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LIBERI E LONGEVI

Università degli
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Federico II
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di **SCAMPIA**



SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA



Sindrome sideropenica e fragilità

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Il sottoscritto

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara che

negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

GUIDOTTI, BAYER, MENARINI, ASTRA, BOEHRINGER, BRUNO
FARMACEUTICI, DAIICHI-SANKYO

Epidemiologia e Prevalenza

CARENFER

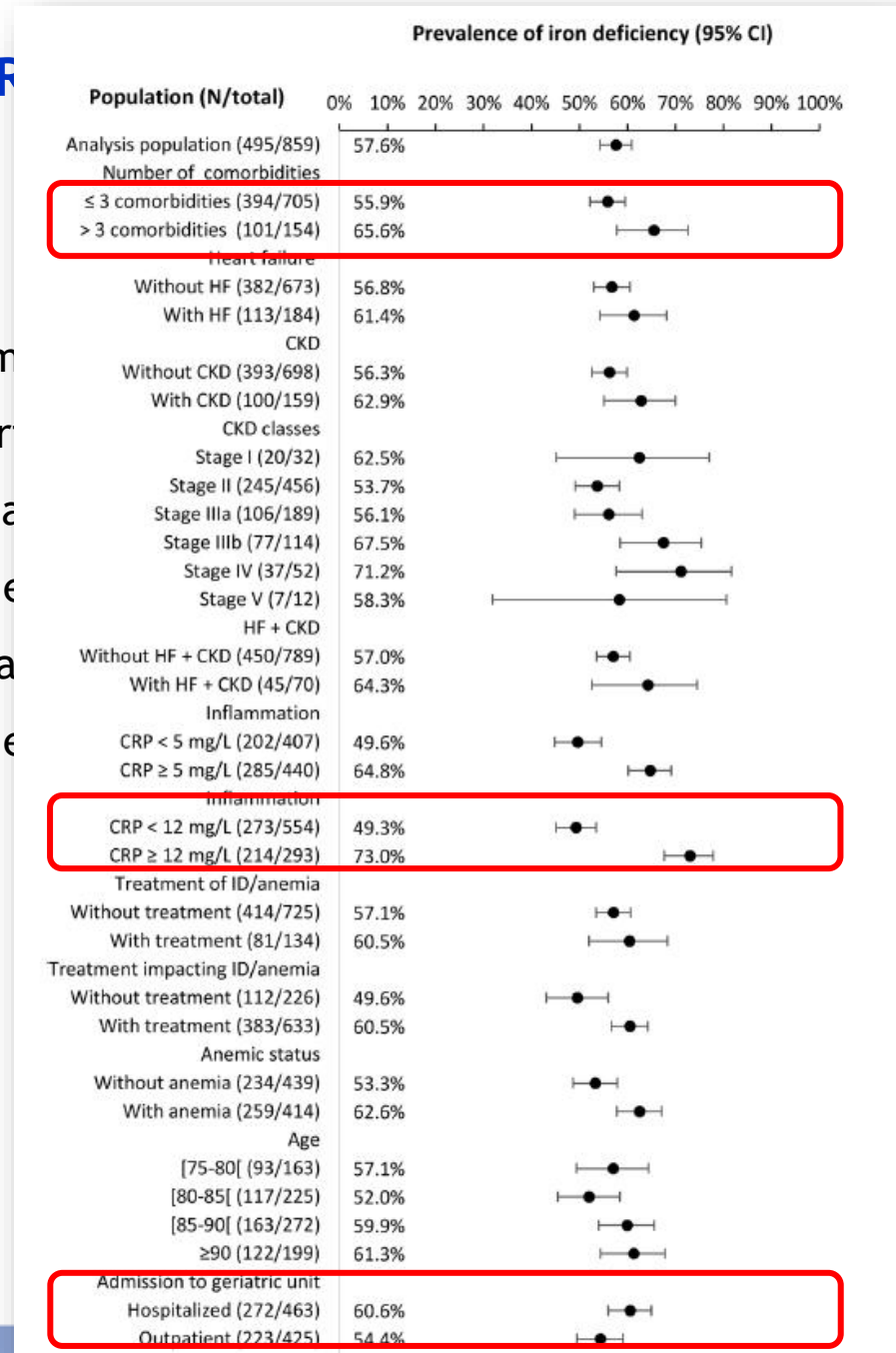
Table 1 Patient characteristics

Characteristics	N	Analysis population (N=888)
✓ ID prevalence 57.6% (95% CI, 54.3-60.9) in the whole cohort (62.6% in anemic and 53.3% in non-anemic pts; $p = 0.0062$).		
✓ ID was absolute in 56.2% and functional in 43.8%.		
✓ Higher ID prevalence in patients with >3 comorbidities (65.6% vs. 55.9%; $p = 0.0274$) and CRP ≥ 12 mg/L (73.0% vs. 49.3%; $p < 0.001$)		
✓ Higher prevalence in hospitalized patients (60.6%) than in outpatients (54.4%)		

Comorbidity was reported in almost all patients (95.2%), the main comorbidities were arterial hypertension (67.5%), diabetes (21.5%), heart failure (21.3%), ischemic heart disease (19.5%), CKD (18.7%) and cancer (10.0%).

Fougere B et al. BMC Ger 2024

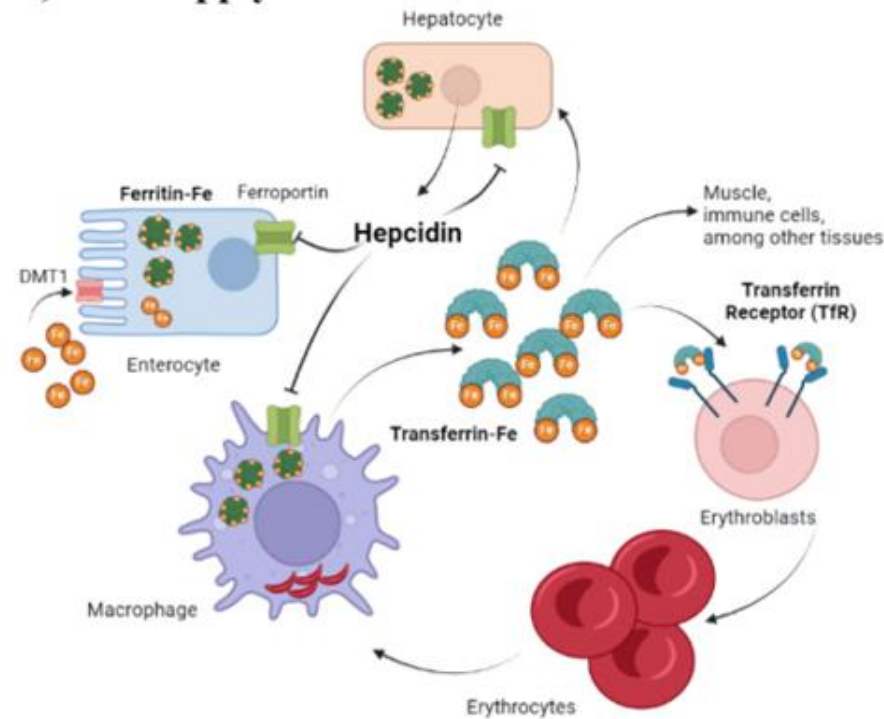
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Iron Metabolism Regulation

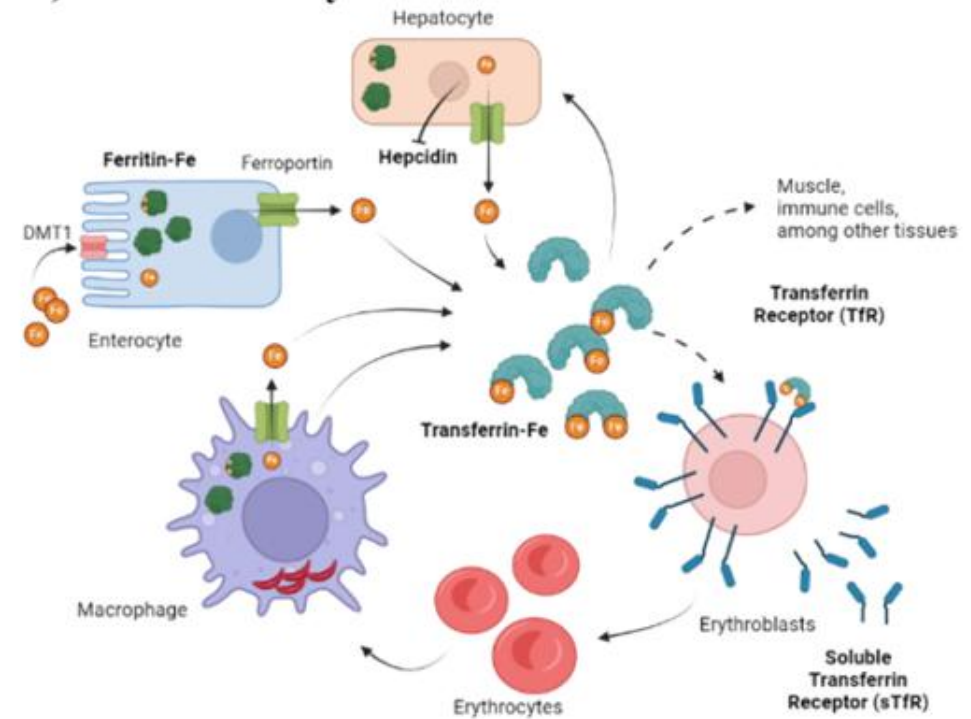
Iriarte-Gahete M et al. Blood Reviews 2024

A) Iron supply



- Aumento saturazione della transferrina
- Completamento depositi di ferritina in enterociti, macrofagi ed epatociti
- Rilascio di epcidina dagli epatociti
- Legame epcidina a ferroportina e blocco esportazione del Fe nel flusso sanguigno
- Accumulo di ferro nei macrofagi di milza e fegato
- Maggiore disponibilità di Fe per la sintesi di emoglobina

B) Iron deficiency



- Limitata disponibilità di ferro assorbito nel flusso sanguigno dagli enterociti attraverso la ferroportina
- Riduzione della saturazione della transferrina
- Inadeguato apporto ai tessuti
- Blocco trascrizione epcidina
- Sovraespressione TfR e secrezione monomero solubile (sTfR) dai precursori eritroidi e sistema monocito-macrofagico

Iron Deficiency assoluta e funzionale

Table 2 Common diseases associated with iron deficiency anemia in elderly patients

Chronic blood loss

- Esophagitis and gastritis
- Gastric and duodenal ulcer
- Esophageal and gastric cancer
- Large hiatal hernia
- Angiodysplasia
- Colonic cancer
- Colonic polyps
- Hematuria
- Uterine bleeding
- Drugs (non-steroidal inflammatory drugs, salicylates, anticoagulants)

Malabsorption

- Helicobacter pylori*
- Autoimmune gastritis
- Celiac disease
- Proton pump inhibitors

Adapted from Lopez *et al.*²³, Goddard *et al.*²⁶, Rockey and Cello⁵¹, Joosten *et al.*⁵² and Hershko and Camaschella⁵³ with permission.

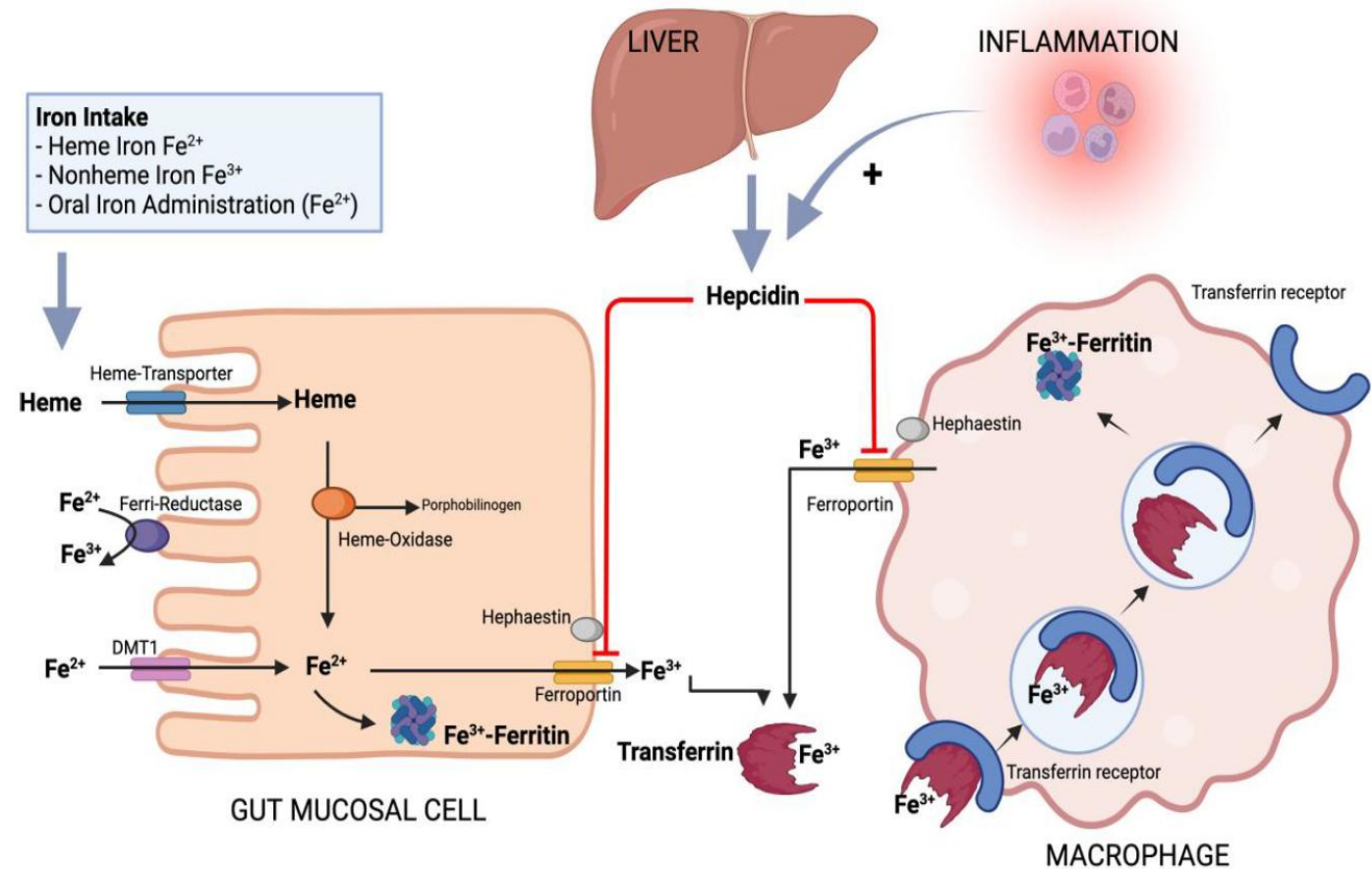
ID assoluta nel paziente anziano

- ✓ Ferritina sierica ≤ 100 ng/mL and
- ✓ TSAT $< 20\%$
- ✓ Soppressione produzione epcidina e degradazione ferroportina
- ✓ \uparrow assorbimento Fe a livello gastroduodenale ed esportazione di Fe dai macrofagi ed epatociti verso la circolazione

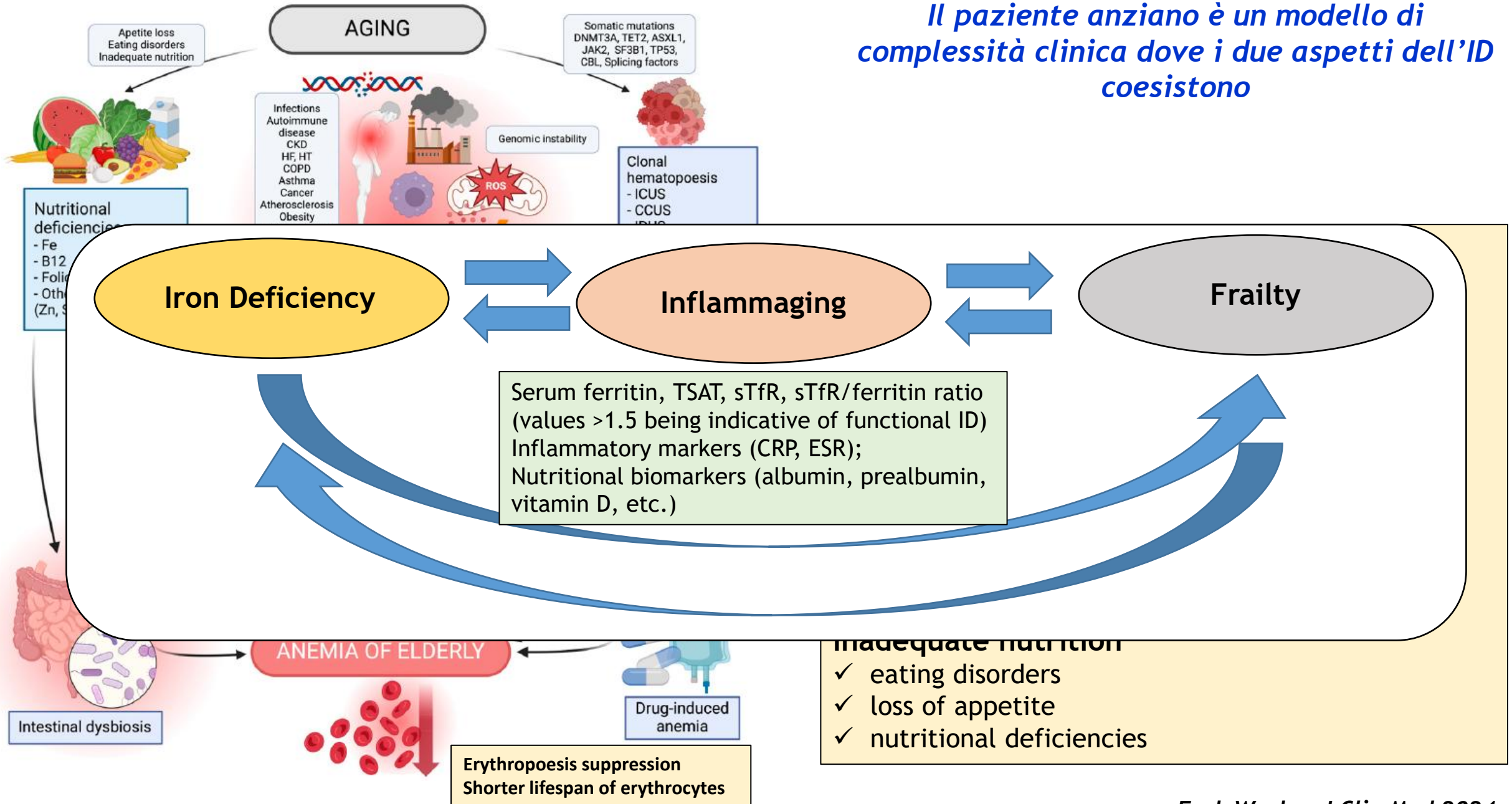
Marianela Iriarte-Gahete Blood reviews 2024
Camaschella C Blood reviews 2019
Joosten E. Geriatr Gerontol Int 2017

ID funzionale nel paziente anziano

- ✓ Ferritina sierica normale o elevata (100-300 ng/mL)
- ✓ TSAT <20%
- ✓ Riserve di ferro presenti ma non disponibili per l'eritropoiesi
- ✓ Elevati livelli di epcidina indotti da citochine infiammatorie (IL-6, IL-1 β) ed LPS
- ✓ Maggiore degradazione della ferroportina
- ✓ Ritenzione di Fe nei macrofagi del SRE
- ✓ Ridotto assorbimento gastroduodenale di Fe
- ✓ Ridotta biodisponibilità del Fe plasmatico
- ✓ Eritropoiesi ferro-ristretta



Il paziente anziano è un modello di complessità clinica dove i due aspetti dell'ID coesistono



Iron Deficiency e Fragilità una combinazione Pericolosa

Funzione Muscolare e Sarcopenia

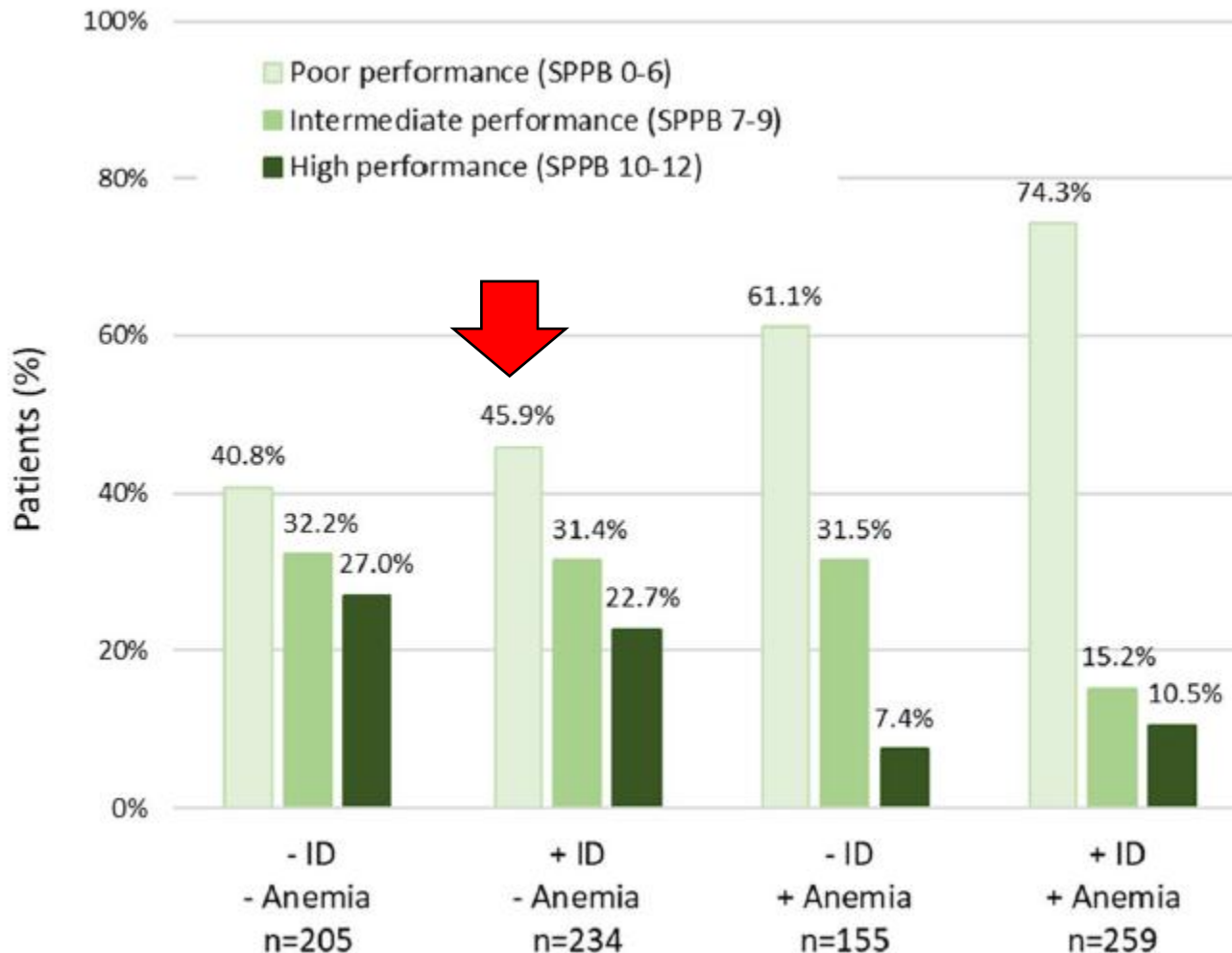
Funzione cognitiva

Sistema CV e Scompenso cardiaco

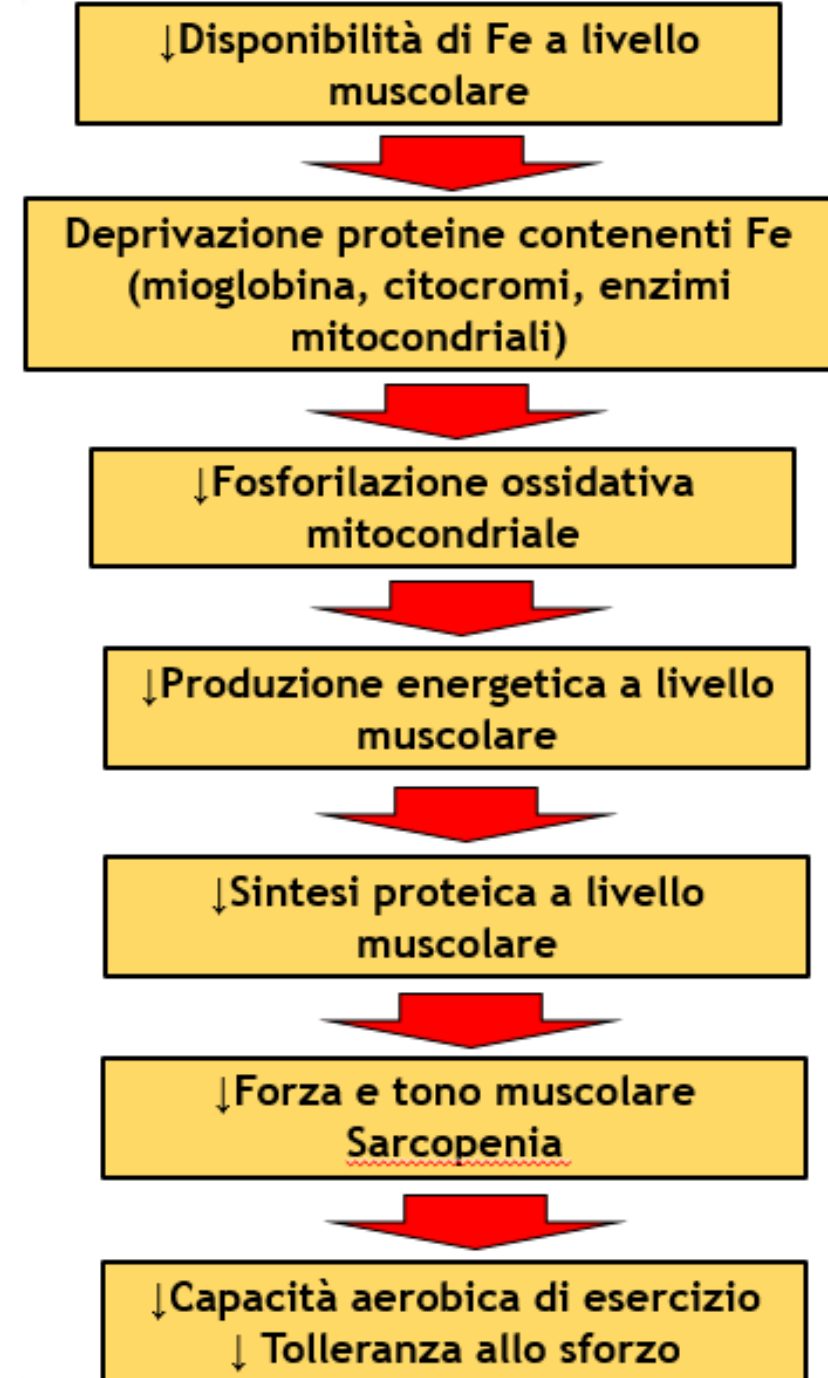
Performance fisica e rischio di
cadute

Sistema immunitario

Physical performance (SPPB score) of older patients according to iron deficiency (ID) and/or anemia



Fougere B et al. BMC Ger 2024



Serum iron level is independently associated with sarcopenia: a retrospective study

- ✓ 286 adult patients hospitalized between 2019 and 2021
- ✓ 117 diagnosed with sarcopenia
- ✓ serum iron, total iron binding capacity (TIBC), transferrin and TSAT measured

Correlation between Iron Status and sarcopenia-related indices

	Handgrip strength	6-m walk test	5-time chair stand test	Balance test	RSMI
Ferritin	0.080	0.031	0.044	0.065	0.134*
Serum iron	0.229**	- 0.200**	- 0.181**	- 0.177**	0.228**
TIBC	0.123*	- 0.134*	- 0.145*	- 0.135*	0.131*
TSAT	0.206**	- 0.100	- 0.124*	- 0.088	0.190**
Transferrin	0.157**	- 0.171**	- 0.177**	- 0.141*	0.119*

- ✓ Serum iron, TIBC, and transferrin levels decreased significantly in the sarcopenia group ($p < 0.05$)
- ✓ They were negatively associated with handgrip strength, relative skeletal muscle index (RSMI) and multiple test performances ($p < 0.05$)

Logistic Regression Model for prediction of Sarcopenia

Variable	Coefficient	OR (95% CI)	P
Sex, male vs female	1.296	3.65 (1.67–7.98)	0.001**
Age, > 65 years vs ≤ 65 years	1.687	5.4 (2.25–12.95)	<0.001***
BMI, > 24 kg/m ² vs ≤ 24 kg/m ²	- 1.799	0.17 (0.08–0.36)	<0.001***
Serum iron, > 10.95 μmol/L vs ≤ 10.95 μmol/L	- 0.942	0.39 (0.16–0.93)	0.034*

Table 4 Stepwise multiple regression analysis of risk factors associated with fatigue and functional status on admission and during hospital stay in total population.

	Beta coefficient	SE	p value
Fatigue			
Charlson Comorbidity Index	0.104	0.042	0.014
Iron deficiency or not	-0.534	0.227	0.019
Previous iron supplementation or not	0.061	0.192	0.971
Age	-0.074	0.237	0.269
Gender ^a	0.768	0.239	<0.001
C-reactive protein	0.093	0.264	0.173
SPPB on admission			
Charlson Comorbidity Index	0.030	0.453	0.651
Iron deficiency or not	-0.529	0.268	0.049
Previous iron supplementation or not	-0.063	0.789	0.331
Age	-0.067	0.018	0.297
Gender ^a	1.405	0.324	<0.001
C-reactive protein	-0.007	0.863	0.916
Handgrip strength	0.104	0.018	<0.001
Barthel Index on admission			
Charlson Comorbidity Index	-0.031	0.455	0.649
Iron deficiency or not	3.913	1.797	0.031
Previous iron supplementation or not	-0.097	0.416	0.158
Age	-0.068	0.992	0.322
Gender	0.152	0.916	0.057
C-reactive protein	-0.107	0.575	0.117
Handgrip strength	0.242	0.116	0.039
knee extension strength	0.065	0.817	0.415

Table 4 Stepwise multiple regression analysis of risk factors associated with fatigue and functional status on admission and during hospital stay in total population.

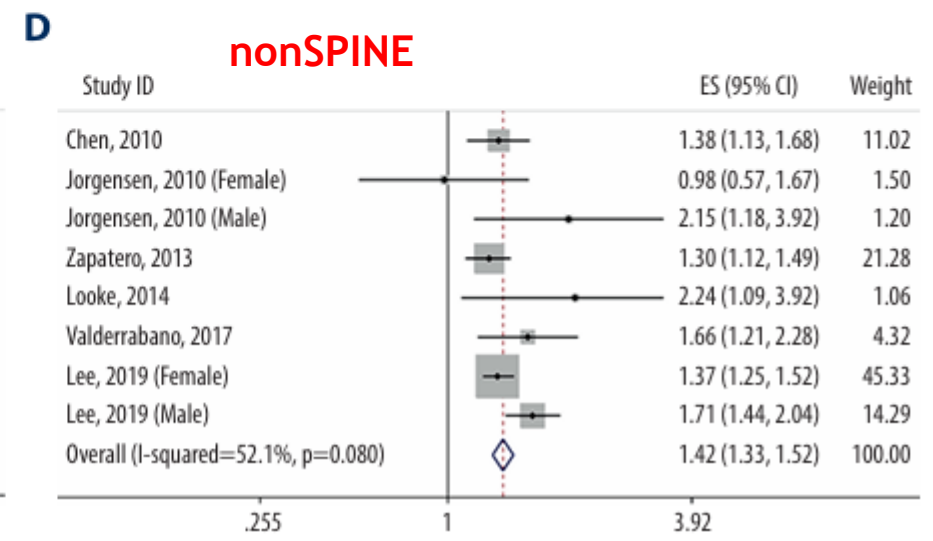
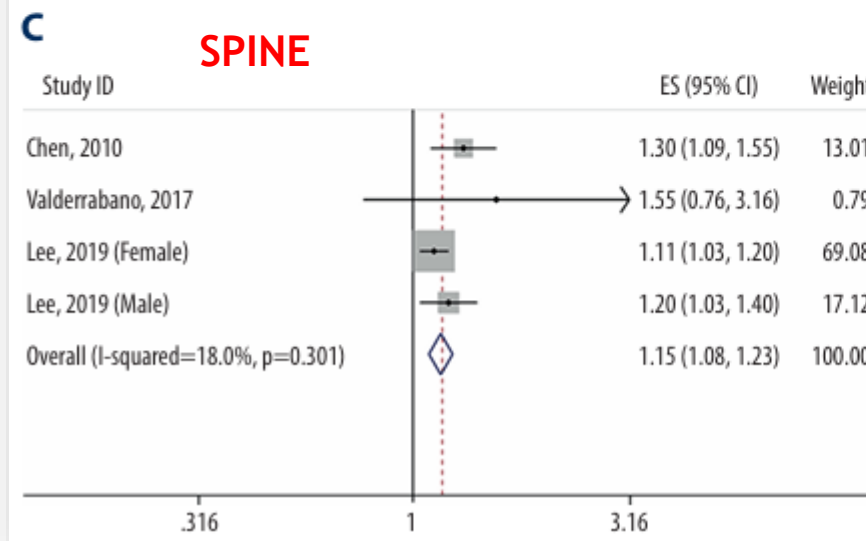
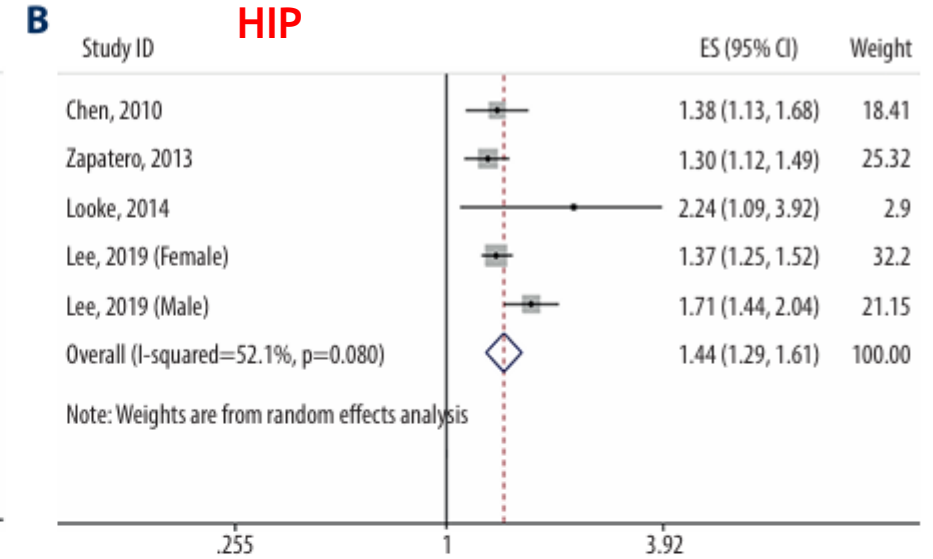
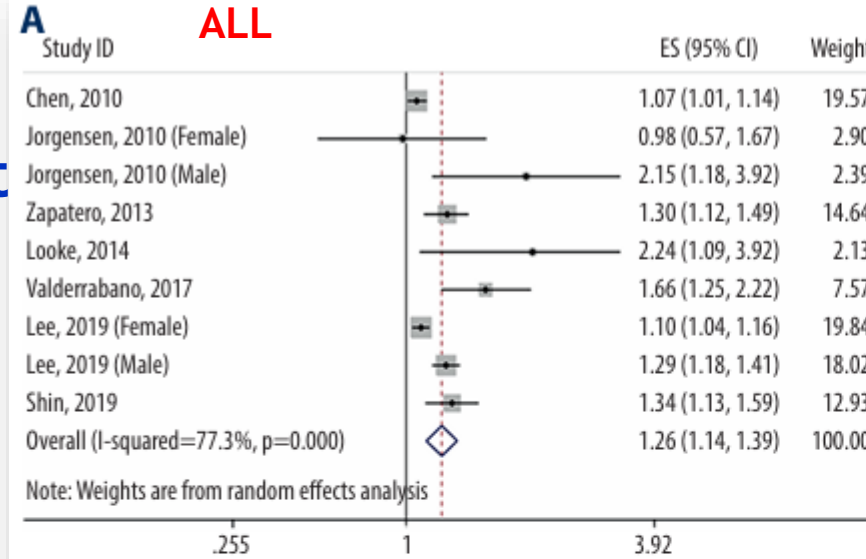
	Beta coefficient	SE	p value
Changes in Barthel Index			
Charlson Comorbidity Index	-0.872	0.336	0.010
Iron deficiency or not	-3.917	1.830	0.034
Previous iron supplementation or not	0.045	0.657	0.512
Actual iron supplementation or not	-0.042	0.552	0.581
Age	0.005	0.071	0.944
Gender	0.113	0.594	0.113
C-reactive protein	-0.109	0.565	0.119
Changes in handgrip strength	0.641	0.274	0.020
Changes in knee extension strength	0.099	0.402	0.163
Changes in knee extension strength			
Charlson Comorbidity Index	-0.065	0.925	0.356
Iron deficiency or not	-0.052	0.680	0.498
Previous iron supplementation or not	-0.108	0.514	0.132
Actual iron supplementation or not	1.150	0.495	0.021
Age	0.047	0.668	0.505
Gender	0.124	0.730	0.085
C-reactive protein	0.116	0.657	0.099

TSAT (%)	20.8 ± 3.8	11.0 ± 3.2	27.6 ± 11.9***
Hb (g/dl)			
Male	11.8 ± 2.1	11.1 ± 1.9	12.4 ± 2.1**
Female	11.3 ± 1.7	10.7 ± 1.5	11.7 ± 1.7***
Length of hospital stay	16 (14-21)	14 (14-21)	18 (14-20)

Iron Deficiency e Fratture da Fragilità

L'Anemia è un predittore

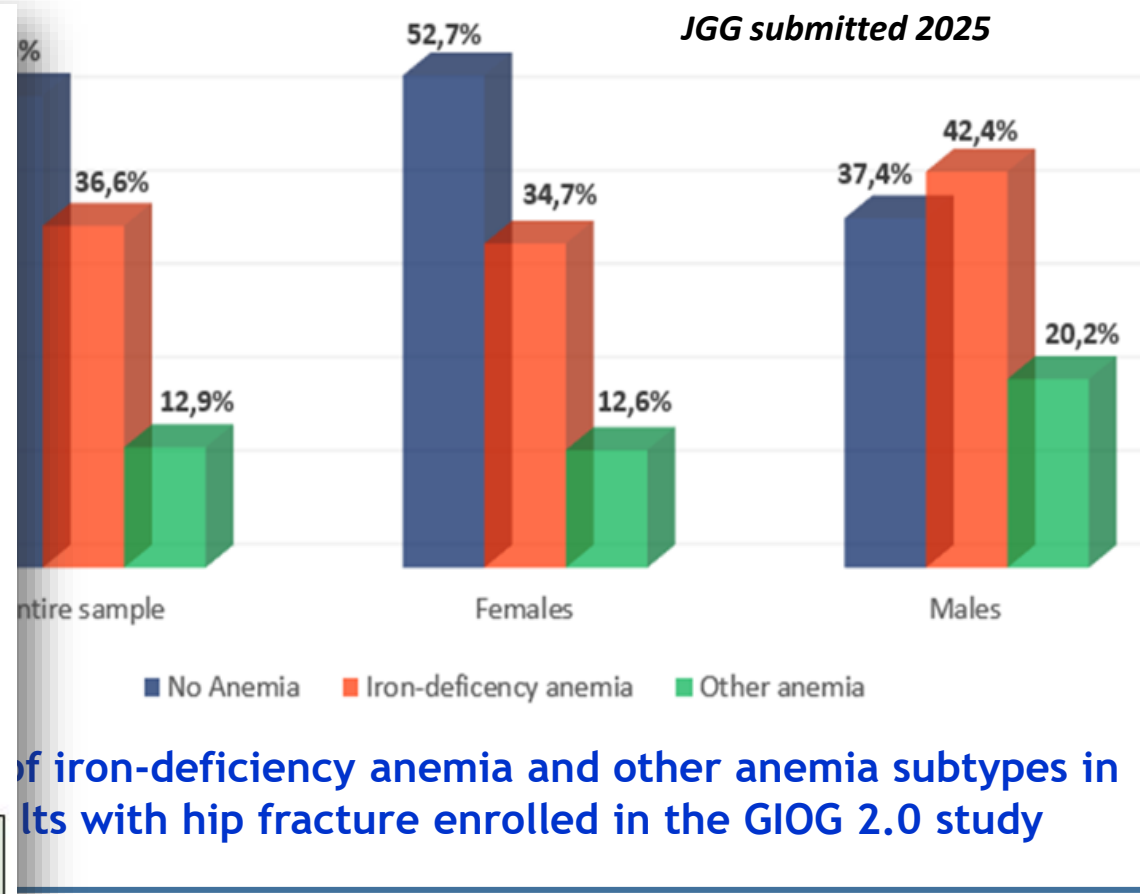
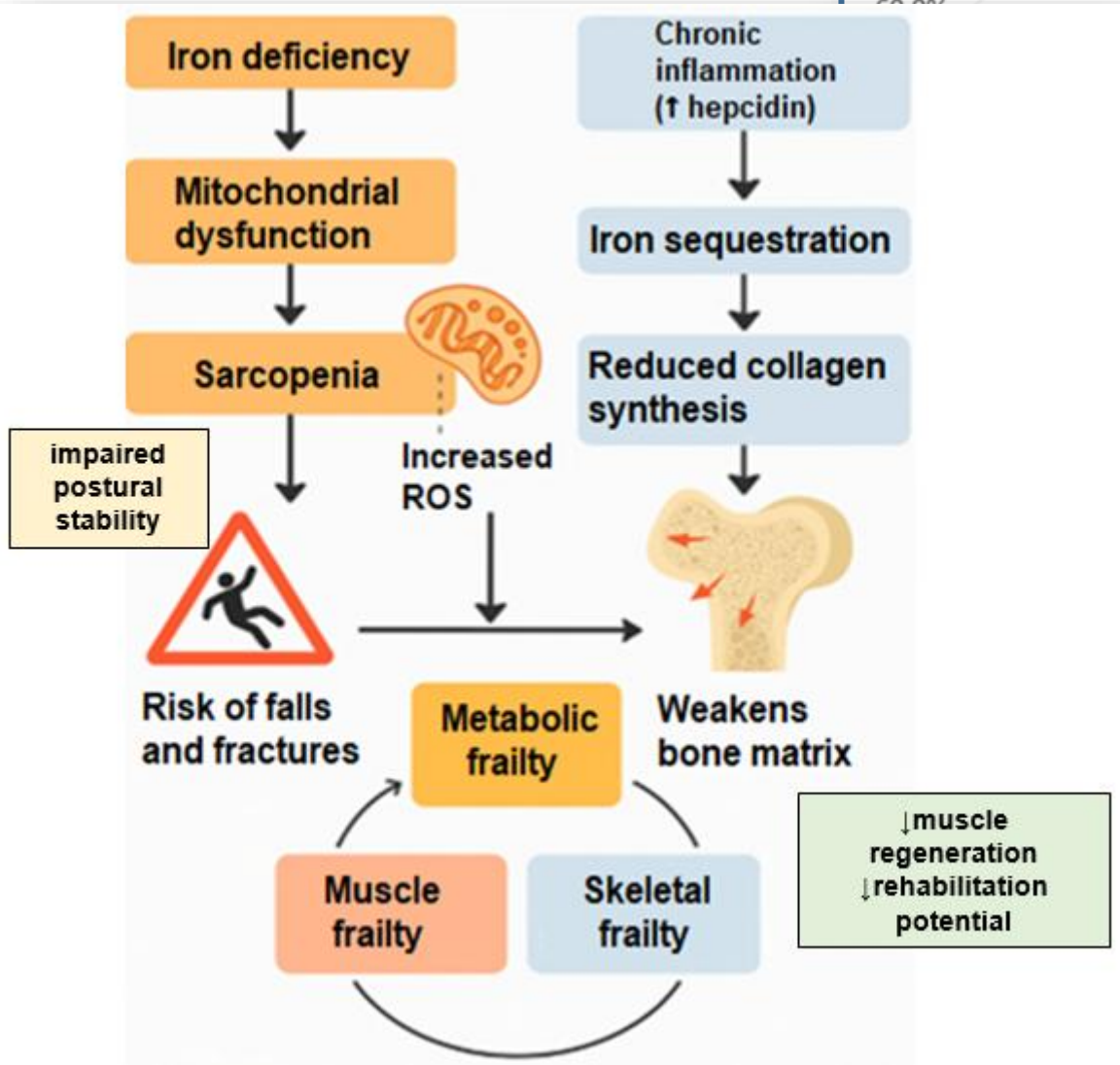
- To estimate the association between anemia and fracture incidence via a systematic review and meta-analysis
- Males with anemia had a 1.51-fold higher fracture risk, females had a 1.09-fold higher fracture risk.



Three-year National report from the Gruppo Italiano di Orto geriatria (GIOG) in the management of hip-fractured patients

Aging Clin Exp Res 2020

- more than 1/3 of hip fracture patients have low ferritin
- these patients have a 2-fold incidence of mortality in the first 30 days
- exploratory cohort studies show that independent risk factors are the following:



Association of the European Cardiology position paper on frailty with heart failure

Short Heart Failure Frailty Score (S-HFFS)

CLINICAL DOMAIN:

1. Does the patient have the following comorbidities?
2. Has the patients had an unintentional weight loss (> 5% of weight) in the past 6 months
3. Has the patient had ≥ 2 falls over the past 12 months?

FUNCTIONAL DOMAIN:

4. Does the patient have any limitations in:
 - a. toileting/bathing?
 - b. dressing?
5. Does the patient have any limitation in their mobility?
6. 30-second chair stand test result

PSYCHO-COGNITIVE DOMAIN:

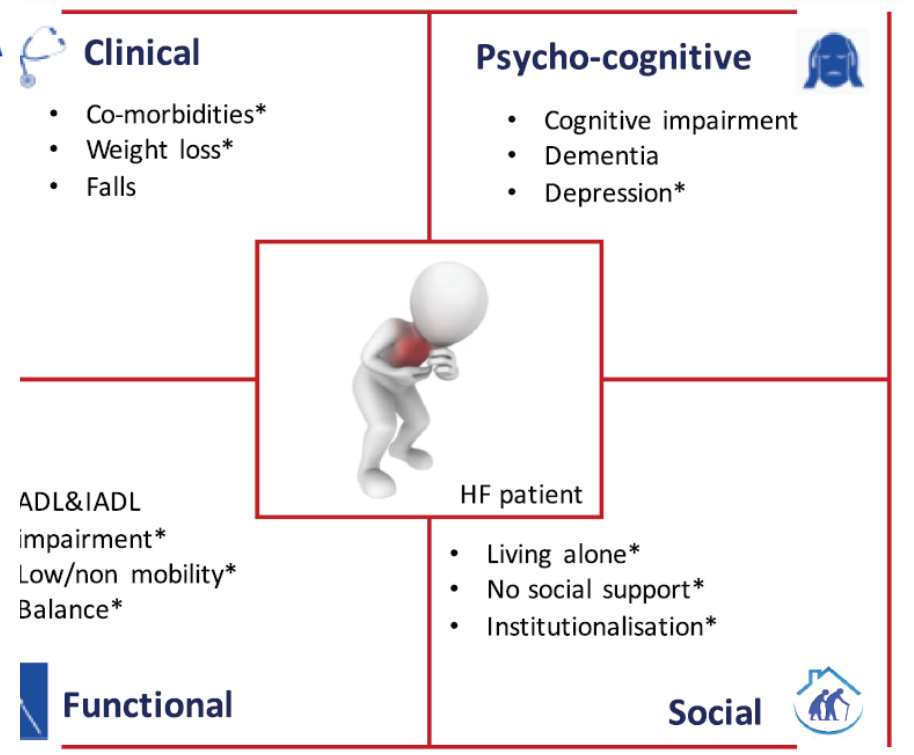
7. Does the patient have a diagnosis or treatment for dementia
8. Does the patient have a diagnosis or treatment for depression

SOCIAL DOMAIN:

9. Where the patient live?
10. Does the patient have the availability of someone (family/friends/social support/carer), if needed

Heart failure: A paper developed by Delphi

, Nancy M. Albert⁵,
 er⁹, Stefan D. Anker¹⁰,
 oks¹⁵, Miguel Camafort¹⁶,
 Wolfram Doehner²¹,
 Gomez-Mesa²⁵,
 Kamlesh Khunti²⁹,
 33, Giuseppe Maltese^{34,35},
 imo Piepoli^{40,41},
 Angela Sciacqua⁴⁶,
 Anna Strömberg⁵¹,
 an⁵⁵, Maurizio Volterrani¹,
 cco Metra⁶¹ and



- 4x-fold increased risk to become frail and frailty may occur in up to 45% of the HF patients and its detection is crucial
- It is associated with increased risk of all-cause mortality, all-cause readmissions and HF readmissions among older HF patients

**Additional burden
failure patients be
anaemia syndrome
BIOSTAT-CHF stu**

Isolated ID remained an independent predictor of all-cause mortality [1.53 (1.03-2.28), $p=0.03$] as well as combined outcomes [1.30 (1.05-1.70), $p=0.045$] (incidence of hospitalizations and/or mortality) while isolated anaemia and CKD were only associated with all-cause mortality after adjustments for the BIOSTAT-CHF risk models

Having ID, either alone or on top of anaemia and/or CKD, was associated with a lower overall summary KCCQ score, an impaired 6-min walk test During a median follow-up of 21.2 (IQR 16-27) months, 899 (41.7%) patients died or were hospitalized for HF.

2151 patients with HF from the BIOSTAT-CHF cohort stratified by (TSAT <20%), anaemia (WHO) and/or CKD

Table 2 Results of the Cox proportional hazards models for the association between the studied syndromes with all-cause mortality and the combined endpoint

Conditions (no. of patients)	All-cause mortality				Combined endpoint			
	Model A		Model B		Model A		Model B	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
No comorbidities (398)	1 [Reference]							
Isolated ID (430)	1.66 (1.12–2.46)	0.011	1.53 (1.03–2.28)	0.03	1.43 (1.10–1.86)	0.006	1.30 (1.05–1.70)	0.045
Isolated anaemia (76)	2.3 (1.28–4.12)	0.005	1.90 (1.06–3.41)	0.02	1.63 (1.06–2.51)	0.023	1.4 (0.91–2.15)	0.11
Isolated CKD (209)	2.53 (1.66–3.86)	<0.001	1.66 (1.08–2.55)	0.02	1.60 (1.18–2.16)	<0.002	1.18 (0.87–1.61)	0.27
IDA (231)	3.33 (2.24–4.94)	<0.001	2.58 (1.73–3.85)	<0.001	2.36 (1.79–3.12)	<0.001	1.71 (1.29–2.26)	<0.001
CRIDS (336)	3.08 (2.12–4.48)	<0.001	1.74 (1.18–2.58)	0.004	2.6 (2.06–3.4)	<0.001	1.67 (1.29–2.17)	<0.001
CRAS (106)	5.25 (3.39–8.12)	<0.001	2.62 (1.66–4.14)	<0.001	3.3 (2.39–4.56)	<0.001	1.87 (1.34–2.61)	<0.001
CRAIDS (365)	4.93 (3.46–7.03)	<0.001	2.42 (1.66–3.53)	<0.001	3.62 (2.84–4.6)	<0.001	1.94 (1.50–2.51)	<0.001

Model A = univariable analysis. Model B = adjusted for BIOSTAT-CHF models, but without haemoglobin.²³

CI, confidence interval; CKD, chronic kidney disease; CRAIDS, cardio-renal anaemia iron deficiency syndrome; CRAS, cardio-renal anaemia syndrome; CRIDS, cardio-renal iron deficiency syndrome; HR, hazard ratio; ID, iron deficiency; IDA, iron deficiency anaemia.

OPTimal PHARMacological therapy for patients with heart failure: Rationale and design

Riccardo T

Background HF medical therapy

	HFrEF	HFmrEF	HFpEF
<i>Background HF medical therapy</i>			
B-blockers	632 (91)	213 (87)	151 (75)
ACEi/ARB	125 (18)	82 (34)	100 (50)
ARNI	430 (61.8)	132 (53.6)	100 (50)
• <50%	45.2%	37.1%	37.5%
• 50 to <100%	30.4%	37.9%	37.5%
• ≥ 100%	24.4%	25%	25%
MRA	507 (72.7)	164 (66.3)	100 (50)
• <50%	55.9%	67.7%	67.5%
• 50 to <100%	35.8%	27.4%	27.5%
• ≥ 100%	8.3%	4.9%	4.9%
SGLT2i	455 (65.3)	139 (55.2)	100 (50)
• Dapagliflozin, %	72.2	82.0	82.0
• Empagliflozin, %	27.8	18.0	18.0
Diuretics	100 (71.4)	100 (50)	100 (50)
IV iron in the last 6 months	21 (3.1)	6 (2.3)	6 (3.0)
Potassium binders	20 (2.9)	7 (2.7)	7 (3.5)
Ivabradine	48 (7.0)	16 (6.3)	16 (8.0)

Data are presented as n (%)

✓ A prospective, multicenter, observational study enrolling adult patients with symptomatic HF, regardless of EF, across 32 Italian HF centers

Recommendation Table 5 — Recommendations for the management of iron deficiency in patients with heart failure

LLGG ESC 2023

Recommendations	Class ^a	Level ^b
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life. ^{c 12,41,47–49}	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization. ^{c 12,41,43–46}	IIa	A

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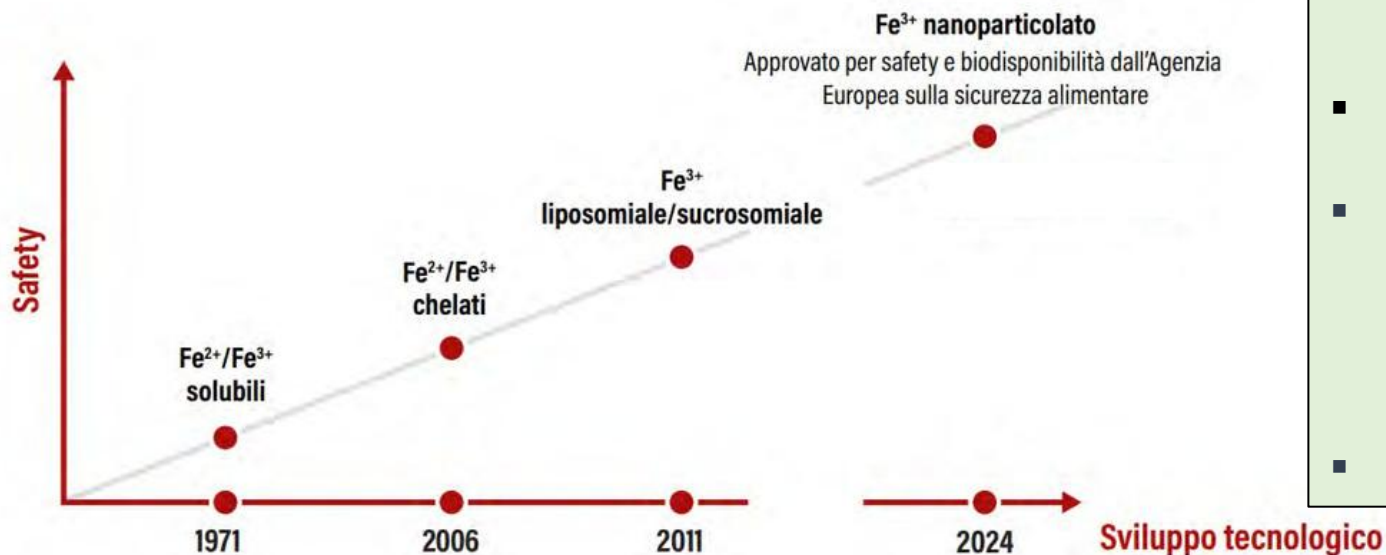
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Strategie Terapeutiche (1)

- Ferro orale prima linea terapeutica, ma i Sali ferrosi bivalenti tradizionali (solfato, fumarato, gluconato) hanno limitata efficacia e scarsa tollerabilità gastrointestinale negli anziani con malassorbimento, multimorbidità e infiammazione cronica
- Introduzione di formulazioni orali di nuova generazione (idrossido di ferro adipato tartrato IHAT, polimaltoso ferrico, ferro liposomiale, sucrosomiale), assorbimento meno dipendente da DMT1 e meno influenzato dall'epcidina

L'EVOLUZIONE TECNOLOGICA DELLA SAFETY DEL FERRO



- IHAT è Fe³⁺ nanoparticolato, con un core ferritina-mimetico, che lo rende altamente biodisponibile, senza produrre radicali liberi
- Combina idrossido di ferro con acido adipico (adipato) e acido tartarico (tartrato), creando una molecola stabile
- IHAT essendo un analogo sintetico della ferritina viene assorbito esclusivamente con meccanismo endocitosico, non determinando danni ossido-riduttivi alla mucosa intestinale e non alterando il microbiota
- Terapia a lungo termine, terapia domiciliare

Strategie Terapeutiche (2)

- Ferro endovena: Provata efficacia FCM nella popolazione geriatrica con ID anemia in condizioni di fragilità (HF, CKD stadi 3-5 in ESA), dimostrati miglioramento funzionale, dell'ADL, mobilizzazione precoce, durata degenza
- Superamento dei limiti dell'assorbimento della formulazione orale
- Ripristino rapido del bilancio del ferro in condizioni di maggiore urgenza clinica
- Buon profilo di tollerabilità e sicurezza

Table 1. Clinical evidence on iron supplementation in older adults with fragility fractures and safety of intravenous therapy

Study	Design	Population	Intervention	Main results	Adverse events
Tagliafico et al., 2021	Prospective cohort	≥85 years	IV FCM (500–1000 mg)	+1.7 g/dL Hb in 4 weeks	No serious events
Muñoz et al., 2017	European multicenter	Surgical older adults	Preoperative FCM	↓ transfusions, ↓ LOS average 2-3 days	<3% mild reactions
Haddad et al., 2023	Geriatric cohort	≥75 years	Postoperative FCM	↑ Hb, ↓ delirium	Well tolerated
Bager et al., 2022	RCT, n=172	Hip fractures	FCM vs control	↓ length of stay	No significant events

Limiti

- ✓ Complessità organizzativa
- ✓ Reazioni avverse sistemiche
- ✓ Alti costi
- ✓ Ipofosfemia (CMF)
- ✓ Bassa fattibilità nella popolazione fragile e in alcuni ambienti di cura

Erythropoietic response after intravenous iron in patients with heart failure and reduced ejection fraction with and without background treatment with sodium-glucose cotransporter 2 inhibitors

Association of sodium-glucose

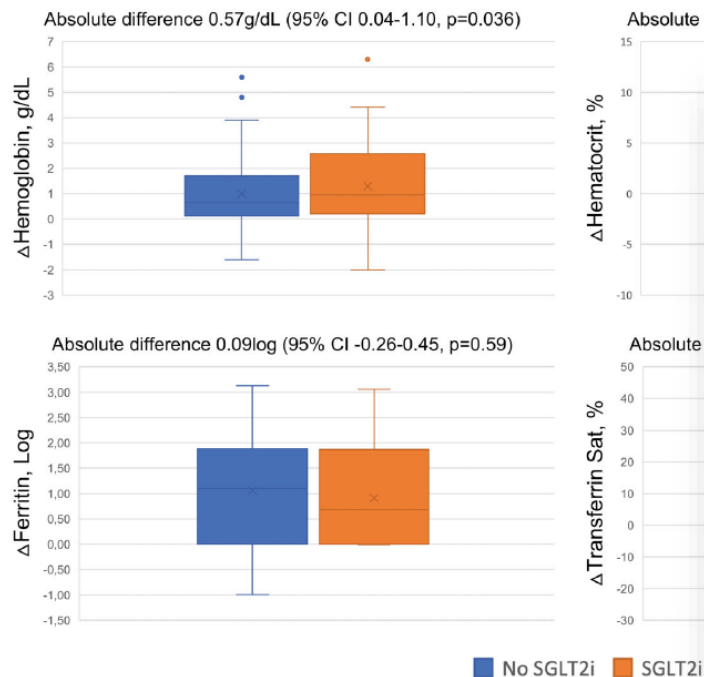
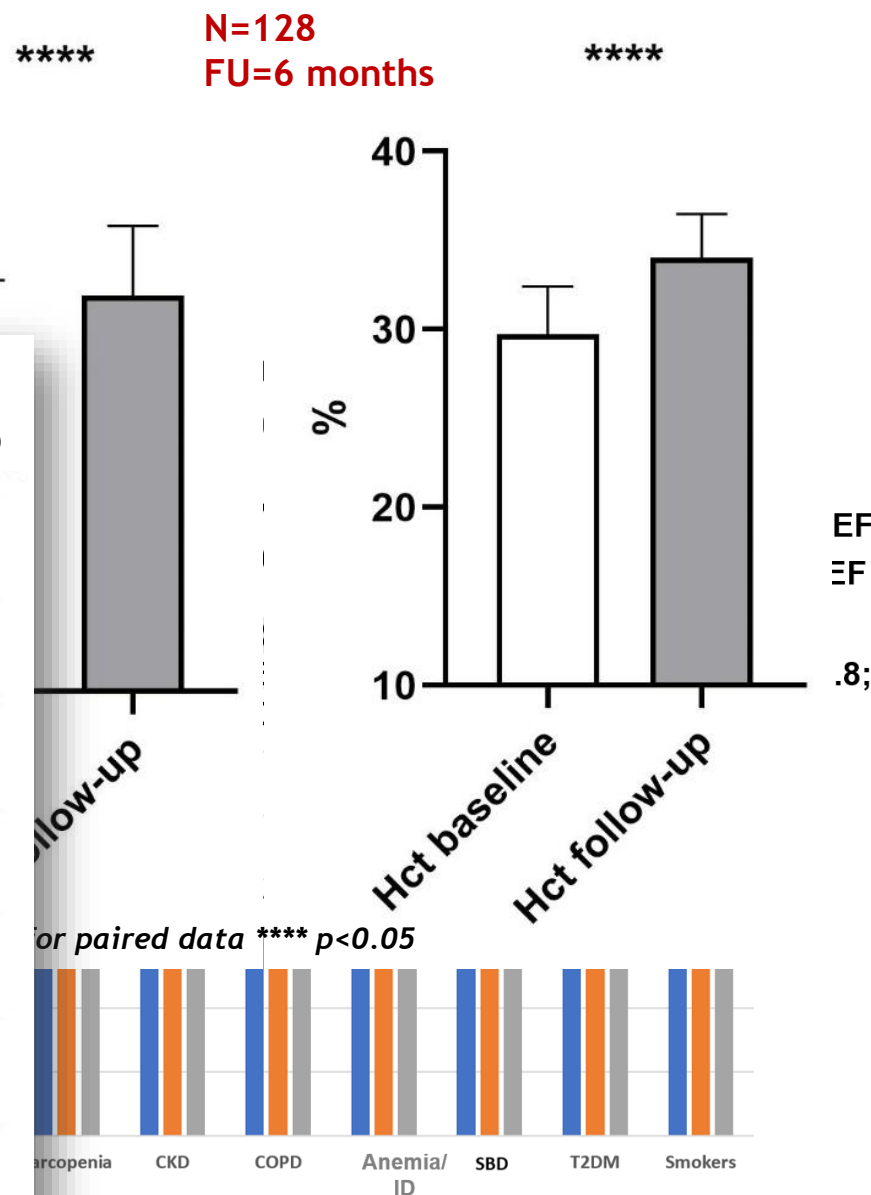
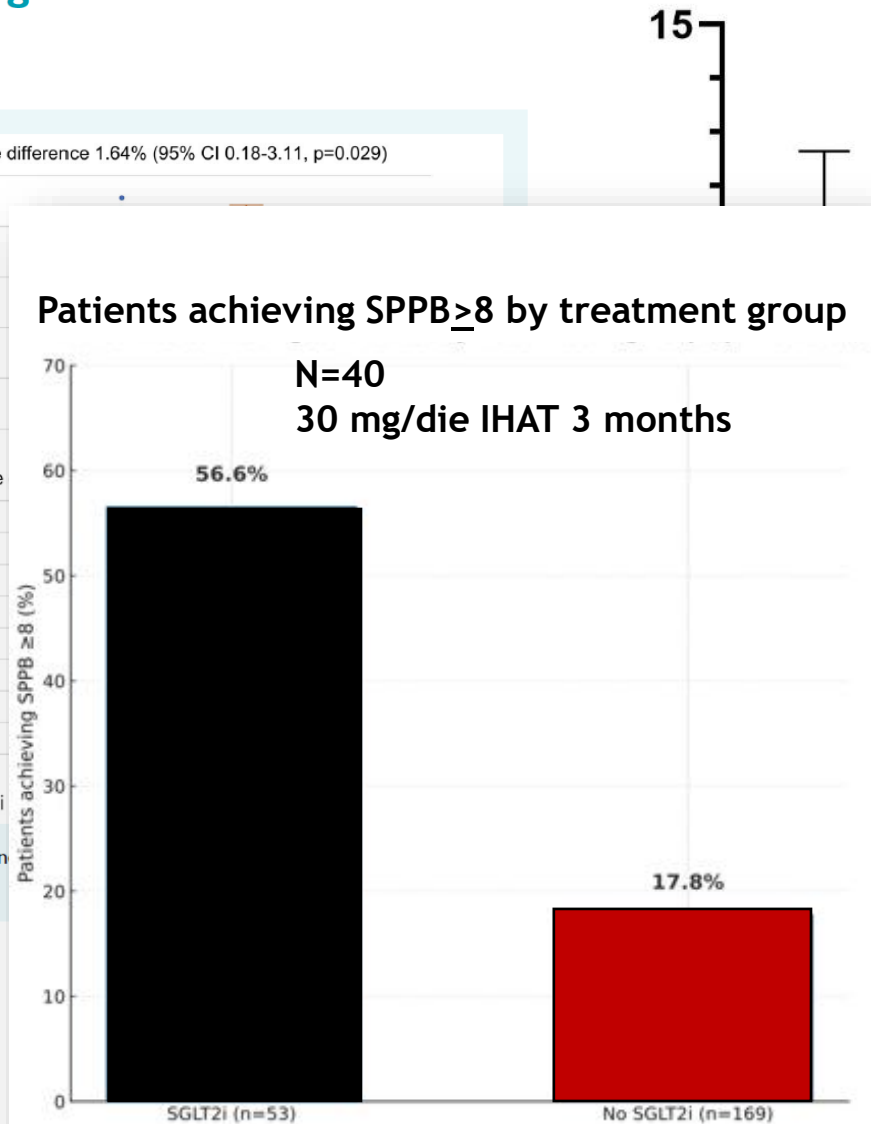


Figure 1 Change in haemoglobin, haematocrit and iron biomarkers post-intravenous iron in patients with heart failure and reduced ejection fraction with and without background treatment with sodium-glucose cotransporter 2 inhibitor (SGLT2i) use at baseline. CI, confidence interval.

Marques P et al. EJHF 2023



G., Sciacqua A., et al., Eur J HF 2024

Considerazioni finali...il punto di vista geriatrico

- ❖ La valutazione della condizione di Iron deficiency/anemia (Hb, ferritina, TSAT, sTfR) contribuisce alla comparsa e progressione della fragilità, pochissimi studi mirati
- ❖ Deve essere parte integrante del processo di cura del paziente anziano soprattutto in condizioni di fragilità, poichè espressione della aumentata vulnerabilità sistemica con implicazioni importanti sul recupero funzionale e sulla prognosi nei differenti settings
- ❖ Differenziare tra ID assoluta e funzionale e identificare le cause trattabili (perdita, deficit nutrizionali, etc.)
- ❖ Pianificare il trattamento dell'ID, ottimizzare la disponibilità del ferro e considerare benefici (QoL, sintomi) e rischi soprattutto nei fragili
- ❖ Considerare target personalizzati in accordo all'età, comorbilità, fragilità e aspettativa di vita (evitare dosaggi troppo elevati, accettare il compromesso di una lieve anemia, prediligere il miglioramento dei sintomi ottenibili con modesti incrementi dell'assetto marziale, le nuove formulazioni di ferro valida alternativa al ferro e.v.)
- ❖ Coinvolgimento dei care-givers nelle terapie croniche soprattutto orali



UMG
Dubium sapientiae initium

Invecchiare non è una malattia è un privilegio

