I. INTERNÍ
KARDIOANGIOLOGICKÁ
KLINIKA LF MU A FNUSA

FAKULTNÍ
NEMOCNICE
U SV. ANNY
V BRNĚ

MUNI
MED

MARKERS OF IRON DEFICIENCY IN PATIENTS WITH HEART FAILURE DECOMPENSATION

M. Bakošová, J. Godava, E. Ozábalová, H. Poloczková, T. Honek, P. Hude, J. Máchal, H. Bedáňová, J. Frantová, J. Horák, P. Němec, J. Krejčí

IRON DEFICIENCY - A COMMON COMORBIDITY IN PATIENTS WITH HEART FAILURE

Iron deficiency (ID) occurs in 40% to 50% of patients with chronic heart failure and up to 80% of patients with acute heart failure.

ID worsens heart failure syndrome by affecting energy metabolism in myocardium and skeletal muscle, oxidation-reduction balance and contractile function.

There are several reasons: inflammation, neurohormonal activation, use of antiplatelet drugs, congestion in the GIT, chronic kidney disease...

ID worsens functional status and performance, is associated with a higher degree of negative remodeling, progression of HF and a higher risk of hospitalization for HF

NEWS IN DIAGNOSE IN ESC GUIDELINES UPDATE

Screening and treatment of ID in patients with heart failure by intravenous administration of ferric carboxymaltose is recommended by the Guidelines for Diagnosis and Treatment of HF since 2016.

> Indication was extended for HFmrEF in patients after acute HF decompensation in 2021.

> The definition of ID was based on ferritin and T-sat values.

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.[720,722,724]	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.[512]	IIa	B

1_Sean P. Murphy, Inflammation in Heart Failure: JACC State-of-the-Art Review, Journal of the American College of Cardiology, 2020

NEWS IN DIAGNOSE IN ESC GUIDELINES UPDATE

According to the 2023 Update of the Guidelines
> indication for HFmrEF regardless of previous cardiac decompensation
> ID was defined as T-sat < 20% OR ferritin < 100 ng/ml
> level of evidence for treatment was up-graded to A

T-sat based orientation is now preferred because inflammation is present in heart failure[1] - and ferritin is an acute phase parameter that may be elevated in inflammation.
On the other hand, it looks like that low ferritin may not always be associated with true iron deficiency.

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

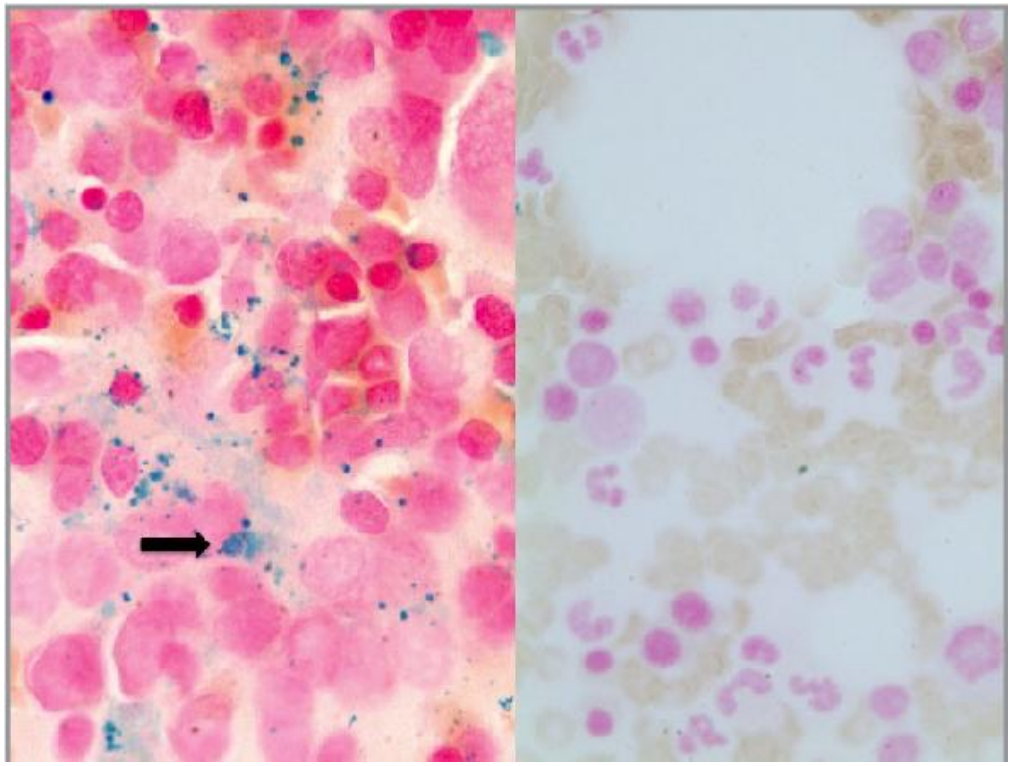
1_Sean P. Murphy, Inflammation in Heart Failure: JACC State-of-the-Art Review, Journal of the American College of Cardiology, 2020

LET´S TALK ABOUT T-SAT

Studies on which ESC Guidelines 2021 are defined, were based on classic diagnostic criteria (ferritin <100ug/L or 100 – 299, if T-sat < 20%)

Studies showed that patients with HF who meet definition with a low serum ferritin level but T-sat of more than 20% may not exhibit ID on bone marrow staining and have a lower risk of hospitalization for HF.[2]

Analyses from previous trials suggested that intravenous iron did not have a treatment effect in patients with a transferrin saturation of more than 20%.[3,4,5]



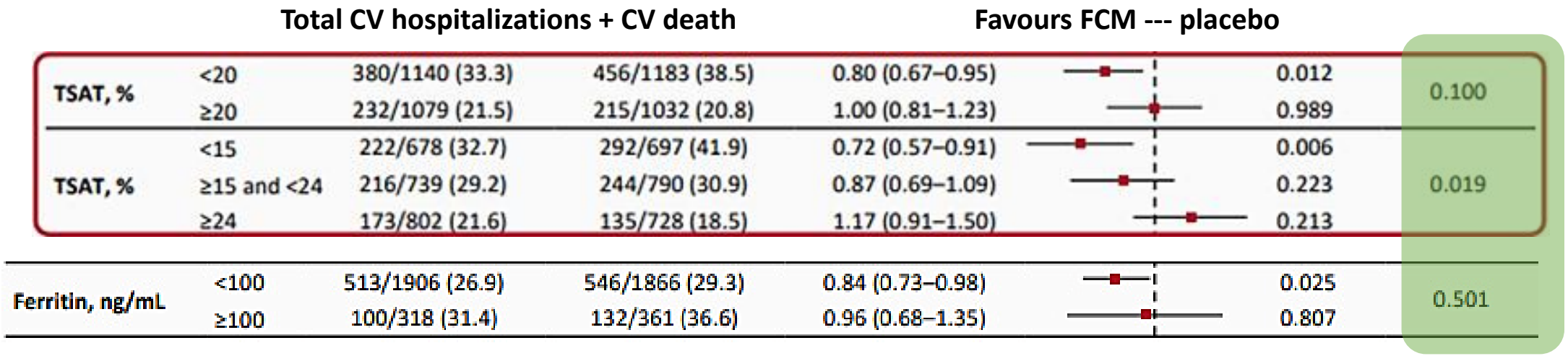
2_Grote Beverborg N, Klip IT, Meijers WC, Circ Heart Fail 2018
3_Martens, Mullens, NEJM, 2023
4_Anker SD, Eur J Heart Fail 2018

T-SAT IN TRIALS

- Comparing AFFIRM-AHF (2021) and IRONMAN (2022) with the latest HEART-FID study (2023), there are more patients with low ferritin but higher, i.e. normal T-sat, who did not benefit so much from iron carboxymaltose.[3]

trial	HEART-FID (2023)	AFFIRM-AHF (2021)	IRONMAN (2022)
T-sat (median)	23,9%	15,2%	15%

- According to subgroup analysis from HEART-FID, low T-sat appears to be a more important predictor of i.v. iron treatment effect than low ferritin alone (without low T-sat)

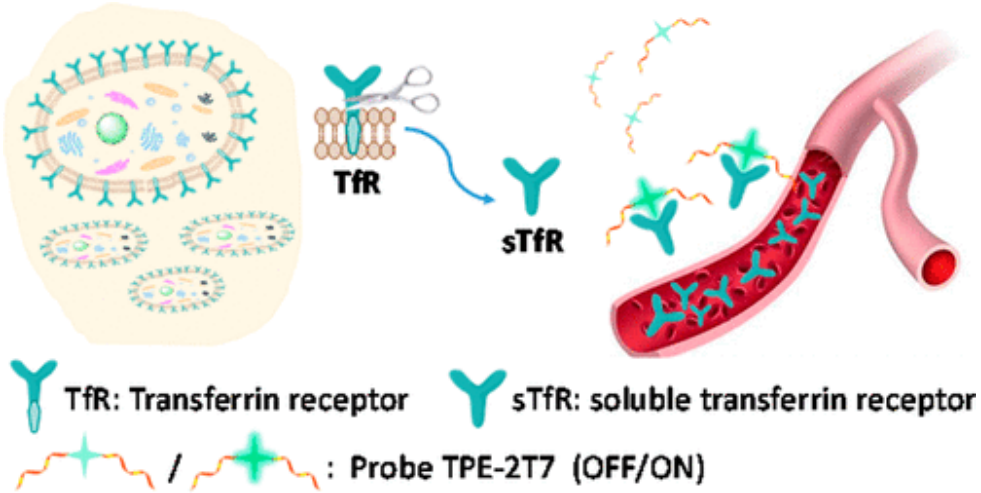


OTHER PARAMETER TO EXPLORE: SOLUBLE TRANSFERRIN RECEPTOR (sTfR)

sTfR is a sensitive marker of ID, higher sTfR mean higher cell „hunger“ for iron

Expression of the sTfR on red blood cell precursors increases as a response to depleted iron

Because sTfR is insensitive to inflammation, it can detect ID in patients with preexisting inflammatory states.



sTfR - WHAT DO WE KNOW ABOUT IT?

Studies are still ongoing to define a cut off value for sTfR.

According to a recent study of 1,236 patients, elevated sTfR (cut-off defined in the study as >1.63 mg/L) was associated with worse exercise tolerance in patients who had normal values of other commonly used iron metabolism parameters.[6]

In current recommendation for the use of sTfR for ID detection in patients with inflammatory conditions, a cut-off > 1.78 mg/l is appropriate, as well as a combination of sTfR and ferritin (sTfR/ferritin index)[7]

6_Ras-Jiménez, JPM, 2023 7_Lifelinelaboratory.com, 2023

STUDY AIM, METHODS, POPULATION

Objective: to compare diagnostic parameters of ID in groups of patients with heart failure according to their circulatory compensation

Method: collecting ID parameters including sTfR

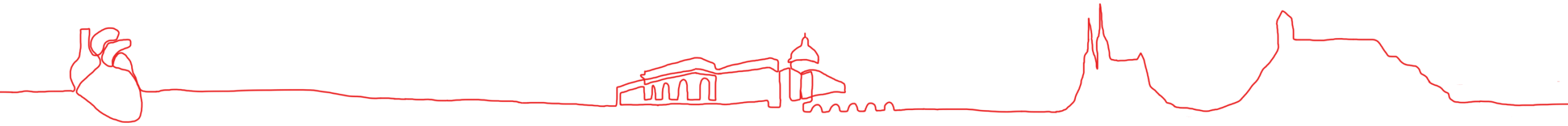
Compare ID parameters of patients with acute decompensation of HF and stable outpatients

98 pacients

- Stable outpatients (54)
- Hospitalized patients (44)

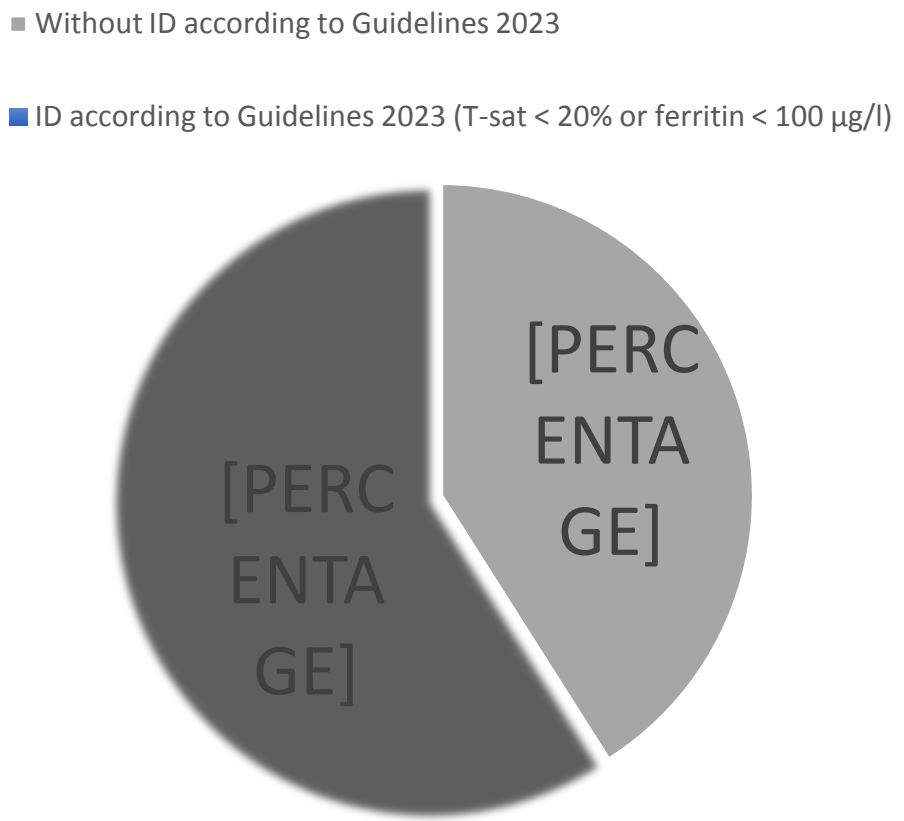
RESULTS: AMBULANT vs. HOSPITALIZED COMPARISON

Levels (median)	All patients	Outpatients	Hospitalized	P-value
T-sat	0,189	0,21	0,163	0,0702
Ferritin (µg/L)	131,70	111,45	156,85	0,2589
sTfR (mg/L)	1,62	1,60	1,66	0,1367
Serum iron (µmol/L)	11,90	13,65	10,25	0,2087
CRP (mg/L)	6,08	5,00	7,20	0,0007
NTproBNP (pg/mL)	1621,50	1186,5	3098,50	<0,0001
Hemoglobin (g/l)	141,50	144,5	130,00	0,5230

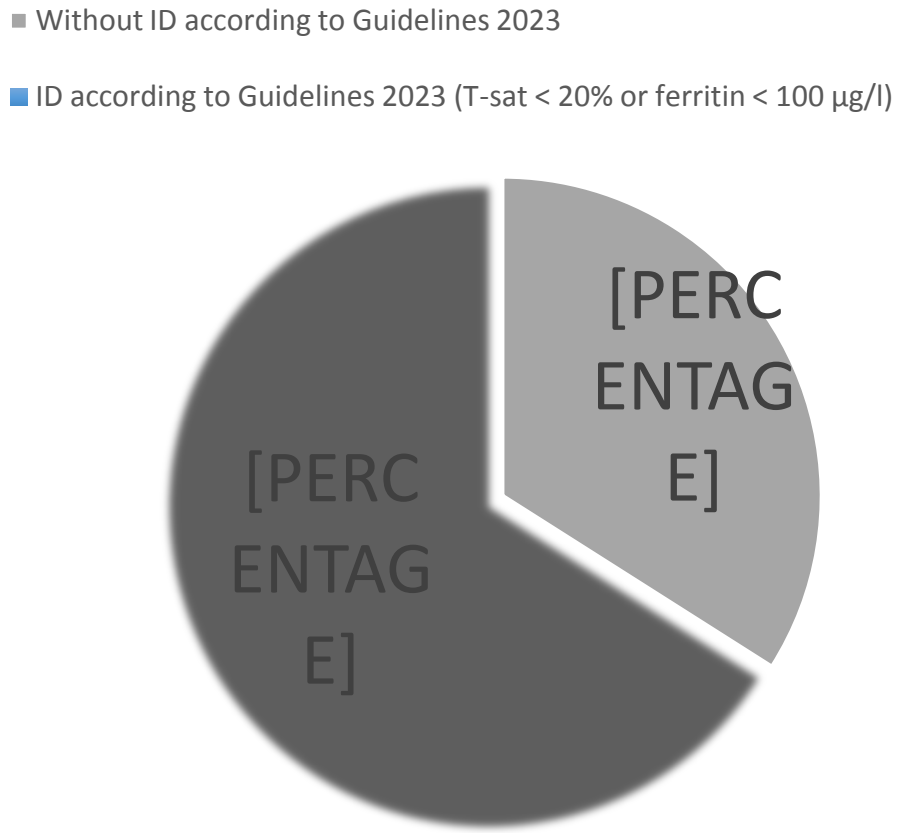


PREVALENCE OF ID: COMPARISON OF GROUPS

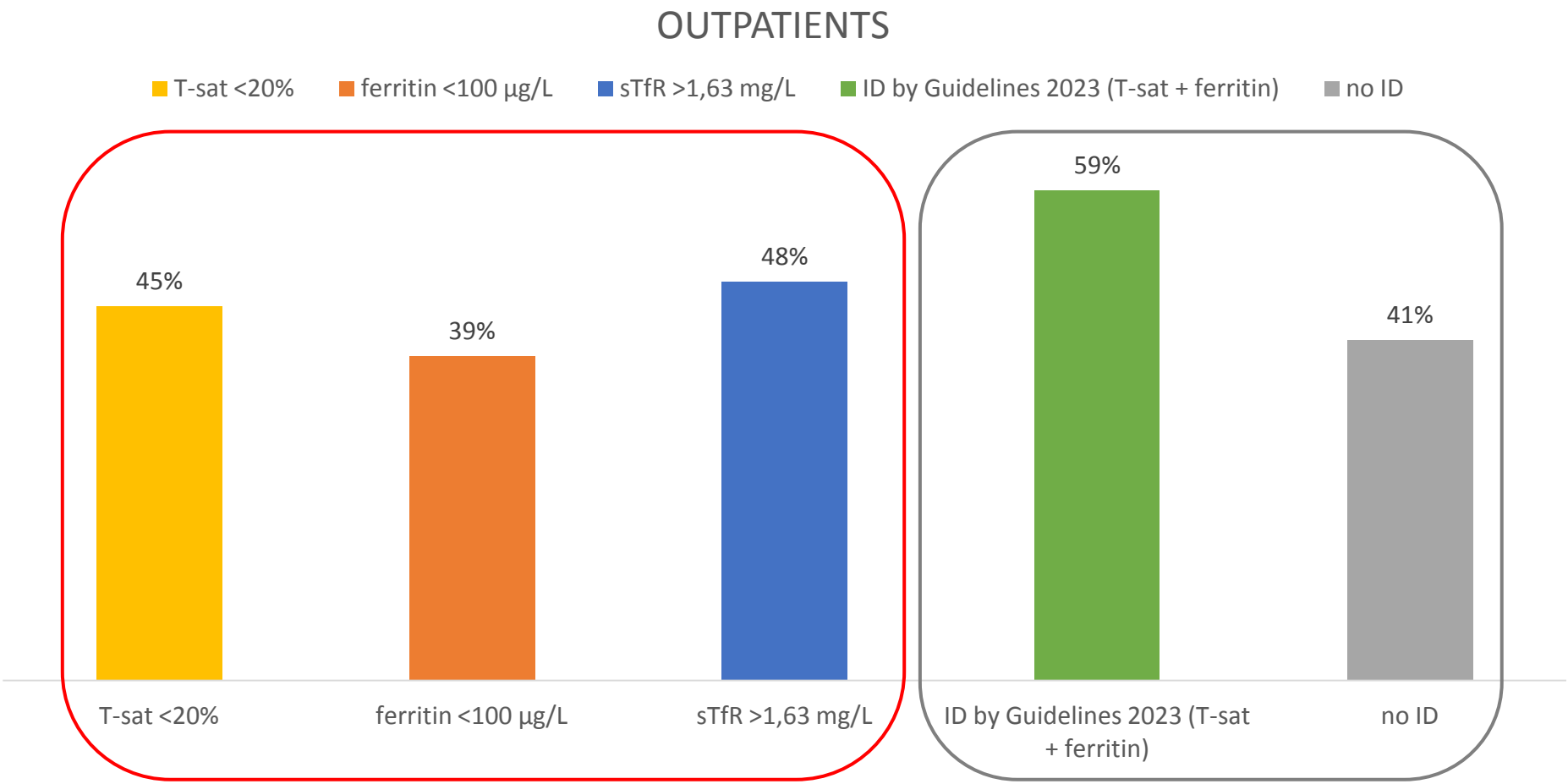
OUTPATIENTS



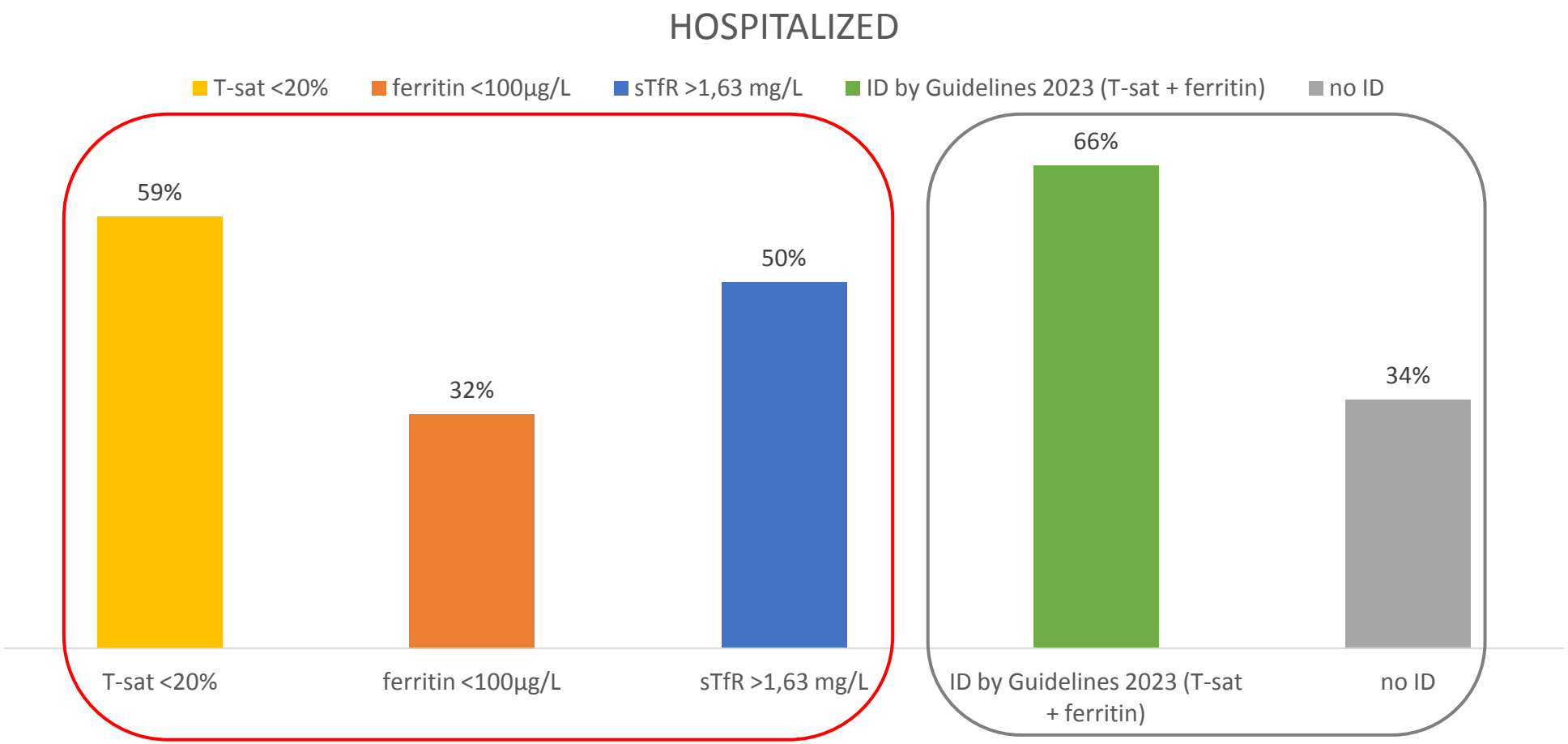
HOSPITALIZED

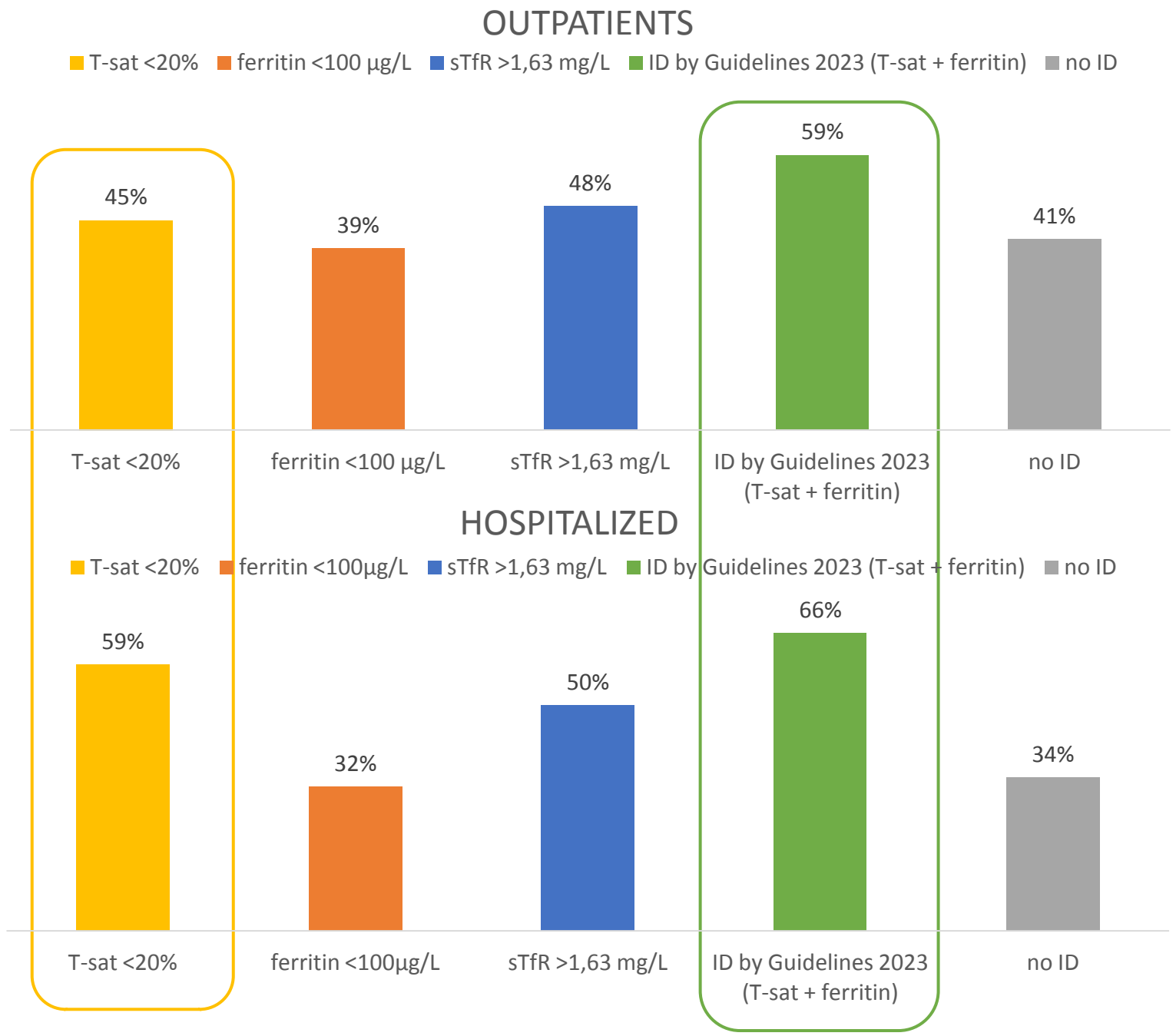


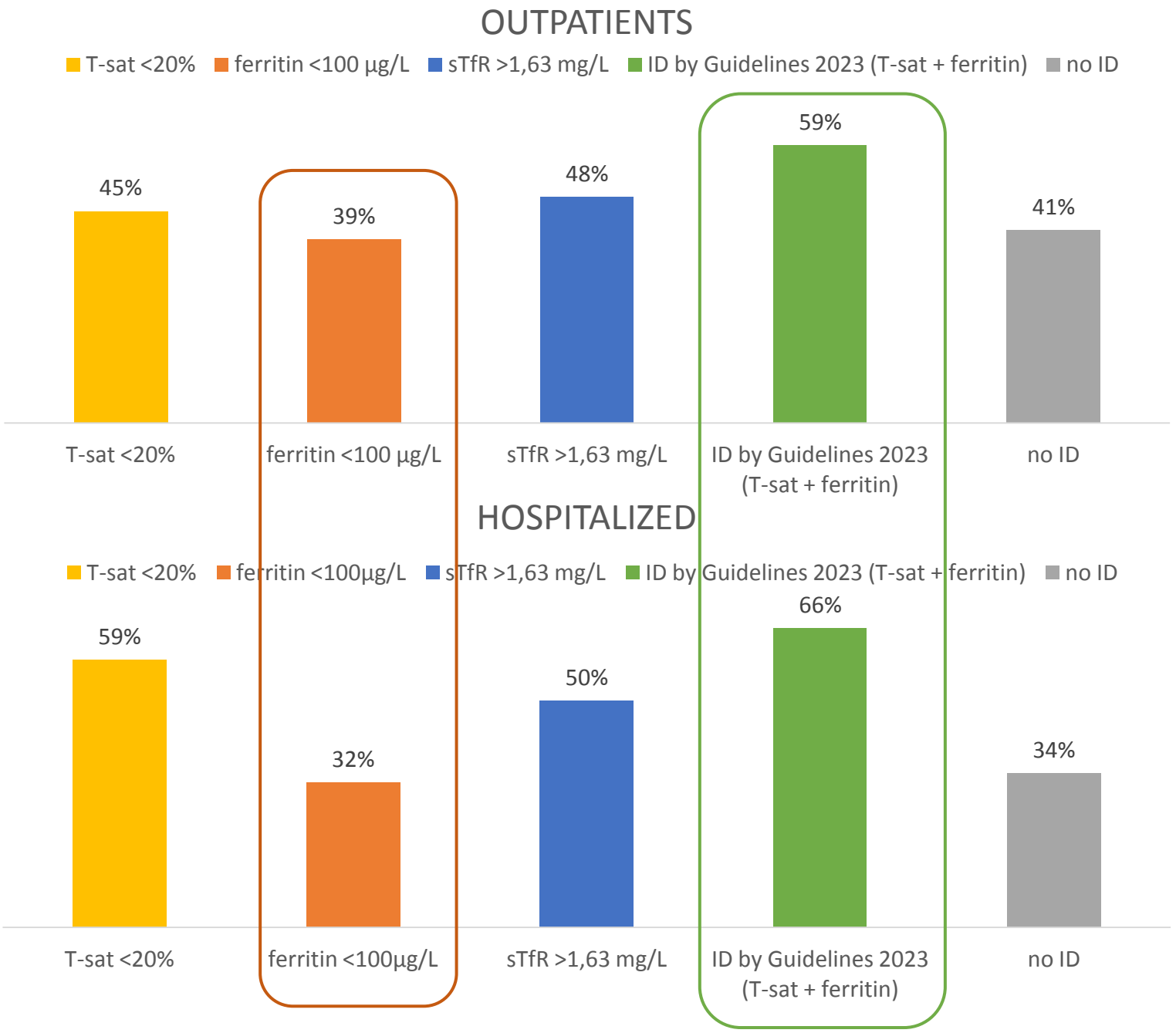
PREVALENCE OF ID BY VARIOUS PARAMETERS: OUTPATIENTS

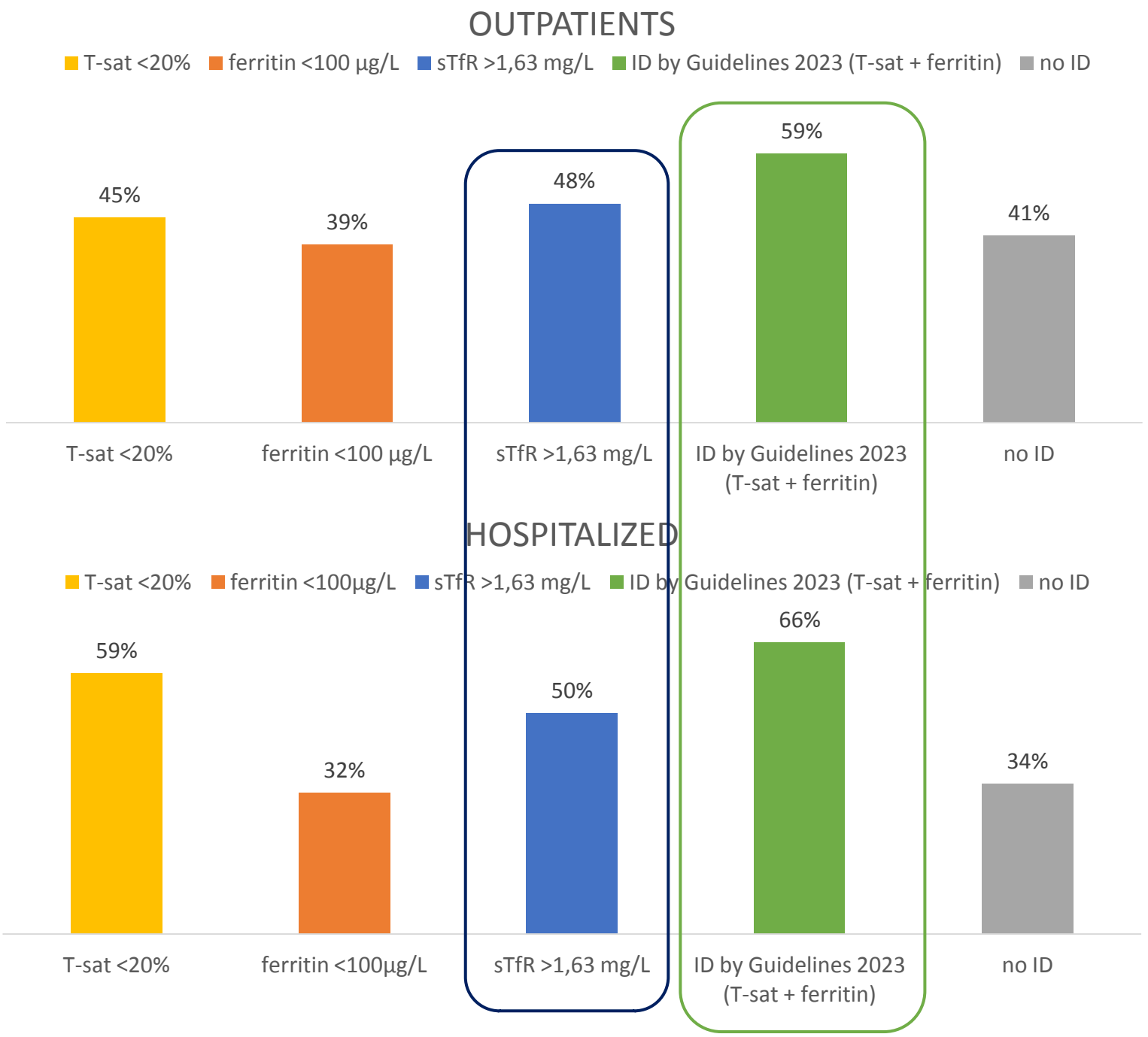


PREVALENCE OF ID BY VARIOUS PARAMETERS: HOSPITALIZED




OUTPATIENTS
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
45%
39%
48%
59%
41%
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
HOSPITALIZED
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
59%
32%
50%
66%
34%
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID


OUTPATIENTS
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
45%
39%
48%
59%
41%
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
HOSPITALIZED
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
59%
32%
50%
66%
34%
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID


OUTPATIENTS
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
45%
39%
48%
59%
41%
T-sat <20%
ferritin <100 µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
HOSPITALIZED
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID
59%
32%
50%
66%
34%
T-sat <20%
ferritin <100µg/L
sTfR >1,63 mg/L
ID by Guidelines 2023 (T-sat + ferritin)
no ID

REGRESSION ANALYSIS

Results of univariate models with NYHA characteristics showed that ferritin seems like the poorest predictor of patients' performance status among all iron parameters.

T-sat, serum iron and sTfR seem to be more precise parameters according to this analysis.

ROC curves of relation to NYHA, p-values for odds ratio

T-sat, p=0,00378

Ferritin, p=0,4259

Serum iron, p=0,00008

sTfR, p=0,001764

CONCLUSIONS I

- The prevalence of ID in heart failure is high, especially in acute decompensation, which was confirmed by our results.
- In the search for optimal diagnostic parameters, it turns out that ferritin is not an optimal marker.
- A statistically significant association was found between a functional status and individual parameters for T-sat, serum iron and sTfR, but not for ferritin.

CONCLUSIONS II

- None of the individual parameters has a higher sensitivity than a Guidelines definition (T-sat<20% or ferritin <100µg/L)
- Guidelines definition is likely to have lower specificity and include patients with false positive ID findings, who will not benefit from treatment (HEART-FID subanalysis)
- In outpatients, the detection according to sTfR is most similar to Guidelines, in hospitalised patients according to T-sat
- T-sat and maybe sTfR might be better predictors of treatment response than the ID definition from the Guidelines
- Possibly a rehabilitation of the importance of serum iron can be in order

I. INTERNÍ
KARDIOANGIOLOGICKÁ
KLINIKA LF MU A FNUSA

FAKULTNÍ
NEMOCNICE
U SV. ANNY
V BRNĚ

MUNI
MED

THANK YOU FOR YOUR ATTENTION

bakosova.maria@fnusa.cz

www.fnusa.cz