FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

Il trattamento del paziente con sovraccarico marziale
CLINICA

Federica Pilo

U.O Ematologia e CTMO
Cagliari

DISCLOSURE

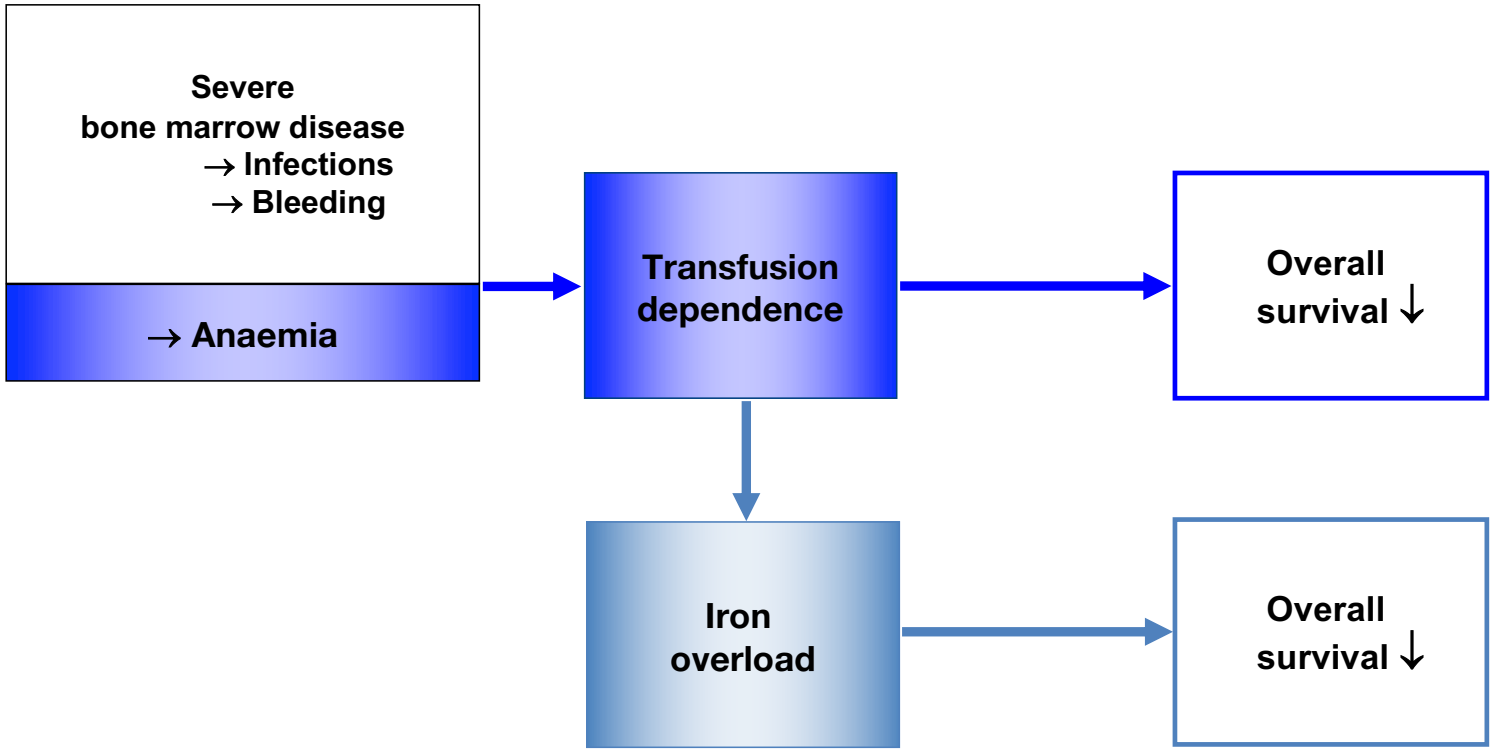
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS					X	X	
CELGENE/BMS						X	

AGENDA

- What we know and what we don't know about iron chelation

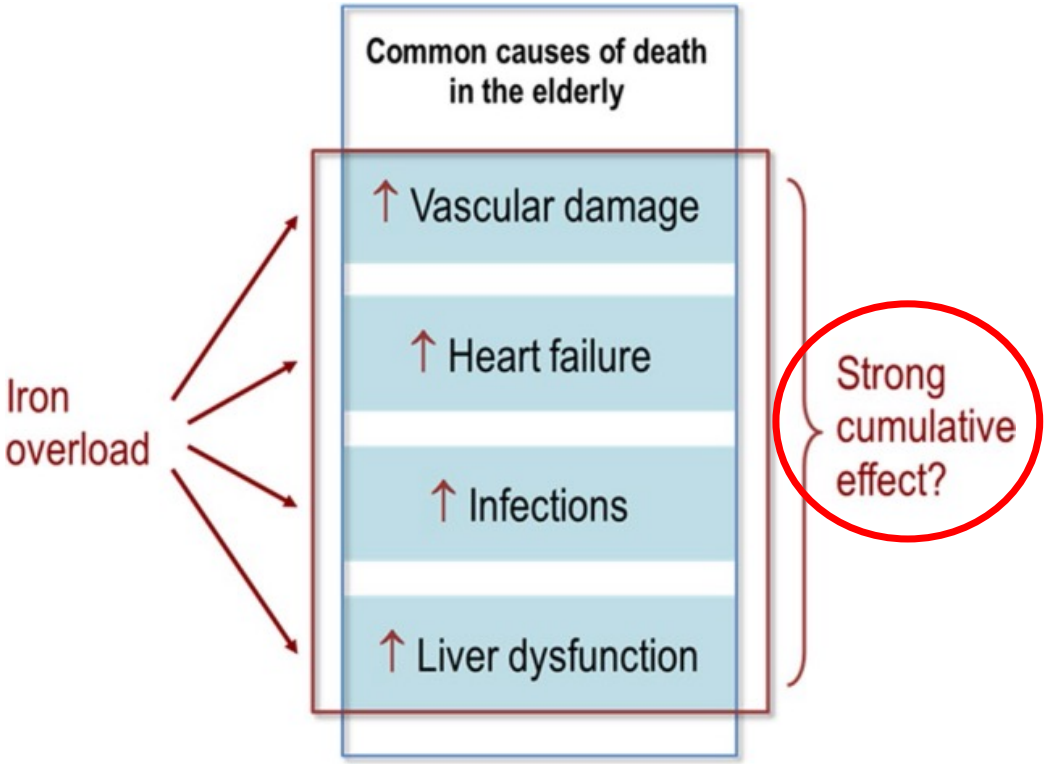
- Highlights of new clinical models involved uncommon iron biomarkers

Independent impact of iron overload and transfusion dependency on survival in patients with MDS

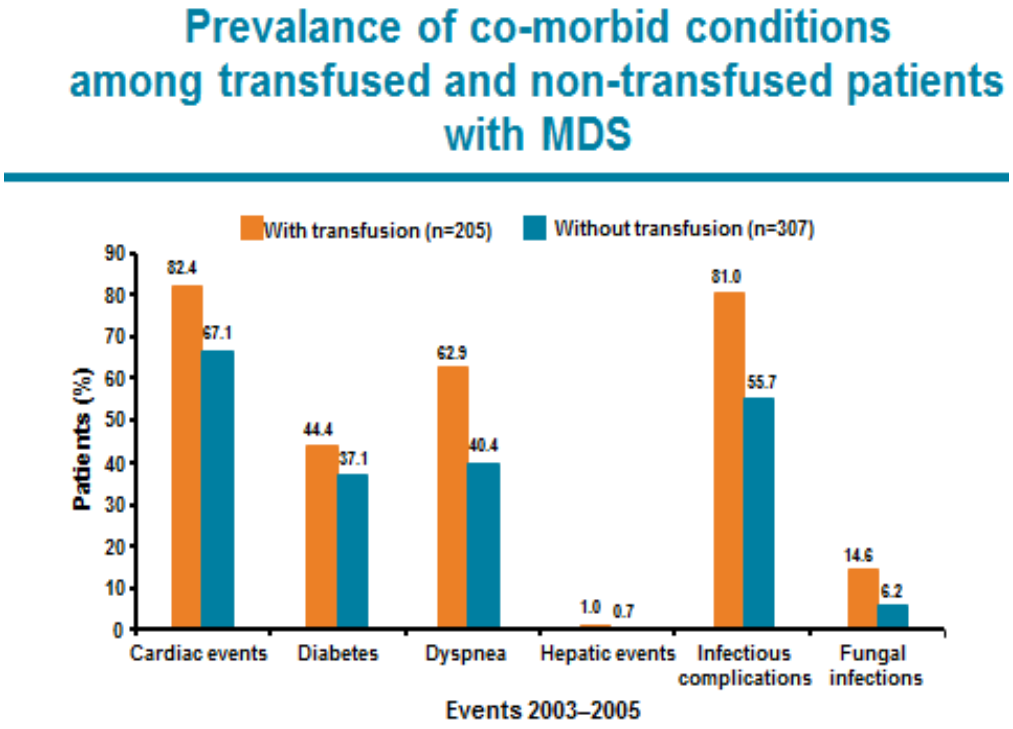


Gattermann N, Rachmilewitz EA. Ann Hematol. 2011;90:1-10.

Iron-related complications overlap with age-related clinical problems



Gattermann N. Int J Hematol. 2018 Jan;107(1):55-63

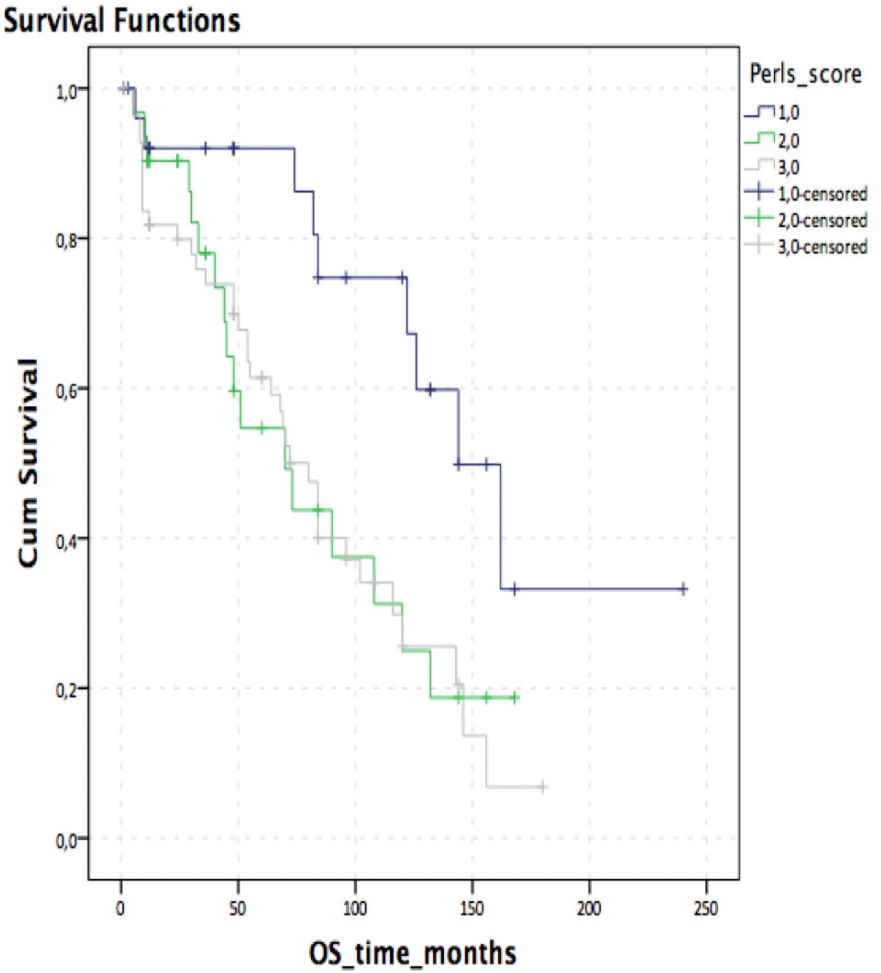


Goldberg S *et al. J Clin Oncol* 2010;28:2847–2852

› Acta Haematol. 2021;144(3):332-336. doi: 10.1159/000510111. Epub 2020 Oct 2.

Perls Stain Grade in Bone Marrow Aspirate Correlates with Overall Survival in Low-Risk Myelodysplastic Patients

Federica Pilo [1], Giovanni Caocci [2], Giannalisa Mele [1], Giorgio La Nasa [1]



3700 Increased Bone Marrow Iron at Diagnosis Is Associated with Inferior Prognosis in Patients with Myelodysplastic Syndromes

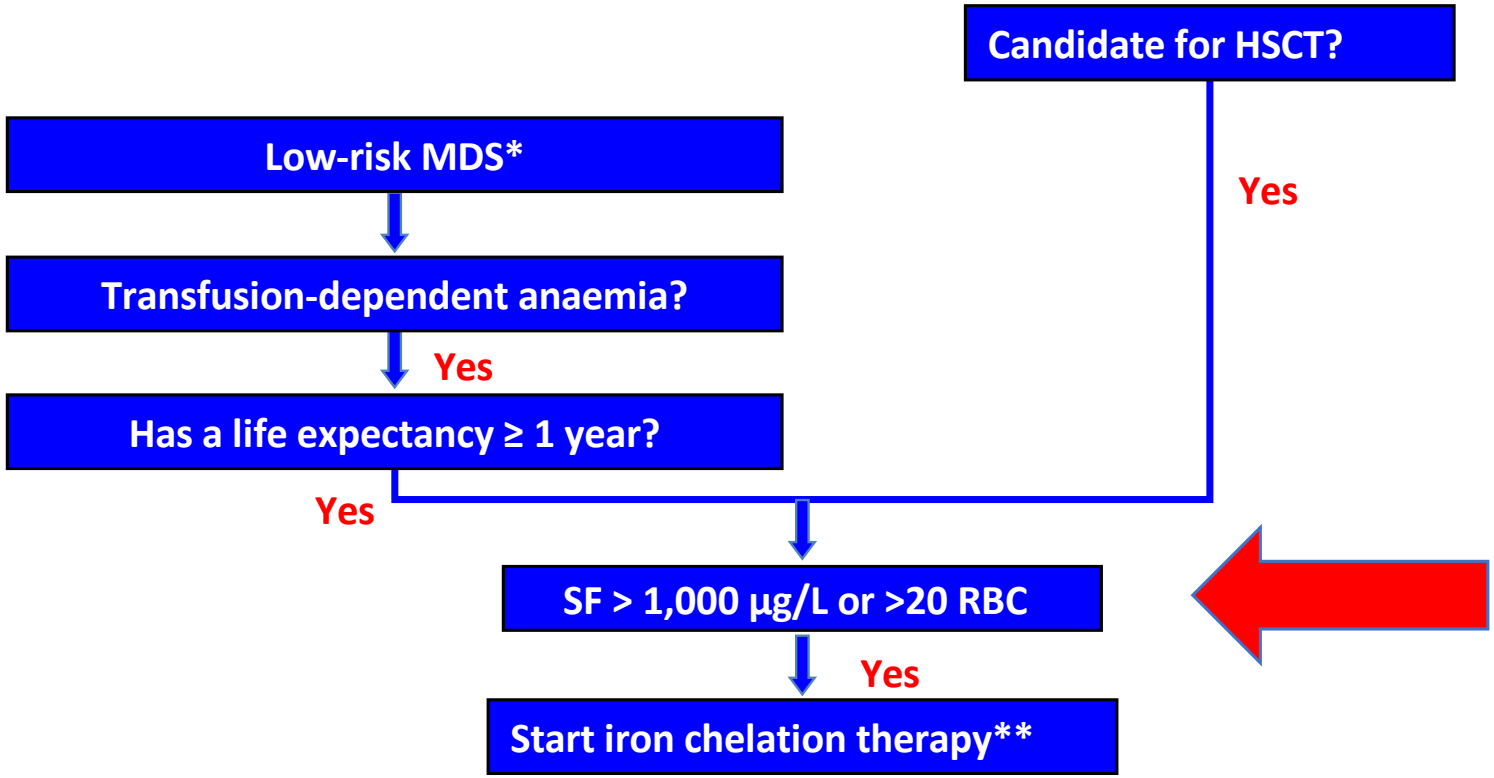
Program: Oral and Poster Abstracts
Session: 637. Myelodysplastic Syndromes — Clinical and Epidemiological: Poster III
Hematology Disease Topics & Pathways:
Epidemiology, Clinical Research, Clinically Relevant, Diseases, Registries, Myeloid Malignancies, Clinical Practice (e.g. Guidelines, Health Outcomes and Services, and Survivorship, Value; etc.)

Monday, December 13, 2021, 6:00 PM-8:00 PM

Annika Kasprzak, MD[1], **Sandra Becker**[2*], Martina Rudelius, MD[3*], Corinna Strupp, MD[1*], Kathrin Nachtkamp, MD[1*], Judith Strapatsas, MD[1*], Barbara Hildebrandt[4*], Norbert Gattermann, MD[1] and Ulrich Germing, MD[1*]*

Conclusion: Increased tissue iron in the bone marrow at the time of diagnosis is associated with inferior survival in patients with MDS, primarily in patients with higher risk MDS. At diagnosis, patients are not yet transfusion-dependent. This suggests that increased iron reflects a prolonged period of increased duodenal iron uptake as a consequence of ineffective erythropoiesis. Therefore, increased marrow iron at the time of MDS diagnosis seems to be a surrogate parameter of hematopoietic insufficiency, which is the real cause of inferior prognosis.

Iron chelation algorithm for MDS



*Includes IPSS Low and Int-1.
**Duration: as needed to maintain serum ferritin < 1,000 µg/L.

Bennett JM, et al. Am J Hematol. 2008;83:858-61.
Gattermann N. Int J Hematol. 2008;88:24-9.

Indication to start chelation

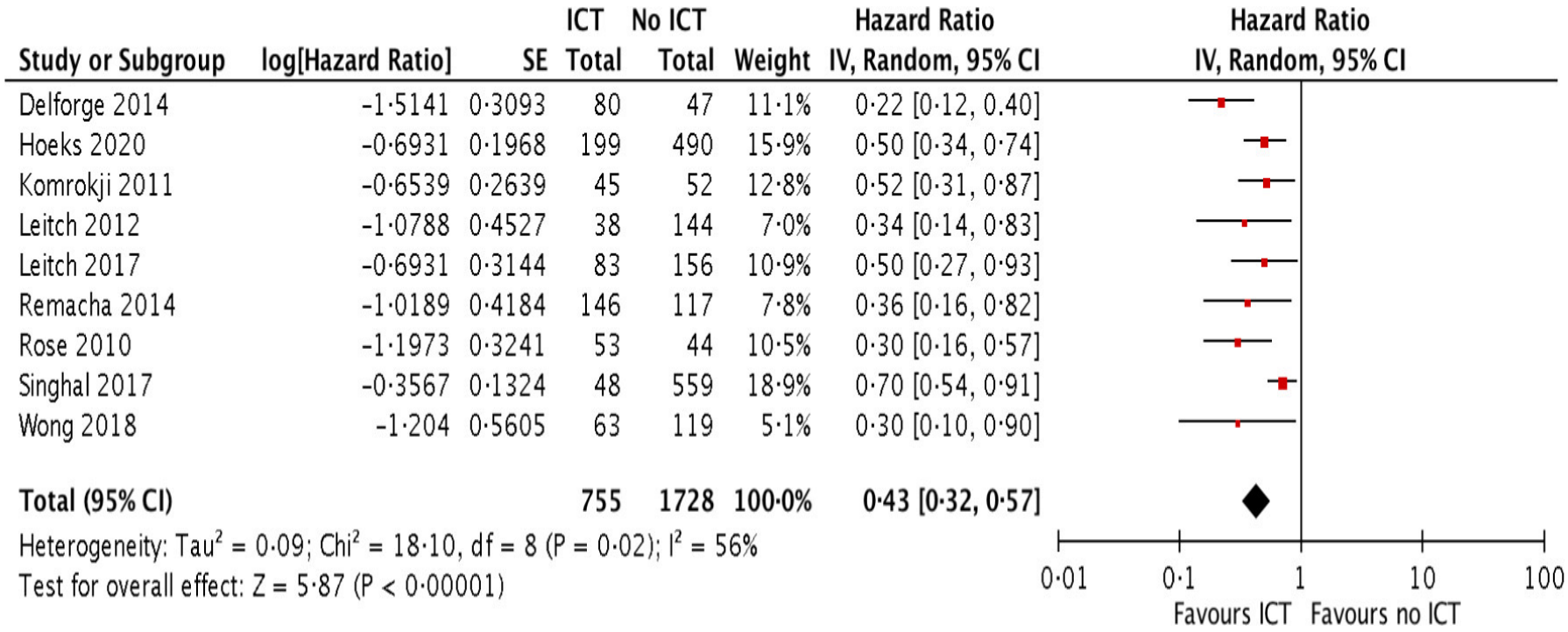
» Bulky iron accumulation (serum ferritin / number of transfusions)

» Life expectancy

Concept: development of organ damage require:

- **overload (bulky disease)**
- **time (years)**

Iron chelation therapy in patients with low- to intermediate-risk myelodysplastic syndrome: A systematic review and meta-analysis



Br J Haematol, Volume: 197, Issue: 1, Pages: e9-e11, First published: 19 December 2021, DOI: (10.1111/bjh.17998)

Studies demonstrating a survival benefit of chelation therapy

Study	N	Design	Survival	Non-chelated patients	Chelated patients	*P* value
Leitch 2008	36	Retrospective	Median overall OS	40 mo	Not reached	0.003
			4-year survival rate	43%	64%	0.003
Rose 2010	97	Prospective follow-up	Median OS from diagnosis	53 mo	124 mo	**<0.0003**
			Median OS with adequate vs weak chelation	NA	124 vs 85 mo	**<0.001**
Neukirchen 2012[a]	188	Matched pair analysis	Median OS	49 mo	75 mo	0.002
Neukirchen 2012[b]	417	Retrospective, registry	Median time to death in transfusion-dependent patients	30 mo	67 mo	NR
Komrokji 2011	97	Retrospective	Median OS	34 mo	59 mo	0.013
Delforge 2012	186	Retrospective	Median OS in Low/Int-1	37 mo	126 mo	**<0.001**
Zeidan 2012	4226	Retrospective, registry	Median survival	47 wk	110 wk	0.003
			HR for 27–52 wks on DFX	1	0.77	NR
			HR for ≥53 wks on DFX	1	0.34	NR
de Witte 2012	1000	Prospective, registry	Adjusted HR	1	0.51 (0.19–1.32)	NS
Delforge 2014	127	Retrospective follow-up	Median OS	3.1 yrs	10.2 yrs	**<0.001**
Remacha 2015	263	Retrospective	Median OS	Not reached	153 mo	**<0.001**
Langemeijer 2016	195/573	Registry	Adjusted HR	1.3 (0.95–1.7)	1	0.01
Lyons 2017	599	Prospective, registry	Median OS from diagnosis	47.8 mo	All 86.3 mo ICT >6 mo 98.7 mo	**<0.0001**
Leitch 2018	239	Prospective, registry	Median OS from transfusion dependence	2.1 yrs	5.2 yrs	**<0.0001**

» DFX, deferasirox; ICT, iron chelation therapy; mo, months; NR, not reported; NS, not significant; yrs, years

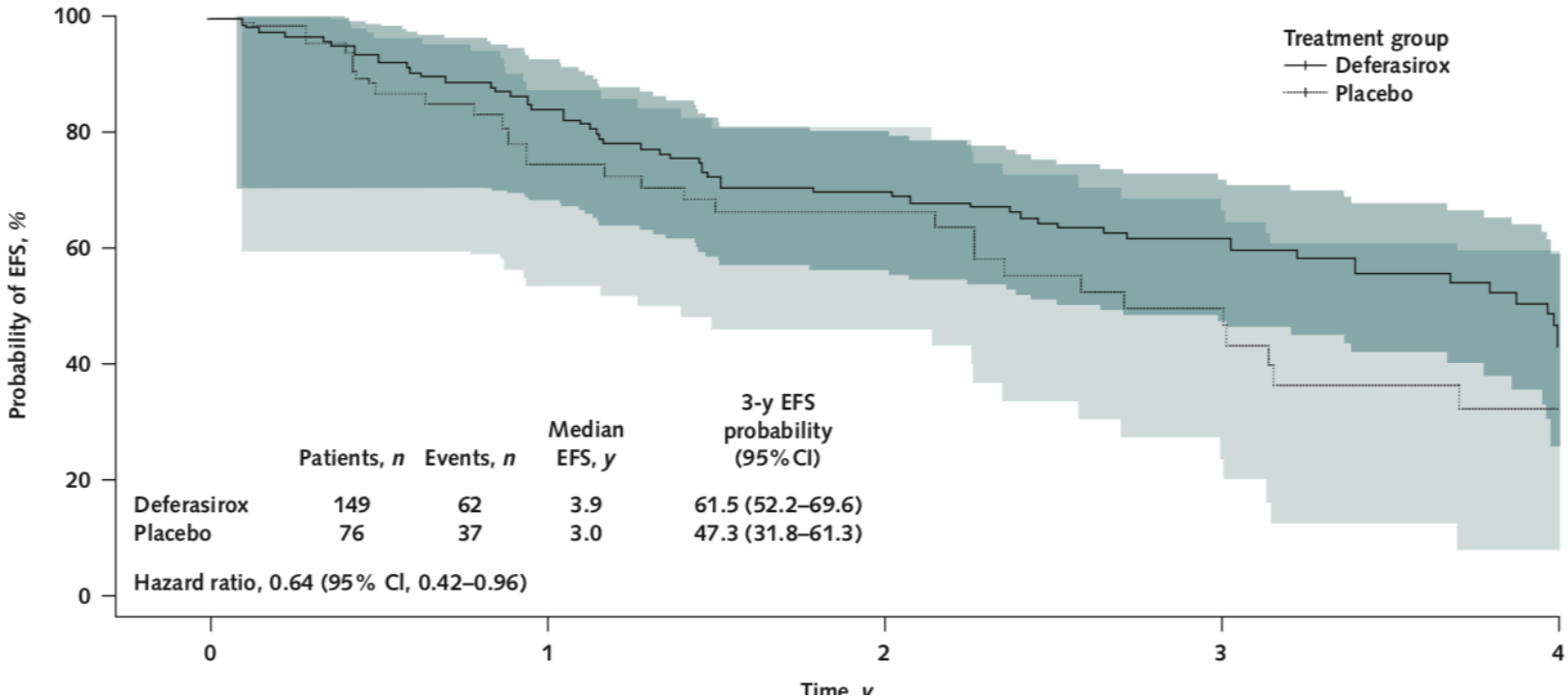
Annals of Internal Medicine

ORIGINAL RESEARCH

Iron Chelation in Transfusion-Dependent Patients With Low- to Intermediate-1–Risk Myelodysplastic Syndromes

A Randomized Trial

Emanuele Angelucci, MD; Junmin Li, MD; Peter Greenberg, MD; Depei Wu, MD; Ming Hou, MD; Efreen Horacio Montaño Figueroa, MD; Maria Guadalupe Rodriguez, MD; Xunwei Dong, MD; Jagannath Ghosh, MS; Miguel Izquierdo, MD; and Guillermo Garcia-Manero, MD; on behalf of the TELESTO Study Investigators*



A 36.4% risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm (HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

Ann Intern Med. 2020;172:513-522

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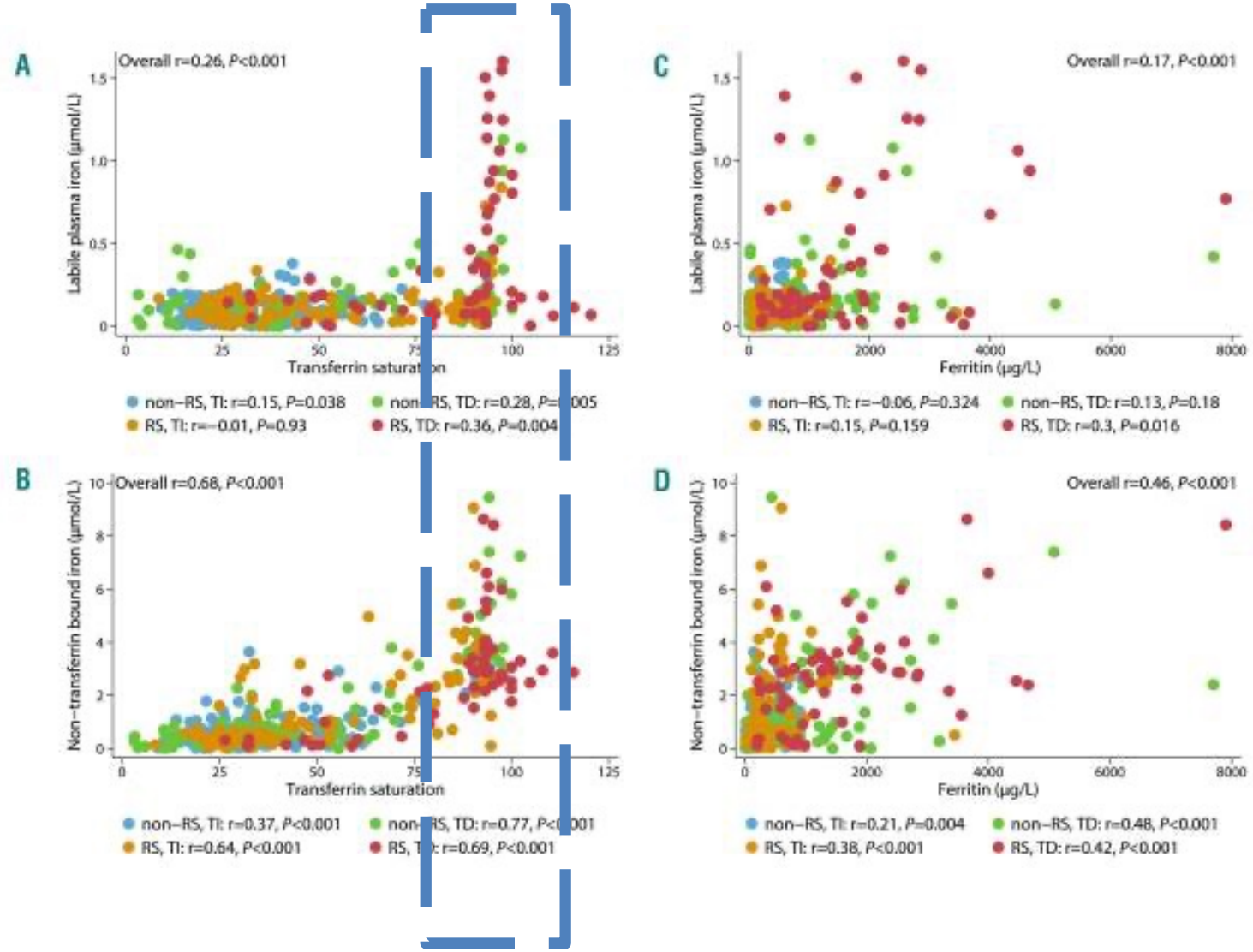
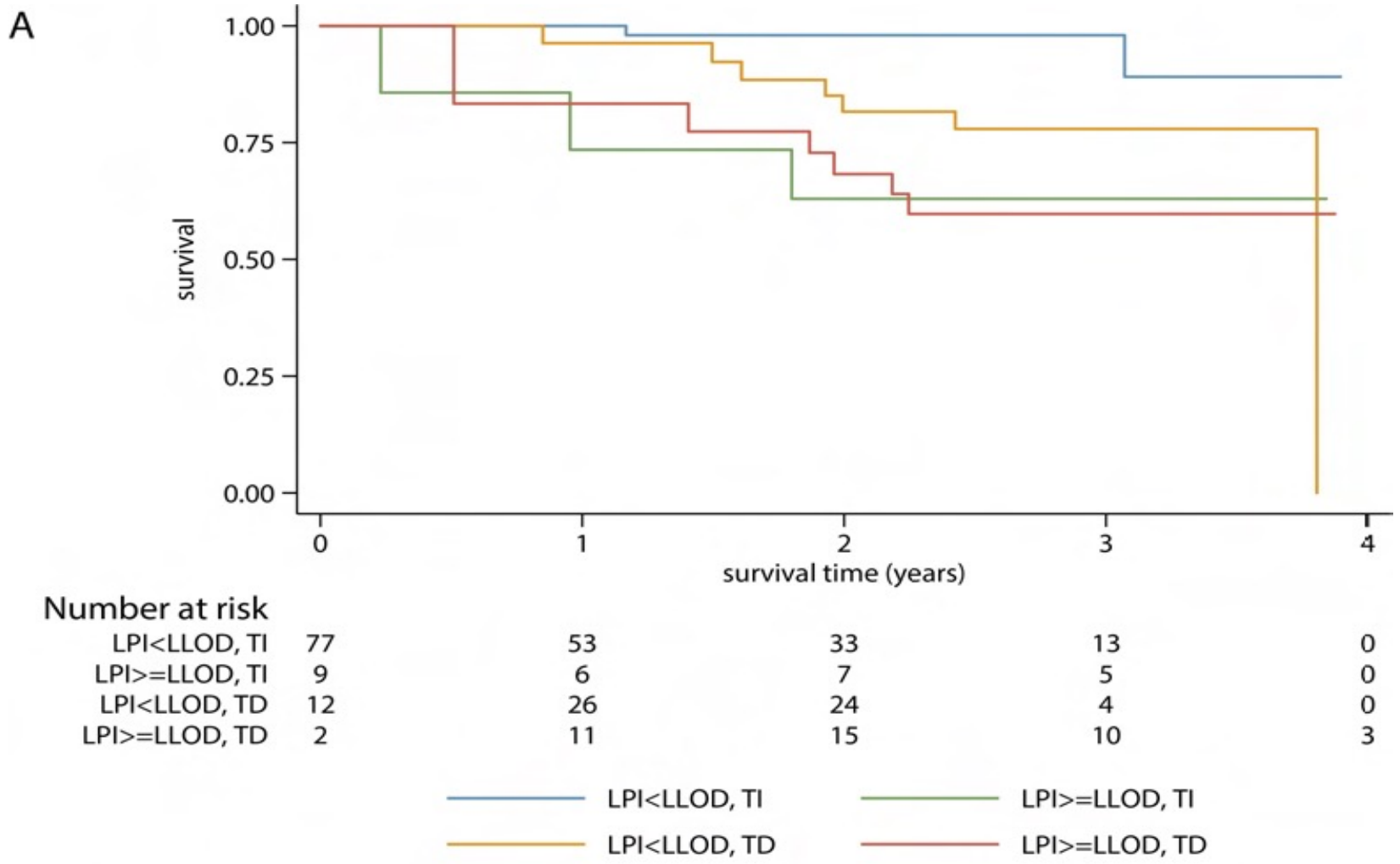
Iron overload detection: new prospective

PRESENT	FUTURE
• ferritin, transferrin saturation • blood transfusion intake, • MRI	• NTBI, LPI/LCI , • ROS (peroxides, superoxide, peroxides/superoxide ratio) • Reduced glutathione (GSH) • Lipid peroxidases (MDA) • Hepcidin, GDF 11 e 15 • Erythroferrone, • 8-OHdG and OGG1 activity



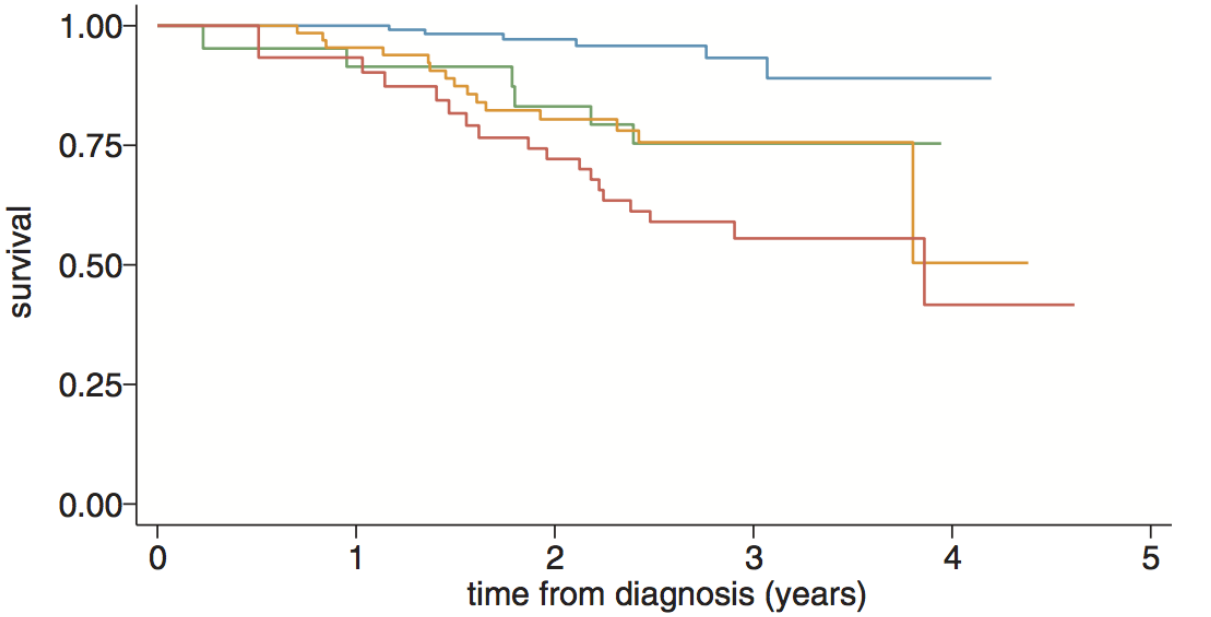
de Swart L. Haematologica. 2017 Nov 9

Labile plasma iron levels predict survival in patients with lower-risk Myelodysplastic syndromes



de Swart L. Haematologica. 2017 Nov 9

Toxic iron species in lower-risk myelodysplastic syndrome patients: course of disease and effects on outcome



- **LPI** was positively correlated TSAT LPI values increased exponentially at TSAT values above 80%.
- **MDA** levels were within the reference range in the non RS-TI group and above the upper limit of the reference range in all other subgroups with the highest levels in the RS-TD group
- **RS-MDS** have the highest levels for markers that reflect iron toxicity.
- **LPI levels above the LLOD are associated with inferior overall and progression-free survival, irrespective of transfusion status.**

M. Hoeks et all, Leukemia 2020

The effects of secondary iron overload and iron chelation on a radiation-induced acute myeloid leukemia mouse model

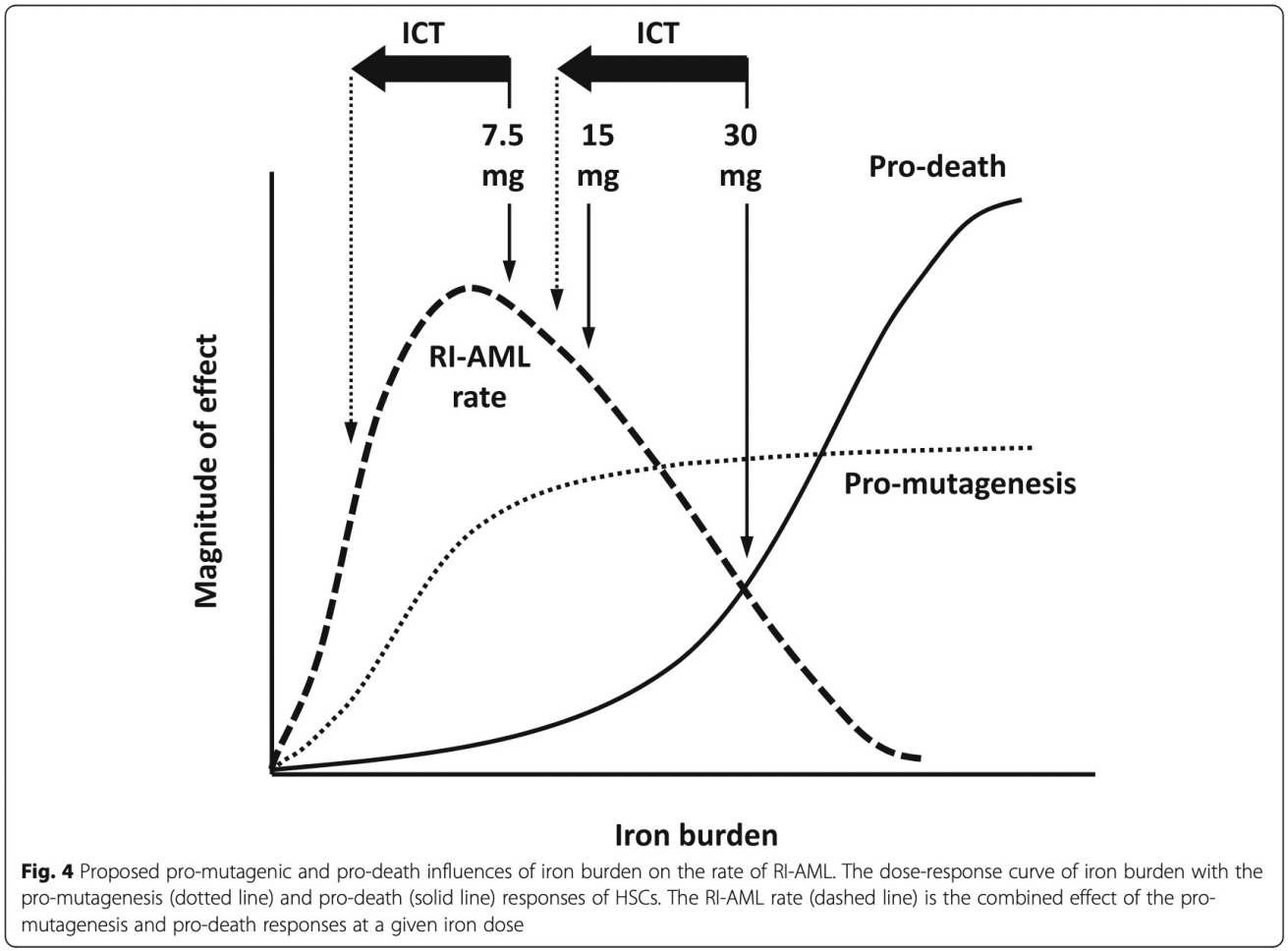


Fig. 4 Proposed pro-mutagenic and pro-death influences of iron burden on the rate of RI-AML. The dose-response curve of iron burden with the pro-mutagenesis (dotted line) and pro-death (solid line) responses of HSCs. The RI-AML rate (dashed line) is the combined effect of the pro-mutagenesis and pro-death responses at a given iron dose

Chan et al. BMC Cancer (2021) 21:509

Thanks for your very kind attention

federica.pilo@aob.it