Relation of Iron Status to Prognosis After Acute Coronary Syndrome

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Iron deficiency has been extensively researched and is associated with adverse outcomes in heart failure. However, to our knowledge, the temporal evolution of iron status has not been previously investigated in patients with acute coronary syndrome (ACS). Therefore, we aimed to explore the temporal pattern of repeatedly measured iron, ferritin, transferrin, and transferrin saturation (TSAT) in relation to prognosis post-ACS. BIOMArCS (BIOMarker study to identify the Acute risk of a Coronary Syndrome) is a prospective, multicenter, observational cohort study conducted in The Netherlands between 2008 and 2015. A total of 844 patients with post-ACS were enrolled and underwent high-frequency (median 17) blood sampling during 1 year follow-up. Biomarkers of iron status were measured batchwise in a central laboratory. We analyzed 3 patient subsets, including the case-cohort (n = 187). The primary endpoint (PE) was a composite of cardiovascular mortality and repeat nonfatal ACS, including unstable angina pectoris requiring revascularization. The association between iron status and the PE was analyzed using multivariable joint models. Mean age was 63 years; 78% were men, and >50% had iron deficiency at first sample in the case-cohort. After adjustment for a broad range of clinical variables, 1 SD decrease in log-iron was associated with a 2.2-fold greater risk of the PE (hazard ratio 2.19, 95% confidence interval 1.34 to 3.54, p = 0.002). Similarly, 1 SD decrease in log-TSAT was associated with a 78% increased risk of the PE (hazard ratio 1.78, 95% confidence interval 1.17 to 2.65, p = 0.006). Ferritin and transferrin were not associated with the PE. Repeated measurements of iron and TSAT predict risk of adverse outcomes in patients with post-ACS during 1 year follow-up.

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Iron metabolism is important to maintain biologic function, and disbalance can lead to, for example, iron deficiency (ID).[1] ID is a prevalent co-morbidity in heart failure (HF) and independently associated with mortality and with reduced functional capacity and quality of life.[2] Correction of ID with intravenous ferric carboxymaltose has been shown to improve prognosis compared with placebo.[3,4] Therefore, iron status screening and treatment of ID of symptomatic, systolic HF patients have a class IC and class IIa recommendation, respectively.[5] However, despite a high prevalence,[6−9] iron status has been insufficiently addressed in patients with coronary heart disease (CHD), and therefore, the prognostic value and clinical implications remain unclear. A recent meta-

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analysis, comprising a total of 7 studies on 2,821 participants with acute coronary syndrome (ACS), showed that patients with baseline ID may have worse prognosis.[10] Nevertheless, these previous studies have an important caveat because baseline ID is a binary snapshot of iron status that fails to capture the dynamic process of iron homeostasis and disease progression. Therefore, we applied a joint model approach to investigate if the temporal pattern of iron status based on repeatedly measured biomarkers is associated with prognosis in patients post-ACS admission.

Methods

The BIOMArCS (BIOMarker study to identify the Acute risk of a Coronary Syndrome), prospective, multicenter, observational cohort study enrolled 844 patients with post-ACS in 18 centers in The Netherlands between 2008 and 2015. This study and the case-cohort design and its rationale have been described previously.[11,12] Briefly, the overarching goal of this study was to identify clinically relevant biomarkers and investigate their temporal pattern in relation to cardiovascular (CV) events. Patients aged >40 years who were hospitalized for ACS, including ST-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris (UAP) with an additional CV risk factor, were included. Patients underwent repeat venipuncture during 1 year after initial hospitalization: at admission, discharge, and afterwards every 2 weeks during the first half year and monthly thereafter with a median of 17 samples per patient (p.p.) (interquartile range [IQR] 12 to 20). A subset of patients (68) underwent additional high-frequency sampling at day 1 to 4 to assess the temporal evolution and normalization in the early phase after index admission. Blood sampling was terminated if the patient underwent coronary artery bypass grafting, HF hospital admission, or a deterioration of renal function (estimated glomerular filtration rate <30 ml/min/1.73 m^2) to avoid bias in biomarker levels. The primary endpoint (PE) was a composite of CV mortality and repeat nonfatal ACS, including UAP requiring urgent coronary revascularization, which was adjudicated by a Clinical Event Committee blinded to biomarker data.

All participants provided written informed consent before study procedures. Management was according to the guidelines at the time and at the discretion of the treating physician. This study was conducted in compliance with the Declaration of Helsinki and was approved by the institutional review boards at all participating centers. BIOMArCS has been registered in The Netherlands Trial Register with the unique identifiers: NTR1106 and NTR1698.

Nonfasting blood samples were first handled on site within 4 hours after venipuncture, and aliquots were stored at −80°C before transport under controlled conditions to Erasmus MC, Rotterdam for long-term storage. Iron status biomarkers included iron, ferritin, and transferrin, which were measured in serum using the quantitative sandwich electrochemiluminescence immunoassay ECLIA (Roche Diagnostics, Mannheim, Germany) on a Cobas immunoassay analyzer. After follow-up ended, blood samples were analyzed batchwise in a central laboratory. Analysts were blinded to patient data. Additionally, transferrin saturation (TSAT) was calculated in the context of this analysis using the formula:[13]

$$TSAT = \frac{Serum\ iron\ (\mu mol/L)}{Total\ iron\ binding\ capacity\ (TIBC)\ =\ transferrin\ (g/L)\ *\ 25} \times\ 100\ \%$$

ID has a heterogenous definition throughout literature. We defined ID as ferritin <100 μg/L (absolute), indicating depleted iron stores, or ferritin 100 to 300 μg/L with TSAT <20% (functional), indicating inadequate mobilization or mismatch, according to the main consensus in HF.[5,14,15] This definition has a sensitivity of 82% for identifying ID based on the gold standard bone marrow staining.[15]

For this current analysis, we used 3 subsets of the BIOMArCS study (Figure 1):

1. Case-cohort (n = 187) consisting of a random sample of 150 patients (142 event-free patients and 8 patients with the event (PE)) taken from the cohort, complemented with the remaining 37 patients with the event. Therefore, this set includes all 45 events. A total of 1,478 and median of 8 blood samples (IQR 4 to 11) p.p. were available.
2. Post-30 days set (n = 158) consisting of the case-cohort minus the patients who experienced the event during or lacked biomarker measurements after the first 30 days. This set includes 28 events (of the 45) with a total of 1,119 and median of 7 blood samples (IQR 5 to 9) p.p.
3. Stabilization set (n = 191) consisting of 142 event-free patients from the case-cohort plus an additional 49 event-free patients (who underwent high-frequency sampling) from the cohort with a total of 1,507 and median of 8 blood samples (IQR 5 to 10) p.p.

Normality was assessed by visually exploring histograms and Q-Q plots. Continuous variables with a normal distribution are presented as mean and SD, whereas non-normally distributed continuous variables are presented as median and IQR. Categorical variables are presented as counts and percentages. Differences in ID and number of events between quartiles of biomarker levels were evaluated using the chi-square test.

The values of iron, ferritin, transferrin, and TSAT were log-transformed and then standardized. The obtained Z scores were used for further analyses to allow for direct comparison between markers. The association between iron status and the PE was analyzed using multivariable joint models that simultaneously analyzed longitudinal biomarker data and time-to-event data.

We ran the following joint models on the case-cohort and post-30 sets:

1. Univariable or unadjusted.

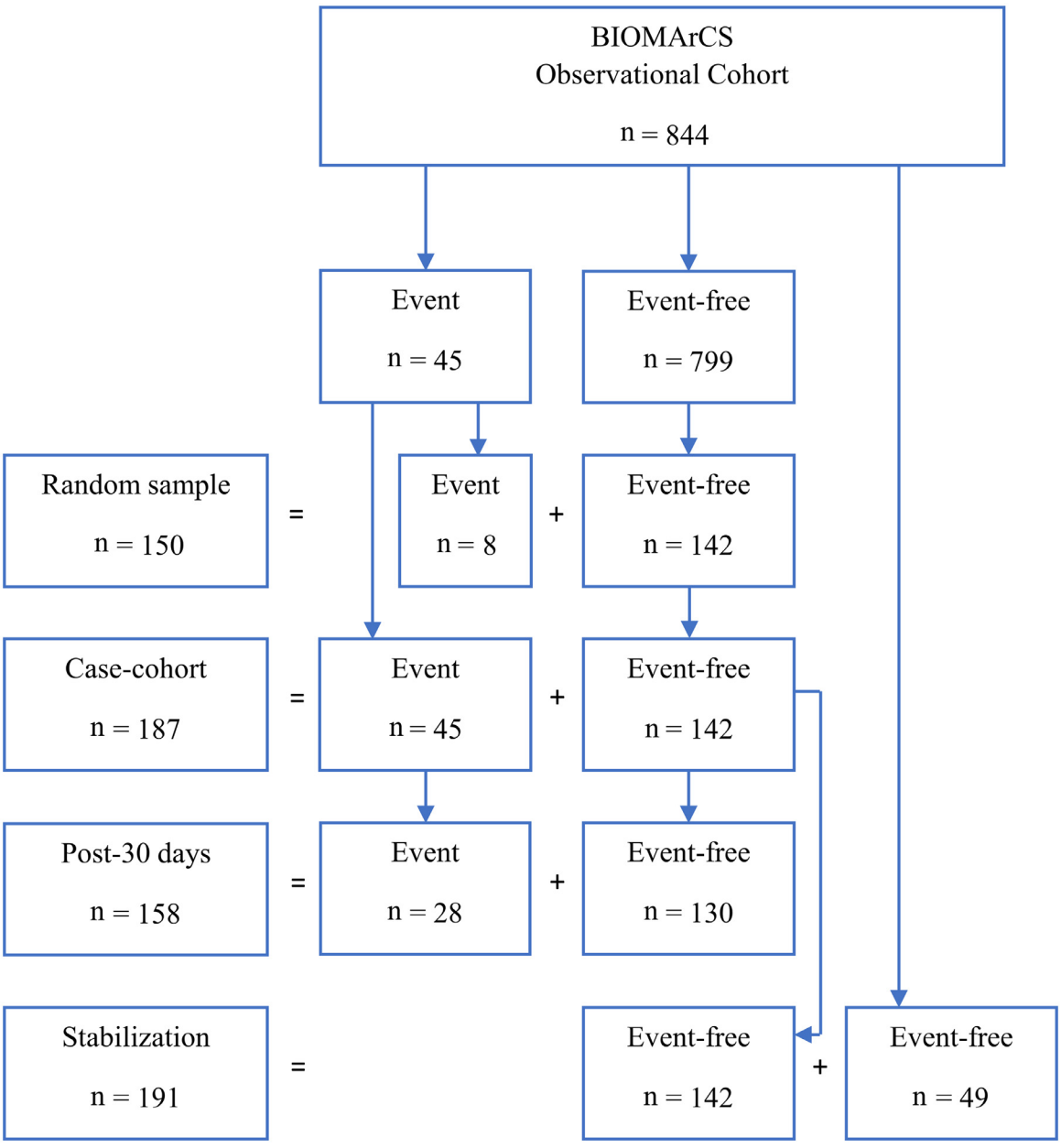

Figure 1. Flowchart of patient subsets.

2. Adjusted for Global Registry of Acute Coronary Events (GRACE) risk score and gender.
3. Adjusted for GRACE risk score, gender, body mass index, smoking status, diabetes mellitus, hypercholesterolemia, coronary artery bypass grafting, valvular heart disease, stroke, peripheral vascular disease, statin use, vitamin K antagonist use, and repeated measurements of log-transformed estimated glomerular filtration rate.[16]

Covariates were selected based on previous literature on ID and potential confounders in known ACS risk prediction tools. The Cox proportional hazards regression sub model was only adjusted for GRACE risk score. The GRACE risk score was calculated based on the model developed by Eagle et al[17] containing age, pulse, systolic blood pressure, initial serum creatinine, positive initial enzymes, ST-segment depression, previous myocardial infraction (MI), previous congestive HF, and in-hospital percutaneous coronary intervention.

For the visualization of the temporal (case-cohort), time-to-event (post-30 set) and stabilization patterns (stabilization set), we used linear mixed effects models. We used 2 cubic splines to allow for nonlinearity, which were placed on different knots based on optimal Akaike's and Bayesian information criteria. Random slopes and intercepts were also included to model patient-specific trajectories. A biomarker was considered stabilized if the change in average level between 2 consecutive days was <1%.

Results are presented as hazard ratios (HRs) per 1 SD decrease in log-biomarker level with corresponding 95% confidence intervals (CIs) and represent the instantaneous risk of the PE at any given time point during follow-up. The $p < 0.05$ (2-sided) was considered statistically significant. Data were analyzed using R Statistical Software version 3.6.3 (Vienna, Austria), using mvJMBayes function within the "JMBayes" package for joint models.

Results

Clinical characteristics for each of the 3 sets are presented in Table 1. Mean age was between 62 and 64 years. More than 75% were men. The most common admission diagnosis was STEMI. The median GRACE risk score at baseline was >109 (intermediate risk). More than a quarter of the patients had previous MI. Chronic HF was not common (<5%).

Table 1
Characteristics of study population in post-30 set (n = 158), case-cohort (n = 187) and stabilization set (n = 191)

Variable	Post-30 (n = 158)	Case-cohort (n = 187)	Stabilization (n = 191)
Age (years)	63.5 ± 10.5	63.4 ± 11.0	62.4 ± 10.6
Men	123 (78%)	147 (79%)	148 (77%)
White	152 (96%)	179 (96%)	183 (96%)
Admission diagnosis			
ST-segment elevation myocardial infarction	69 (44%)	81 (43%)	93 (49%)
Non-ST-segment elevation myocardial infarction	66 (42%)	78 (42%)	74 (39%)
Unstable angina pectoris	23 (15%)	28 (15%)	24 (13%)
Culprit coronary artery			
Right	54 (34%)	61 (33%)	59 (31%)
Left main	6 (4%)	6 (3%)	6 (3%)
Left anterior descending	55 (35%)	62 (33%)	68 (36%)
Left circumflex	23 (15%)	26 (14%)	27 (14%)
Cardiovascular risk factors			
Diabetes mellitus	32 (20%)	41 (22%)	33 (17%)
Hypertension	84 (53%)	99 (53%)	101 (53%)
Hypercholesterolemia	76 (48%)	92 (49%)	92 (48%)
Family history of coronary artery disease	75 (59%)	91 (60%)	87 (53%)
Smoking status			
Current smoker	65 (41%)	77 (41%)	80 (42%)
Former smoker	48 (30%)	56 (30%)	50 (26%)
Never smoker	45 (28%)	54 (29%)	61 (32%)
Global Registry of Acute Coronary Events risk score	113 (91 − 132)	113 (91 − 132)	109 (89 − 129)
Prior cardiovascular disease			
Myocardial infarction	51 (32%)	57 (30%)	50 (26%)
Coronary artery bypass grafting	16 (10%)	23 (12%)	14 (7%)
Percutaneous coronary intervention	47 (30%)	52 (28%)	44 (23%)
Stroke	20 (13%)	25 (13%)	19 (10%)
Peripheral vascular disease	15 (9%)	19 (10%)	12 (6%)
Chronic heart failure	7 (4%)	8 (4%)	4 (2%)
Valvular heart disease	5 (3%)	6 (3%)	3 (2%)
Physical examination			
Body mass index (kg/m2)	27.7 ± 3.7	27.6 ± 3.8	27.6 ± 3.6
Heart rate (bpm)	70 (70 − 80)	72 (61 − 83)	73 (62 − 84)
Systolic blood pressure (mmHg)	140 (120 −157)	140 (123 − 157)	137 (117 − 152)
Killip class I	148 (94%)	170 (91%)	177 (93%)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	90 (72 − 113)	92 (73 − 115)	97 (76 − 120)
Medication at discharge			
Aspirin	152 (96%)	172 (92%)	183 (96%)
P2Y12 inhibitor	149 (94%)	169 (90%)	177 (93%)
Vitamin K antagonist	14 (9%)	16 (9%)	14 (7%)
Statin	151 (96%)	172 (92%)	183 (96%)
Beta-blocker	135 (85%)	155 (83%)	167 (88%)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	135 (85%)	155 (83%)	159 (84%)
Iron status at first sample			
Iron (μmol/L)	15 (11 − 18)	13 (10 − 17)	14 (10 − 18)
Ferritin (μg/L)	158 (88 − 281)	180 (112 − 301	182 (116 − 301)
Transferrin (g/L)	2.4 (2.2 − 2.7)	2.4 (2.2 − 2.7)	2.4 (2.2 − 2.7)
Transferrin saturation (%)	23 (20 − 28)	22 (16 − 28)	23 (16 − 29)
Iron deficiency*	73 (47%)	94 (54%)	82 (51%)

Values are in mean ± standard deviation, median (interquartile range 25th - 75th percentile) or n (%).
* Iron deficiency is defined as serum ferritin level <100 μg/L or ferritin 100 − 300 μg/L with a transferrin saturation of <20%.

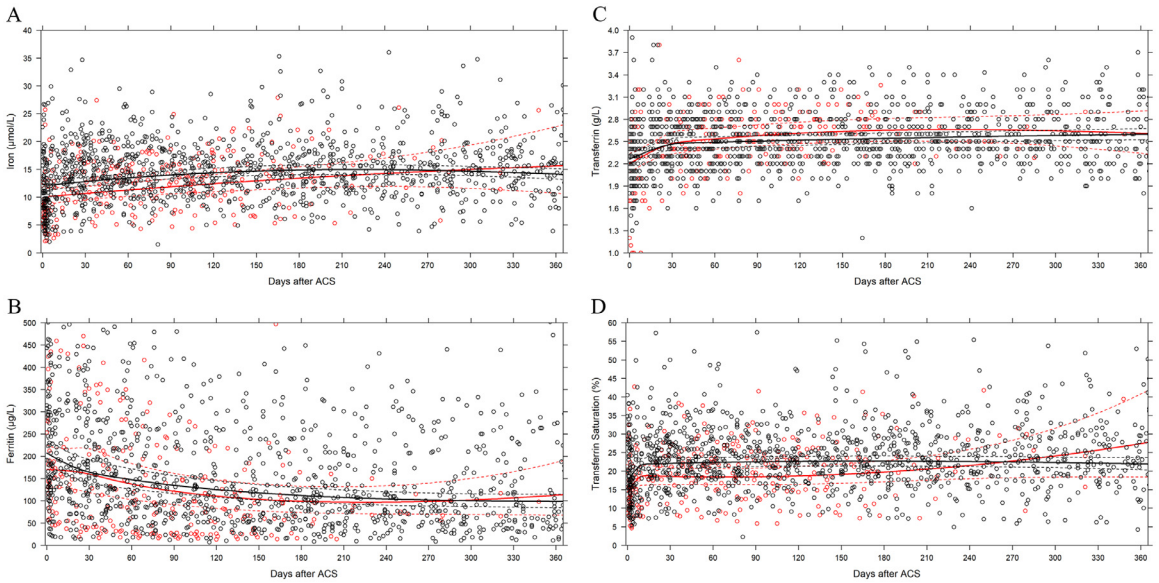

Figure 2. Temporal pattern showing the longitudinal evolution of the average estimated biomarker level (based on LME model) during 1 year follow-up post-ACS in event versus event-free patients (n = 187) for iron (*A*), ferritin (*B*), transferrin (*C*), and TSAT (*D*). Patients who reached the PE are presented in red and those who did not in black. Solid bold lines represent the mean values, and dashed lines represent the corresponding 95% CI. Dots represent the individual measurements. LME = linear mixed effect.

Biomarkers of iron status were relatively similar in level at the first sample across the 3 sets, except for ferritin, which seemed lower in the post-30 set (Table 1). ID (binary variable) at first sample was prevalent with around 50% across the 3 sets. ID in the case-cohort was significantly more prevalent in the lowest quartile of iron level at first sample compared with the highest (100% vs 30%, p <0.001). A similar pattern was observed for ferritin (88% vs 48%, p <0.001) and TSAT (100% vs 16%, p <0.001). Transferrin showed an opposite pattern (45% vs 71%, p = 0.045). There was no significant difference in event rate across quartiles of biomarker levels at first sample.

Exploratory Cox PH regression analysis of ID in the case-cohort revealed a trend, albeit not significant, toward increased risk for the PE with a univariable HR 1.80 (95% CI 0.89 to 3.15, p = 0.068) and adjusted (GRACE risk score) HR 1.67 (95% CI 0.89 to 3.15, p = 0.111).

Biomarker level change throughout follow-up is visualized in Figure 2 for each of the iron status biomarkers in the case-cohort. The longitudinal evolution is the average estimated biomarker level for event versus event-free patients during 1 year follow-up post-ACS. Overall, levels are lower in event patients, with the exception of transferrin, and seem to increase over time above the level of event-free patients, although toward the end of follow-up,

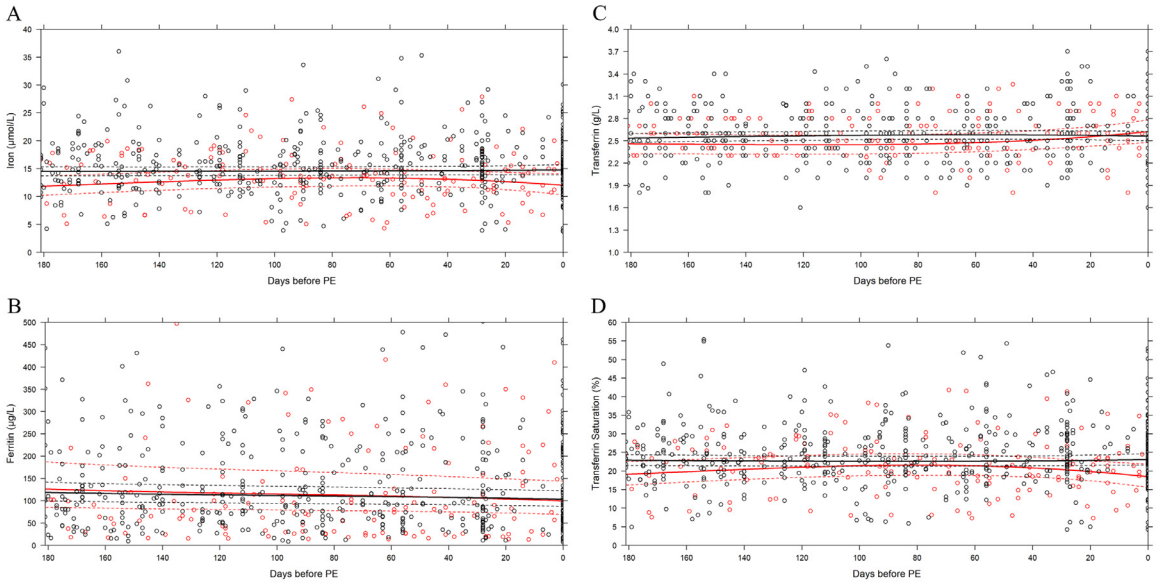

Figure 3. Time-to-event pattern showing the longitudinal evolution of the average estimated biomarker level during follow-up leading up to the PE in event patients versus end-of-follow-up in event-free patients (n = 158) for iron (*A*), ferritin (*B*), transferrin (*C*), and TSAT (*D*). See previous figure legend.

the CI is broad, so caution when interpreting is required. Average ferritin level stays above the absolute ID threshold of 100 μg/L in both groups. Notably, TSAT showed a divergent pattern with an increasing trend in event patients from below the 20% threshold to above, whereas in event-free patients, the levels were mostly above the threshold and remained considerably stable throughout follow-up.

Figure 3 shows the time-to-event pattern in the post-30 set. In this figure, the *x* axis is reversed, showing the period leading up to the PE or end-of-follow-up. There is no clear discernible pattern; however, iron and TSAT levels are lower during the entire follow-up in event patients and slowly decrease the weeks before the event, whereas they remain stable in event-free patients.

The stabilization or washout pattern of biomarkers in the event-free patients from the stabilization set during the first 30 days is presented on the left in Figure 4. On the right are all the individual measurements throughout 1 year of follow-up. Iron showed a J-shaped curve with an initial high level and steep decrease in the first few days, whereas TSAT showed a low-amplitude S-shaped curve. A straight line was observed for ferritin (decreasing) and transferrin (increasing). Iron had a peak at day 0 with an average of 15 μmol/L and stabilized at day 21. Ferritin also had a peak at day 0 with an average of 210 μg/L and stabilized at day 1. Transferrin had a peak at day 32 with an average of 2.5 g/L and stabilized at day 1. TSAT had a peak at day 31 with an average of 23% and stabilized at day 24, considering the S-shaped curve.

Repeated measurements of iron and TSAT were significantly associated with the PE in the joint model analysis of the case-cohort, but ferritin and transferrin were not (Table 2). After adjustment for a broad range of clinical variables (model 3), the adjusted HR (aHR) per 1 SD decrease in iron level was 2.19 (95% CI 1.34 to 3.54, p = 0.002), whereas this was 1.78 (95% CI 1.17 to 2.65, p = 0.006) for TSAT.

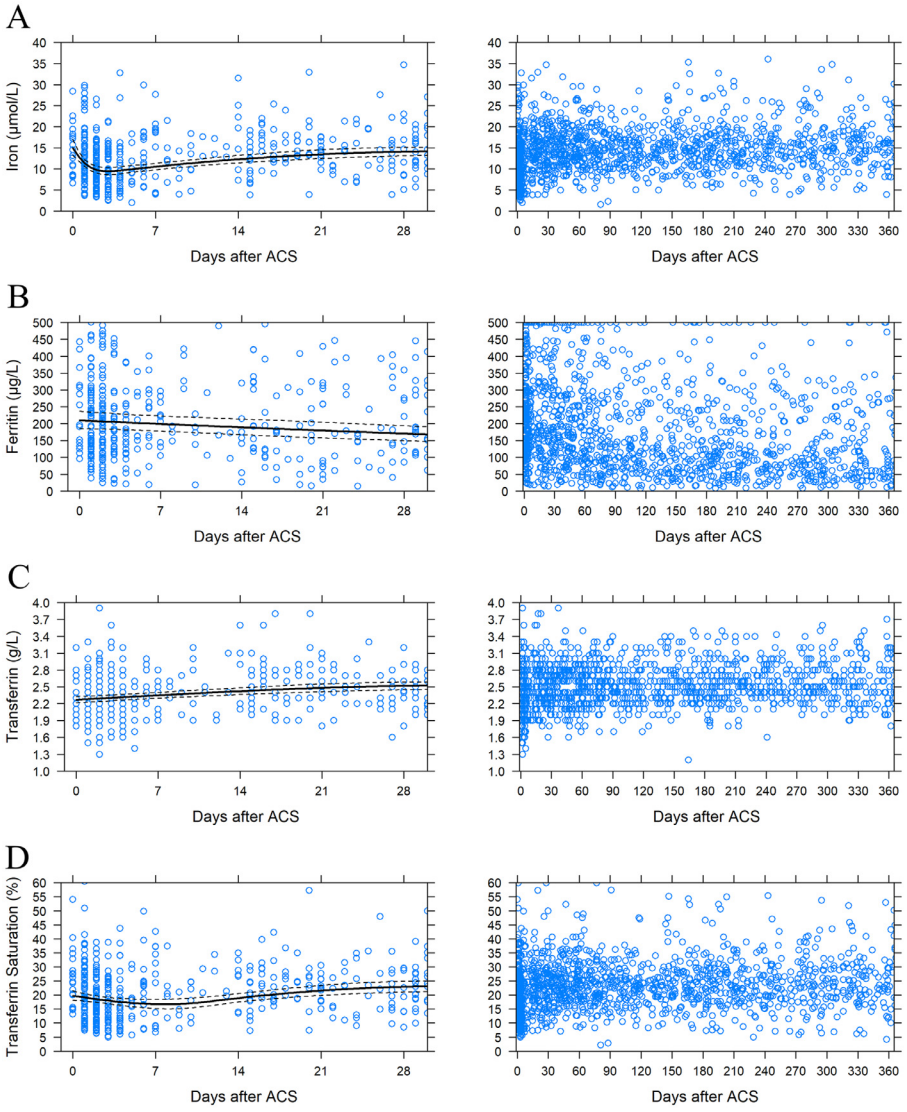

Figure 4. Stabilization pattern showing the longitudinal evolution of the average estimated biomarker level during first 30 day post-ACS (*left*) and the individual measurements during 1 year follow-up post-ACS (*right*) in event-free patients (n = 191) for iron (*A*), ferritin (*B*), transferrin (*C*), and TSAT (*D*). Solid bold lines represent the mean values, and dashed lines represent the corresponding 95% CI. Dots represent the individual measurements.

Table 2
Association of iron status with primary endpoint in case-cohort (n = 187)

Biomarker	Model	Hazard ratio* (95% confidence interval)	*P*-value
Iron	1†	2.13 (1.27 − 3.32)	**0.006**
	2‡	2.06 (1.25 − 3.26)	**0.006**
	3§	2.19 (1.34 − 3.54)	**0.002**
Ferritin	1	1.00 (0.68 − 1.37)	0.934
	2	0.97 (0.68 − 1.38)	0.830
	3	0.96 (0.69 − 1.36)	0.808
Transferrin	1	0.95 (0.63 − 1.35)	0.800
	2	0.96 (0.66 − 1.39)	0.818
	3	0.95 (0.63 − 1.39)	0.832
Transferrin saturation	1	1.82 (1.22 − 2.61)	**0.006**
	2	1.79 (1.15 − 2.66)	**0.006**
	3	1.78 (1.17 − 2.65)	**0.006**

* Per 1 standard deviation decrease of the log-transformed biomarker level.
† Unadjusted.
‡ Adjusted for Global Registry of Acute Coronary Events risk score and gender.
§ Adjusted for Global Registry of Acute Coronary Events risk score, gender, body mass index, smoking status, diabetes, hypercholesterolemia, coronary artery bypass graft, valvular heart disease, stroke, peripheral vascular disease, statin use, vitamin K antagonist use and repeatedly measured log-transformed estimated glomerular filtration rate.

In contrast to the case-cohort, removal of the initial 30-day phase rendered the association of iron and TSAT not significant in the analysis of the post-30 set, despite a trend for worse prognosis (Table 3). The aHR per 1 SD decrease in iron level was 1.45 (95% CI 0.81 to 2.38, p = 0.162). Similarly, the aHR was 1.28 (95% CI 0.77 to 1.99, p = 0.288) for TSAT.

Table 3
Association of iron status with primary endpoint in post-30 set (n = 158)

Biomarker	Model	Hazard ratio* (95% confidence interval)	*P*-value
Iron	1†	1.52 (0.87 − 2.53)	0.146
	2‡	1.53 (0.80 − 2.68)	0.168
	3§	1.45 (0.81 − 2.38)	0.162
Ferritin	1	1.08 (0.74 − 1.66)	0.748
	2	1.06 (0.72 − 1.61)	0.784
	3	1.03 (0.69 − 1.56)	0.886
Transferrin	1	1.08 (0.69 − 1.74)	0.786
	2	1.04 (0.67 − 1.64)	0.866
	3	1.03 (0.65 − 1.63)	0.872
Transferrin saturation	1	1.35 (0.80 − 2.21)	0.238
	2	1.35 (0.84 − 2.03)	0.204
	3	1.28 (0.77 − 1.99)	0.288

* Per 1 standard deviation decrease of the log-transformed biomarker level.
† Unadjusted.
‡ Adjusted for Global Registry of Acute Coronary Events risk score and gender.
§ Adjusted for Global Registry of Acute Coronary Events risk score, gender, body mass index, smoking status, diabetes, hypercholesterolemia, coronary artery bypass graft, valvular heart disease, stroke, peripheral vascular disease, statin use, vitamin K antagonist use and repeatedly measured log-transformed estimated glomerular filtration rate.

Discussion

In this analysis of patients with post-ACS from the BIOMArCS study, we show that repeated measurements of decreased iron and TSAT levels, in contrast to ferritin and transferrin, are associated with an increased risk for the composite PE of CV mortality and repeat nonfatal ACS including UAP requiring urgent coronary revascularization during 1-year follow-up. Moreover, we demonstrate that there is no clear divergent pattern in temporal and time-to-event evolution of biomarker levels between event and event-free patients, although iron and TSAT seemed to decrease somewhat before the PE. Both the stabilization pattern and day were different between biomarkers, illustrating that there is considerable variability present between them.

ID is a prevalent condition with 43% in a meta-analysis of patients with ACS.[10] A limited number of studies reported on prognosis in the presence of baseline ID and showed increased risk for CV events.[10] Furthermore, Meroño et al[8] also showed that ID results in worse exercise capacity and worse quality of life in the recovery phase post-ACS, although no effect on CV morbidity or mortality was shown. A retrospective subgroup analysis of 836 patients with ACS (29% ID) from the AtheroGene cohort study showed a 52% increased risk for CV mortality or MI during 4-year follow-up.[9] In our study, ID was more prevalent (~50%), and while not our primary focus, ID did reveal a trend toward increased risk (67%) for a similar endpoint but did not reach significance. This could be due to shorter follow-up and lower endpoint cases (45 vs 111) or patient selection compared with AtheroGene. Regardless, we cannot unequivocally state that ID is directly related with the PE because ferritin levels were not associated with the PE in longitudinal analysis and could be due to underlying anemia or proinflammatory state.

Iron and TSAT were the best indicators of ID and showed similar performance in a study of HF patients.[15] Similarly, we showed in patients with post-ACS that ID (according to the same definition) was 100% prevalent in the lowest quartile of iron and TSAT level at first sample. The utility of serum iron itself for the assessment of iron status is limited because of diurnal variation in level, especially in nonfasting samples.[18] Duarte et al[19] showed that in patients admitted with ACS and in the lower tertile of serum iron level had a higher rate of mortality and HF at 1 year but not reinfarction. Likewise, Steen et al[20] failed to demonstrate an association between catalytic iron and risk of MI in 1,701 patients with ACS. In contrast, we showed that a 1 SD decrease in serum iron was associated with >twofold greater risk for CV mortality and repeat ACS. A retrospective cohort study showed that excessively low or high baseline serum iron level (U-shaped relation) without anemia is an independent risk factor for major adverse CV and cerebrovascular events (MACCE) in patients with CHD complicated with chronic HF.[21] In our study, chronic HF was uncommon and accounted for in the GRACE risk score, and we found no association between higher iron levels and adverse outcome.

TSAT ≤20% as single parameter was highly correlated with bone marrow ID in HF patients,[15] and patients below

this threshold saw most benefit from ferric carboxymaltose.[3] In an observational study of 252 older patients with ACS (60% ID), baseline TSAT level <20% was independently and inversely associated with an increased risk for mortality.[7] Our study confirms this association based on repeated measurement of TSAT for CV mortality and repeat nonfatal ACS.

The role of ferritin in atherosclerosis and prognosis in patients with ACS is subject to diverging perspectives. Some studies even suggest a cytoprotective effect of ferritin,[22] whereas a prospective study in healthy Finnish men actually showed that elevated serum ferritin >200 mg/L was associated with a 2.2-fold greater risk of MI.[23] Duarte et al[19] showed that both low (<111) and high (>219) serum ferritin levels were associated with higher incidence of HF during hospitalization and mortality in patients with ACS. Moreover, a high serum ferritin level of 316 μg/L was an independent predictor of 1-year mortality. In contrast, Dominguez-Rodriguez et al[24] showed in patients with STEMI who underwent primary PCI that lower baseline serum ferritin levels were predictive of MACE at 30 days. Our study on repeated measures did not show any association of ferritin with CV mortality and repeat nonfatal ACS. This could be due to ferritin being falsely elevated as an acute phase protein in the early phase post-ACS or as a marker of ongoing low-grade vascular inflammation,[25] thereby masking a possible ID. An alternative noteworthy indicator that unlike ferritin is not affected by inflammation is the soluble transferrin receptor or soluble transferrin receptor/ferritin index,[26] which was strongly associated with long-term CV mortality and future MI in patients with CHD from AthereoGene.[27]

Hasić et al[28] described the changes in iron status parameters in patients with ACS during day 1 to 7 of hospital admission. A significant decrease in iron and total iron binding capacity along with a significant increase in ferritin were observed. Our study also showed a considerable decrease in iron, but in contrast, we showed that although average ferritin level was somewhat higher in event patients, it decreased in the first week(s). It is unclear how prevalent ID was in their study, and anemia status was unknown in ours.

Considering the heterogeneity in definition across studies and multitude of indicators of iron status, there is a clear need for a standardized way of iron assessment with appropriate cut-off values for the ACS population. Like in HF patients, ID could be a potential target in the management of patients with CHD with potential prognostic benefit. Therefore, routine screening in this population, especially in the acute phase, should be considered for improved risk stratification. Further research in the form of a randomized controlled trial investigating the effectiveness and safety of an intervention with iron supplementation on long-term adverse outcomes in patients with post-ACS with or without ID could then be conducted.

To the best of our knowledge, this is the first study to evaluate the prognostic value of repeated measurements of several iron status biomarkers in patients with post-ACS. We analyzed high-frequency blood samples using multivariable joint models in 3 subsets of BIOMArCS that was specifically designed to investigate the longitudinal evolution of biomarkers, providing valuable information on their temporal pattern and relation with prognosis.

However, some limitations should be acknowledged. First, the analysis in the post-30 set could be underpowered because only 28 events were available. Another explanation could be that the impact of alterations in iron status on prognosis after the acute phase might be less prominent because of underlying inflammation as a possible reason. This could explain the discrepancy in association and significance level compared with the analysis of the case-cohort. Furthermore, variability in sampling moment[18] could have affected biomarker measurements. Additionally, sampling was not terminated in case of possible bleedings which could have affected the results. Last but not least, residual confounding could be an issue, despite extensive adjustment for a wide range of relevant confounders in the joint models. In particular, anemia, a predictor of adverse outcomes in ACS,[29] or more importantly, repeated measurements of hemoglobin were not available. Although previous literature has demonstrated ID was independently associated with adverse outcomes regardless of additional adjustment for hemoglobin,[9] we are unaware of how this might have affected the results of our study on the temporal pattern of iron status.

In conclusion, our analysis of subsets of BIOMArCS shows that repeated measurements of iron and TSAT predict CV mortality and repeat nonfatal ACS including UAP requiring urgent coronary revascularization during 1 year follow-up in patients with post-ACS. No clear discernible differences in biomarker patterns between event and event-free patients are observed by visually exploring the temporal evolution or time-to-event patterns.

Disclosures

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