Con il Patrocinio di

Azienda Ospedaliero - Universitaria Parma

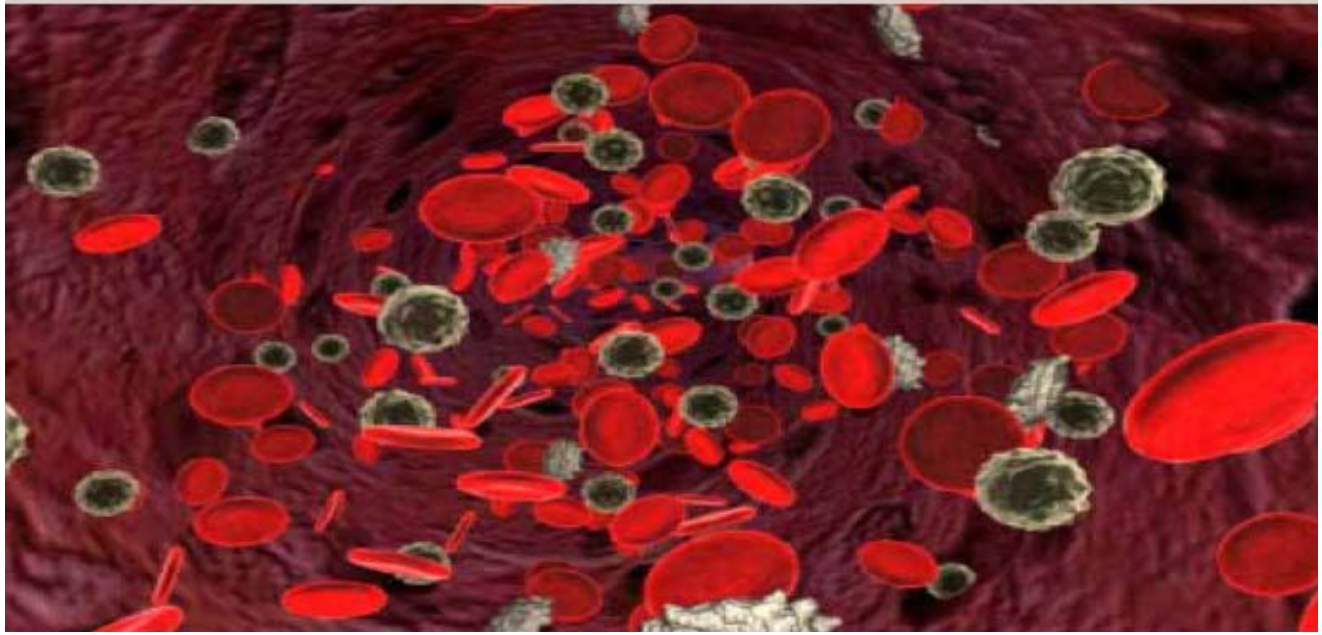
AUSL Parma

SIMTI

CENTRO NAZIONALE SANGUE

# CARENZA ED ECCESSO DI FERRO

## NUOVE CONOSCENZE ED APPROCCIO TERAPEUTICO

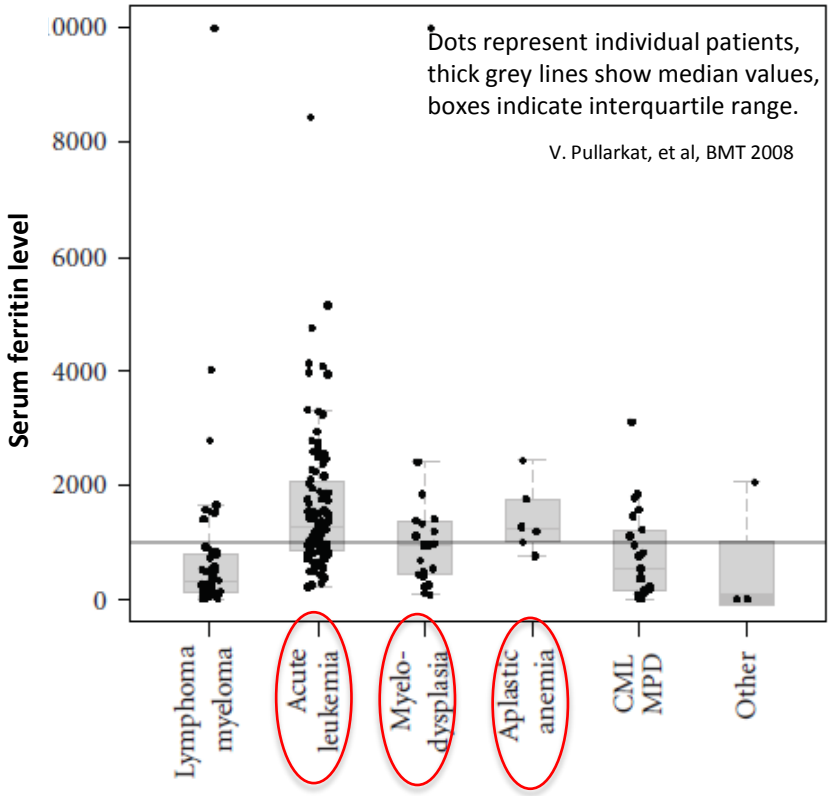


Esperienze dei
Sovraccarichi di Ferro nel
Trapianto Ematopoietico

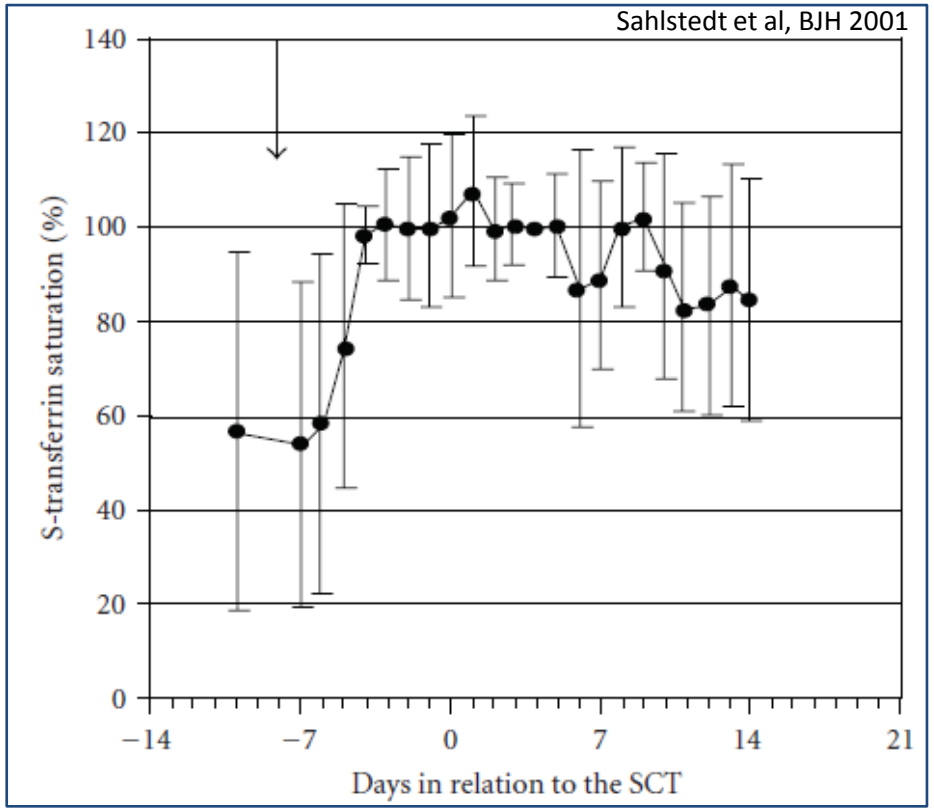
Prof. Franco Aversa
Ematologia e CTMO
Università di Parma
franco.aversa@unipr.it

# Iron Overload in Patients Undergoing Hematopoietic Stem Cell Transplantation

## IO by disease

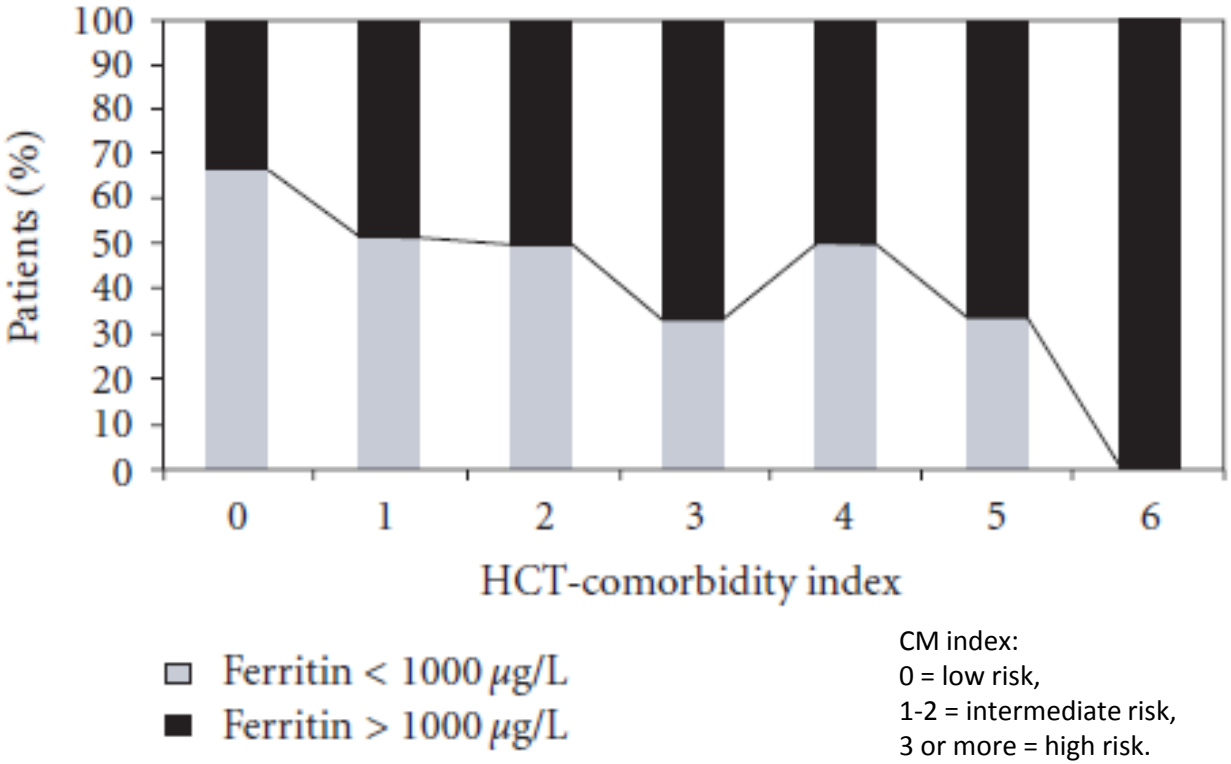



## IO by conditioning regimen




Mean ± SD serum level of the calculated transferrin saturation in 10 allogenic SCT patients during the peritransplantation period. Arrow indicates onset of the conditioning regimen

# Association of pre-transplantation serum ferritin levels and morbidity.




CM index:
0 = low risk,
1-2 = intermediate risk,
3 or more = high risk.

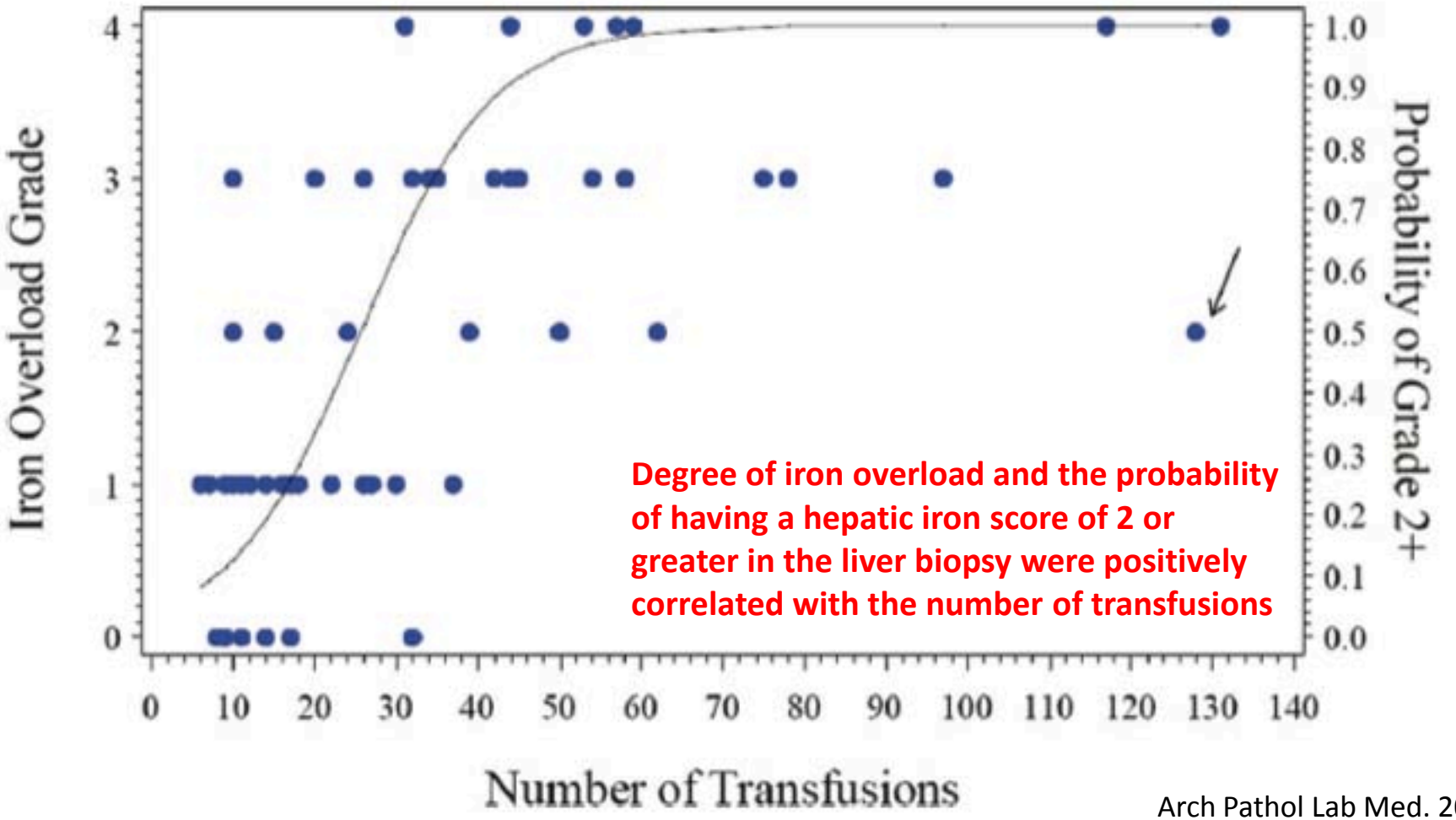
Serum ferritin levels correlate with the HSCT-comorbidity index

Iron overload is associated with a significantly higher HSCT comorbidity index

Platzbecker et al, BBMT 2008

# Iron Overload in Allogeneic Hematopoietic Stem Cell Transplant Recipients

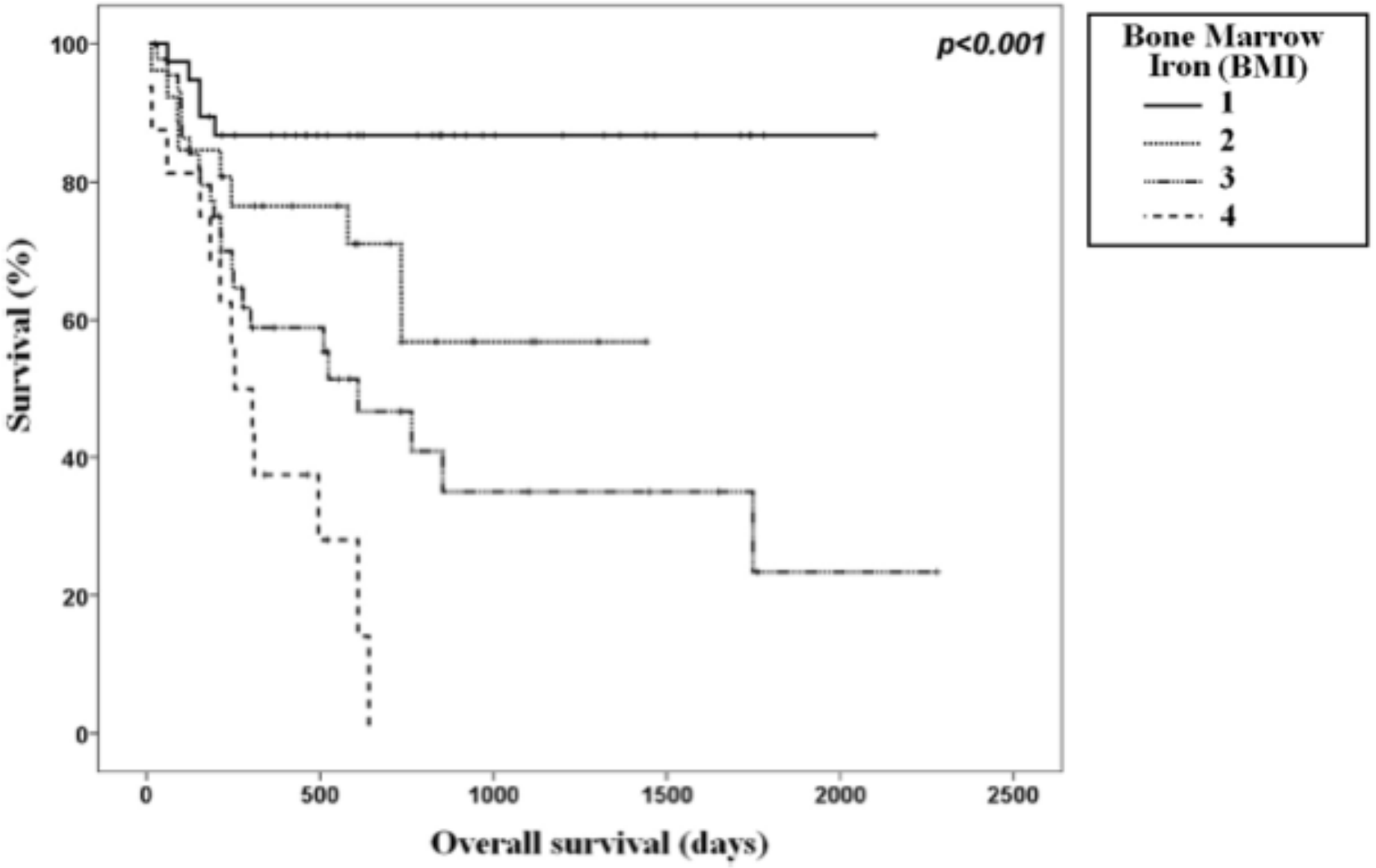
*Sharif Ali, MD; Jason D. Pimentel, MD; Javier Munoz, MD; Veena Shah, MD; Rick McKinnon, MT(ASCP); George Divine, PhD; Nalini Janakiraman, MD*




**Degree of iron overload and the probability of having a hepatic iron score of 2 or greater in the liver biopsy were positively correlated with the number of transfusions**

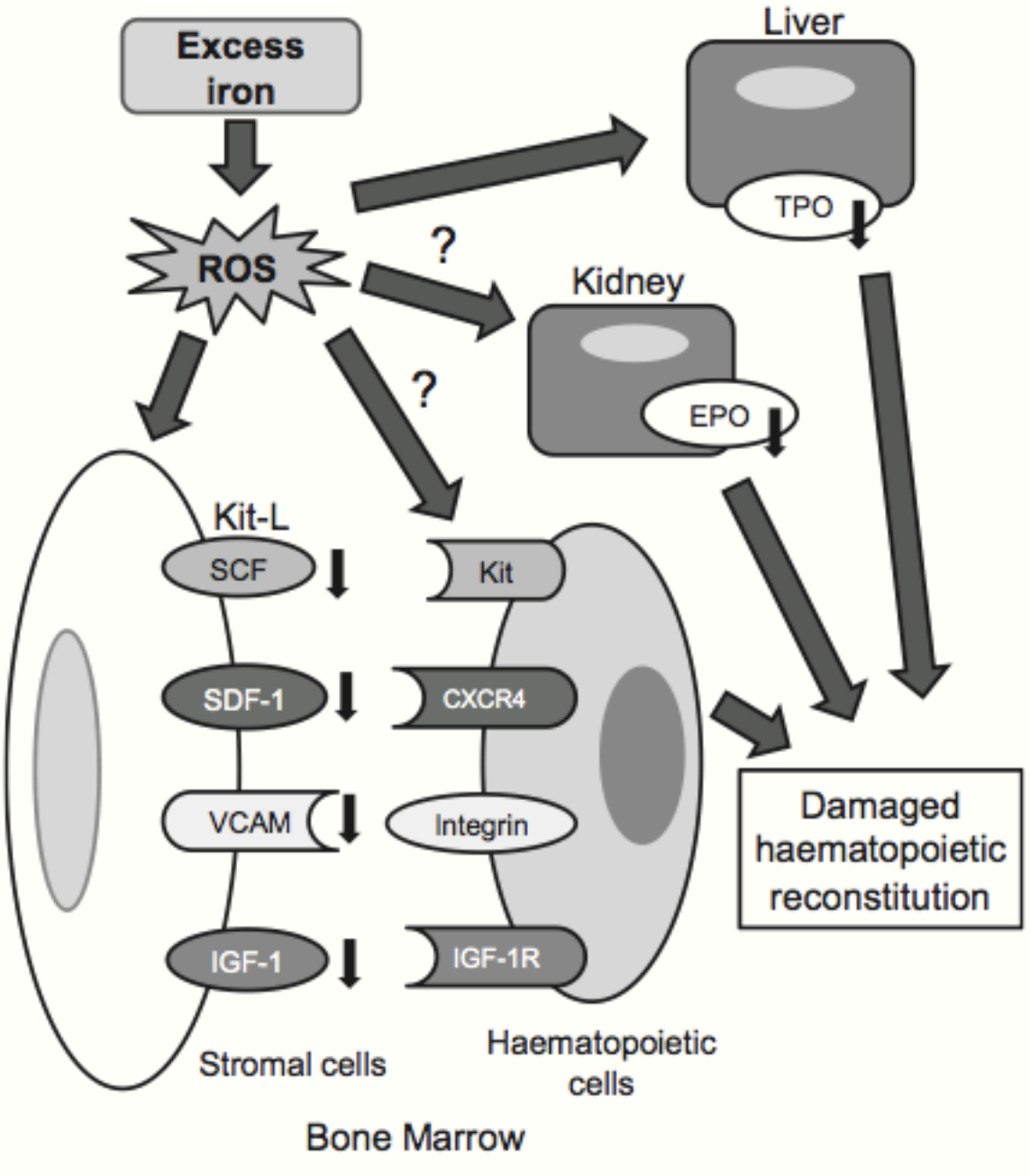
Arch Pathol Lab Med. 2012.

Increased BM Iron Scores are strongly correlated with Elevated Serum Ferritin Levels and poorer OS after AlloHSCT.
A single center experience




Sivgin et al.

Clinical Lymphoma, Myeloma & Leukemia, October 2016




Excess iron increases ROS in bone marrow and liver.

ROS:
a) damage hematopoietic stromal cells,
b) reduce some molecules for hematopoiesis,
c) reduce production of TPO in the liver and EPO in the kidney.

The disturbance of hemato-poietic supporting machinery can be one of the negative effects induced by iron overload.

European Journal of Haematology 2014

# Factors Affecting Stem Cell Mobilization for Autologous Hematopoietic Stem Cell Transplantation

Zübeyde Nur Özkurt, Zeynep Arzu Yeğin, Elif Suyanı, Şahika Zeynep Akı, Kadir Acar, Münci Yağcı, and Gülsan Türköz Sucak*

- Rate of mobilization failure =11.8% (14/118)
- CD34+ →negatively correlate with ferritin and transferrin saturation.
- *serum ferritin levels → higher in mobilization failure*.
- **Hypothesis**: oxidative stress induced by excess iron and/or the inflammatory milieu of the malignancy which might as well cause increased ferritin levels may alter or blunt the cytokine response or the functions of adhesion molecules and micro-enviromental interactions of HSCs

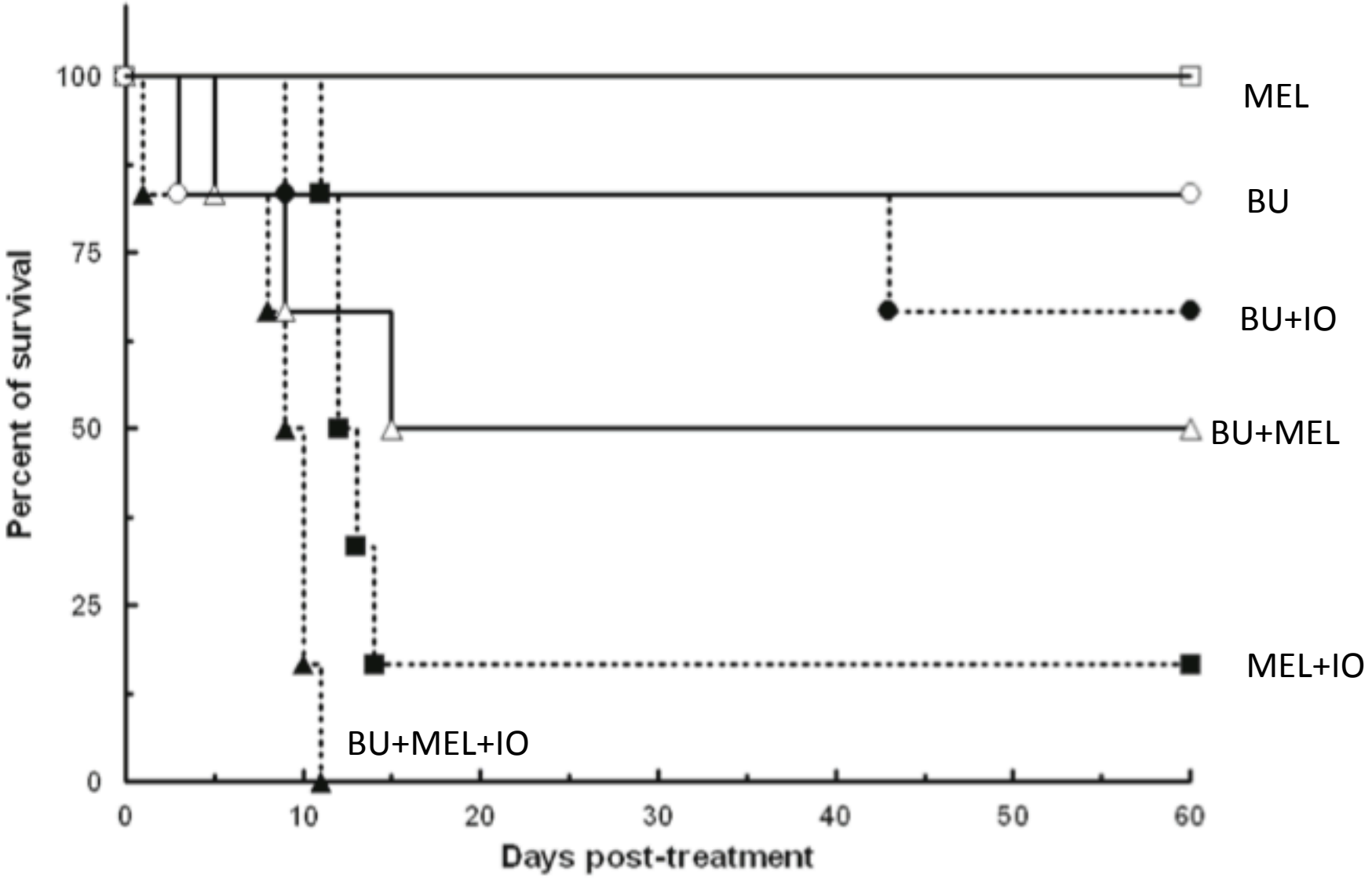
Journal of Clinical Apheresis 25:280–286 (2010)

# Iron Overload Exacerbates Busulfan-Melphalan Toxicity Through a Pharmacodynamic Interaction in Mice

- Iron excess increases the toxicity of melphalan or busulfan melphalan combination.
- BU clearance alteration was exacerbated in iron overloaded mice demonstrating a PK interaction.
- Iron overload increased melphalan toxicity without altering its PK, suggesting a PD interaction between iron and melphalan.

Bouligand et al. Pharm Res (2016) 33:1913–1922

**Survival (control vs iron) not treated or treated by busulfan (Bu), melphalan (Mel) or by the combination (Bu Mel). Survival of not treated mice was 100%.**




Bouligand et al.

Pharm Res (2016) 33:1913–1922

# Iron Overload: Predictor of Adverse Outcome in Hematopoietic Stem Cell Transplantation

G.T. Sucak, Z.A. Yegin, Z.N. Özkurt, Ş.Z. Akı, and M. Yağci

250 pts, median age, 34 (16–71) yrs , Auto 102, allo 148 (2003-08).

**Mucositis.**

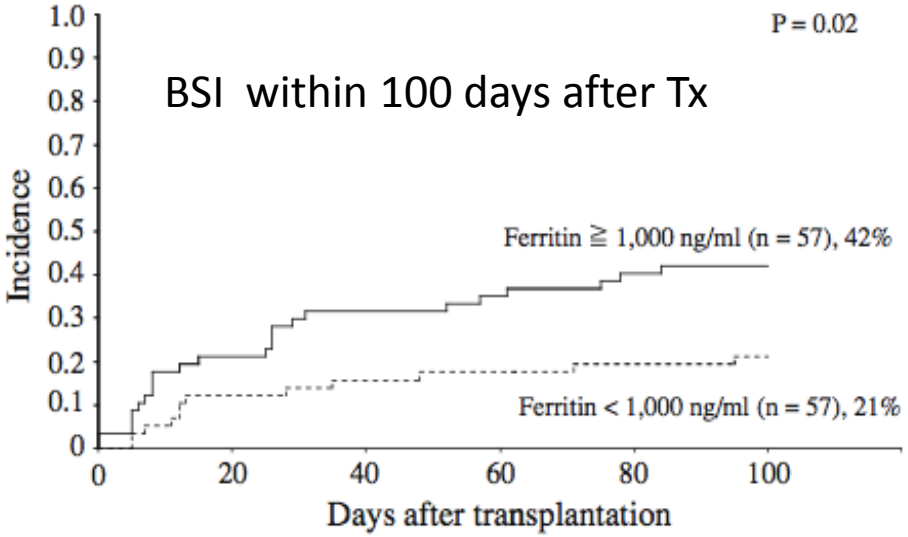
***Patients with grade III-IV mucositis exhibited significantly higher pre-HSCT ferritin concentrations***.

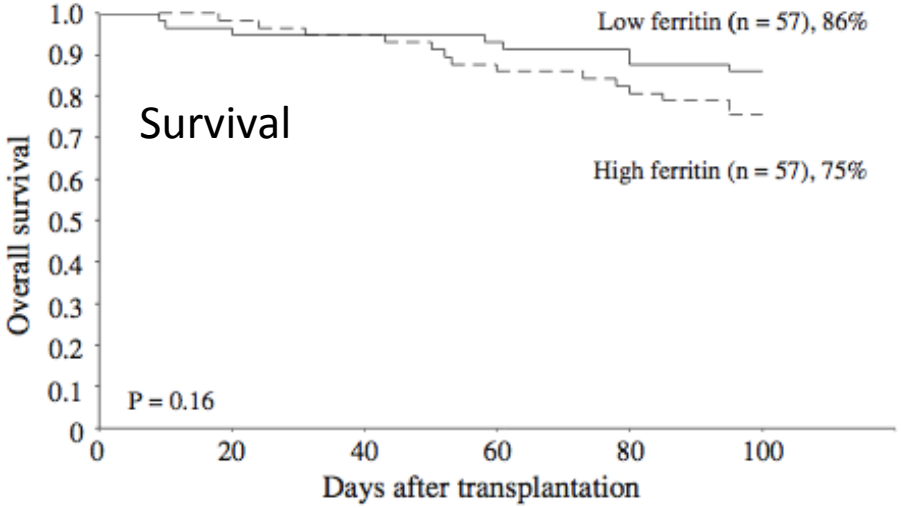
Pre-HSCT serum ferritin concentration >500 ng/mL correlated with severe mucositis in autoHSCT, with a positive predictive value (PPV) of 21.4% and a negative predictive value (NPV) of 94.1%.
No linear relationship was observed between severe mucositis and high ferritin concentration in the alloHSCT.

*Transplantation Proceedings,* 42, 1841–1848 (2010)

# Pretransplant serum ferritin is associated with bloodstream infections within 100 days of allogeneic stem cell transplantation for myeloid malignancies

Takayoshi Tachibana · Masatsugu Tanaka · Hirotaka Takasaki · Ayumi Numata · Satomi Ito · Reina Watanabe · Rie Hyo · Rika Ohshima · Maki Hagihara · Rika Sakai · Shin Fujisawa · Naoto Tomita · Hiroyuki Fujita · Atsuo Maruta · Yoshiaki Ishigatsubo · Heiwa Kanamori




Int J Hematol (2011) 93:368–374

# Increased Bone Marrow Iron Stores Is an Independent Risk Factor for Invasive Aspergillosis in Patients With High-Risk Hematologic Malignancies and Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

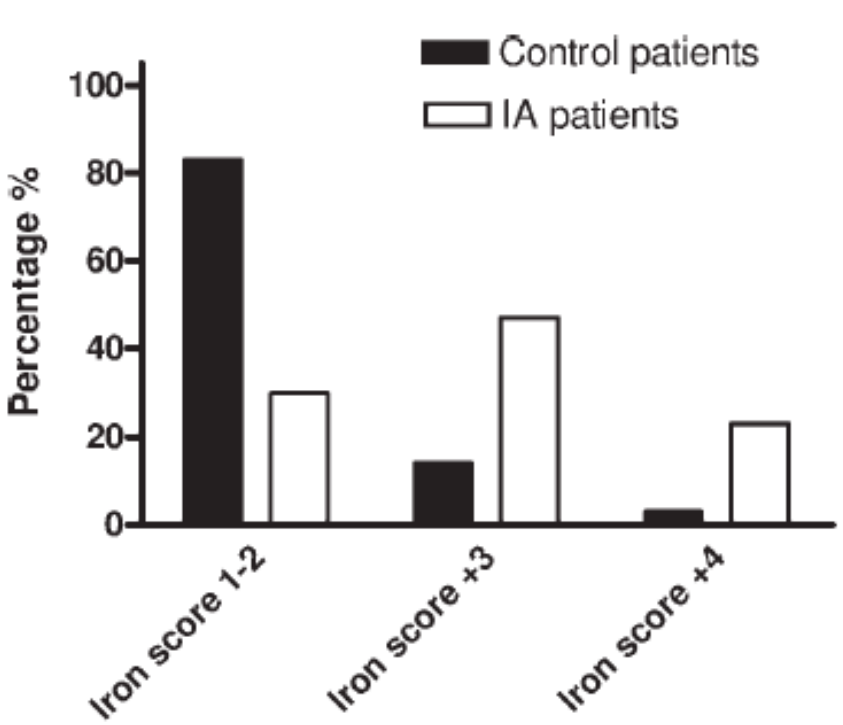



**FIGURE 1.** Distribution of patients with normal (1 or 2) or increased (≥3) bone marrow iron stores scores. IA indicates invasive aspergillosis.

Dimitrios P. Kontoyiannis,

CANCER September 15, 2007 / Volume 110 / Number 6

Host animals can limit the growth of pathogenic microorganisms in vivo by significantly reducing free iron levels.

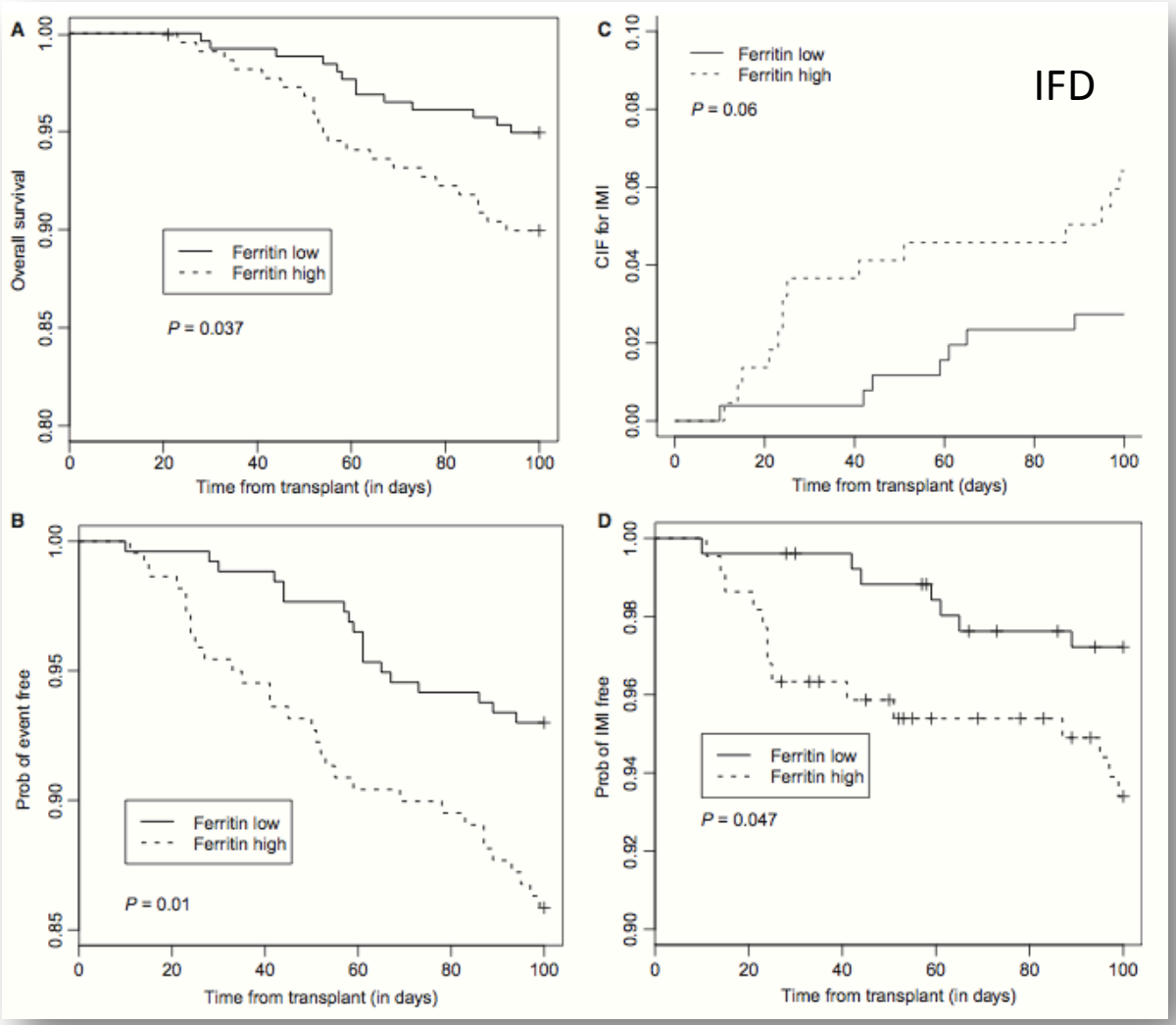
*A. fumigatus* is capable of growth in media containing concentrations of human serum which are inhibitory to the growth of most fungal pathogens.

Siderophores produced by A. fumigatus are responsible for its ability to access transferrin-bound iron, likely permitting its growth in the presence of serum

*Hissen AH, et al. Infect Immun. 2005;73:5493*

# Impact of pretransplant serum ferritin level on risk of invasive mold infection after allogeneic hematopoietic stem cell transplantation

Sanjeet S. Dadwal[1], Bernard Tegtmeier[1], Xueli Liu[3], Paul Frankel[3], James Ito[1], Stephen J. Forman[2], Vinod Pullarkat[2]




European Journal of Haematology, 2014

# Iron Overload: Predictor of Adverse Outcome in Hematopoietic Stem Cell Transplantation

G.T. Sucak, Z.A. Yegin, Z.N. Özkurt, Ş.Z. Akı, and M. Yağci

**Acute GvHD**

Incidence: 20.3%,

Distribution: skin (43%), liver (13%), GI (20%), L+GI (6%), S+GI (16%).

*Iron status → significantly higher in the group with **hepatic GvHD**.*

No significant effect of pre-HSCT iron status was observed in other forms of acute GvHD.

**SOS/VOD.**

Incidence 29.7%.

*Iron status → significantly higher in the group with **SOS***

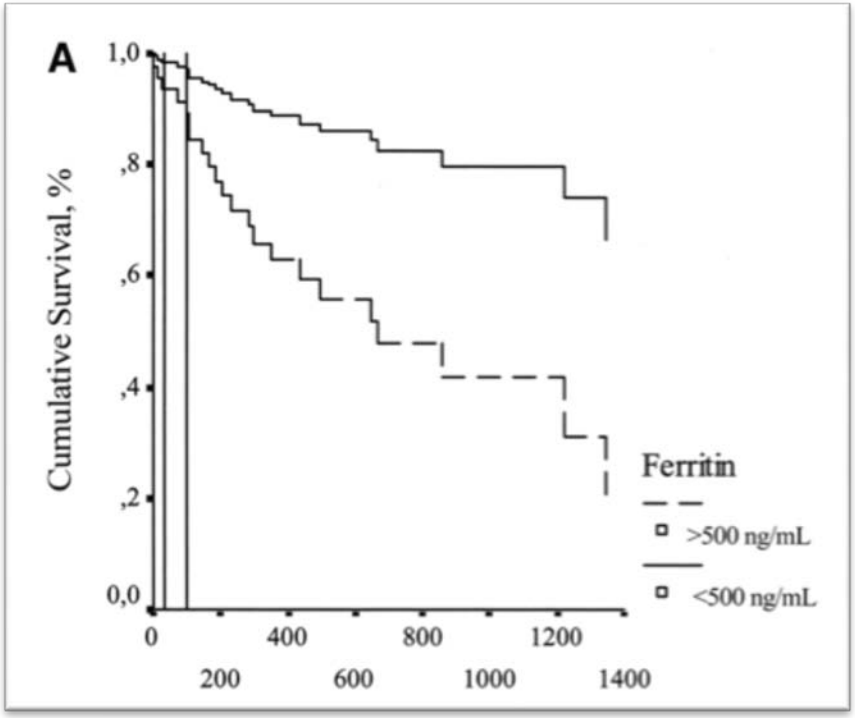
*Transplantation Proceedings,* 42, 1841–1848 (2010)

# Iron Overload: Predictor of Adverse Outcome in Hematopoietic Stem Cell Transplantation

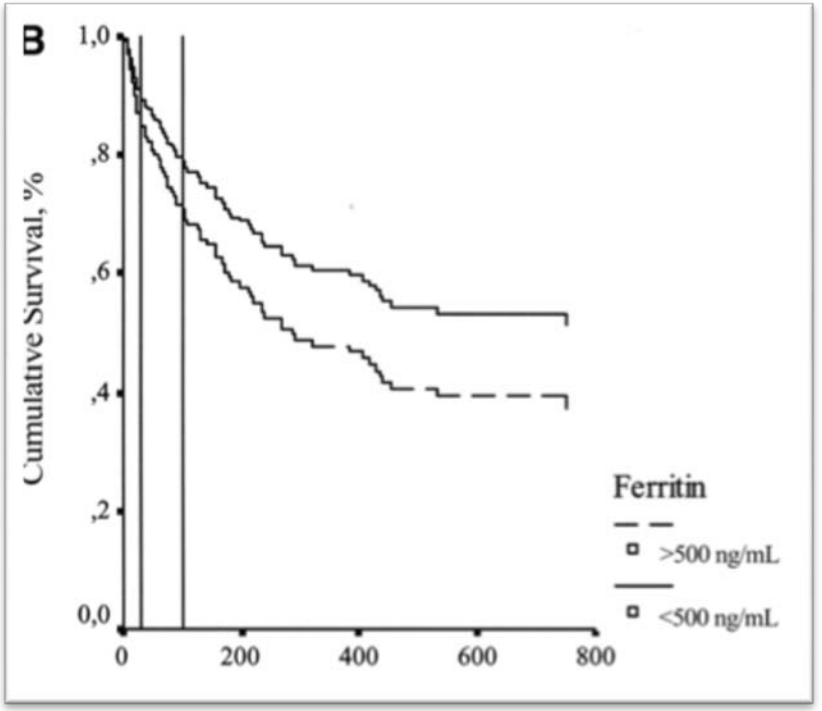
G.T. Sucak, Z.A. Yegin, Z.N. Özkurt, Ş.Z. Akı, and M. Yağci

**TRM.**

**AutoHSCT (2.9%)**




**AlloHSCT (9.5%),**

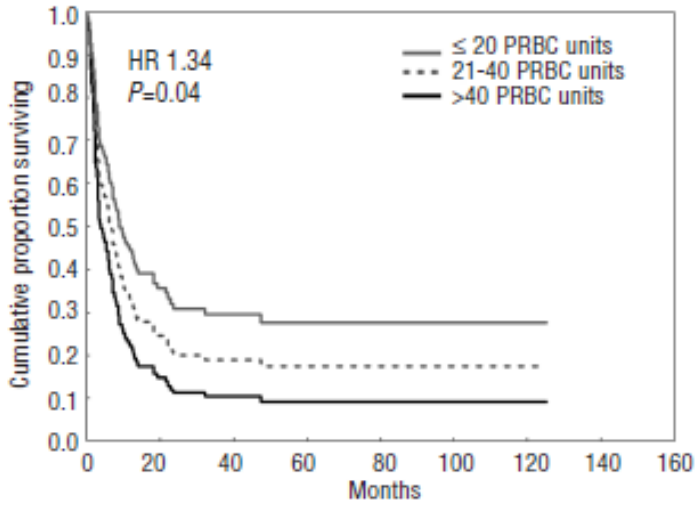


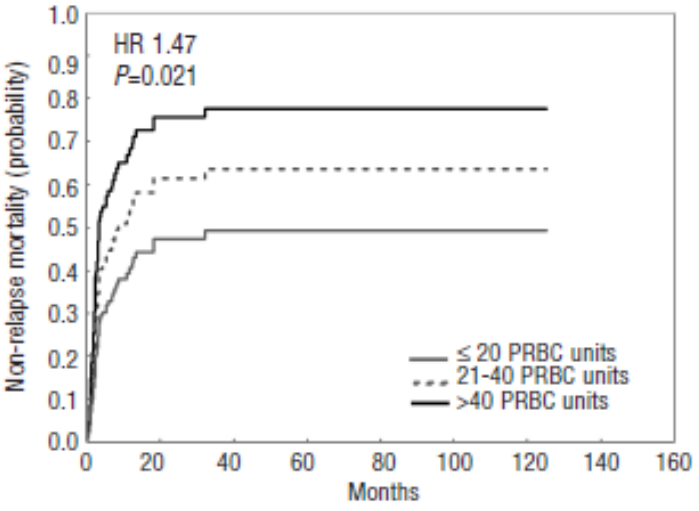

*Transplantation Proceedings,* 42, 1841–1848 (2010)

# Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study

Alessandrino et al. Haematologica 2010

## outcome by transfusion burden

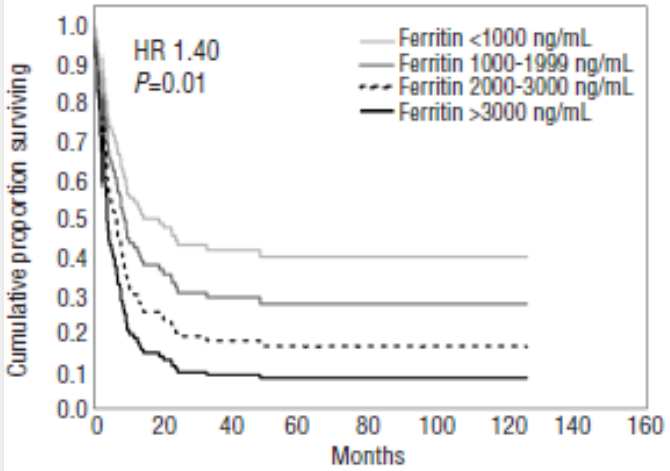


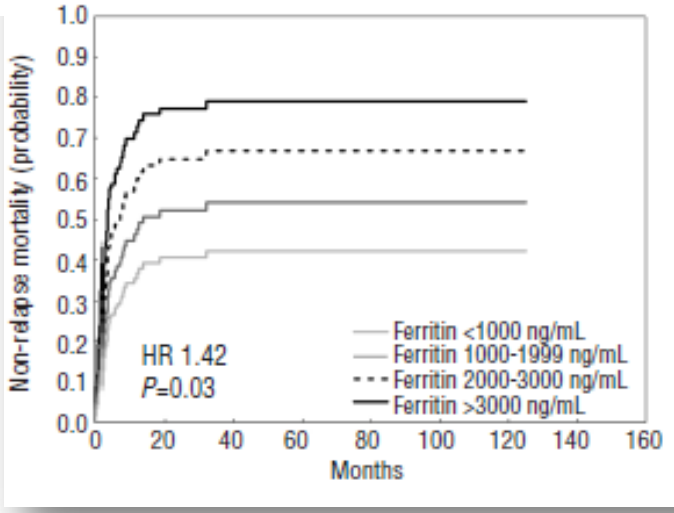




OS

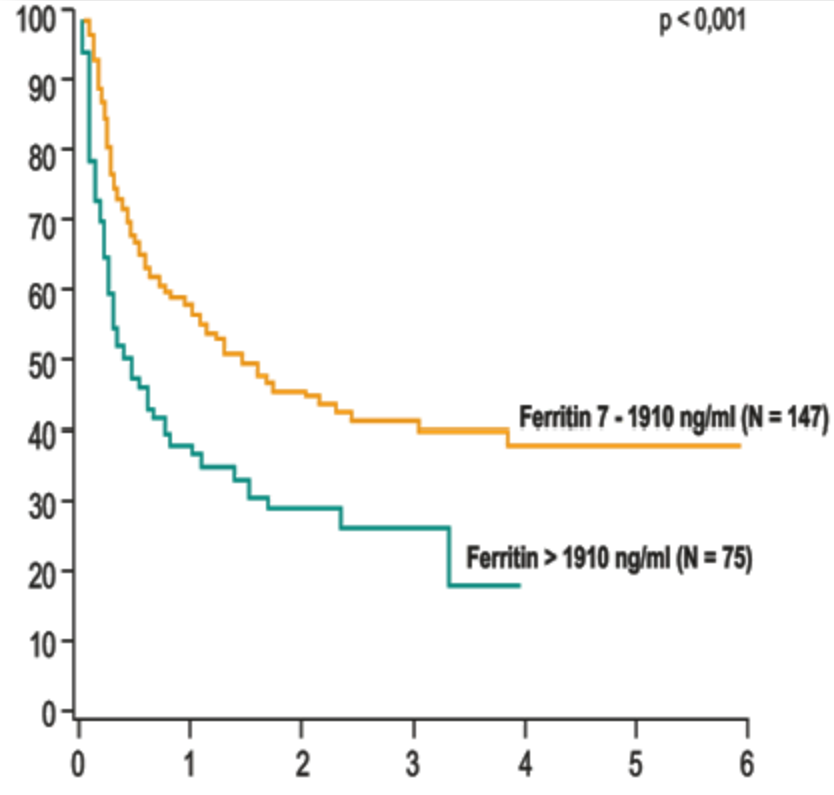
NRM

## outcome by ferritin level



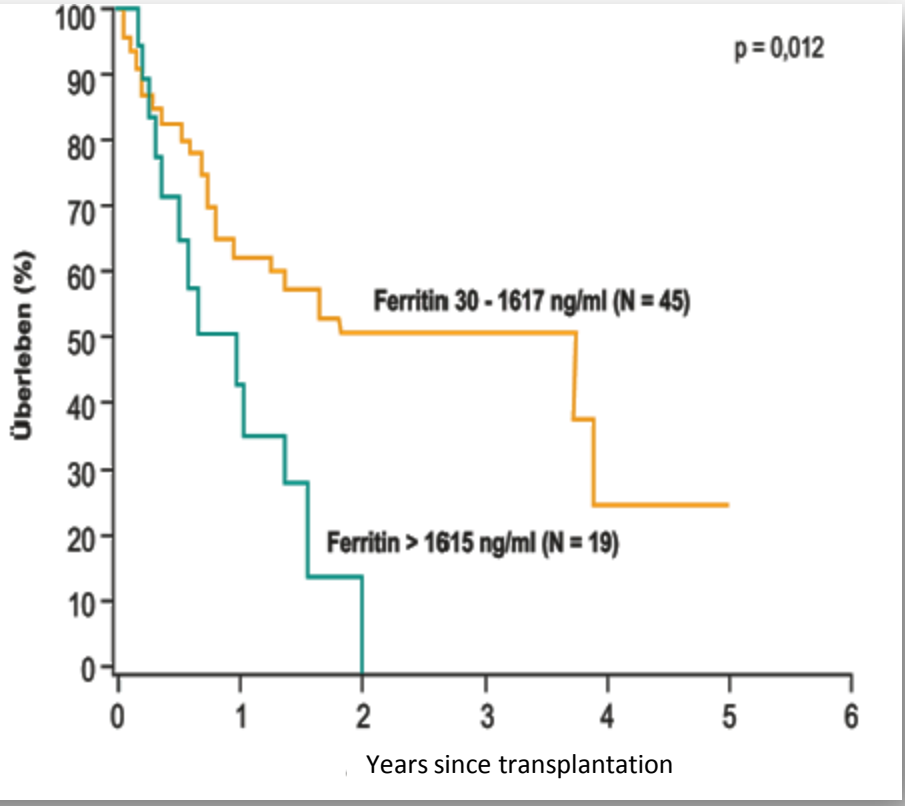



# Pre-transplant serum ferritin and survival by conditioning regimen




Myeloablative conditioning (MAC)

Mahindra A et al. Br J Haematol 2009

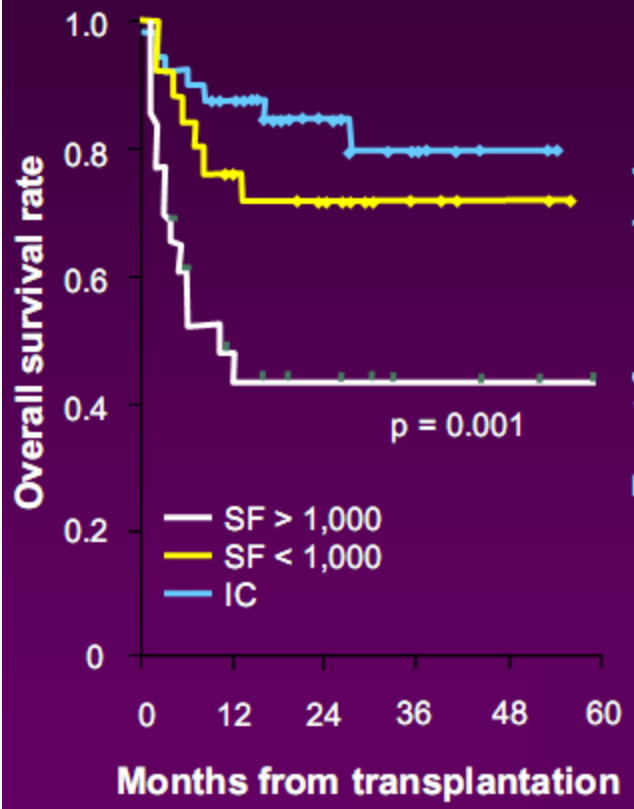


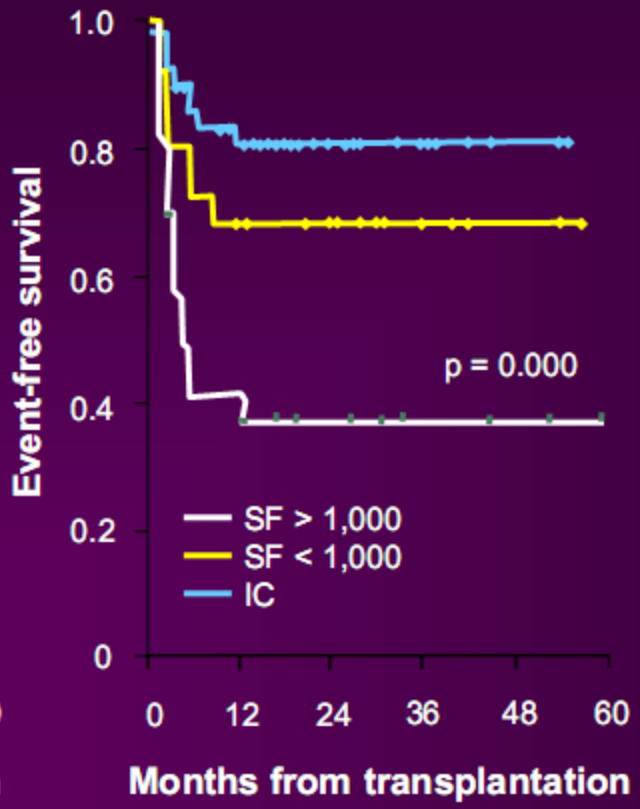

Non-myeloablative (RIC)

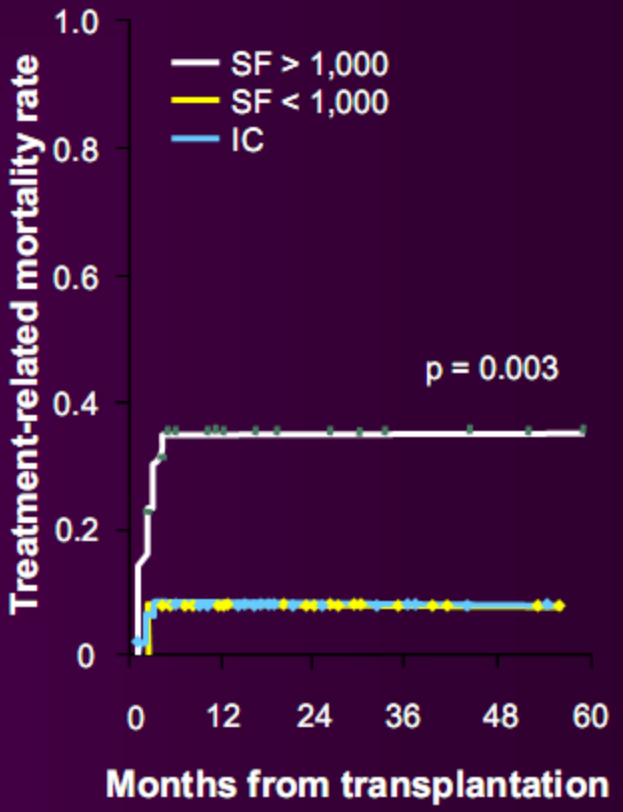
Mahindra A et al. Bone Marrow Transplant 2009

# Iron chelation

## Prior to SCT




ICT = iron chelation therapy;
— SF > 1,000 = patients with serum ferritin ≥ 1,000 µg/L at the time of HSCT;
— SF < 1,000 = patients with serum ferritin < 1,000 µg/L at the time of HSCT, without ICT;
— IC = patients with serum ferritin decreased to < 1,000 µg/L with ICT before HSCT.

Lee JW, et al. Bone Marrow Transplant. 2009

# Which Patients Undergoing AlloHSCT Could Benefit from Treatment of Iron Overload ?

- All pts who are transfusion dependent and are potential candidate to HSCT should receive iron chelation therapy
- If iron overload has occurred in patients for whom a MAC has been planned, an attempt should be performed to reduce body iron stores.
- The accomplishment of the reduction of iron overload ***should not cause a delay in HSCT***.
- Body iron excess should be reduced at
  - Complete and sustained Engraftment
  - Stop Immunosuppression.

Alessandrino et al. AJH 2011

## Iron overload (IO) can persist after HSCT, potentially for many years.

- In pediatric patients, IO decreases over time as a result of utilization of storage iron for growth.
- Late effects may differ between thalassemic and non-thalassemic patients due to the distribution of tissue iron (parenchymal vs macrophage) in different disease states.
- IO can mimic exacerbation of *hepatic GVHD*, leading to unnecessary continuation or intensification of immuno-suppressive therapy.

# Assessing Iron Load in the HSCT Patient

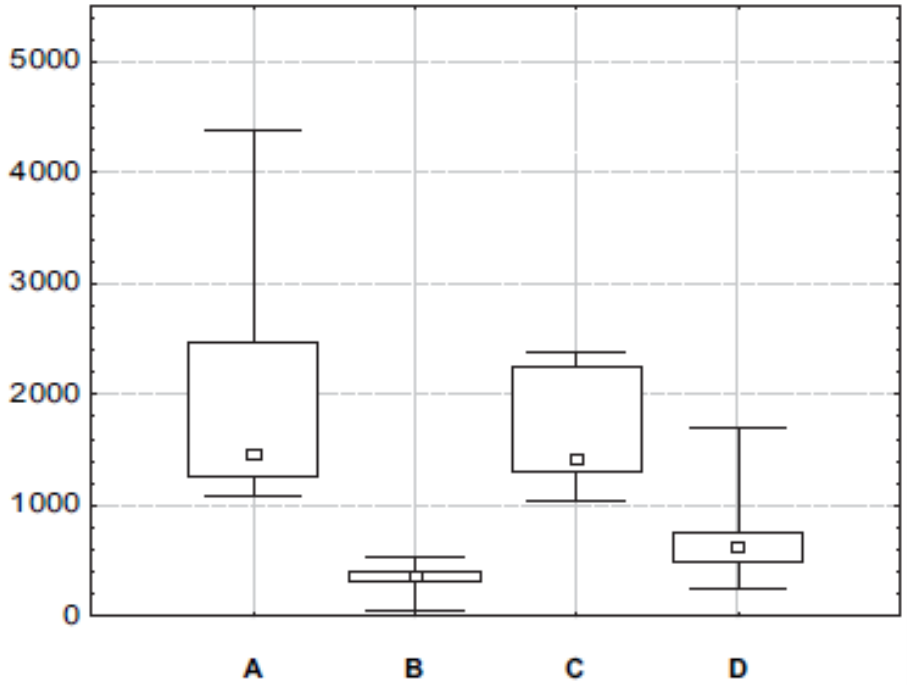
- Ferritin levels increase in conditions of iron overload → simple surrogate marker for body iron load.
- Serum ferritin levels are subject to fluctuation due to:
  - inflammation, liver damage, infection, GVHD→ all result in elevated serum ferritin levels and overestimation of iron load.
- Serial ferritin measurements compensate for fluctuations.
- As 90% of excess iron is deposited in the liver, assessment of LIC provides an accurate measure of whole-body iron levels. *Noninvasive MRI techniques are more often used instead of the liver biopsy.* An additional advantage of MRI is its ability to measure cardiac iron, which does not correlate with serum ferritin or hepatic iron.

# Iron Overload in Patients Receiving Allogeneic Hematopoietic Stem Cell Transplantation: Quantification of Iron Burden by a Superconducting Quantum Interference Device (SQUID) and Therapeutic Effectiveness of Phlebotomy

ASBMT American Society for Blood and Marrow Transplantation

Busca et al.

**Impact of phlebotomy on serum ferritin level and LIC.**




A: ferritin level before phlebotomy
B: after completion of the program (P<.001).

C: LIC before phlebotomy
D: after completion of the program (P<.001).

*Biol Blood Marrow Transplant 16: 115-122 (2010)*

# Which Is The Most Appropriate Iron Chelation Treatment for MDS Patients Before and After HSCT?

- Phlebotomy → first choice therapy (± EPO)
  - 6 ml/kg blood withdrawal at 14-day interval
  - target iron status is serum ferritin inside the normal laboratory range and transferrin saturation <45%
- For those patients who cannot be phlebotomized → deferoxamine or deferasirox
- Iron-chelating therapy should be continued until ferritin <500 ng/ml.

Alessandrino et al. AJH 2011

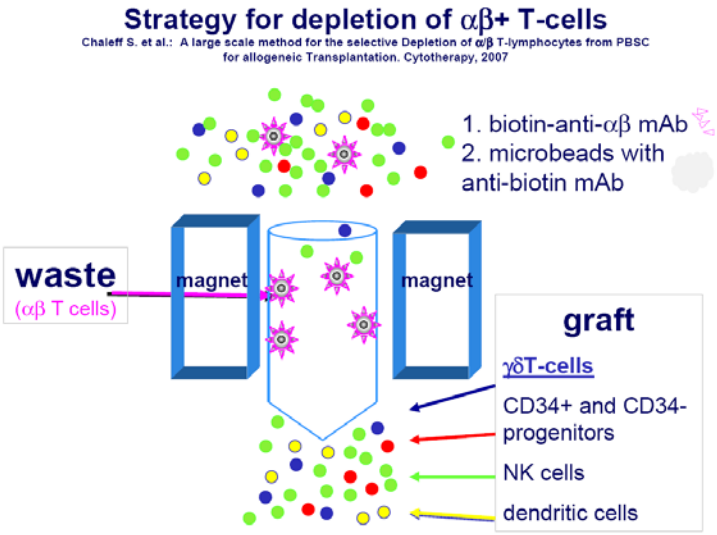
# Risk factors for HSCT failure

- **Host related**
  - Age
  - Comorbidities
- **Disease related**
  - Disease/Genetics
  - Status at transplant
- **Procedure related**
  - Conditioning regimen
  - Quality of the graft
  - GvHD prophylaxis

***HSCT «package»***

**Efficient TCRα/β+ cell depletion**
→ Potentially reducing the risk of GvHD

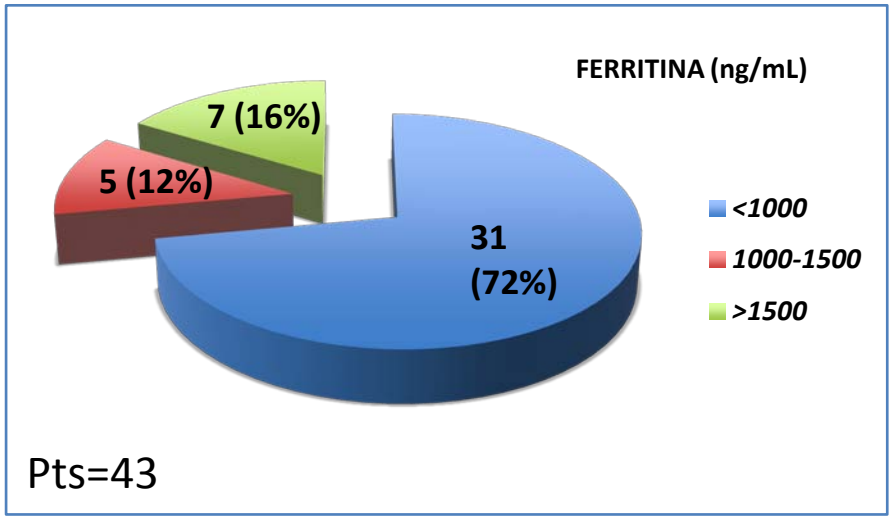
**Maintenance of stem cells and facilitating cells (TCRγδ T cells, NK cells)**
→ might facilitate engraftment,
→ exerts a GvL effect and reduces the risk for infections.

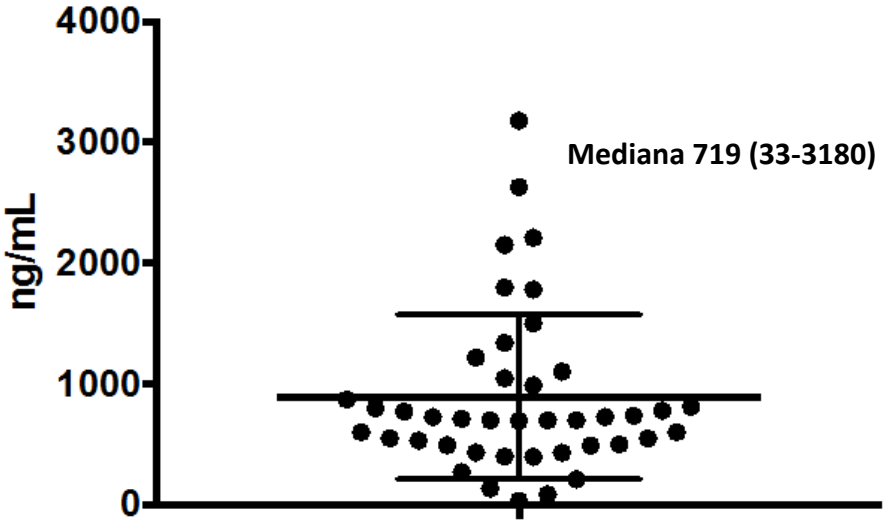


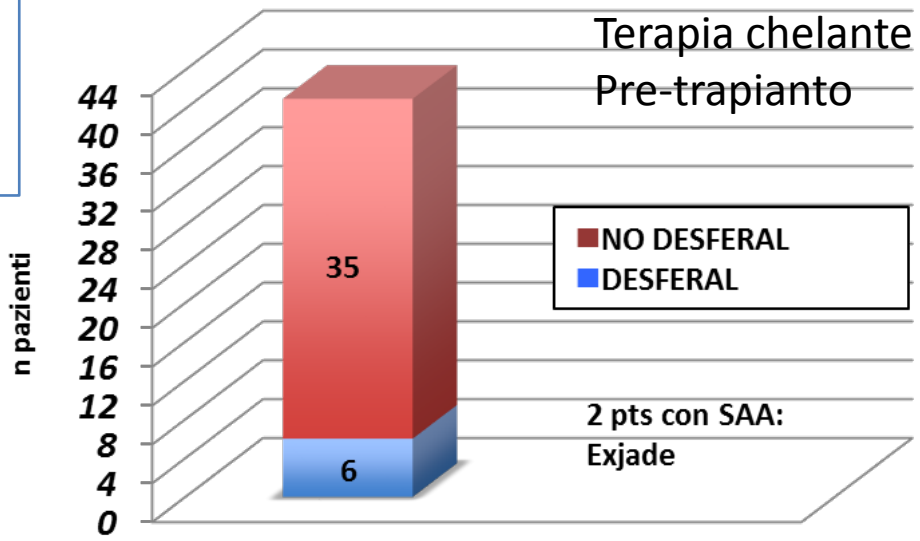

# GRAFT COMPOSITION

## (median of 40 procedures)

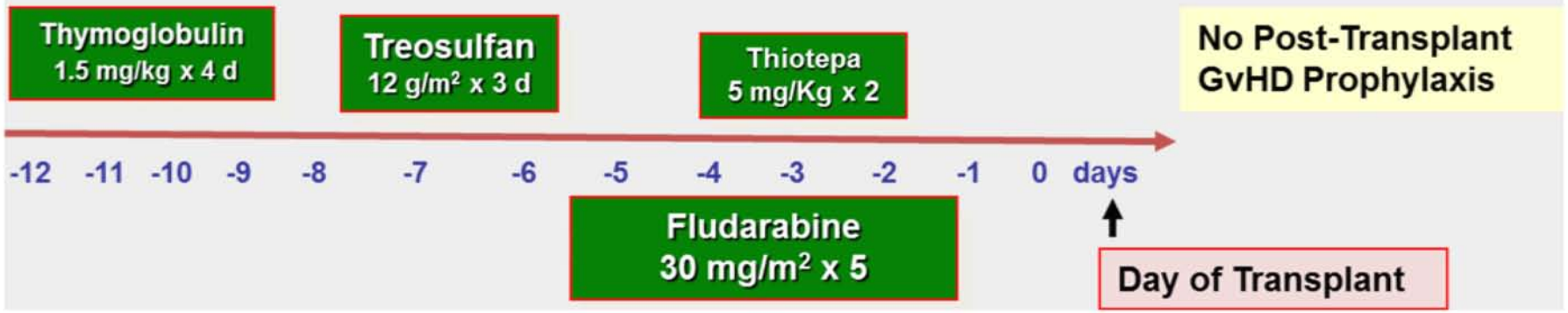
| | CD34 | CD3 | | | CD20 | NK |
|---|---|---|---|---|---|---|
| | | Total CD3 | γδ | αβ | | |
| cells/kg Median | $11 \times 10^6$ | $4.3 \times 10^6$ | $4 \times 10^6$ | $4{,}8 \times 10^4$ | $4.8 \times 10^4$ | $30 \times 10^6$ |
| (Range) | (5-19) | (1-35.7) | (1-34) | (0,4-37) | (1.8-32) | (8-91) |

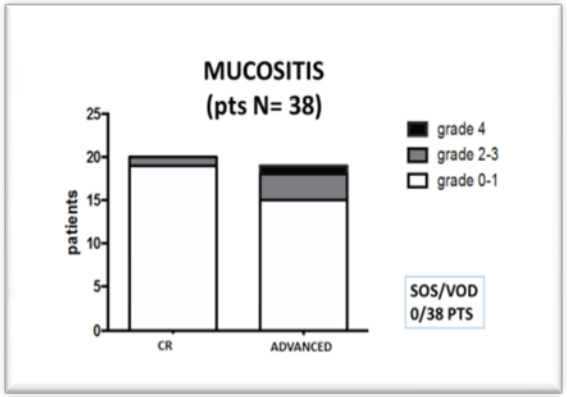

FERRITINA (ng/mL)
7 (16%)
5 (12%)
31
(72%)
<1000
1000-1500
>1500
Pts=43


4000
3000
2000
1000
0
ng/mL
Mediana 719 (33-3180)

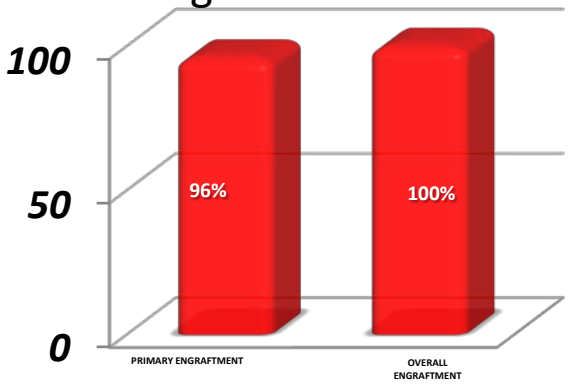

Terapia chelante
Pre-trapianto
n pazienti
44
40
36
32
28
24
20
16
12
8
4
0
35
6
NO DESFERAL
DESFERAL
2 pts con SAA:
Exjade

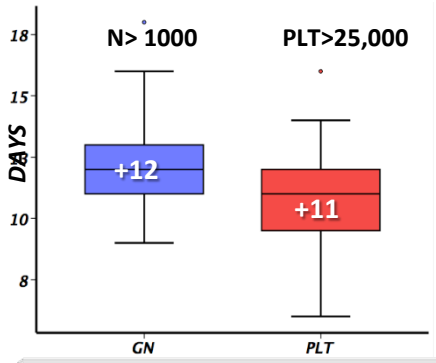
# Chemotherapy alone-based conditioning regimen

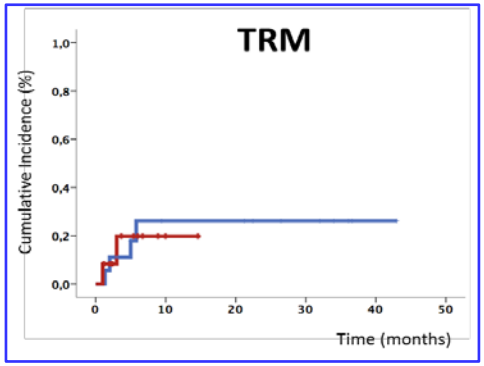


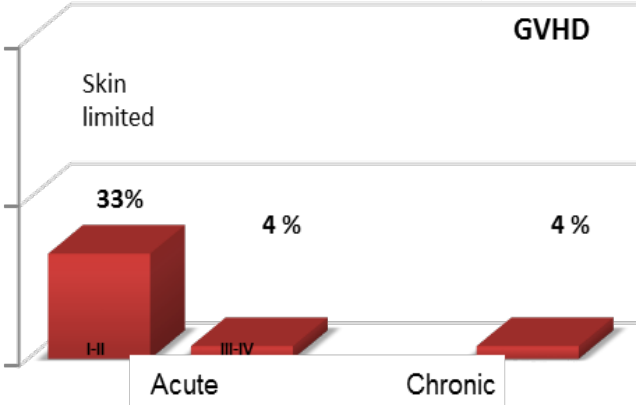




## Engraftment



# Conclusioni

- Sovraccarico di ferro pre- e post-trapianto rimane un fattore di rischio per TRM
  - Sicuramente nel trapianto convenzionale
  - Forse NO nel trapianto T depletato
- Utile la chelazione pre- e post-trapianto
  - Ma non ritardare trapianto se urgente
- Flebotomia +/- EPO: prima linea