

# Changes in iron metabolism after primary PCI in patients with STEMI and ischemia-reperfusion injury

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**Abstract.** Within the present study, the aim was to investigate the dynamic changes in iron metabolism parameters in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) and to evaluate their association with the occurrence of ischemia-reperfusion injury (IRI). The present single-center, prospective observational study enrolled 68 patients with STEMI undergoing primary PCI from January to December 2024. Clinical characteristics, laboratory data and echocardiographic findings were collected. Patients were classified into IRI (n=30) and non-IRI (n=38) groups based on predefined IRI criteria. Venous blood samples were obtained pre- and post-PCI to measure ferritin, hepcidin, heme and heme oxygenase-1 (HO-1) levels. Statistical analyses were conducted to compare the changes in these iron metabolism indices between the two groups. Among the 68 enrolled patients, the incidence of IRI was 44.1%. Ferritin showed a significant increase post-PCI. The rise in ferritin and hepcidin was more pronounced in the IRI group compared with the non-IRI group. Although both IRI and non-IRI groups exhibited an upward trend in heme and HO-1 after PCI, the elevation in heme was higher in the IRI group in comparison with the HO-1. Differences in heme and HO-1 between IRI and non-IRI groups were not statistically significant. In conclusion, post-PCI rises in ferritin and hepcidin were more pronounced in patients with STEMI and IRI, while heme and HO-1 showed non-significant upward trends. These results indicated an association between altered iron/heme metabolism and IRI and therefore support further evaluation of ferritin/hepcidin as candidate biomarkers, pending validation in larger multicenter studies with multivariable adjustment.

## Introduction

ST-segment elevation myocardial infarction (STEMI) is characterized by complete occlusion of a major coronary artery and represents a severe clinical presentation of ischemic heart disease. Global data indicate that ischemic heart disease affected an estimated 254.28 million people and caused 8.99 million deaths worldwide in 2021 (1). Rapid restoration of coronary blood flow is key in salvaging ischemic myocardium and improving patient outcomes. Primary percutaneous coronary intervention (PCI) has become the most established method for treating STEMI and can effectively restore flow in the infarct-related artery. However, the reperfusion process itself may paradoxically induce further myocardial injury, known as ischemia-reperfusion injury (IRI) (2). IRI markedly increases the final infarct size and contributes to adverse left ventricular remodeling, ultimately affecting long-term cardiac function and increasing the risk of heart failure. The underlying mechanisms of IRI are complex and multifactorial, involving oxidative stress, inflammation, calcium overload and mitochondrial dysfunction. Specifically, abrupt reperfusion induces a burst of reactive oxygen species that damages cell lipids, proteins and DNA; inflammatory cell activation and cytokine release further exacerbate endothelial and myocardial injury; calcium overload promotes cardiomyocyte hypercontracture and activation of calcium-dependent enzymes and mitochondrial dysfunction impairs ATP production and triggers cell death (2). Therefore, IRI has become a challenging clinical issue with limited treatment options currently available.

Iron metabolism serves a key role in maintaining normal myocardial function. Iron is an important component of hemoglobin and myoglobin, participating in the transport and storage of oxygen and is also important for the energy metabolism of cardiomyocytes (3). Dysregulation of iron metabolism, particularly iron overload, has been associated with the occurrence and development of a number of cardiovascular diseases, including atherosclerosis, heart failure and myocardial ischemia-reperfusion injury (3). Excess iron can catalyze the production of reactive oxygen species (ROS) through the Fenton reaction, resulting in oxidative stress and lipid peroxidation, which damage cell membranes and organelles (4). Furthermore, iron overload may activate inflammatory pathways, including NF- $\kappa$ B-mediated signaling and downstream cytokine release, such as TNF- $\alpha$  and IL-6, thereby exacerbating inflammatory responses and further

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injuring cardiomyocytes (5). Ferritin, hepcidin, heme and heme oxygenase-1 (HO-1) are key regulatory factors of iron metabolism whose roles in cardiovascular diseases have garnered increasing attention (3,5). Ferritin is a notable intracellular iron-storage protein, and serum ferritin is commonly used as a surrogate marker of body iron stores, although it may also be influenced by inflammation and tissue injury (3,5). Hepcidin is the key hormone in regulating iron homeostasis, predominantly produced by the liver and it inhibits iron absorption and release. Heme is the prosthetic group of hemoglobin and myoglobin and exhibits pro-oxidative and pro-inflammatory effects, whereas HO-1 is a protective enzyme with antioxidant and anti-inflammatory properties that can degrade heme. Given that iron overload, oxidative stress and inflammation are all central to IRI pathology, it was hypothesized that disordered iron metabolism may serve an important role in IRI following direct PCI in patients with STEMI (5).

The present study aimed to investigate the dynamic changes in iron metabolism indices (including ferritin, hepcidin, heme and HO-1) in patients with STEMI following direct PCI and analyze the association between these indices and IRI. The present study aimed to expand the current understanding of the role of iron metabolism in the development of IRI and discuss whether these iron metabolism indices could serve as potential biomarkers and therapeutic targets for IRI.

## Materials and methods

**Study population.** From January to December 2024, patients diagnosed with acute STEMI who underwent emergency PCI at Beijing Shijitan Hospital (Beijing, China) were consecutively enrolled in the present single-center, prospective, observational study. The inclusion criteria ensured patients: i) Were aged  $\geq 18$  years; ii) had STEMI determined by clinical presentation and electrocardiography (ECG), consistent with the Fourth Universal Definition of Myocardial Infarction (6); iii) were in a stable condition; iv) demonstrated willingness to participate within the present study with signed informed consent; and v) were in receipt of direct primary PCI reperfusion therapy. The exclusion criteria encompassed: i) Advanced malignancy; ii) severe hepatic or renal failure; iii) active bleeding or marked hematological disorders; iv) serious trauma, major surgery or a notable bleeding event within the previous 3 months; v) immune system disorders or use of corticosteroids or immunosuppressants; vi) pregnancy or lactation; vii) or the inability to complete follow-up or related assessments in the present study, for other reasons.

A total of 68 patients with STEMI who met the aforementioned criteria and completed follow-up were ultimately included. Based on whether IRI occurred after PCI, patients were categorized into an IRI group and a non-IRI group. Clinical characteristics and indicators were compared between the two groups.

The present study conformed to the relevant ethical principles for biomedical research involving human subjects outlined in the Declaration of Helsinki. The present study protocol was reviewed and approved by the Medical Ethics Committee of Beijing Shijitan Hospital (Beijing, China; approval no. IIT2024-040). All participants provided written informed consent prior to participation in the present study.

**Treatment protocol.** All enrolled patients underwent primary PCI within the standardized STEMI management pathway of Beijing Shijitan Hospital, which aligned with contemporary guideline recommendations (7). Before PCI, patients received a loading dose of aspirin (300 mg) and an oral P2Y12 (adenosine diphosphate) receptor inhibitor (300 mg clopidogrel or 180 mg ticagrelor). Periprocedural anticoagulation was administered (typically intravenous unfractionated heparin), with bivalirudin used when clinically indicated. After PCI, dual antiplatelet therapy was continued and guideline-directed secondary prevention therapy was prescribed as appropriate, including high-intensity statins,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Additional medications (such as nitrates, diuretics or mineralocorticoid receptor antagonists) were used according to the clinical condition of the patient.

**Definition and assessment of IRI.** To the best of our knowledge, currently, there is no fully standardized criterion for defining IRI. Therefore, consistent with prior clinical evidence (8,9) and guideline documents (6,7) using ECG ST-segment resolution and angiographic perfusion abnormalities as surrogates of impaired myocardial reperfusion/microvascular dysfunction after primary PCI, IRI in the present study was assessed using ECG, angiographic and biomarker indicators (6-9). Specifically, within 2 h post-PCI, incomplete ST-segment resolution ( $<50\%$ ) or new ST-segment elevation on the ECG, together with either the occurrence of an angiographic 'no-reflow'/'slow-flow' phenomenon during PCI or a markedly elevated peak cardiac troponin level ( $>5$ -fold the 99th percentile upper reference limit), was considered to be consistent with IRI (2,8-9).

### Clinical assessment and laboratory examination

**Clinical data.** Baseline data, including patient sex, age, major cardiovascular risk factors (hypertension, diabetes mellitus, smoking history and hyperlipidemia) and past cardiovascular history, were collected. Preoperative venous blood samples ( $\sim 10$  ml in total) were drawn to assess routine parameters such as complete blood count, liver and renal function tests, lipid profiles, fasting blood glucose and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

**Iron metabolism parameters.** Fasting venous blood samples (5 ml) were collected both pre-PCI (as soon as possible after admission) and post-PCI ( $24 \pm 4$  h after the procedure). Samples were placed in anticoagulant or clot-activator tubes and separated and stored according to the specific assay requirements. Iron metabolism-related indicators included: i) Serum ferritin, which was measured using the Human FE (Ferritin) ELISA kit (cat. no. RXG60096; Quanzhou Ruixin Biotechnology Co., Ltd.) and expressed in ng/ml; ii) hepcidin, determined by the Human Hepcidin ELISA kit (cat. no. RX105169H; Quanzhou Ruixin Biotechnology Co., Ltd.) and expressed in ng/ml; iii) heme (iron protoporphyrin IX), which was measured by the Heme Microplate Assay kit (cat. no. abs580148; Absin Bioscience Inc.) and expressed in  $\mu\text{mol/l}$ ; and iv) HO-1, which was also measured by the HO1 ELISA Kit (cat. no. RX102881H; Quanzhou Ruixin Biotechnology Co., Ltd.) and expressed in ng/ml. Samples were stored and transported in accordance with the manufacturer's instructions. Each assay

was performed in duplicate, and the arithmetic mean of the duplicate measurements was used for statistical analysis.

#### *Diagnostic tests and biomarker measurements.*

**Echocardiography.** Transthoracic echocardiography was performed within 24 h of admission to measure left ventricular ejection fraction (LVEF) and cardiac structural parameters.

**ECG.** Routine 12-lead ECGs were conducted upon admission, 2 h post-PCI, 24 h post-PCI and during any clinical events such as chest pain or arrhythmias.

**Cardiac enzymology.** Venous blood samples were collected every 4 h preoperatively and postoperatively until peak levels were reached and began to decline. Subsequent sampling intervals and duration were determined based on the condition of the patient. Serum cardiac troponin I (cTnI) was quantitatively measured using the Access hsTnI high-sensitivity cardiac troponin I chemiluminescent immunoassay kit (cat. no. B52699; Immunotech SAS) on a Beckman Coulter Access immunoassay system in the clinical laboratory of Beijing Shijitan Hospital. The maximum cTnI value recorded during the present study period for each patient was designated as the peak cTnI and used for subsequent statistical analysis.

**Statistical analysis.** Statistical analyses were performed using SPSS (version 27; IBM Corp.). Normality of continuous variables was assessed using the Shapiro-Wilk test and homogeneity of variances was evaluated using Levene's test. Continuous variables are presented as the mean  $\pm$  SD when normally distributed and as the median and interquartile range (IQR) when non-normally distributed. Between-group comparisons (IRI vs. non-IRI) were conducted using the independent-samples Student's t-test when data were normally distributed with equal variances, while Welch's Student's t-test was used for normally distributed data with unequal variances and the Mann-Whitney U test was applied for non-normally distributed variables. Categorical variables are expressed as n (%) and were compared using the  $\chi^2$  or Fisher's exact test, as appropriate. Comparisons between two time points within the same participants (pre-PCI vs. post-PCI) were performed using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. For analyses of changes over time, the change value ( $\Delta$ =post-PCI-pre-PCI) was calculated for each participant and compared between groups using the independent-sample Student's t-test. Welch's t-test or Mann-Whitney U test, as appropriate. Heme and ferritin were presented as median with IQR at all time points for consistent reporting. All tests were two-tailed and  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Demographic characteristics.** A total of 68 patients with STEMI who underwent primary PCI were enrolled in the present study. There were 57 male (83.8%) and 11 female patients (16.2%). The average age of the patients was 63.0 years. Regarding past medical history, hypertension and hyperlipidemia were the most common comorbidities in this cohort, with 49 (72.1%) and 41 (60.3%) patients, respectively. A total of 27 patients (39.7%) had a history of smoking, and 19 patients

(27.9%) had diabetes. Among them, 30 patients developed IRI, accounting for 44.1% (Table I).

**Clinical characteristics of patients with STEMI and IRI.** Based on the presence or absence of IRI, the 68 enrolled patients with STEMI who received primary PCI were divided into an IRI group (n=30) and a non-IRI group (n=38). Compared with the non-IRI group, the IRI group appeared to be younger ( $59.4 \pm 12.7$  vs.  $65.7 \pm 11.9$  years) and there was no statistically significant difference in the sex ratio. Common cardiovascular risk factors (hypertension, diabetes, smoking and hyperlipidemia) also showed no statistically significant differences between the two groups. With regard to culprit vessels, the IRI group exhibited a higher proportion of left anterior descending artery involvement (73.3 vs. 42.1%), but the difference was not statistically significant. Regarding peak TnI levels, the median in the IRI group was higher (49,155.7 vs. 12,504.0 ng/l), although the difference was not statistically significant. Notably, the IRI group had a significantly higher NT-proBNP level upon admission compared with the non-IRI group (480.7 vs. 58.6 pg/ml), suggesting a greater cardiac burden. Differences in high-sensitivity CRP, LVEF and serum creatinine were not statistically significant between the two groups. The neutrophil count in the IRI group ( $6.7 \pm 1.6 \times 10^9$  cells/l) was higher compared with that in the non-IRI group ( $5.6 \pm 1.4 \times 10^9$  cells/l), approaching statistical significance, indicating that more active inflammatory responses may exist in the IRI group. Serum iron levels in the IRI and non-IRI groups were 13.5 and 9.8  $\mu$ mol/l, respectively, with no significance observed. Overall, there were no major differences in sex, age or risk factors among patients with IRI and without IRI, however the IRI group exhibited higher NT-proBNP levels and neutrophil count (Table I).

**Changes in iron metabolism indices (ferritin, hepcidin, heme and HO-1) in patients with STEMI after primary PCI.** Results showed that ferritin was significantly increased after PCI in patients with STEMI. The median ferritin levels before PCI were 61.2 (29.2-84.7) ng/ml and rose to 85.1 (64.2-124.1) ng/ml post-PCI. The median hepcidin level before PCI was 27.6 ng/ml and after PCI remained at 27.6 ng/ml, with no significant change. The median heme level before PCI was 8.9  $\mu$ mol/l and rose to 14.8  $\mu$ mol/l post-PCI but this was not significant. For HO-1, the median value increased from 13.1 ng/ml pre-PCI to 17.7 ng/ml post-PCI, also without statistical significance, but displaying an increasing tendency (Table II).

**Characteristics of serum ferritin and hepcidin changes in patients with STEMI and IRI.** After primary PCI, iron metabolism indices in patients with STEMI exhibited certain changes. In the IRI group, pre-PCI serum ferritin was lower compared with that in the non-IRI group [median, 57.2 (15.0-67.6) vs. 72.1 (37.9, 101.6) ng/ml], whereas post-PCI ferritin levels were 89.1 (62.4-124.3) and 75.6 (65.0-116.5) ng/ml in the IRI and non-IRI groups, respectively; neither difference was statistically significant. However, the median change in ferritin in the IRI group was an increase of 51.1 ng/ml, significantly higher than the decrease of 6.9 ng/ml in the non-IRI group. Meanwhile, the mean pre-PCI hepcidin levels in the IRI and non-IRI groups were 20.6 and 27.1 ng/ml, respectively and the mean

Table I. Baseline characteristics of patients with and without reperfusion injury following acute myocardial infarction.

Variable	Total (n=68)	No reperfusion injury (n=38)	Reperfusion injury (n=30)	P-value
Sex (women), n (%)	11 (16.2)	5 (13.2)	6 (20)	0.930
Age, years (mean $\pm$ SD)	63.0 $\pm$ 12.6	65.7 $\pm$ 11.9	59.4 $\pm$ 12.7	0.229
Diabetes, n (%)	19 (27.9)	8 (21.1)	11 (36.7)	0.409
Smoking, n (%)	27 (39.7)	11 (28.9)	16 (53.3)	0.188
Hyperlipidemia, n (%)	41 (60.3)	25 (65.8)	16 (53.3)	0.244
Hypertension, n (%)	49 (72.1)	27 (71.1)	22 (73.3)	0.943
PtoB time, h (%)				0.893
<3	8 (11.8)	5 (13.2)	3 (10.0)	
3-5	44 (64.7)	25 (65.8)	19 (63.3)	
6-12	16 (23.5)	8 (21.0)	8 (26.7)	
Culprit vessel (LAD), n (%)	38 (55.9)	16 (42.1)	22 (73.3)	0.326
Infarction location (anterior wall), n (%)	38 (55.9)	16 (42.1)	22 (73.3)	0.135
Proximal lesion, n (%)	33 (48.5)	19 (50.0)	14 (46.7)	0.821
NT-proBNP, pg/ml	137.4 (27.6-480.7)	58.6 (13.5-155.3)	480.7 (197.3-512.4)	0.026
hsCRP, mg/l	2.0 (1.1-2.9)	1.5 (0.6-2.2)	2.1 (2.0-2.9)	0.340
Peak cTnI, ng/l	37,932.7 (5,654.1-79,109.0)	12,504.0 (4,723.0-43,861.9)	49,155.7 (14,641.0-102,639.0)	0.106
Creatinine, $\mu$ mol/l (mean $\pm$ SD)	76.6 $\pm$ 16.4	77.4 $\pm$ 17.7	75.8 $\pm$ 14.5	0.825
Left ventricular ejection fraction, %	58.0 (53.0-61.0)	59.0 (53.0-63.0)	56.0 (49.0-59.0)	0.277
Hemoglobin, g/l	144.0 (137.0-157.0)	141.0 (137.0-145.0)	153.0 (132.0-158.0)	0.298
Blood glucose, mmol/l	8.9 (7.8-10.5)	8.5 (8.0-9.1)	9.7 (7.8-10.9)	0.325
Neutrophil count, $\times 10^9$ cells/l (mean $\pm$ SD)	6.0 $\pm$ 1.6	5.5 $\pm$ 1.4	6.7 $\pm$ 1.6	0.053
Serum iron, $\mu$ mol/l (mean $\pm$ SD)	13.0 $\pm$ 5.6	9.8 $\pm$ 6.3	13.5 $\pm$ 7.1	0.199

Data are presented as the median (IQR) unless otherwise specified. IQR, interquartile range; LAD, left anterior descending artery; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hsCRP, high-sensitivity CRP; PtoB, pain-to-balloon time; cTnI, cardiac troponin I.

Table II. Changes in iron metabolism markers before and after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction.

Variable	Total (n=68)	Pre-operative (n=68)	Post-operative (n=68)	P-value
Ferritin, ng/ml	68.8 (55.5-114.8)	61.2 (29.2-84.7)	85.1 (64.2-124.1)	0.020
Hepcidin, ng/ml	27.6 (20.5-30.9)	27.6 (20.5-29.0)	27.6 (21.3-32.0)	0.425
Heme, $\mu$ mol/l	12.6 (7.9, 19.7)	8.9 (6.8, 17.5)	14.8 (9.8, 20.1)	0.124
HO-1, ng/ml	16.1 (2.0, 32.7)	13.1 (2.0, 32.7)	17.7 (2.2-28.9)	0.544

Data are presented as the median (IQR). IQR, interquartile range; HO-1, heme oxygenase-1.

post-PCI levels were 27.0 and 27.1 ng/ml, respectively, with no statistically significant differences between groups at either time point. Notwithstanding the lack of a statistically significant baseline difference, post-PCI hepcidin values tended to converge; the mean increase in hepcidin was 7.7 ng/ml in the IRI group, significantly greater compared with the 1.1 ng/ml increase observed in the non-IRI group (Table III).

*Characteristics of serum heme and HO-1 changes in patients with STEMI and IRI.* Pre-PCI median heme levels in the IRI

and non-IRI groups were 10.4 and 8.9  $\mu$ mol/l, respectively, while the post-PCI median levels were 13.0 and 17.4  $\mu$ mol/l, respectively. There was no statistically significant difference between the groups. The median heme changes for the IRI and non-IRI groups was an increase of 0.4 and 5.1  $\mu$ mol/l, respectively, with no statistically significant difference. For HO-1, the IRI and non-IRI groups had pre-PCI median levels of 13.1 and 18.7 ng/ml, respectively and post-PCI levels of 15.2 and 24.7 ng/ml, respectively, with no statistically significant differences between the groups. The median HO-1 changes

Table III. Pre- and post-operative levels of ferritin and hepcidin in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, stratified by reperfusion injury.

A, Ferritin				
Variable	Total (n=68)	Reperfusion injury (n=30)	No reperfusion injury (n=38)	P-value
Pre-operative, ng/ml	61.2 (29.2-84.7)	57.2 (15.0-67.6)	72.1 (37.9-101.6)	0.112
Post-operative, ng/ml	85.1 (64.2-124.1)	89.1 (62.4-124.3)	75.6 (65.0-116.5)	0.780
Change, ng/ml	34.8 (-10.9-63.9)	51.1 (37.4-64.9)	-6.9 (-20.5-33.1)	0.016
B, Hepcidin				
Variable	Total (n=68)	Reperfusion injury (n=30)	No reperfusion injury (n=38)	P-value
Pre-operative, ng/ml (mean ± SD)	23.9±9.1	20.6±11.1	27.1±4.7	0.094
Post-operative, ng/ml (mean ± SD)	27.0±9.2	27.0±10.5	27.1±8.0	0.974
Change, ng/ml (mean ± SD)	4.1±6.5	7.7±6.7	1.1±4.4	0.016

Ferritin values are presented as median (IQR) for consistent reporting across time points. IQR, interquartile range.

Table IV. Pre- and post-operative levels of heme and HO-1 in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction.

A, Heme				
Variable	Total (n=68)	Reperfusion injury (n=30)	Non-reperfusion injury (n=38)	P-value
Pre-operative, μmol/l	8.9 (6.8, 17.5)	10.4 (7.2, 17.5)	8.9 (5.0, 16.4)	0.544
Post-operative, μmol/l	14.8 (9.8, 20.1)	13.0 (10.4, 23.2)	17.4 (9.8, 19.6)	0.975
Change, μmol/l	4.3 (-4.2, 6.3)	0.4 (-4.7, 4.6)	5.1 (-2.3, 6.9)	0.307
B, HO-1				
Variable	Total (n=68)	Reperfusion injury (n=30)	Non-reperfusion injury (n=38)	P-value
Pre-operative, ng/ml	13.1 (2.0-32.7)	13.1 (1.5-29.1)	18.7 (2.9-33.8)	0.314
Post-operative, ng/ml	17.7 (2.2-28.9)	15.2 (2.0-25.1)	24.7 (3.2-35.9)	0.289
Change, ng/ml	1.1 (-0.1-1.7)	0.1 (-3.8-1.7)	1.2 (0.2-2.0)	0.230

Data are presented as the median (IQR) for consistent reporting across time points. IQR, interquartile range; HO-1, heme oxygenase-1.

in the two groups showed an increase of 0.1 and 1.2 ng/ml, respectively, without a statistically significant difference observed (Table IV).

### Discussion

The present study aimed to investigate the changes in iron metabolism indices (ferritin, hepcidin, heme and HO-1) in patients with STEMI after primary PCI, grouping them by the presence or absence of IRI. The findings revealed that post-PCI ferritin was significantly increased compared with pre-PCI levels among patients with STEMI. The ferritin elevation in patients with IRI was significantly greater compared with that in the non-IRI group. Likewise, the change in hepcidin in

patients with IRI was also higher compared with the non-IRI group. Although no statistically significant difference was observed between groups, both heme and HO-1 levels tended to increase after primary PCI and, compared with patients without IRI.

IRI is a complex and multifactorial pathophysiological process in patients with STEMI undergoing primary PCI. The reported incidence of IRI ranges from 11-48% (2). In the present study, the incidence of IRI was 44.1%. The occurrence of IRI is associated with multiple factors, including ischemic duration, ischemic severity, reperfusion strategy and the baseline disease status of the patient. In the present study, the IRI group exhibited a significantly higher NT-proBNP level upon admission compared with the non-IRI group (P=0.026),

suggesting a heavier cardiac burden, consistent with previous findings that elevated NT-proBNP is associated with the extent of myocardial damage and the severity of IRI (10). Furthermore, although it did not reach statistical significance ( $P=0.053$ ), the IRI group had a higher granulocyte count, suggesting inflammation may serve a role in the development of IRI (11).

The present findings demonstrated that, despite the lack of statistically significant baseline differences, the IRI group of patients with STEMI experiencing IRI after PCI displayed a significantly greater ferritin elevation ( $P=0.016$ ) compared with the non-IRI group. These findings indicate an association between dysregulated iron metabolism and IRI; however, given the observational design, causality cannot be inferred and residual confounding cannot be excluded. Ferritin is the major iron-storage protein, and its elevated level generally reflects increased iron content in the body or disordered iron metabolism (12). During IRI, myocardial cell damage and necrosis lead to the release of intracellular iron to the circulation, raising ferritin levels (13). Furthermore, ROS produced during IRI can promote the release and degradation of ferritin, further exacerbating iron overload (14). Free iron can catalyze ROS production through the Fenton reaction, resulting in lipid peroxidation, protein oxidation and DNA damage, aggravating myocardial damage and apoptosis (15). Simultaneously, iron overload may activate inflammatory cascades and promote the release of inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6, further worsening the inflammatory injury of IRI (16). Hepcidin is a key hormone regulating iron metabolism, functioning mainly by inhibiting iron absorption and release. The present study showed that the magnitude of change in hepcidin in patients with IRI was also significantly higher compared with that in patients without IRI ( $P=0.016$ ), potentially being associated with inflammatory response, as inflammation can elevate the synthesis and release of hepcidin, promoting intracellular iron retention and exacerbating iron overload and oxidative stress injury (17).

The present study demonstrated that heme levels exhibited an upward trend post-PCI in patients with STEMI both in the IRI and non-IRI groups. However, the difference between the groups was not statistically significant. Notably, although there were no statistically significant differences in heme levels between the two groups before PCI ( $P=0.544$ ) and after PCI ( $P=0.975$ ), the heme levels in the IRI group were higher compared with those in the non-IRI group. This trend suggests that heme may serve a role in the pathophysiological mechanisms of IRI. One possible explanation is that patients in the IRI group had higher baseline heme levels, reflecting an inherent susceptibility to oxidative stress and inflammation, which are primary drivers of IRI. This may predispose these patients to greater myocardial injury upon reperfusion. Heme is a component of hemoglobin and myoglobin, serving a key role in oxygen transport and storage. During IRI, myocardial cell damage and hemolysis can lead to the release of heme into the bloodstream (18). Free heme possesses pro-oxidant and pro-inflammatory properties, exacerbating tissue damage caused by IRI (19). It can catalyze the production of ROS through Fenton reactions, leading to lipid peroxidation, protein oxidation and DNA damage (20). Additionally, heme can activate inflammatory cascades, including TLR4-mediated signaling

and downstream NF- $\kappa$ B activation, thereby promoting the release of inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6, thereby further intensifying the inflammatory response and tissue injury (16,19). Furthermore, it should be noted that the magnitude of heme level changes in the IRI group was smaller compared with the non-IRI group (a median increase of 0.4  $\mu$ mol/l in the IRI group vs. a median increase of 5.1  $\mu$ mol/l in the non-IRI group;  $P=0.307$ ), although this difference did not reach statistical significance. This may suggest an impaired capacity for clearance or metabolism of free heme in patients with IRI. Reduced clearance efficiency could lead to sustained elevated heme levels in these patients, thereby exacerbating oxidative damage. However, the role of heme is not entirely detrimental. Previous studies have indicated that lower concentrations of heme may induce the expression of HO-1, exerting antioxidant and anti-inflammatory protective effects (21,22). Therefore, the role of heme in IRI may be dualistic, with its ultimate effect depending on its concentration, duration of action and the physiological state of the organism.

HO-1 is a protective enzyme with antioxidant and anti-inflammatory properties that catalyzes the degradation of heme into biliverdin, carbon monoxide and free iron (21). In the present study, HO-1 levels exhibited an upward trend post-PCI in both the IRI and non-IRI groups of patients with STEMI, although the difference between the groups was not statistically significant. Upregulation of HO-1 may represent an endogenous protective mechanism of the body attempting to counteract the oxidative stress and inflammatory responses induced by IRI (22). The protective effects of HO-1 are primarily mediated through its degradation products biliverdin, carbon monoxide and bilirubin. Biliverdin and bilirubin are effective antioxidants that can scavenge ROS and inhibit lipid peroxidation (23). Carbon monoxide exerts anti-inflammatory, anti-apoptotic and vasodilatory effects (24). However, the modest increase in HO-1 observed in the present study suggests that this protective mechanism may be insufficient to fully offset the damage caused by IRI. This insufficiency could be due to inadequate induction of HO-1 during the IRI process or the inhibition of HO-1 activity.

The results of the present study indicate that there were differences in the magnitude of changes in heme and HO-1 levels post-PCI between the IRI and non-IRI groups of patients with STEMI, although these differences did not reach statistical significance. In the IRI group, the median change in heme was an increase of 0.4  $\mu$ mol/l, whereas in the non-IRI group it was an increase of 5.1  $\mu$ mol/l ( $P>0.05$ ). For HO-1, the median change in the IRI group was an increase of 0.1 ng/ml, compared with an increase of 1.2 ng/ml in the non-IRI group ( $P=0.230$ ). These findings suggest that, although both groups exhibited trends of increased heme and upregulated HO-1 post-PCI, the increases in heme and HO-1 were smaller in the IRI group. However, because these between-group differences were not significant, any mechanistic interpretation should be made with caution.

Based on the observed associations between changes in iron metabolism parameters and IRI, therapeutic strategies targeting iron handling and downstream oxidative/inflammatory pathways (such as iron chelation, antioxidant therapy or HO-1 modulation) merit further investigation. Notably, the present observational study did not establish causality

or therapeutic efficacy; therefore, these strategies should be evaluated in adequately powered randomized clinical trials and mechanistic studies before clinical application. Iron chelators can mitigate oxidative stress damage by binding free iron ions, thereby inhibiting Fenton reactions and reducing the generation of ROS (25). In addition, iron chelators can decrease iron-mediated inflammatory responses, further protecting myocardial cells. Another potential therapeutic target is antioxidants, which can directly scavenge ROS, inhibit lipid peroxidation and protein oxidation, thereby alleviating oxidative stress damage (26). Furthermore, a number of antioxidants can enhance endogenous protective mechanisms by upregulating HO-1 expression. The direct use of HO-1 inducers or HO-1 gene therapy may also serve as potential therapeutic strategies (18); however, further research is needed to verify their safety and efficacy.

The present study exhibits a number of limitations that should be considered when interpreting the results. First, the sample size was relatively small, which may have resulted in insufficient statistical power, especially in subgroup analyses such as comparisons between the IRI and non-IRI groups. Second, the single-center design may have limited the generalizability of the findings. Third, as an observational study, multivariable adjustment was not performed; therefore, residual confounding cannot be excluded, and the observed associations should be interpreted as simple associations rather than evidence of causality. Given the sample size and event number, more complex multivariable models may increase the risk of overfitting. Future larger multicenter prospective studies with multivariable analyses and mechanistic investigations are warranted.

In conclusion, following primary PCI in patients with STEMI, the levels of ferritin and hepcidin increased, with more pronounced post-PCI rises in patients with IRI. Heme and HO-1 showed upward trends without statistically significant inter-group differences. Overall, these findings support an association between altered iron/heme metabolism and the occurrence of IRI, suggesting that serial ferritin and hepcidin assessment may be explored as candidate biomarkers for early risk stratification, while iron-related pathways merit further investigation as potential therapeutic targets. However, given the single-center observational design, the limited sample size and the lack of multivariable adjustment, the results of the present study should be interpreted cautiously and require further determination in larger multicenter cohorts with multivariable analyses.

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### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

ZW conceived and designed the present study, analyzed data and wrote the manuscript. ZW, YZ, KZ and XH contributed to data acquisition. JP interpreted data and revised the manuscript. ZW and YZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (Beijing, China; approval no. IIT2024-040). All procedures conformed to the Declaration of Helsinki. Written informed consent was obtained from all the participants before enrolment.

### Patient consent for publication

The participants provided written consent for the publication of their anonymized data.

### Competing interests

The authors declare that they have no competing interests.

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