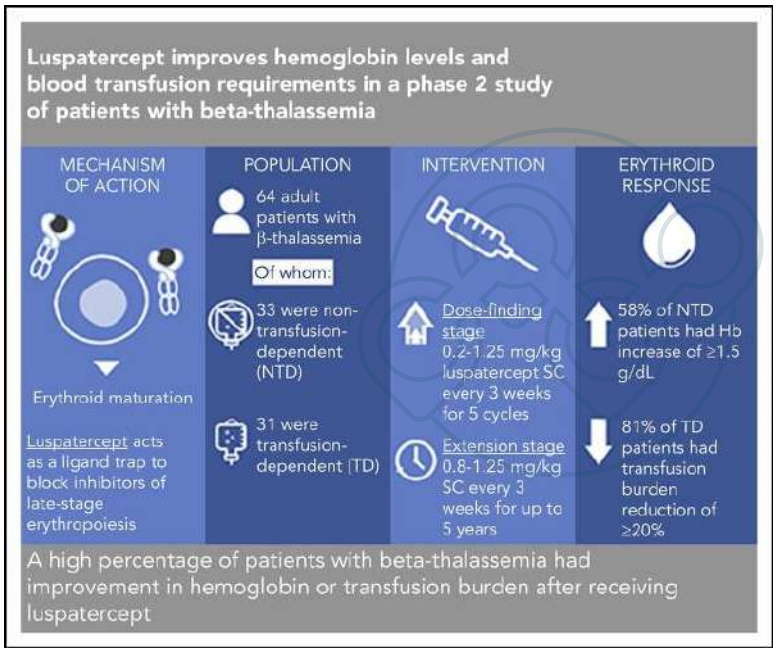


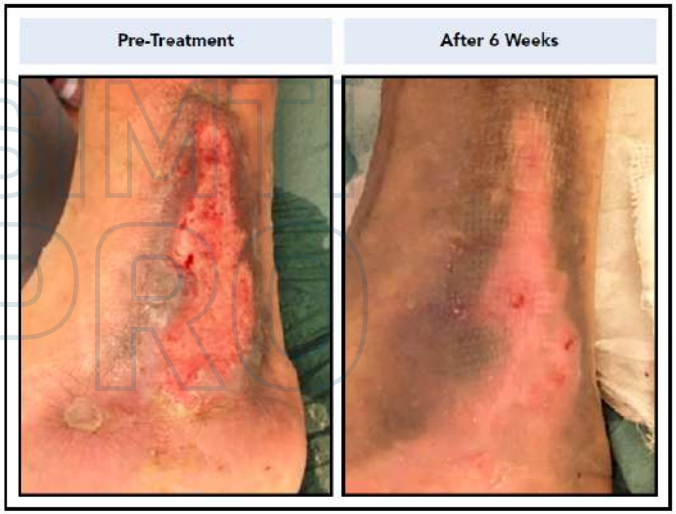
Smad 2,3 signaling
inhibits RBC Maturation



Reduced Smad 2,3 signaling -
promotes RBC Maturation

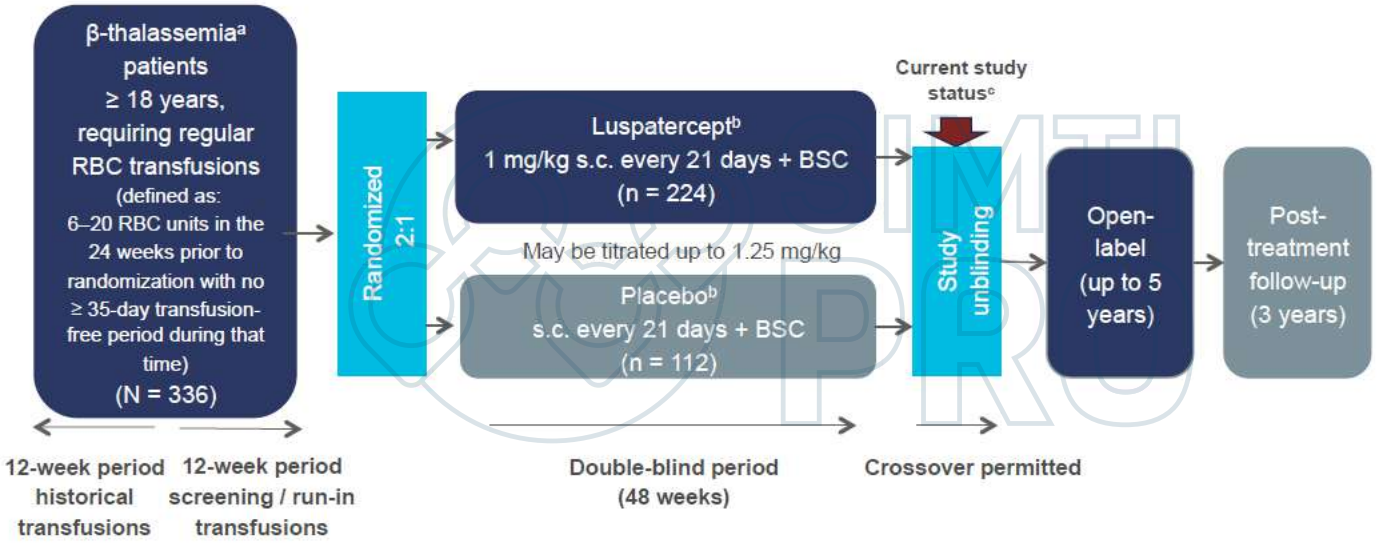
Luspatercept: key findings from the phase 2 trial





Piga A et al. Blood 2019;133:1279-1289.

BELIEVE: a randomized, double-blind, placebo-controlled, phase 3 study of luspatercept in adults with TDT



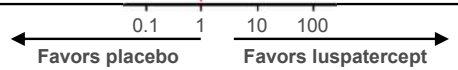
[a] β-thalassemia or hemoglobin E / β-thalassemia (β-thalassemia with mutation and / or multiplication of α-globin was allowed. [b] RBC transfusions and iron chelation therapy to maintain each patient's baseline hemoglobin level. [c] The trial is fully enrolled and patients continue to receive treatment or follow-up. BSC, best supportive care; RBC, red blood cell; s.c., subcutaneously.

Cappellini MD et al. N Engl J Med 2020;382:1219-1231.

BELIEVE Trial

Primary endpoint: Subgroup analysis favors luspatercept

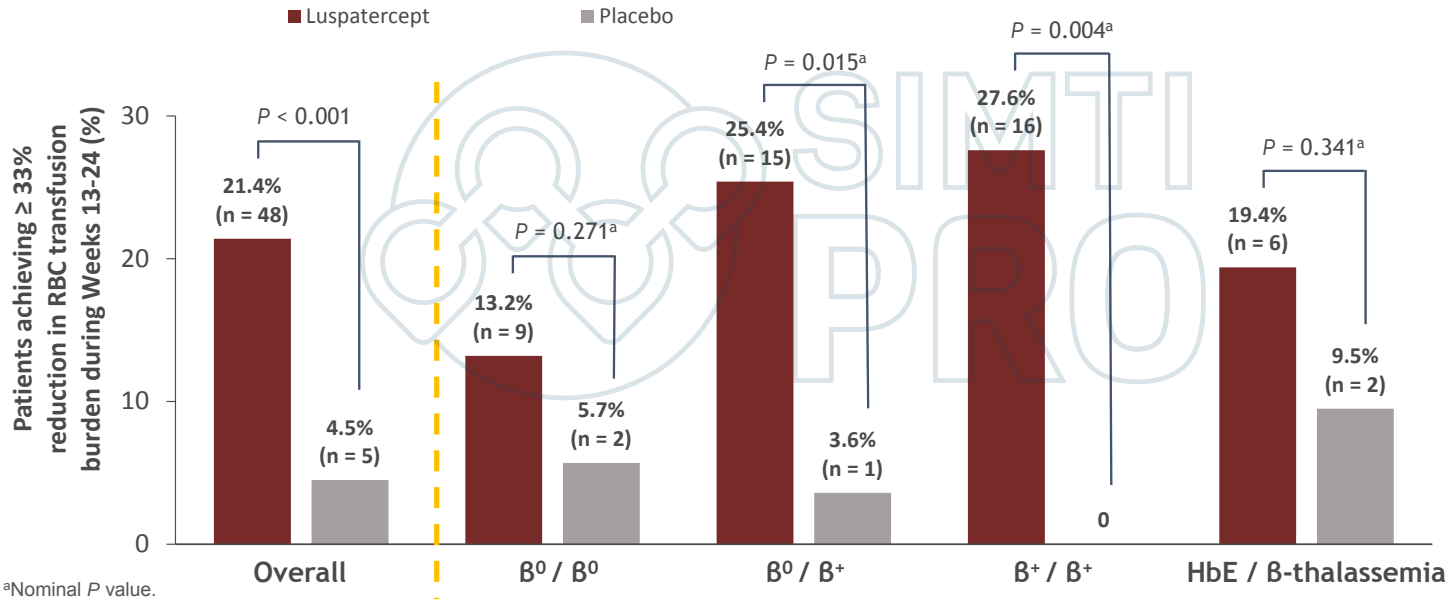
Sub-groups	Luspatercept n/N (%)	Placebo n/N (%)	OR (95% CI)	*P* value
Overall	48/224 (21.4)	5/112 (4.5)	5.79 (2.24, 14.97)	< 0.0001
Region: North America & Europe	23/100 (23.0)	1/51(2.0)	14.94 (1.95, 114.12)	0.0009
Region: Middle East & North Africa	11/52 (21.2)	2/26 (7.7)	3.22 (0.66, 15.77)	0.1351
Region: Asia–Pacific	14/72 (19.4)	2/35 (5.7)	3.98 (0.85, 18.62)	0.0629
Age: ≤ 32 years	22/129 (17.1)	4/63 (6.3)	3.00 (0.98, 9.20)	0.0476
Age: > 32 years	26/95 (27.4)	1/49 (2.0)	17.50 (2.27, 134.98)	0.0004
Splenectomy: Yes	31/129 (24.0)	2/65 (3.1)	9.72 (2.22, 42.53)	0.0003
Splenectomy: No	17/95 (17.9)	3/47 (6.4)	2.94 (0.81, 10.69)	0.0918
Sex: Female	35/132 (26.5)	4/63 (6.3)	5.33 (1.80, 15.80)	0.0011
Sex: Male	13/92 (14.1)	1/49 (2.0)	8.05 (1.01, 64.16)	0.0218
β-thalassemia Gene: β^0/β^0	9/68 (13.2)	2/35 (5.7)	2.54 (0.48, 13.51)	0.2708
β-thalassemia Gene: Non-β^0/β^0	39/155 (25.2)	3/77 (3.9)	8.35 (2.47, 28.23)	< 0.0001
Baseline Transfusion Burden: ≤ 6 units/12 weeks	27/112 (24.1)	3/56 (5.4)	5.61 (1.60, 19.65)	0.0033
Baseline Transfusion Burden: > 6 units/12 weeks	21/112 (18.8)	2/56 (3.6)	6.16 (1.38, 27.44)	0.0082
Baseline Hemoglobin: < 9 g/dL	22/87 (25.3)	4/51 (7.8)	3.78 (1.25, 11.42)	0.0128
Baseline Hemoglobin: ≥ 9 g/dL	26/137 (19.0)	1/61 (1.6)	14.17 (1.85, 108.79)	0.0012
Baseline Liver Iron: ≤ 3 mg/g dry weight	12/70 (17.1)	1/37 (2.7)	7.18 (0.88, 58.63)	0.0335
Baseline Liver Iron: > 3 to ≤ 7 mg/g dry weight	13/51 (25.5)	0/30 (0)	Infinity	0.0053
Baseline Liver Iron: > 7 to ≤ 15 mg/g dry weight	10/38 (26.3)	1/19 (5.3)	5.41 (0.67, 43.34)	0.0741
Baseline Liver Iron: > 15 mg/g dry weight	13/65 (20.0)	3/26 (11.5)	1.79 (0.47, 6.78)	0.3831



The BELIEVE Trial studied adult patients.

Achievement of ≥ 33% reduction in RBC transfusion burden during Weeks 13-24 (according to genotype)

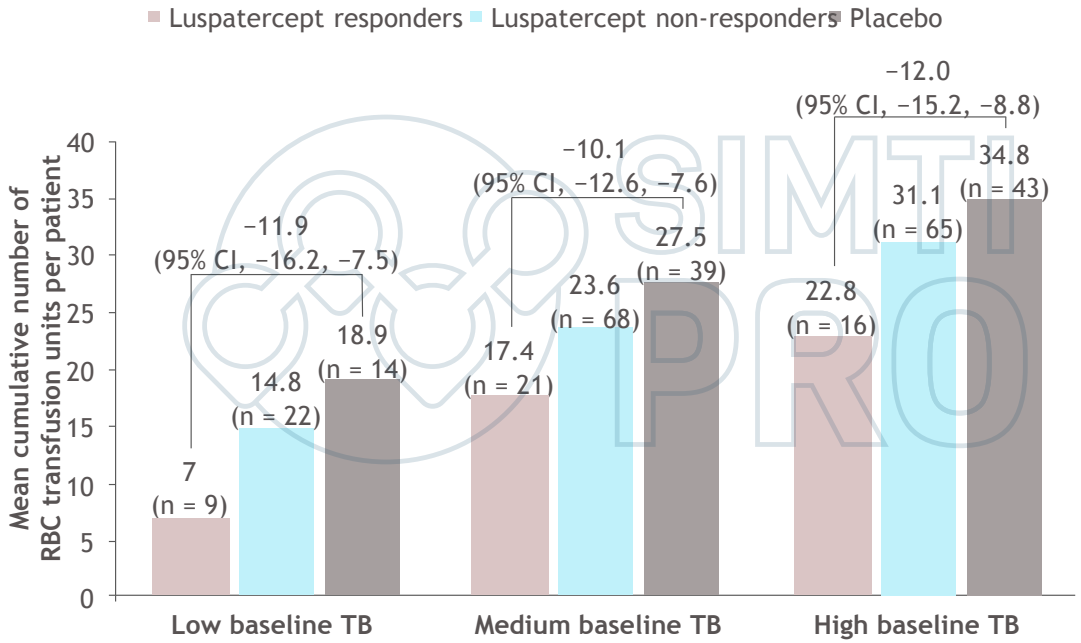
A greater proportion of luspatercept-treated patients achieved ≥ 33% reduction from baseline in RBC transfusion burden during Weeks 13-24 versus placebo, regardless of β-globin genotype



[a]Nominal *P* value.
Data cutoff: May 11, 2018.

BELIEVE trial

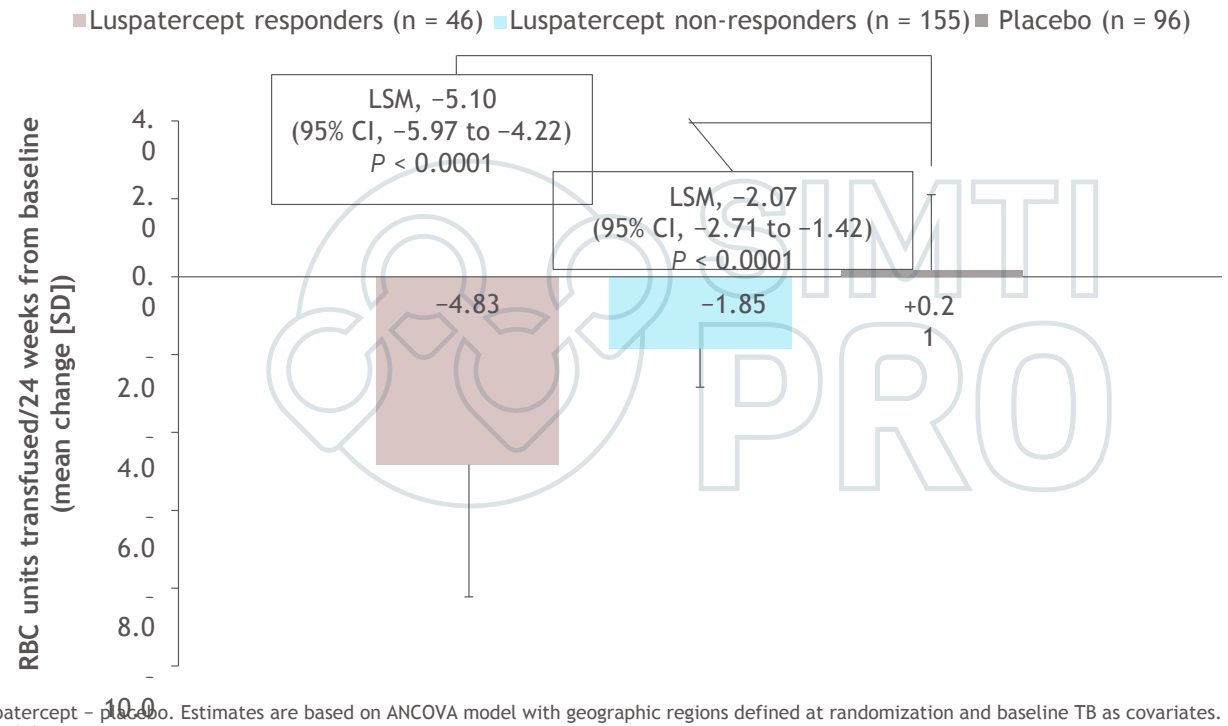
Mean cumulative number of RBC transfusion units by level of baseline TB through week 48



Baseline low, medium, and high TB were defined as receipt of ≤ 10, > 10 to ≤ 15, and > 15 RBC units/24 weeks, respectively.

BELIEVE

Mean change in RBC units transfused during weeks 25–48

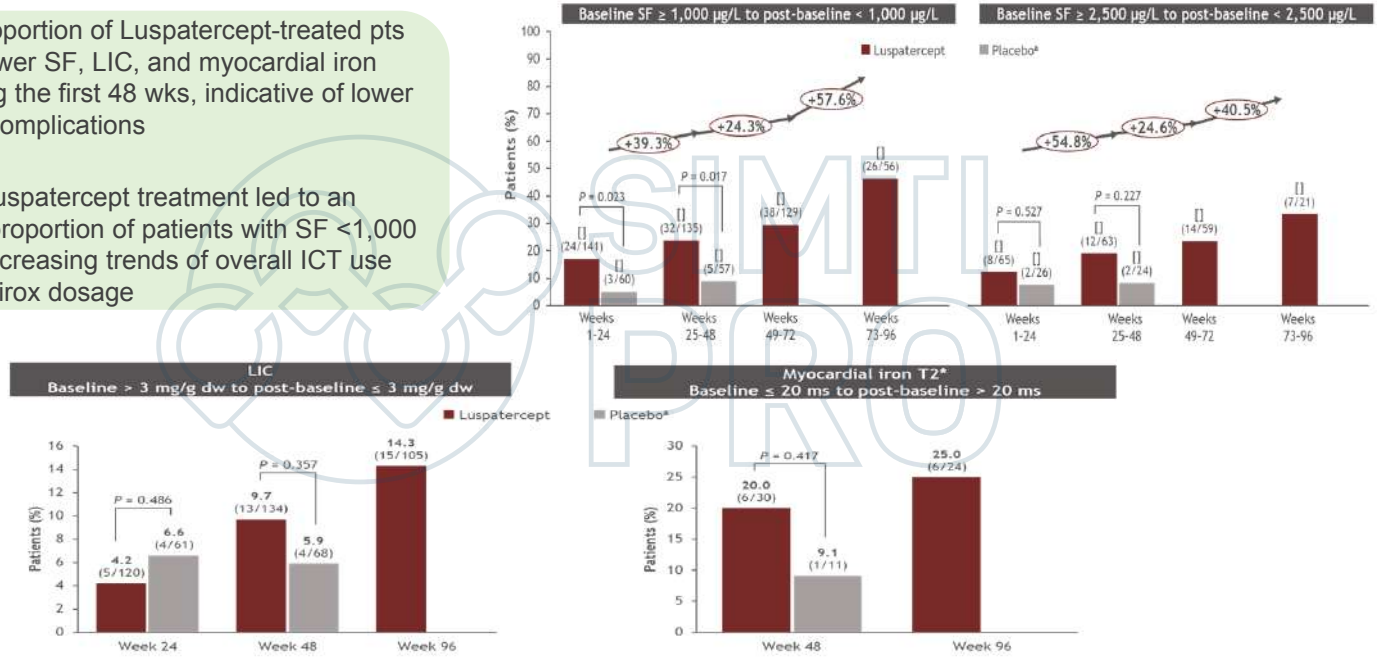


LSM is luspatercept − placebo. Estimates are based on ANCOVA model with geographic regions defined at randomization and baseline TB as covariates.
SD, standard deviation.

BELIEVE

Longitudinal effect of luspatercept on iron overload and iron chelation therapy

- A higher proportion of Luspatercept-treated pts shifted to lower SF, LIC, and myocardial iron levels during the first 48 wks, indicative of lower risk of IOL complications
- Long-term luspatercept treatment led to an increasing proportion of patients with SF <1,000 µg/L and decreasing trends of overall ICT use and deferasirox dosage



P values are estimated from Cochran–Mantel–Haenszel test. Patients with LIC ≥ 3 mg/g dw are considered to have iron overload. Myocardial iron T2* < 20 ms indicates increased cardiac risk. [a]Placebo patients evaluated up to Week 48.

Hermine O et al. Blood 2021;136:Presentation 1697.

BELIEVE Trial

Safety Summary

Treatment-Emergent Adverse Events, n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Patients with at least 1 TEAE (any grade)	214 (96.0)	101 (92.7)
Patients with at least 1 grade TEAE (grade ≥ 3)[b]	65 (29.1)	17 (15.6)
Patients with at least 1 serious TEAE[c]	34 (15.2)	6 (5.5)
Patients with at least 1 TEAE resulting in the following:		
Death[d]	0	1 (0.9)
Study drug discontinuation	12 (5.4)	1 (0.9)

[a] Safety population. [b] No one organ class or system was predominant.[c] Anemia was the only serious TEAE occurring in > 1% of patients in either arm (luspatercept, n = 3 [1.4%]; placebo, n = 0 [0%]). [d] TEAE of acute cholecystitis resulted in death in 1 of 109 (0.9%) placebo patients; no luspatercept-treated patients died due to TEAEs. TEAE, treatment-emergent adverse event.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

TEAEs by frequency ≥ 10% in Either Arm (all grades)

n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Back pain	61 (27.4)	32 (29.4)
Upper respiratory tract infection	59 (26.5)	36 (33.0)
Headache	58 (26.0)	26 (23.9)
Bone pain	**44 (19.7)**	**9 (8.3)**
Arthralgia	**43 (19.3)**	**13 (11.9)**
Pyrexia	36 (16.1)	23 (21.1)
Cough	32 (14.3)	12 (11.0)
Fatigue	30 (13.5)	14 (12.8)
Oropharyngeal pain	28 (12.6)	12 (11.0)
Diarrhea	27 (12.1)	11 (10.1)
Dizziness	**25 (11.2)**	**5 (4.6)**
Asthenia	22 (9.9)	11 (10.1)
Myalgia	22 (9.9)	11 (10.1)
Pharyngitis	20 (9.0)	13 (11.9)

[a] Safety population.

The BELIEVE Trial studied adult patients.

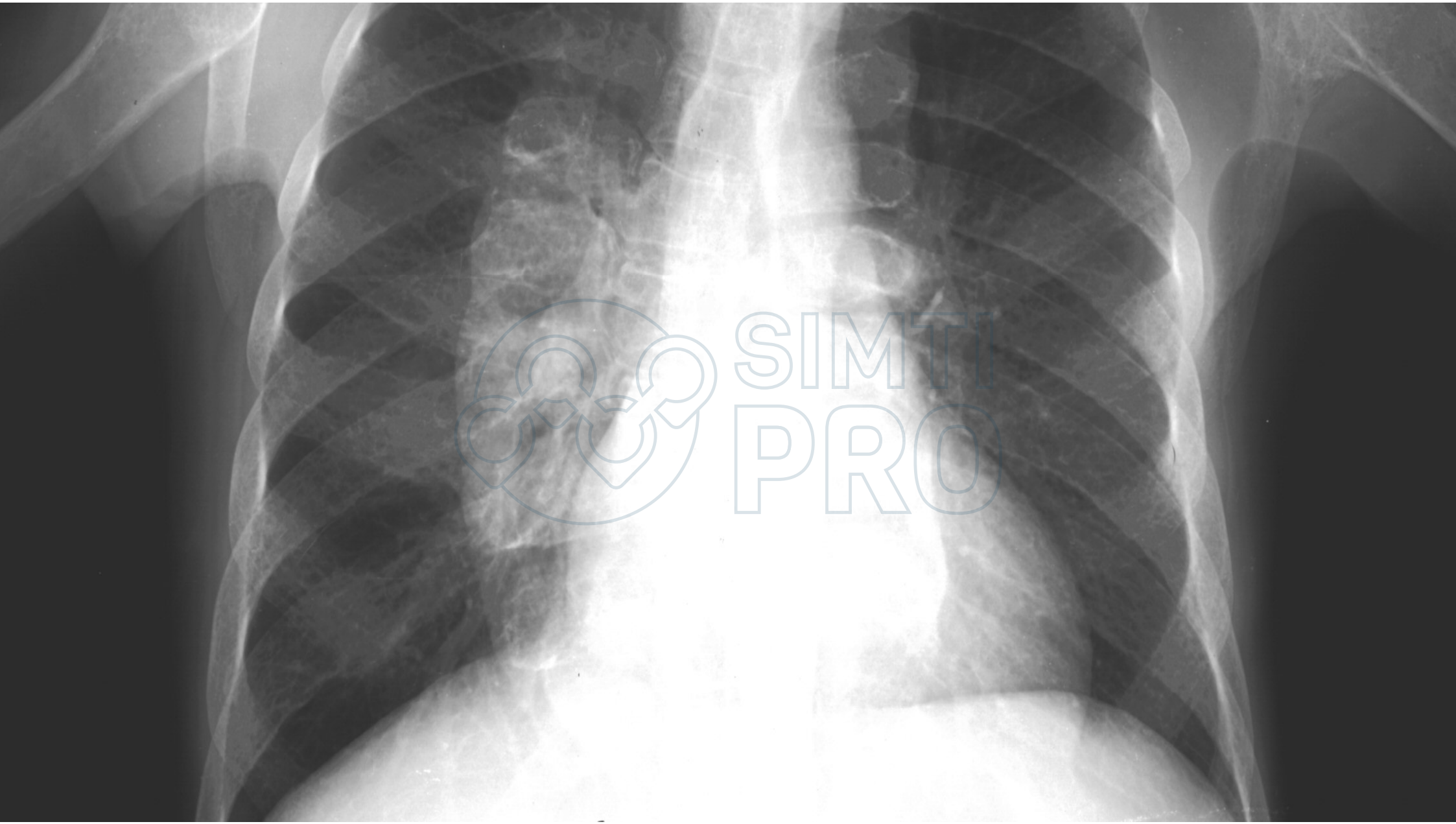
BELIEVE Trial

Grade 3–4 TEAEs by frequency ≥ 1% in Either Arm

n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Anemia	7 (3.1)	0
Increased LIC	6 (2.7)	1 (0.9)
Hyperuricemia	6 (2.7)	0
Hypertension	4 (1.8)	0
Syncope	4 (1.8)	0
Back pain	3 (1.3)	1 (0.9)
Bone pain	3 (1.3)	0
Blood uric acid increased	3 (1.3)	0
Increased AST	3 (1.3)	0
Increased ALT	2 (0.9)	3 (2.8)
Thromboembolic events[b]	2 (0.9)	0

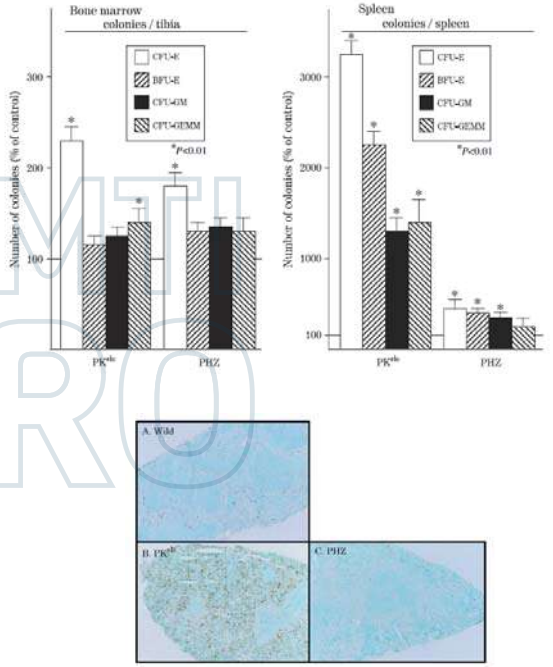
In total, thromboembolic events (all grades) were reported in **8/223 (3.6%)** luspatercept-treated patients (deep venous thrombosis, pulmonary embolism, portal vein thrombosis, ischemic stroke, thrombophlebitis, superficial phlebitis) and 1/109 (0.9%) placebo-treated patients (phlebitis). In all cases, patients had multiple risk factors for thromboembolic events

[a] Safety population. [b] Thromboembolic events included as a TEAE of interest; other events occurring in < 1% of patients are not shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
The BELIEVE Trial studied adult patients.

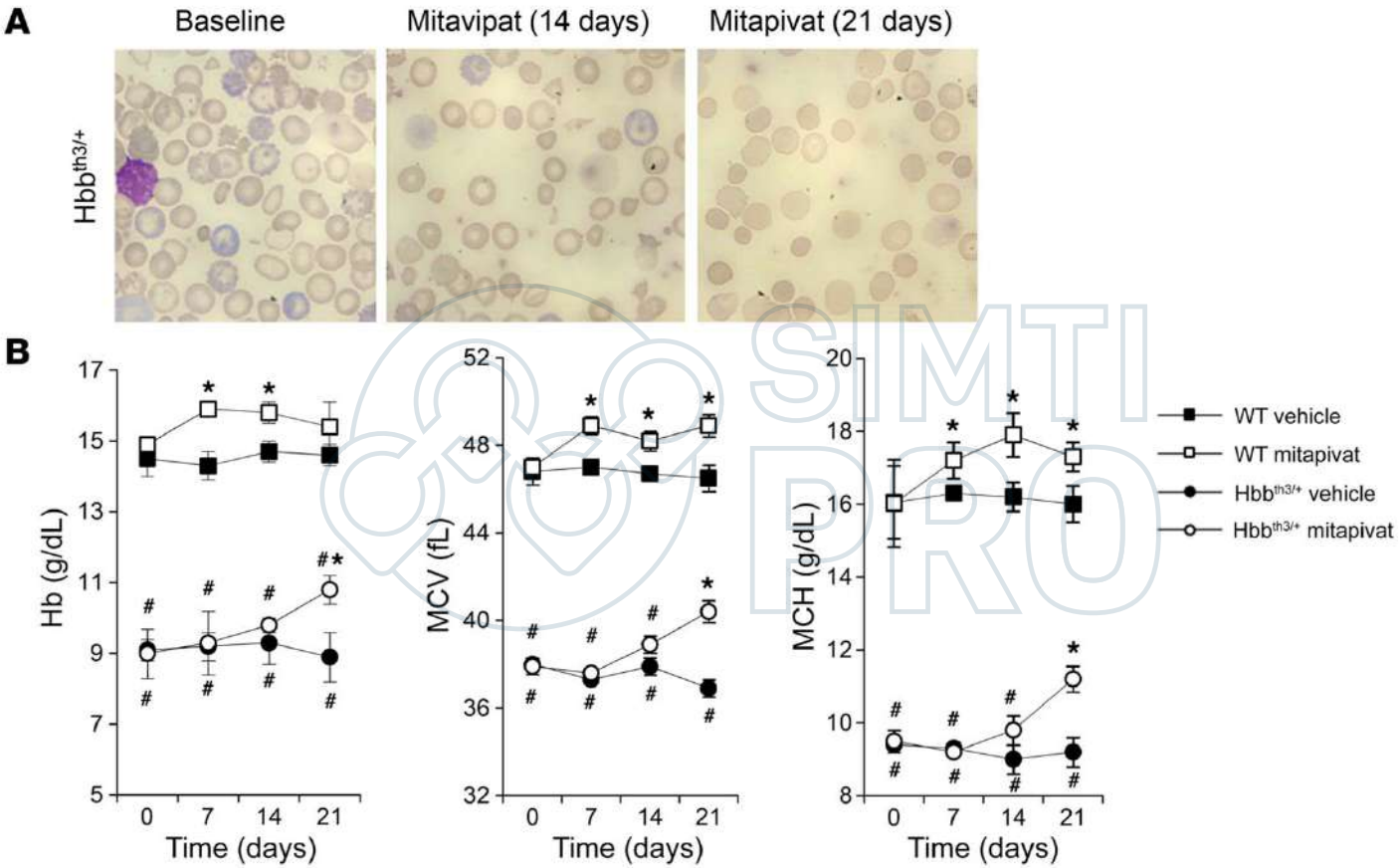

SIMTI
PRO

Mitapivat (PK activator)

- Metabolic disturbance in PK deficiency alters not only the survival of RBCs but also the maturation of erythroid progenitors, resulting in ineffective erythropoiesis. ATP supply appears to be insufficient in thalassemic RBCs to maintain membrane fitness and clearance of globin precipitates
- Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the RBC-specific form of PK (PK-R)
- Mitapivat has already shown efficacy and safety in clinical trials of patients with PK deficiency
- In mouse models β-thalassemia, mitapivat increased ATP levels, reduced markers of ineffective erythropoiesis, and improved anemia, RBC survival, and indexes of iron overload



Aizawa S *et al. Exp Hematol* 2005;33:1292-1298; Yang H *et al. Clin Pharmacol Drug Dev* 2019;8:246-259; Grace *RF et al. N Engl J Med* 2019;381:933-944; Matte A *et al. Haematologica* 2016;101:18(S135) (abs).



Matte A, *JCI*, 2021

Interim data from phase 2 trial

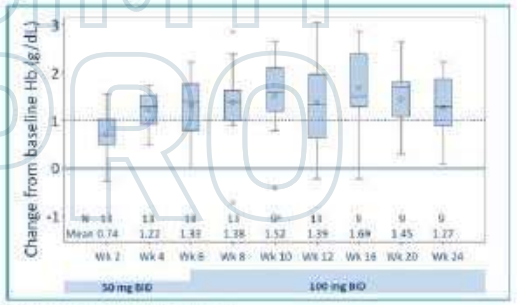
- Hb increase of ≥1.0 g/dL in 8 of 9 patients at 12 weeks with favorable changes in markers of erythropoiesis and hemolysis
- AEs occurring in >3 patients included insomnia, dizziness, cough, dyspepsia, fatigue, headache, nasal congestion, nausea, and upper respiratory tract infection

Table. Patient demographics and characteristics at baseline

Baseline characteristics	Total (N = 18)
Median (range) duration of treatment, weeks	20.6 (1.1–50.0)
Male/female, n	5/13
Age, median (range), years	43.5 (29–67)
Race, n (%)	
Asian	9 (50.0)
White	4 (22.2)
Native Hawaiian or other Pacific Islander	1 (5.6)
Other[a]	4 (22.2)
Thalassemia type, n (%)	
α	5 (27.8)
β	13 (72.2)
Hb, median (range), g/dL	8.43 (5.6–9.8)
Indirect bilirubin, median (range), mg/dL	1.17 (0.31–5.52)
Lactate dehydrogenase, median (range), U/L	249 (126–613)
Erythropoietin, median (range), mU/mL	70.5 (15–11,191

Hb, hemoglobin.
Splenectomy and prior transfusions were reported in 2 patients each at baseline.
[a]Includes patients who reported more than 1 category, and 1 not reported.

Figure. Hb change over time



BID, twice daily; Hb, hemoglobin; Wk, week.
Solid blue line indicates baseline, dashed blue line indicates Hb 1 g/dL above baseline. Boxes represent interquartile range, lines in boxes indicate medians, diamonds indicate means, whiskers and outliers (circles) calculated with Tukey's method.
[a]4 patients were not evaluated at Week 10 due to a protocol amendment eliminating this visit.

Kuo KHM *et al. Blood* 2020;136:2600 (abs).

Mitapivat (PK activator) trials

Agent	Clinical Trials*	Design	n‡, population, age	Key efficacy measures
PK activator				
Mitapivat (AG-348)	● NCT03692052 ● Active, not recruiting†	● Phase 2 ● Open-label	● n = 20 ● NTDT (including α-thalassemia) with Hb ≤10 g/dL ● ≥18 yr	● Hb increase ≥1 g/dL§ ● Hb, Reticulocytes, bilirubin, LDH, haptoglobin, ● EPO, nRBC, sTfR
	● ENERGIZE-T ● NCT04770779 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● n = 240 ● TDT (including α-thalassemia) ● ≥18 yr	● Transfusion reduction (≥50%§, ≥33%) / ● independence ● Transfusion requirement ● SF, TSAT, TIBC
	● ENERGIZE ● NCT04770753 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● n = 171 ● NTDT (including α-thalassemia) with Hb ≤10 g/dL ● ≥18 yr	● Hb increase ≥1 g/dL§ ● PRO ● Hb, Hb increase ≥1.5 g/dL ● Reticulocytes, bilirubin, LDH, haptoglobin, EPO, ● SF, TSAT

Musallam KM *et al. Am J Hematol* 2021;

Am J Hematol. 2009 May;84(5):317-8.

The influence of treatment in specialized centers on survival of patients with thalassemia major

Forni GL, Puntoni M, Boeri E, Terenzani L, Balocco M.