Iron deficiency and all-cause mortality after myocardial infarction

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INSTITUT KLINICKÉ A EXPERIMENTÁLNÍ MEDICÍNY
KLINIKA KARDIOLOGIE

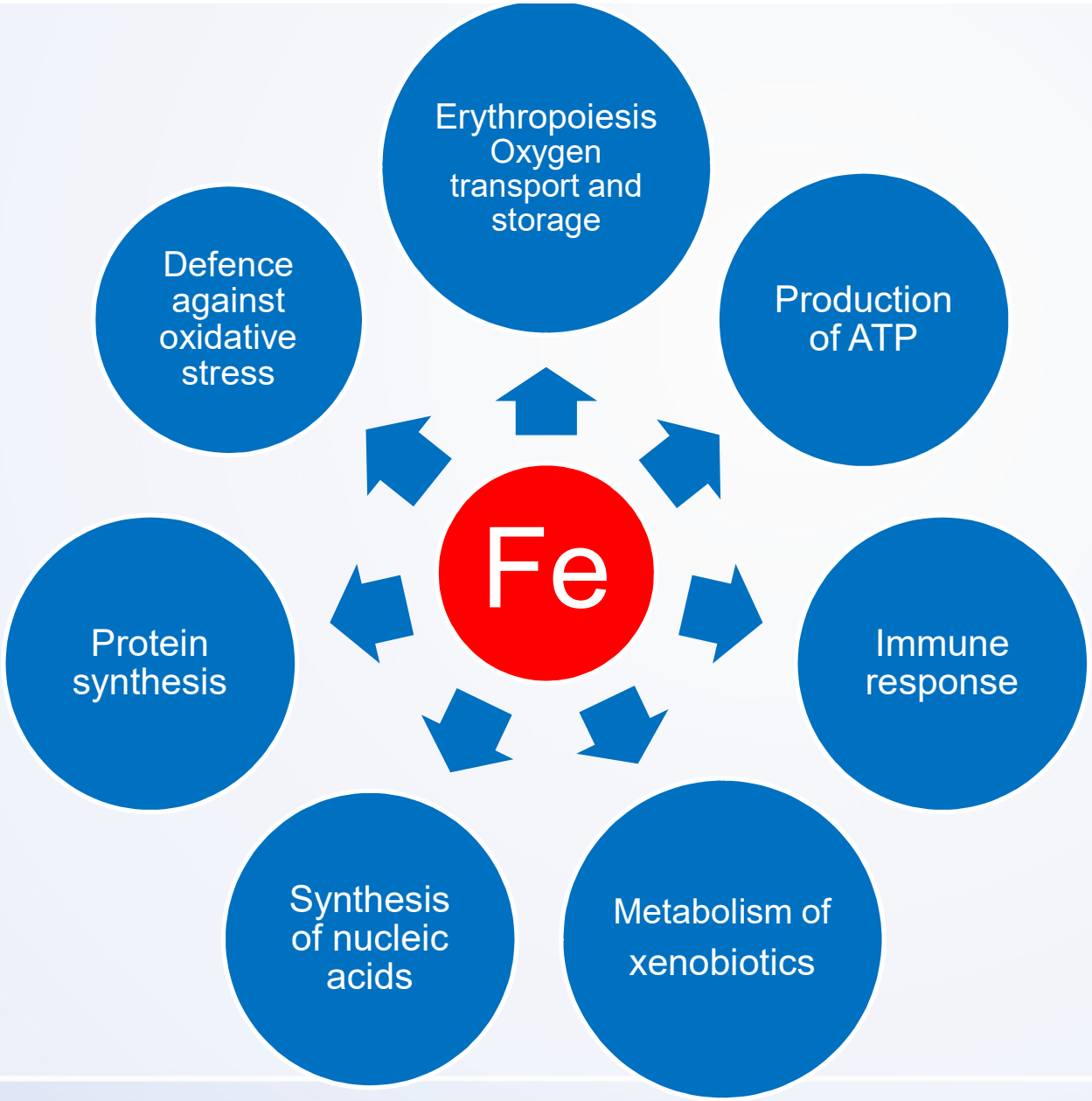
Introduction

Aims

Methods

Results

Conclusion


Erythropoiesis
Oxygen transport and storage
Production of ATP
Immune response
Metabolism of xenobiotics
Synthesis of nucleic acids
Protein synthesis
Defence against oxidative stress
Fe

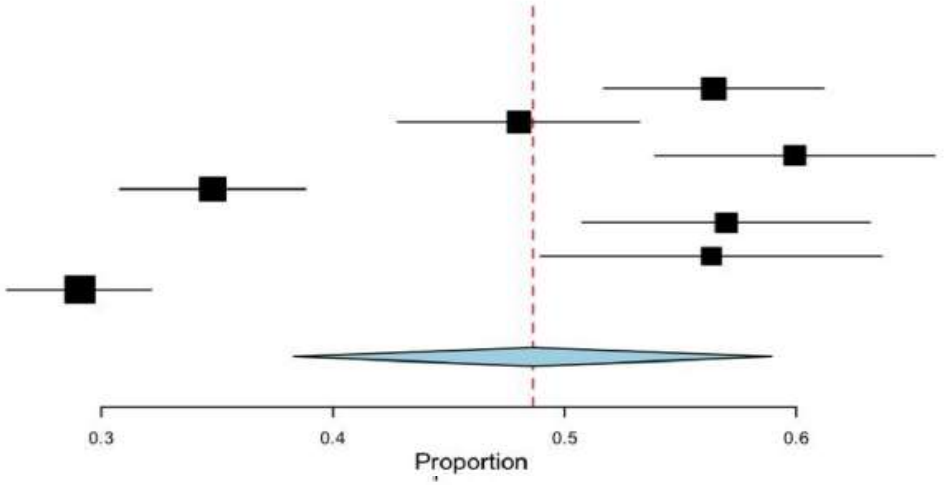
Iron deficiency (ID) in patients with myocardial infarction (MI)

- Altered cellular metabolism
- Increased oxidative stress and apoptosis
- Decreased activity of cardioprotective signaling of eNOS/sGC/protein-kinase G

ID in patients with MI

A) Prevalence of iron deficiency

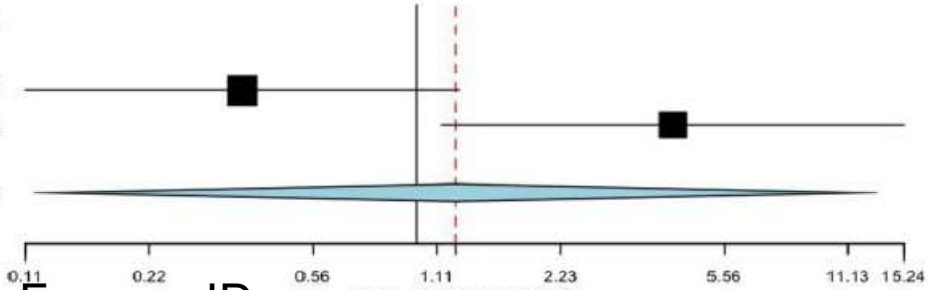
Studies	Estimate (95% C.I.)	Ev/Trt
Cosentino 2020	0.564 (0.517, 0.612)	237/420
Fujinaga 2013	0.480 (0.428, 0.532)	169/352
Gonzales-D'gregorio 2018	0.599 (0.539, 0.660)	151/252
Martins 2015	0.348 (0.308, 0.388)	189/543
Merono 2017	0.570 (0.508, 0.632)	139/244
Paeres 2018	0.563 (0.490, 0.637)	98/174
Zeller 2019	0.291 (0.260, 0.321)	243/836
Overall (I^2=9686 % , P< 0.001)	**0.486 (0.383, 0.589)**	**1226/2821**



Prevalence of ID 43 %

B) In-hospital pooled cardiovascular and overall mortality

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Cosentino 2020	0.376 (0.111, 1.267)	4/237	8/183
Fujinaga 2013	4.177 (1.145, 15.241)	11/169	3/183
Overall (I^2=8585 % , P=0.008)	**1.239 (0.117, 13.134)**	**15/406**	**11/366**



Favours ID

Favours non-ID

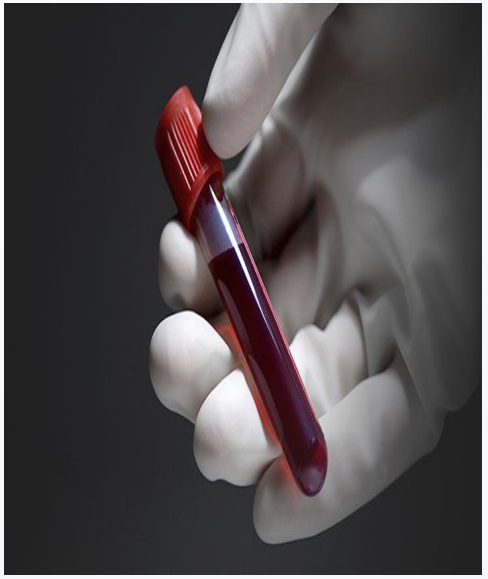
Aims

1. To compare association of different ID definitions with all-cause mortality in patients with first type of MI

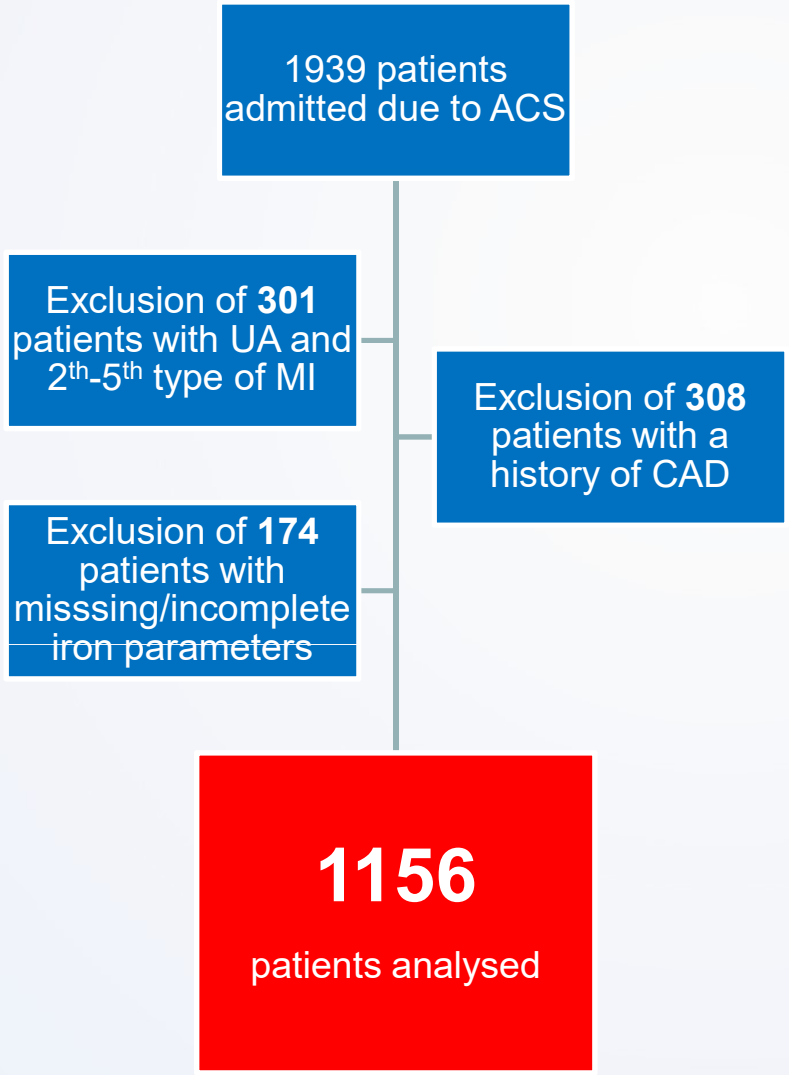
2. To analyse additional predictive value of ID to GRACE score

Methods

Prospective registry of patients admitted to IKEM with a diagnosis of ACS since June 2017

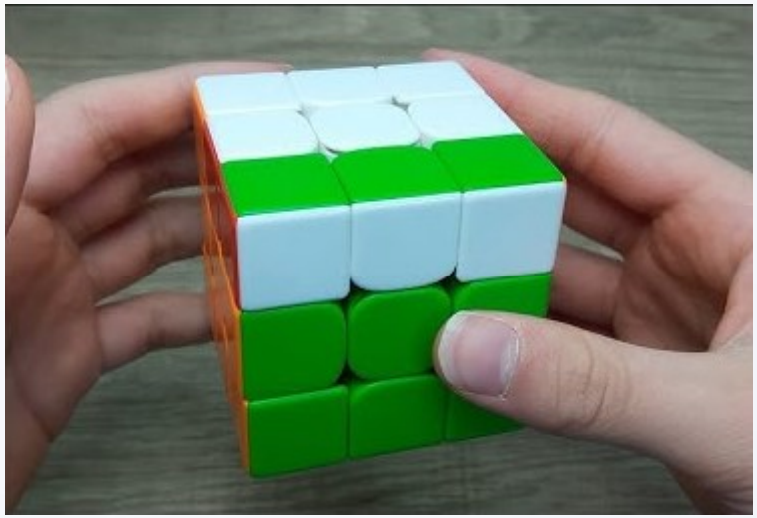


1st day after admission: study blood samples


1939 patients admitted due to ACS
Exclusion of **301** patients with UA and 2th-5th type of MI
Exclusion of **308** patients with a history of CAD
Exclusion of **174** patients with misssing/incomplete iron parameters
1156
patients analysed

Methods

Decision tree analysis for cut-offs of ID parameters



Restricted cubic spline model

Results

1156 patients

Mean age 64 ±12 years

Women 25 %

Median follow-up 3,4 years

Mortality 16,8 %

Results I

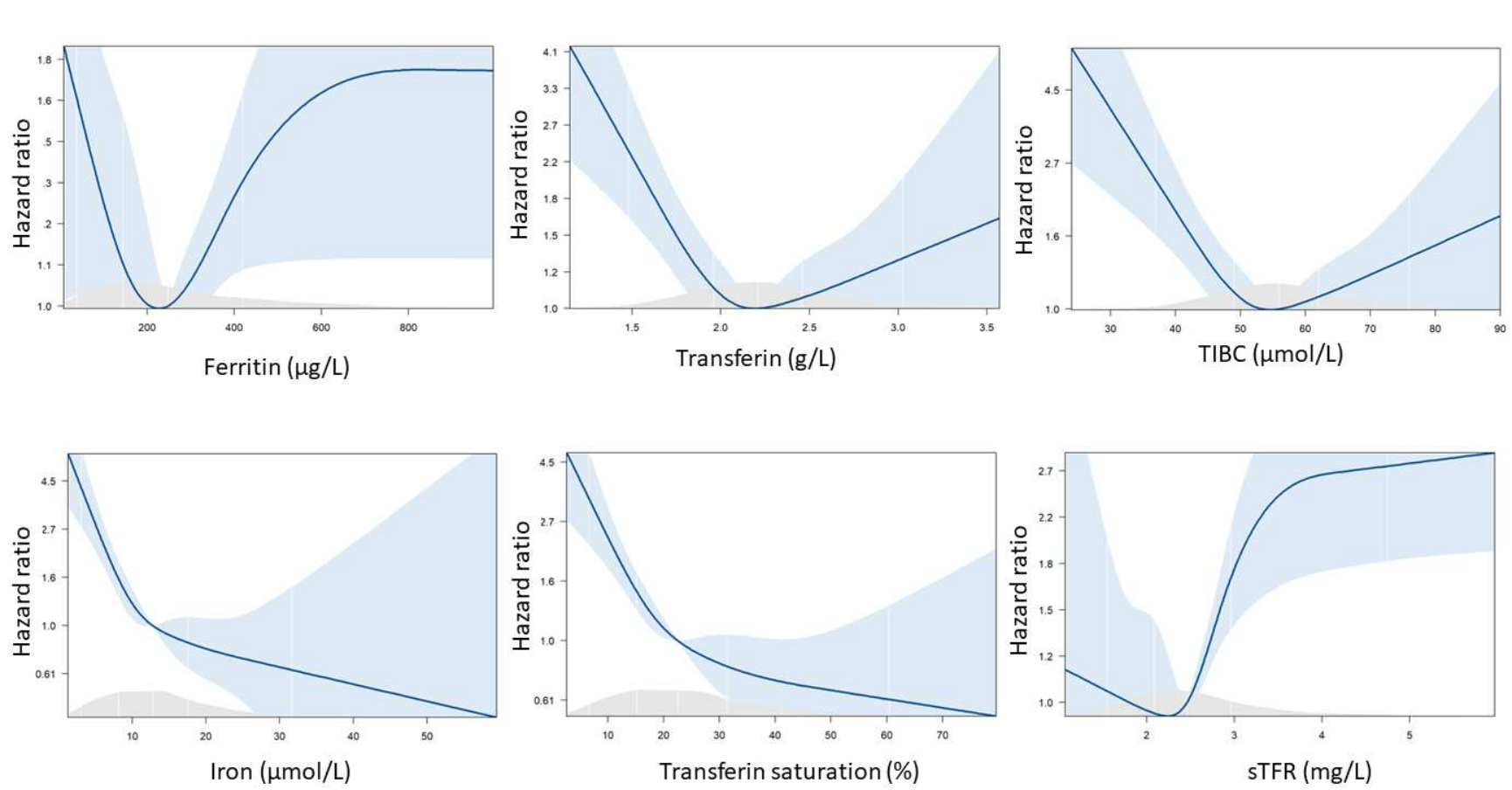


Fig.1: Restricted cubic splines model for various ID parameters and all-cause mortality
Adjusted for age. Grey area: histogram; modrá oblast: 95% confidence interval

Results II

Tab 1: Comparison of additional predictive value of ID parameters to GRACE score

	6 months				
	AUC	Δ AUC	p	Δ Brier	p
Iron ≤13 µmol/L	82.6 (77.1—88.0)	2.5 (1.1—3.9)	0.001	−0.1(−0.2— −0.001)	0.01
TSAT <20 %	81.7 (76.2—87.2)	1.6 (0.1—3.2)	0.04	−0.1 (−0.2— −0.01)	0.047
Ferritin <30 µg/L	79.9 (74.3—85.6)	−0.2 (−0.3—0.001)	0.04	0.01 (−0.001—0.001)	0.74
Ferritin <100 µg/L	80.0 (74.3—85.8)	−0.1 (−0.6—0.5)	0.90	−0.001 (−0.1—0.01)	0.19
Guideline	80.5 (74.7—86.2)	0.4 (−0.7—1.5)	0.5	−0.1 (−0.2—−0.1)	0.02
Prague criteria	82.9 (77.5—88.2)	2.8 (0.9—4.7)	0.004	−0.3 (−0.4 — −0.1)	0.0003
		Table B			
	12 months				
	AUC	Δ AUC	p	Δ Brier	p
Iron ≤13 µmol/L	81.9 (77.0—86.9)	2.1 (0.7—3.6)	0.004	−0.2 (−0.3—−0.1)	0.005
TSAT <20 %	81.5 (76.6—86.4)	1.7 (0.2—3.2)	0.03	−0.1 (−0.3—0.1)	0.096
Ferritin <30 µg/L	79.8 (74.8—84.8)	−0.01 (−0.4—0.4)	0.96	0.01 (−0.001—0.001)	0.90
Ferritin <100 µg/L	79.8 (74.7 84.9)	0.001(0.5 0.5)	1.0	0.001 (0.1 0.01)	0.19
Guideline	80.2 (75.1—85.3)	0.4 (−0.6—1.4)	0.4	−0.1 (−0.2 — −0.1)	0.044
Prague criteria	82.4 (77.6—87.2)	2.6 (0.7—4.5)	0.007	−0.3 (−0.6— −0.1)	0.001

52 % patients with serum iron (S-Fe) ≤13 µmol/L
58 % patients had ID according to Prague ID criteria (at least 1 of 2 parameters: S-Fe ≤12.8 µmol/L and/or sTfR ≥3 mg/L)

Baseline characteristics

	Iron >12.8 & sTfR<3	Iron ≤12.8 & sTfR<3	Iron >12.8 & sTfR≥3	Iron ≤12.8 & sTfR≥3	p
	(n=490) 42,4 %	(n= 394) 34,1 %	(n=83) 7,2 %	(n=189) 16,3 %	
Characteristics					
Age (years)	**62,0 ± 11,9**	**64,3 ±12,7***	**66 ±12,7***	**67,6 ±12,2***	**< 0,001**
Male sex, n (%)	376 (77%)	292 (74%) *	60 (72%)	139 (74%)	0,68
STEMI, n (%)	304 (62%)	279 (71%)*	38 (46%)	125 (66 %)	0,001
Anterior MI, n (%)	195 (40%)	175 (44%)	38 (46%)	97 (51%)	0,052
Subacute MI, n (%)	33 (7%)	81 (21%)*	8 (10%)	41 (22%)*	<0,0001
Multi-vessel disease, n (%)	138 (28%)	121 (31%)	26 (31%)	74 (39%)	0,052
CPR before admission, n (%)	14 (3%)	31 (8%)*	1 (1%)	13 (7%)	0,02
Admission HR, min^{-1}	74 ±16	80±20*	77 ±17	82 ±18*	<0,0001
Admission SBP, mmHg	145±26	138±29*	149±23	142±24	0,0002
PCI or CABG, n (%)	**479 (98%)**	**355 (90%)***	**76 (92%)***	**165 (87%)**	**< 0,0001**
Hemoglobin, $g.l^{-1}$	145±13	141±15*	144±19	137±21*	<0,0001
Leukocyte count, $10^9.l^{-1}$	10,5 (8,4-15,2)	11,7 (9,5-15,0)*	10,0 (7,4-11,8)	11,8 (9,1-14,0)*	<0,0001
HbA1c, $mmol.mol^{-1}$	41 (38-46)	42 (39-47)	41 (37-49)	44 (40-53)*	<0,0001
CKD-EPI, $ml/s/1,73m^2$	**1,39±0,30**	**1,28±0,39***	**1,26±0,37***	**1,16±0,42***	**<,0001**
Max. hsTroponin T, ng/L	1047 (314-3088)	2256 (825-5159)*	813 (255-2183)	2011 (685-4045)*	<0,0001

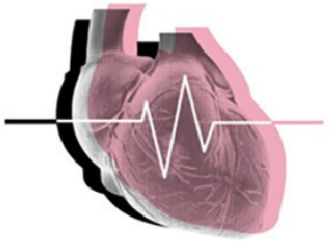
- p< 0,05 vs. S-Fe ≥ 12,8 and sTfR ≤ 13

Baseline characteristics

	Iron >12.8 & sTfR<3	Iron ≤12.8 & sTfR<3	Iron >12.8 & sTfR≥3	Iron ≤12.8 & sTfR≥3	p
	(n=490) 42,4 %	(n= 394) 34,1 %	(n=83) 7,2 %	(n=189) 16,3 %	
Iron metabolism					
Iron, µmol/L	**19,8±7,0**	**8,4±2,9***	**17,6±4,1***	**7,5±2,9***	<0,0001
Ferritin, µg/L	240 (138-391)	292 (180-490)*	189 (97-278)*	230 (103-412)	<0,0001
TSAT, %	**35,9±13,7**	**16,2±5,6***	**29,6±7,1***	**13,6 ± 5,3***	<0,0001
sTfR, mg/L	2,23 ± 0,40	2,33 ± 0,37	3,6 ± 0,85*	4 ± 1,62*	<0,0001
ECHO					
LV EF ≤ 40%, n (%)	69 (14%)	125 (32%)*	16 (19%)	61 (32%)*	< 0,0001
Risk factors					
Arterial hypertension, n (%)	270 (55%)	228 (58%)	54 (65%)	135 (71%)*	0,004
Diabetes mellitus, n (%)	88 (18%	82 (21%)	19 (23%)	82 (43%)*	<0,0001
Current smoking, n (%)	247 (50%)	184 (47%)	32 (39%)	66 (35%)*	0,06
COPD, n (%)	28 (6%)	24 (6%)	5 (6%)	11 (6%)	0,996
History of atrial fibrillation, n (%)	17 (3%)	18 (5%)	7 (8)	24 (13%)	<0,0001
Dialysis, n (%)	2 (0,4 %)	1 (0,3 %)	0 (0%)	1 (0,5%)	0,45
Medications at discharge, n (%)					
ACE inhibitors or ARB, n (%)	382 (78%)	282 (74%)	70 (84%)	144 (79%)	0,16
BB, n (%)	382 (78%)	296 (78%)	68 (82 %)	151 (83%)	0,43
Statins, n (%)	480 (98%)	365 (96 %)	79 (95%)	168 (92%)*	0,004
Aspirin, n (%)	474 (97%)	349 (91%)*	77 (93%)	158 (86%)*	<0,0001
Ticagrelor, n (%)	365 (75%)	226 (59%)*	44 (53%)*	88 (48%)*	<0,0001
Outcome					
Killip class I, n (%)	427 (87%)	276 (70%)*	75 (90%)*	114 (60%)	<0,0001
Death, n (%)	36 (7%)	74 (19 %)*	19 (23%) *	65 (34%) *	<0,0001

- p< 0,05 vs. S-Fe ≥ 12,8 and sTfR ≤ 13

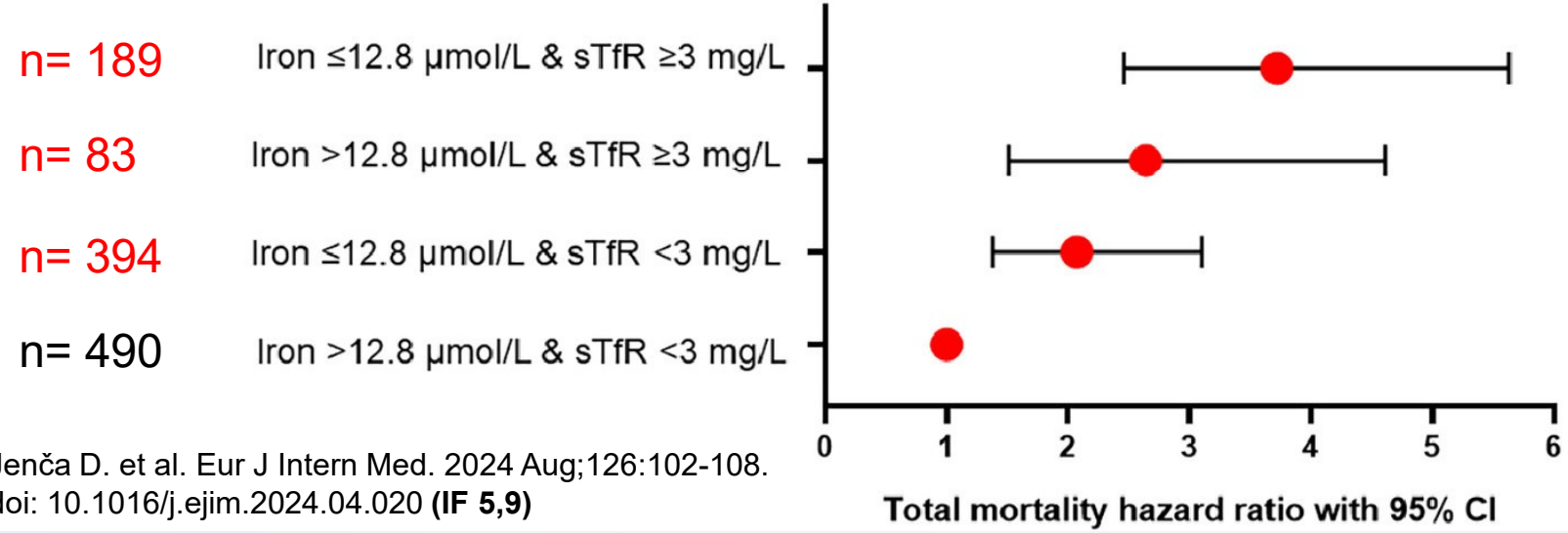
PragueID criteria and prognosis of patients after myocardial infarction



PragueID criteria: Iron ≤12.8 µmol/L & sTfR ≥3 mg/L

Iron deficiency prevalence after MI: 58%

+Fe



Adjusted for GRACE score

Jenča D. et al. Eur J Intern Med. 2024 Aug;126:102-108.
doi: 10.1016/j.ejim.2024.04.020 **(IF 5,9)**

PragueID criteria	Prevalence	Unadjusted	Adjusted (model 2)*
Iron >12.8µmol/L & sTfR<3 mg/L	ref	ref	ref
Iron ≤12.8µmol/L & sTfR<3 mg/L	394 (34.1)	2.79 (1.87-4.15)	1.75 (1.16-2.64)
Iron >12.8µmol/L & sTfR≥3 mg/L	83 (7.2)	3.27 (1.88-5.70)	2.05 (1.15-3.64)
Iron ≤12.8µmol/L & sTfR≥3 mg/L	189 (16.3)	5.76 (3.83-8.66)	2.56 (1.64-3.99)

* Adjusted for age, gender, HF history, CKD-EPI, admission systolic blood pressure and heart rate, absence of PCI, Killip class, ejection fraction <35 % at discharge

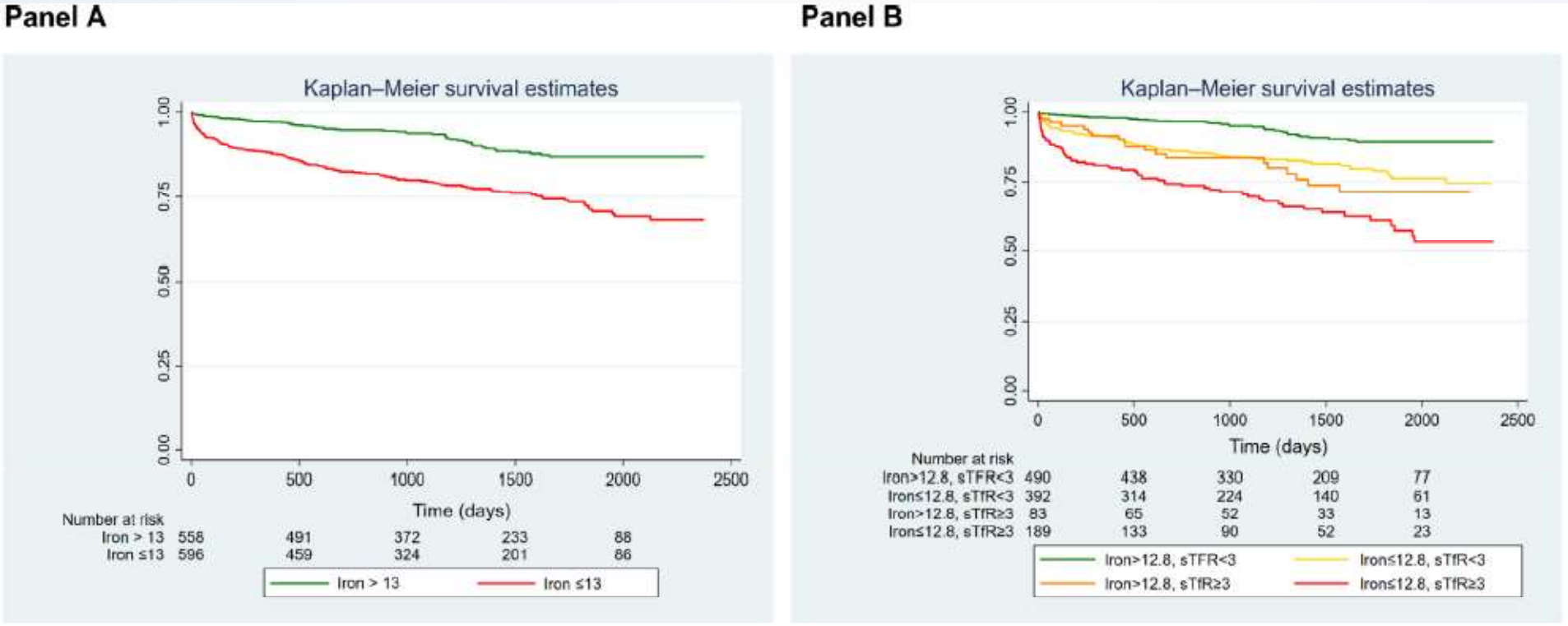


Fig. Kaplan-Meier survival curves
A for serum iron
B for PragueID criteria

Study limitations

- Single-centre study
- Retrospective analysis
- Single measurement of iron parameters

Conclusions

- ID is very common among patients with MI
- ID criteria based on combination of S-Fe and sTfR provide the best predictive value for mortality
- The role of parenteral iron substitution in ID patients with MI has to be addressed in RCT

Thank you for your attention