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Original Article Iron deficiency and all-cause mortality after myocardial infarction

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ARTICLE INFO ABSTRACT Keywords: Background: Data on the clinical significance of iron deficiency (ID) in patients with myocardial infarction (MI) Myocardial infarction are conflicting. This may be related to the use of various ID criteria. Iron deficiency We aimed to compare the association of different ID criteria with all-cause mortality after MI. Outcomes Methods: Consecutive patients hospitalized for their first MI at a large tertiary heart center were included. We Mortality evaluated the association of different iron metabolism parameters measured on the first day after hospital Criteria admission with all-cause mortality. Results: From the 1,156 patients included (aged 64±12 years, 25 % women), 194 (16.8 %) patients died during the median follow-up of 3.4 years. After multivariate adjustment, iron level ≤13 µmol/L (HR 1.67, 95 % CI 1.19–2.34) and the combination of iron level \leq 12.8 µmol/L and soluble transferrin receptor (sTfR) \geq 3 mg/L (HR 2.56, 95 % CI 1.64-3.99) termed as PragueID criteria were associated with increased mortality risk and had additional predictive value to the GRACE score. Compared to the model including iron level, the addition of sTfR improved risk stratification (net reclassification improvement 0.61, 95 % CI 0.52-0.69) by reclassifying patients into a higher-risk group. No association between ferritin level and mortality was found. 51 % of patients had low iron levels, and 58 % fulfilled the PragueID criteria. Conclusion: Iron deficiency is common among patients with the first MI. The PragueID criteria based on iron and

Conclusion: Iron deficiency is common among patients with the first MI. The PraguelD criteria based on iron and soluble transferrin receptor levels provide the best prediction of mortality and should be evaluated in future interventional studies for the identification of patients potentially benefiting from intravenous iron therapy.

1. Introduction

Iron is an essential element required for normal mitochondrial function [1,2] oxygen transport, synthesis of proteins and nucleic acids, and normal immune system function. Although iron is environmentally abundant, iron deficiency (ID) is one of the most common nutritional deficits worldwide affecting approximately two billion people [3].

In cardiovascular disease, the effect of ID has been best described in patients with heart failure (HF) [4]. ID affects approximately 50 % of HF patients and is associated with worse functional capacity, impaired quality of life, increased mortality, and hospitalization rate, irrespective of anemia presence [5]. Treatment with intravenous ferric

carboxymaltose in patients with HF and ID improves symptoms, functional capacity, and quality of life, and reduces the risk of hospital admissions for HF and cardiovascular causes [6,7] Despite that, there is no consensus on ID definition in HF [8,9] The most commonly used are the guideline-recommended ID criteria based on ferritin and transferrin saturation [8,10] However, other criteria have been used as well [9,11]

Much less is known about ID effects in patients with myocardial infarction (MI). A systematic review and meta-analysis of 7 studies including a total of 2821 patients described worse long-term outcomes in the ID population, whereas short-term outcomes were heterogeneous across studies [12]. However, ID did not affect prognosis in MI patients with cardiogenic shock [13]. A small sample size and different criteria

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Fig. 1. Restricted cubic splines of different iron metabolism parameters and all-cause mortality after myocardial infarction.

for ID definitions may explain this heterogeneity in study outcomes. Furthermore, several criteria use ferritin to define ID. Nonetheless, ferritin is a positive acute phase reactant, thus the inflammatory reaction to MI may influence it [14]. Besides, ferritin has been suggested as a leakage product from damaged cells [15]. Therefore, ferritin may not be a good marker of ID in patients with MI.

For selecting patients potentially benefiting from intravenous iron therapy, the definition of ID is important. However, ID criteria currently used are based only on a consensus, while ID definition based on hard outcomes is missing. Misclassification of patients may dilute the therapy effect. This issue is further supported by an animal model of MI, which has shown no effect of iron supplementation in normal iron status [16]. Thus, the correct definition of ID is of great clinical importance. Until now, no previous study compared the association of different ID criteria with total mortality after MI.

To address this issue, the present study aimed to compare the prognostic significance of diverse criteria of iron deficiency measured on the first day after hospital admission in a large cohort of consecutive patients hospitalized for their first myocardial infarction at a large tertiary heart center.

2. Methods

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2.1. Population

This study used data from the prospective Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry (AMBI-TION registry) [17]. The registry collects clinical data and biospecimens from consecutive patients hospitalized for acute coronary syndrome since June 2017 at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, a tertiary heart center with around-the-clock coronary intervention service. The Fourth Universal Definition of Myocardial Infarction has been used [18]. Patients underwent a detailed interview during their hospital stay, and additional information was obtained from medical record abstraction and laboratory studies. For this analysis, we included consecutive patients enrolled between June 2017 and February 2023 with type I MI and no previous history of coronary artery disease. Iron metabolism was measured in the central laboratory from blood samples collected on the morning of the first day after hospital admission. Death was ascertained through December 1st, 2023. Mortality data were provided by the Institute of Health Information and Statistics of the Czech Republic (UZIS), which keeps a list of all deceased persons and dates of death in the Czech Republic by law. All patients signed informed consent. This study was approved by a local ethics committee and complies with the Declaration of Helsinki.

2.2. Primary outcome

The primary outcome of the analysis was all-cause mortality.

2.3. GRACE score

The Eagle model estimates for death within 6 months after discharge was used [19]. Variables included in the model were age, heart rate, systolic blood pressure, creatinine level, troponin elevation, ST segment depression on initial ECG, previous history of MI and heart failure, and PCI.

2.4. Statistical methods

Continuous variables are presented as mean and SDs or medians and IQRs. Hazard ratios (HR) are shown with a 95 % confidence interval (CI). Nominal variables are shown as counts and percentages.

We have used restricted cubic splines adjusted for age to detect a nonlinear association between different parameters of iron metabolism and the primary outcome. Furthermore, we have used decision tree analysis to set the cut points for ID definition. The Cox regression model was used to analyze the association of different ID criteria with the outcome.

The Global Registry of Acute Coronary Events (GRACE) score has been recommended by the guidelines to stratify patients' risk after MI [20]. To analyze the additional predictive value of different ID criteria to the GRACE score, we have used the difference in the area under the receiver operating characteristic curve (AUC), the Brier score, and the continuous net reclassification improvement (NRI).

Statistical analyses were conducted with R statistical software

Table 1

Population demographics.

Characteristics	1ron > 12.8 & s1fR < 3 (n = 490)	$1 \text{ron} \le 12.8 \& \text{sTrR} < 3 (n = 394)$	$\begin{array}{ll} 12.8 \& \$11R<3 (n = 100 > 12.8 \& \$11R \ge 3(n = 83) \end{array}$		р	
Age (vears)	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 %)*	45 (54 %)	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 %)	0.001	
Admission HR, min^{-1}	74 ± 16	80 + 20*	77 + 17	$82 \pm 18^*$	< 0.0001	
Admission SBP, mmHg	145 ± 26	$138\pm29^{*}$	149±23	142 ± 24	0.0002	
Admission DBP, mmHg	$80{\pm}13$	78±15	$82{\pm}14$	79±14	0.10	
Creatinine, μ mol. l^{-1}	81 (70–93)	86 (72–102)*	86 (70–101)	91 (75–118)*	< 0.0001	
CKD-EPI, ml/s/1.73m ²	1.39 ± 0.30	$1.28\pm0.39^{*}$	$1.26 \pm 0.37^{*}$	$1.16 \pm 0.42^{*}$	< 0.0001	
Fasting glucose, mmol/L	7.93 ± 3.42	$8.78\pm3.81^*$	8.24 ± 3.19	9.72 ± 4.84*	< 0.0001	
HbA1c, $mmol.mol^{-1}$	41 (38–46)	42 (39-47)	41 (37–49)	44 (40–53)*	< 0.0001	
Maximal hsTroponin T. ng/L	1047 (314-3088)	2256 (825–5159)*	813 (255–2183)	2011 (685-4045)*	< 0.0001	
Total cholesterol	4.99 ± 1.16	$4.57 \pm 1.12^{*}$	5.09 ± 1.25	$4.60 \pm 1.26^{*}$	< 0.0001	
LDL cholesterol	3.34 ± 1.01	$2.96 \pm 1.03^{*}$	3.45 ± 1.23	$2.97 \pm 1.16^{*}$	< 0.0001	
Leukocyte count, 10^9 .1 ⁻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	
Hemoglobin, g/L	145 ± 13	141 + 15*	144 + 19	$137 \pm 21*$	< 0.0001	
Hemoglobin < 120 n (%)	12 (3 %)	38 (10 %)*	7 (9 %)*	38 (20 %)*	< 0.0001	
LV FF (%)	50 (40-55)	40 (35–50)*	50 (40-55)	40 (35-50)*	< 0.0001	
LV EF $< 40\%$ n (%)	69 (14 %)	125 (32 %)*	16 (19 %)	61 (32 %)*	< 0.0001	
PCI or CABG, $n(\%)$	479 (98 %)	355 (90 %)*	76 (92 %)*	165 (87 %)*	< 0.0001	
Killin class L n (%)	427 (87 %)	276 (70 %)*	75 (90 %)	114 (60 %)*	< 0.0001	
Risk factors	(2) (0) (0)	2,0 (,0,0)	, , , , , , , , , , , , , , , , , , , ,	111 (00 /0)	0.0001	
Arterial hypertension n (%)	270 (55 %)	228 (58 %)	54 (65 %)	135 (71 %)*	0.001	
Diabetes mellitus, n (%)	88 (18 %)	82 (21 %)	19 (23 %)	82 (43 %)*	< 0.0001	
Current smoking n (%)	247 (51 %)	184 (47 %)	32 (39 %)	66 (35 %)*	0.002	
BML kg/m ²	286 ± 45	28.5 ± 4.8	$30.3 \pm 6.4^*$	29.3 ± 5.2	0.006	
COPD n (%)	28 (6 %)	24 (6 %)	5 (6 %)	11 (6 %)	0.996	
Atrial fibrillation history n	17 (4 %)	18 (5 %)	7 (8)*	24 (13 %)*	< 0.0001	
(%)	17 (170)	10 (0 /0)	, (0)	21(10,70)	0.0001	
Medications on admission						
ACE inhibitors or ABB, n (%)	212 (43 %)	168 (43 %)	36 (43 %)	95 (50%)	0.31	
Statins, n (%)	85 (17 %)	76 (19 %)	15 (18%)	49 (26 %)	0.08	
Antiplatelet therapy, n (%)	47 (10 %)	54 (14 %)	11 (13 %)	45 (24 %)*	0.002	
Anticoagulants, n (%)	20 (4 %)	19 (5 %)	11 (13 %)*	21 (11 %)*	0.0002	
Discharge medication [#]						
ACE inhibitors or ARB, n (%)	382 (78 %)	282 (74 %)	70 (84 %)	144 (79 %)	0.16	
Beta blocker, 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	
Clopidogrel, n (%)	88 (18 %)	136 (36 %)*	34 (41 %)*	73 (40 %)*	< 0.0001	
Prasugrel, n (%)	19 (4 %)	5 (1 %)	3 (4 %)	2 (1 %)	0.05	
Ticagrelor, n (%)	365 (75 %)	226 (59 %)*	44 (53 %)*	88 (48 %)*	< 0.0001	
Anticoagulation, n (%)	52 (11 %)	85 (22 %)*	15 (18 %)	55 (30 %)*	< 0.0001	
Tripple therapy, n (%)	33 (7 %)	48 (13 %)*	10 (12 %)	23 (13 %)*	0.02	
Iron metabolism			()			
Iron, umol/L	19.8 ± 7.0	$8.4 \pm 2.9^{*}$	$17.6 \pm 4.1*$	$7.5 \pm 2.9^{*}$	< 0.0001	
Ferritin, ug/L	240 (138-391)	292 (180-490)*	189 (97–278)*	230 (103-412)	< 0.0001	
Transferrin, g/L	2.25 ± 0.35	$2.1 \pm 0.39^{*}$	$2.4 \pm 0.36^{*}$	$2.31 \pm 0.46*$	< 0.0001	
TIBC, umol/L	56.6 ± 8.9	$53.0 \pm 9.8^{*}$	$60.6 \pm 9.2^{*}$	58.1 ± 11.6	< 0.0001	
TSAT.%	35.9 ± 13.7	$16.2 \pm 5.6^*$	$29.6 \pm 7.1*$	$13.6 \pm 5.3^*$	< 0.0001	
sTFR. mg/L	2.23 ± 0.40	2.33 ± 0.37	$3.60 \pm 0.85^{*}$	$4.0 \pm 1.62^{*}$	< 0.0001	
Scores			2100 - 0100		20.0001	
GRACE	114 ± 23	$122\pm26^{*}$	121 ± 25	$129 \pm 26^*$	< 0.0001	
Outcome						
Death, n (%)	36 (7 %)	74 (19%)*	19 (23 %)*	65 (34 %)*	< 0.0001	
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*p < 0.05 vs. Iron >12.8 & sTfR<3 group.

#missing in patients with in-hospital death.

version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), JMP 17, SPSS version 25.0 (IBM Corporation, Armonk, NY), and STATA version 17 (StataCorp, College Station, TX). All statistical tests and confidence intervals were 2-sided with a significance level of 0.05.

3. Results

In total, 1156 patients (mean age 64 years, 75 % male) hospitalized for their first type I myocardial infarction between June 2017 and February 2023 were included in this analysis. During the median followup of 1224 days (IQR 626-1782), 194 (16.8 %) patients died.

Fig. 1 presents restricted cubic splines of the association between different parameters of iron metabolism and all-cause mortality risk. While there was no association between ferritin level and all-cause mortality, low iron, transferrin, TSAT, total iron binding capacity (TIBC), and high sTfR were associated with increased mortality risk.

3.1. Development of pragueid criteria

In the decision tree model, among the analyzed iron metabolism

Iron≤12.8. sTfR≥3

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Panel A Panel B Kaplan-Meier survival estimates Kaplan-Meier survival estimates 00[.] 8 0.75 0.75 0.50 0.50 0.25 0.25 0.00 500 1000 1500 2000 2500 0.00 Time (days) Number at risk Iron>12.8, sTFR<3 Iron≤12.8, sTfR<3 Iron>12.8, sTfR≥3 Iron≤12.8, sTfR≥3 209 140 33 52 0 500 1000 1500 2000 2500 490 438 330 392 314 224 61 13 23 Time (days) 65 133 83 189 52 90 Number at risk Iron > 13 Iron ≤13 491 459 233 201 558 596 372 88 86 324 Iron>12.8, sTFR<3 Iron≤12.8, sTfR<3

Fig. 2. Kaplan-Meier survival for iron (Panel A) and PragueID (Panel B) categories.

Table 2

Association of different iron deficiency criteria with all-cause mortality.

Iron > 13

Iron ≤13

Iron deficiency criteria	Prevalence n(%)	Unadjusted HR (95 % CI)	Adjusted* HR (95 % CI)	Adjusted** HR (95 % CI)
Iron \leq 13 µmol/L	598 (51.7)	2.78	2.06	1.67
		(2.03-3.82)	(1.50 - 2.84)	(1.19 - 2.34)
TSAT <20 %	468 (40.5)	2.46	1.89	1.38
		(1.85 - 3.28)	(1.41 - 2.53)	(1.01 - 1.90)
Ferritin <30 µg/L	20 (1.7)	1.44	1.58	1.55
		(0.59–3.50]	(0.64–3.84)	(0.63–3.80)
Ferritin <100 µg/	157 (13.6)	1.50	1.37	1.36
L		(1.05 - 2.13)	(0.96–1.95)	(0.93–1.98)
Guideline ID	357 (31.0)	1.69	1.57	1.34
definition		(1.28 - 2.24)	(1.19 - 2.08)	(0.99–1.82)
Prague ID criteria				
2. Iron \leq 12.8	394 (34.1)	2.79	2.07	1.75
µmol/L &		(1.87–4.15)	(1.38–3.10)	(1.16–2.64)
$3 \operatorname{Iron} > 12.8$	83 (7.2)	3.97	2 64	2.05
umol/L &	05 (7.2)	(1.88_5.70)	(151-461)	(1 15 - 3 64)
sTfR≥3 mg/L		(1.00-3.70)	(1.51-4.01)	(1.13-3.04)
4. Iron ≤12.8	189 (16.3)	5.76	3.72	2.56
µmol/L &		(3.83–8.66)	(2.46-5.63)	(1.64–3.99)
sTfR≥3 mg/L				

* Adjusted for GRACE score.

^{**} 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

A 95 % confidence interval is shown in bracelets. Guideline ID criteria were ferritin $<100 \mu$ g/L or TSAT <20 % if ferritin was 100–299 μ g/L.

parameters (iron, transferrin, TSAT, TIBC, TfR), the combination of iron ${\leq}12.8~\mu\text{mol/L}$ and sTfR ${\geq}3.0~\text{mg/L}$ showed the best association with total mortality risk. Based on these cut-points, we have created 4 groups – group 1 with normal iron and normal sTfR, group 2 with low iron and normal sTfR, group 3 with normal iron and high sTfR, and group 4 with low iron and high sTfR. We have termed this classification as PragueID criteria. Population demographics by PragueID criteria are shown in Table 1.

As shown in Fig. 2, the addition of sTfR to iron level can reclassify the risk associated with low iron to intermediate and high, while high sTfR in the presence of normal iron is associated with an intermediate risk.

3.2. Comparison of ID criteria

After adjustment for the GRACE score or other variables affecting

mortality risk after MI, all ID criteria except for ferritin were independently associated with the total mortality (Table 2). The hazard ratio was highest for the Prague ID criteria and iron level. As assessed by the AUC and Brier score (Table 3), only the iron level and Prague ID criteria had additional prognostic value to the GRACE score. When the additional prognostic value of iron or PragueID was compared, there was no difference in AUC, but there was a borderline difference in the Brier score and an improvement in net reclassification improvement (NRI) in favor of the PragueID criteria. Beyond the iron level, PragueID correctly reclassified cases patients into the higher-risk group (Table 4).

Iron>12.8. sTfR≥3

4. Discussion

In the present study, we have analyzed the association of different ID criteria with all-cause mortality in patients hospitalized for their first MI. We show that ID is common among these patients, but the prevalence and prognostic implications differ by the criteria used. Among several criteria evaluated, only iron level and particularly the combination of iron level and soluble transferrin receptor were independently associated with the risk of all-cause mortality and improved risk prediction beyond the guidelines recommended GRACE score.

While ferritin is a guideline-recommended parameter for ID diagnosis in HF, we did not find any association between ferritin level and mortality risk. This finding among MI patients may be explained by the effect of cell necrosis and inflammatory response on ferritin levels. Thus, ferritin should not be used to define ID after MI.

Our observation is in line with previous studies. In patients with chronic HF, TSAT <20 % and serum iron \leq 13 mmol/L were independently associated with death, but lower serum ferritin concentrations were paradoxically associated with better survival [9]. In a study of the prognostic value of temporal changes of iron metabolism parameter in patients with acute coronary syndrome, a decrease in TSAT and iron levels, but not changes in ferritin levels were associated with an increased risk of cardiovascular death and nonfatal ACS [21]. Among patients with coronary artery disease, sTfR was independently associated with an increased risk of cardiovascular death or MI [22]. We add to this evidence the observations that among several criteria of ID, the combination of low iron and high sTfR can identify patients at increased mortality risk, which may have the biggest benefit from iron supplementation.

To the best of our knowledge, this is the first large-scale study among consecutive MI patients evaluating the prevalence and prognostic significance of different ID criteria. We found that 51 % of patients after MI

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Table 3

Table A

Additional predictive value of different iron deficiency criteria to the GRACE score 6 months (Table A) and 12 months (Table B) after hospital discharge.

	6 months				
	AUC	Δ AUC	р	Δ Brier	р
Iron ≤13 µmol/L	82.6 (77.1-88.0)	2.5 (1.1-3.9)	0.001	-0.1(-0.20.001)	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(-0.40.1)	0.0003
		Table B			
	12 months				
Prague criteria Iron ≤13 μmol/L TSAT <20 %	AUC	Δ AUC	р	Δ Brier	р
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)	$\begin{array}{rrrr} 1.0 & -0.001 & (-0.1 - 0.01) \\ 0.4 & -0.1 & (-0.20.1) \end{array}$		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

A 95 % confidence interval is shown in bracelets.

Table 4 Comparison of model discrimination, calibration, and reclassification.

	Discrimination			Calibration		Reclassification			
Time	AUC Iron	AUC PragueID	AUC	р	Brier	р	NRI	NRI+	NRI-
6 months	82.6 (77.1–88.0)	82.9 (77.5–88.2)	0.3 (-1.1-1.7)	0.70	-0.1 (-0.3-0.01)	0.06	0.56 (0.34–0.87)	-10^{-15} (-0.20–0.28)	0.56 (0.52–0.59)
1 year	81.9 (77.0–86.9)	82.4 (77.6-87.2)	0.5 (-1.0-1.9)	0.50	-0.2 (-0.3-0.01)	0.06	0.66 (0.62–0.81)	0.64 (0.55-0.78)	0.01 (-0.004-0.08)
2 years	81.5 (77.3–85.6)	82.2 (78.1-86.3)	0.7 (-0.6-2.1)	0.30	-0.3 (-0.5-0.001)	0.04	0.60 (0.49–0.76)	0.57 (0.44-0.67)	0.03 (-0.01-0.09)
3 years	79.8 (75.6–84.0)	80.3 (76.0-84.6)	0.5 (-0.8-1.9)	0.40	-0.3 (-0.6-0.01)	0.06	0.61 (0.52–0.69)	0.56 (0.50-0.63)	0.04 (-0.009-0.08)

A model with Grace score and Iron class (Iron \leq 13 μ mol/L vs. Iron >13 μ mol/L) was compared with a model including Grace score and PragueID class. A 95 % confidence interval is shown in brackets.

AUC - area under the curve, NRI - net reclassification improvement.

have iron \leq 13 µmol/L and 58 % have ID if PragueID criteria are used. Thus, more than 50 % of patients with the first MI are affected by ID. This is similar to the ID prevalence in HF, among which 43 % of men and 54 % of women had iron \leq 13 mmol/L [9]. After adjustment for other covariates, the mortality risk associated with low iron level in our study was increased by 67 %, and by 156 % in patients with low iron and high sTfR. Interestingly, this risk in MI patients is higher than the 37 % risk increase associated with iron \leq 13 µmol/L among patients with HF [9]. This difference may be partially explained by the addition of antiplatelet therapy in MI patients, which may further worsen the pre-existing ID.

In previous studies, MI was associated with serum iron, TIBC, and TSAT decrease and ferritin increase, with MI severity affecting the magnitude of this change [23,24] Thus, low iron levels may be only a marker of MI severity. However, sTfR as a marker of iron demand is not affected by inflammation [22] and MI severity (Supplementary Table 1). This suggests that ID is not only a marker of MI severity but also a risk factor that may be intervened. Previous studies suggest the biological plausibility of this concept. In an animal model, the deleterious effect of ID was at least in part explained by increased oxidative/nitrosative stress and altered antioxidant defense caused by inhibition of the endothelial nitric oxide synthase (eNOS)/ soluble guanylate cyclase/protein kinase G pathway, leading to eNOS degradation via ubiquitin/proteasome system [25]. Altered energy metabolism is another possible explanation of the deleterious effect of ID in CAD [26,27] In a small study among STEMI patients, application of ultrasmall superparamagnetic iron-oxide within 4 days following an acute myocardial infarction led to smaller infarct size [28]. While our observational study is not able to answer the question of whether ID is a risk marker or a risk factor after MI, identifying ID criteria with the best predictive value sets the ground for future interventional studies with iron supplementation.

4.1. Strengths and limitations of the study

We must admit several limitations of our study. First, iron metabolism was measured at a single time point one day after hospital admission. Because iron parameters dynamically evolve after MI, we were unable to determine how measurements at different time points would affect the prognostic value of ID criteria.

Nevertheless, in a previous study using serial measurement in ACS patients, iron status patterns did not differ in those with and without events [21].

Second, we have used all-cause, rather than cardiovascular mortality, as we were unable to ascertain the cause of death. On the other hand, cardiovascular death is the leading cause of mortality in patients in the first four years after MI [29]. Based on previous studies analyzing the association of ID with total and cardiovascular mortality, we believe that changing the primary study objective would not affect our results [12, 30]

Third, due to the observational nature of our study, no causal inferences can be drawn from our results. Future interventional studies will be needed to evaluate the effects of iron supplementation in patients with ID defined by our criteria.

Fourth, we did not measure hepcidin level, which is considered a key regulator of iron homeostasis [31]. However, in a previous study hepcidine level was not independently associated with the outcome of patients with coronary heart disease [32].

Fifth, because we did not have data on iron supplementation during the study follow-up, we were unable to account for this effect.

The strengths of our study include analysis of various iron status parameters including sTfR and the large single-center cohort of consecutive MI patients with a relatively long follow.

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5. Conclusion

The present study among consecutive patients hospitalized for their first myocardial infarction shows that iron deficiency is present in over 50 % of patients. Among several iron deficiency criteria, the combination of low iron level and high soluble transfer receptor were independently associated with mortality risk and improved risk stratification. The clinical benefit of iron supplementation decision-making based on our criteria will have to be addressed in future studies.

Declartion of competing interest

Dr. Jenča has received consulting fees from Swixx Biopharma. The remaining authors have nothing to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author (PW) upon reasonable request.

Ethical approval information

The study was approved by a local ethics committee. All participants gave their written informed consent prior to data collection.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.04.020.

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