The Predictive Value of Myeloperoxidase for Contrast-Induced Nephropathy After Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction

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Background: Higher serum myeloperoxidase (MPO) in patients with acute coronary syndrome is associated with adverse cardiovascular outcomes. Contrast-induced nephropathy (CIN) is associated with worse prognosis in patients with coronary artery disease following angiography. We have no idea whether patients with higher serum myeloperoxidase have a higher risk of CIN in acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).

Methods: This study involved 436 consecutive patients with AMI who had received PCI. Serum MPO levels were determined using enzyme-linked immunosorbent assay before administration of contrast media. Multivariate logistic regression analysis was used to analyze the independent risk factors for CIN after univariate analysis. The receiver operator characteristic (ROC) analysis was performed to evaluate the predictive value of MPO for CIN.

Results: Among the 436 patients, 79 individuals (18.1%) suffered CIN after the PCI procedure. Patients who developed CIN had significantly higher MPO levels compared to those who did not ([203.8 (150.6–276.2)] versus [138.5 (129.9–149.2)]; $p < 0.001$). Multivariate logistic regression analysis revealed that MPO level (OR 1.023, 95% CI: 1.017–1.029, $p < 0.001$) was an independent risk factor for the incidence of CIN after adjusting for the baseline information, blood indicators and angiography procedural parameters. The area under the ROC curve for predicting CIN of MPO was 0.848, and the optimum cutoff point of MPO was 147.38ug/L; the sensitivity and specificity were 82.3% and 72.3%, respectively.

Conclusion: The results show that MPO is independently associated with an increased risk of CIN with AMI patients undergoing PCI. Further studies are needed to verify these results.

Keywords: myocardial infarction, contrast-induced nephropathy, myeloperoxidase, percutaneous coronary intervention

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Introduction

Contrast-induced nephropathy (CIN) is a common complication experienced by coronary artery disease patients after percutaneous coronary intervention (PCI).¹ CIN negatively affects patients' prognosis, such as prolonging duration of hospitalization and increasing incidence of mortality and end-stage renal disease.² However, there is no specific and effective treatment for CIN at present, although

early identification and intervention can effectively improve the prognosis of patients at higher risk for CIN to some degree. At present, the clinical use of serum creatinine (SCr) level changes to diagnose CIN has some hysteresis.³ Hence, it is crucial to find some new and valuable predictors for predicting CIN.

As a member of the heme peroxidase superfamily, released by activated neutrophils, myeloperoxidase (MPO) has powerful pro-oxidative and pro-inflammatory properties.⁴ Nitric oxide decreased after MPO was activated,⁵ leading to endothelial dysfunction.⁶ Recently, MPO has been recognized as an indicator of instability of plaque and patients with acute coronary syndrome admitted to emergency department because of chest pain are found to have higher MPO level.^{4,7–10} Furthermore, increased MPO is not likely to be specific to cardiac diseases; rather, it has also been associated with a variety of clinical conditions, including the development of atherosclerosis,⁴ together with numerous other inflammatory conditions,¹¹ neurodegenerative disease,¹² lung disorders^{13,14} and cancer,¹⁵ as activation of neutrophils and macrophages can occur in any infectious and inflammatory conditions.

Considering the strong relation between MPO and inflammation and oxidative stress, we speculated that leukocyte activation and, especially, MPO secretion both play a preeminent role in the initiation and extension phases of CIN.¹⁶ In this study, we assessed whether patients with high serum MPO levels are more likely to suffer CIN. We aimed to evaluate whether serum MPO can be used as an early diagnostic marker of CIN onset after PCI in acute myocardial infarction (AMI) patients.

Patients and Methods

Study Population

This was a prospective and observational study (see Figure 1). Between January 2016 and September 2018, 436 patients with AMI who were treated by PCI in the Department of Cardiology, Zhongda Hospital Affiliated to Southeast University were selected. The criteria for admission were: (1) the diagnosis of ST-segment elevation myocardial infarction was in accordance with the 2015 guidelines¹⁷ for the diagnosis and treatment of acute ST-segment elevation myocardial infarction of the Cardiovascular Diseases Branch of the Chinese Medical Association; and (2) the diagnosis of non-acute ST-segment elevation myocardial infarction¹⁸ was in

accordance with the guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndrome formulated by the Cardiovascular Diseases Branch of the Chinese Medical Association. The exclusion criteria were: (1) allergic history of iodine or iodine contrast agents; (2) patients with chronic renal insufficiency stage 5 or maintenance of hemodialysis/peritoneal dialysis; (3) CT, MRI and other contrast agents were performed within two weeks before admission; imaging examinations using other contrast agents were expected during the study period (except for PCI after one week); (4) nephrotoxic drugs had been used in the past two weeks (including high-dose loop diuretics, non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, proprietary Chinese medicines containing aristolochic acid, etc.); and (5) patients with inflammatory diseases, autoimmune diseases, liver dysfunction, thyroid dysfunction, malignant tumors or infectious diseases. The research registration number was ChiCTR1900020824, and this study was approved by the Zhongda Hospital Ethics Committee; all patients provided informed consent.

MPO Assay and Blood Analysis

The blood samples for MPO assay were collected at baseline coronary angiography from the sheath of the radial/femoral artery. Next, the concentration of serum myeloperoxidase (MPO) in patients was determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (produced by Beijing Union Rock Biotechnology Co. Ltd). In the microporous plate coated with anti-MPO antibody, the standard substance and the plasma to be tested were added, followed by the anti-MPO antibody with horseradish peroxidase to form a “sandwich” antigen–antibody complex, which catalyzed the conversion of the substrate TMB into a blue substance that turned yellow after termination. The depth of the color was proportional to the concentration of MPO antigen in the sample. The absorbance (OD) was measured at 450 nm by ELISA. The concentration of the analyte was calculated according to the OD value. SCr concentrations were measured before PCI, 48 h and 72 h after coronary angiography. CIN is currently defined either as an acute decrease in renal function after contrast exposure without evidence of other causes or as an SCr increase of 0.5mg/dL or a 25% increase compared to the baseline SCr level within 48 to 72 h following contrast media administration.¹⁹

Figure 1 Study inclusion and exclusion criteria.

Angiographic Definitions

All patients underwent coronary angiography, and each coronary angiogram was preceded by experienced interventional cardiology using the femoral or radial approach. PCI of diseased vessels was conducted on the basis of coronary angiography findings. In principle, emergency PCI only deals with criminals' vessels. All patients were treated with load-dose double antiplatelet aggregation drugs (aspirin 300mg and clopidogrel 300 mg, or ticagrelor 180 mg) before surgery; Iodixanol (320 mg iodine/mL, GE Healthcare, Piscataway, New Jersey), a kind of iso-osmolar, nonionic contrast agent was administered during all procedures. Antiplatelet drugs and statins were used after surgery; use of vasoactive drugs (such as dopamine, sodium nitroprusside, etc.), intra-aortic balloon pump, platelet membrane glycoprotein II b/III a receptor antagonists,

and the use of β -receptor blockers, angiotensin-converting enzyme inhibitors(ACEIs) or angiotensin receptor blockers (ARBs), nitrates and calcium antagonists was determined by physicians based on respective clinical conditions. During the study period, nephrotoxic drugs (including large doses of loop diuretics, non-steroidal anti-inflammatory drugs other than aspirin, aminoglycosides, amphotericin B and traditional Chinese medicine containing aristolochic acid, etc.) were avoided.

Statistical Analysis

SPSS version 19.0 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis of data. The classified variables are expressed in frequencies and percentages, and compared by using χ^2 and Fisher exact tests. The measurement data were expressed by mean +

standard deviation or median and interquartile range, and comparisons between groups were expressed by independent sample *t*-test or Mann–Whitney *U*-test, where appropriate. Independent risk factors that might affect the occurrence of CIN in univariate analysis were filtered using multiple binary logistic regression analysis. The receiver operating characteristic (ROC) curve and the corresponding area under curve (AUC) were used to find out the best cutoff values of MPO for predicting CIN. Two-sided *p*-values of <0.05 were considered statistically significant.

Results

The study cohort included 436 consecutive patients who underwent PCI. Mean age was 62.9 ± 12.7 years [range: 26–92]), and 335 (76.8%) were male. Baseline creatinine was $86.3 \pm 41.6 \mu\text{mol/L}$; consistently, average GFR was $64.4 \pm 24.5 \text{ mL/min/1.73m}^2$. Of these patients, 116 (26.6%) had diabetes mellitus, 242 (55.5%) had hypertension and 35 (8.0%) had received previous percutaneous coronary intervention. Overall, 79 patients (18.1%) developed CIN after the PCI procedure.

Baseline clinical characteristics of the study population are summarized in Table 1. Elderly patients were more likely to suffer from CIN. Patients with hypertension, diabetes mellitus, old myocardial infarction, and prior PCI on admission ($p < 0.05$) had a higher incidence of CIN. There were no significant differences between the groups regarding gender, body mass index, smoking, systolic blood pressure, stroke, LVEF, prevalence of STEMI or in-hospital medications ($p > 0.05$).

Comparisons between the laboratory parameters of the two groups are shown in Table 2. Patients who developed CIN have significantly higher MPO levels at baseline compared to non-CIN patients: [203.8 (150.6–276.2)] versus [138.5 (129.9–149.2)]; $p < 0.001$). In addition, patients in the CIN group had significantly higher baseline WBC and creatinine levels than those in the non-CIN group ($p < 0.05$). However, patients in the CIN group showed significantly lower levels of lymphocyte and monocyte than patients in the non-CIN group ($p < 0.05$).

Table 3 presents angiography and procedural characteristics of the two groups. The patients with CIN had higher rates of aspiration and emergency PCI. However, no significant differences were found in any other procedural characteristics, such as contrast agent volume, culprit vessel, number of vessels or rates of thrombus among the groups. Also, the proportion of stents implanted and the

Table 1 Baseline Clinical Characteristics Between Patients with CIN and without CIN

Variables	CIN (n=79)	Non-CIN (n=357)	p-value
Age (years)	66.4±12.0	62.1±12.7	0.006
Male, n (%)	55(69.6)	280(78.4)	0.105
BMI (kg/m ²)	25.0±3.6	24.9±3.6	0.820
Systolic BP (mmHg)	128±22.6	129±21.1	0.755
Smoking, n (%)	34(54.0)	178(63.6)	0.196
Hypertension, n (%)	55(69.6)	187(52.4)	0.006
Diabetes mellitus, n (%)	37(46.8)	79(22.1)	<0.001
OMI, n (%)	8(10.1)	7(2.0)	0.002
Pre-PCI, n (%)	14(17.7)	21(4.8)	0.002
Stroke, n (%)	3(3.8)	3(0.8)	0.076
LV (cm)	4.77±1.51	5.01±2.31	0.366
LVEF (%)	45(36–55)	50(40–61)	0.142
Cardiogenic shock, n (%)	7(8.9)	23(6.4)	0.461
Acute heart failure, n (%)	10(12.7)	34(9.5)	0.410
Diagnosis, n (%)			0.814
NSTEMI	52(65.8)	230(64.4)	
STEMI	27(34.2)	127(35.6)	
Medication, n (%)			
Aspirin	77(97.5)	341(95.5)	0.753
β-blocker	60(75.9)	277(77.6)	0.767
ACEI	25(31.6)	146(40.9)	0.128
ARB	19(24.1)	79(22.1)	0.711
CCB	19(24.1)	83(23.2)	0.879
Statins	77(97.5)	343(96.1)	0.748
Loop diuretics	27(34.2)	125(35.0)	>0.99
Spironolactone	27(34.2)	123(34.5)	>0.99

Note: Data are presented as n (%) or median (25th–75th percentile).

Abbreviations: BMI, body mass index; BP, blood pressure; Pre-PCI, pre-percutaneous coronary intervention; LV, left ventricular; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

number and length of stents were similar between patients with CIN and those without CIN ($p > 0.05$).

Obviously, MPO level is significantly linked to the incidence of CIN in the univariate model. Age, hypertension, diabetes, old myocardial infarction, emergency PCI and aspiration were also positively associated with the development of CIN. Multivariate logistic regression analysis revealed that baseline MPO level (OR 1.023, 95% CI: 1.017–1.029, $p < 0.001$), age (OR 1.030, 95% CI: 1.002–1.059, $p = 0.034$), presence of hypertension (OR 2.336, 95% CI: 1.161–4.700, $p = 0.017$), diabetes (OR 2.037, 95% CI: 1.027–4.041, $p = 0.042$), OMI (OR 9.787, 95% CI: 2.402–39.882, $p = 0.001$) and WBC level

Table 2 Baseline Laboratory Data Between Patients with CIN and without CIN

Variables	CIN (n=79)	Non-CIN (n=357)	p-value
MPO (ug/L)	203.8 (150.6–276.2)	138.5 (129.9–149.2)	<0.001
WBC ($\times 10^9/L$)	11.2 $\pm$ 3.4	10.4 $\pm$ 3.7	0.073
Hemoglobin (g/L)	134.3 $\pm$ 21.6	138.4 $\pm$ 20.1	0.113
PLT ($\times 10^9/L$)	216.2 $\pm$ 69.4	214.4 $\pm$ 61.9	0.818
Lymphocyte ($\times 10^9/L$)	1.5 $\pm$ 1.1	1.7 $\pm$ 1.1	0.076
Monocyte ($\times 10^9/L$)	0.45 $\pm$ 0.27	0.49 $\pm$ 0.24	0.118
Pre-creatinine (μ mol/L)	91.7 $\pm$ 40.5	79.0 $\pm$ 45.0	0.017
eGFR	57.8 $\pm$ 11.2	69.8 $\pm$ 16.2	<0.001
Uric acid (mmol/L)	322.4 $\pm$ 112.6	330.4 $\pm$ 94.4	0.521
Urea nitrogen (mmol/L)	5.7 $\pm$ 3.2	6.9 $\pm$ 4.5	0.546
TC (mmol/L)	4.8 $\pm$ 2.5	4.6 $\pm$ 1.2	0.510
TG (mmol/L)	1.9 $\pm$ 1.5	2.2 $\pm$ 1.7	0.705
LDL-C (mmol/L)	2.8 $\pm$ 0.7	2.9 $\pm$ 1.1	0.563
HDL-C (mmol/L)	1.1 $\pm$ 0.3	1.1 $\pm$ 0.4	0.717
Troponin I (ng/mL)	7.26 (0.42–20)	9.08 (0.12–26)	0.426
CK-MB (ng/mL)	12.8 (2.6–23)	18.4 (2.0–27)	0.166
FBG (mmol/L)	8.8 $\pm$ 4.0	8.7 $\pm$ 4.2	0.944

Note: Data are presented as median (25th–75th percentile).

Abbreviations: MPO, myeloperoxidase; WBC, white blood count; PLT, platelet counts; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; CK-MB, creatine kinase-MB; FBG, fasting blood glucose.

Table 3 Baseline Angiographic Data Between Patients with CIN and without CIN

Variables	CIN (n=79)	Non-CIN (n=357)	p-value
Emergency PCI, n (%)	67(84.8)	257(72.0)	0.022
IABP, n (%)	5(6.3)	19(5.3)	0.784
Contrast dose, mL	100 (100–120)	100(100–120)	0.180
Culprit vessel, n (%)			0.889
Left main	1(1.3)	4(1.1)	
Left anterior descending	41(51.9)	174(48.7)	
Left circumflex	11(13.9)	37(10.4)	
Right coronary artery	24(36.4)	131(36.7)	
Number of vessels, n (%)			0.341
1	13(16.5)	55(15.4)	
2	14(17.7)	91(25.5)	
3	52(65.8)	211(59.1)	
Thrombus n (%)	58(73.4)	227(63.6)	0.117
Aspiration, n (%)	58(73.4)	218(61.1)	0.040
Stenting, n (%)	66(83.5)	321(89.9)	0.116
Number of stents, n	0.95 $\pm$ 0.53	1.01 $\pm$ 0.47	0.305
Pre-expansion, n (%)	25(31.6)	151(42.3)	0.099
Length of stents, cm	22.7 $\pm$ 14.1	25.3 $\pm$ 14.1	0.138

Note: Data are presented as n (%) or median (25th–75th percentile).

Abbreviations: PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump.

(OR 1.116, 95% CI: 1.022–1.217, $p=0.014$) were all independent risk factors. However, the level of eGFR (OR 0.211, 95% CI: 0.142–0.421, $p=0.003$) was shown

to be the protective factor for CIN after adjusting for the baseline data, blood parameter and angiography procedural parameters (Table 4).

Table 4 Univariate and Multivariate Logistic Regression Analysis of CIN Risk Factors

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
MPO	1.021	1.016–1.027	<0.001	1.023	1.017–1.029	<0.001
Age	1.028	1.008–1.049	0.007	1.030	1.002–1.059	0.034
Male	0.630	0.367–1.083	0.095	0.871	0.412–1.839	0.716
Hypertension	2.083	1.235–3.513	0.006	2.336	1.161–4.700	0.017
Diabetes mellitus	3.100	1.866–5.150	<0.001	2.037	1.027–4.041	0.042
OMI	5.634	1.979–16.035	0.001	9.787	2.402–39.88	0.001
Pre-PCI	3.446	1.667–7.126	0.001	1.993	0.676–5.874	0.211
WBC	1.060	0.994–1.19	0.074	1.116	1.022–1.217	0.014
Lymphocyte	0.785	0.600–1.027	0.078	0.847	0.412–1.839	0.716
eGFR	0.271	0.181–0.568	<0.001	0.211	0.142–0.421	0.003
Emergency	2.173	1.127–4.188	0.021	2.458	0.909–6.644	0.076
Aspiration	1.761	1.024–3.030	0.041	1.266	0.556–2.883	0.575

Abbreviations: MPO, myeloperoxidase; OMI, old myocardial infarction; Pre-PCI, pre-percutaneous coronary intervention; WBC, white blood count; eGFR, estimated glomerular filtration rate.

Figure 2 Receiver operating characteristic curve of the MPO level in predicting CIN. The optimum cutoff point of MPO was 147.38ug/L, with a sensitivity of 82.3% and a specificity of 72.3%.

According to the ROC curve analysis (Figure 2), the MPO level was an accurate predictor for the development of CIN; the AUC was 0.848 for the baseline MPO level (95% CI: 0.797–0.898, $p < 0.001$). The optimum cutoff point for MPO was 147.38ug/L, with a sensitivity of

82.3% and a specificity of 72.3%. Furthermore, we found that the incidence of CIN in the high MPO group (39.6%; MPO > 147.38ug/L) was significantly higher ($p < 0.001$; Figure 3) compared to the group without elevated MPO (5.1%, MPO < 147.38ug/L).

Discussion

This study found that CIN was a common complication after PCI in AMI patients. This is consistent with previous reports^{20,21} in which the incidence of CIN in patients with AMI after PCI was still as high as 18.1%. In the present study, we evaluated the predictive value of MPO for risk of CIN in AMI patients undergoing PCI. Our data, the first report in the literature on this subject, suggested that high baseline MPO level is a pre-procedural predictor of CIN. Age, hypertension, diabetes mellitus, old myocardial infarction and baseline WBC are also independent predictors of CIN in such patients.

The precise pathophysiologic mechanisms of CIN have not been fully elucidated yet. Possible mechanisms include renal vasoconstriction, decrease of renal blood flow, formation of reactive oxygen species, medullary hypoxia and direct cytotoxicity.^{22–25} In view of the similarity between many mechanisms, such as inflammation and oxidative stress induced by MPO with the pathogenesis of CIN, we speculate that there is an inevitable correlation between the occurrence of CIN and the level of

Figure 3 CIN incidence in different groups.

MPO. Here, we firstly reported that baseline MPO level was independently correlated with risk of CIN in AMI patients undergoing PCI. With respect to the mechanisms underlying this association, The MPO-hydrogen peroxide-chloride system resulted in a variety of chlorinated protein and lipid adducts, which can lead to kidney injury.²⁶ The inflammation induced and exacerbated by MPO antibody complexes in necrotizing glomerulonephritis following MPO is a crucial pathogenic factor in glomerular and tubulointerstitial diseases in hyperlipidemia-induced renal damage in rodents.²⁷ MPO is involved in the adherence of neutrophils to the glomerular basement membrane and the degradation of the basement membrane by oxidants at sites of attachment. Johnson et al²⁸ revealed that MPO-mediated glomerular disease gives rise to glomerular morphologic changes, endothelial and mesangial cell injury, activation of platelets and subsequent proliferative responses mimicking inflammatory and proliferative glomerulonephritis in humans. In particular, the interaction of MPO with nitric oxide metabolism makes the actions of oxidants more complex and may explain the bimodal salubrious and unwholesome effects of the MPO-hydrogen peroxide-chloride system in redox-modulated renal diseases.²⁹ 3-nitrotyrosine, lipid hydroperoxides and other resultant oxidation products accumulate in the fibrotic kidneys and the plasma of chronic renal insufficiency patients, indicating oxidative stress aggravated during the progression of kidney disease.³⁰ Therefore, we propose a hypothesis that MPO and MPO-derived oxidants may participate as mediators of oxidative modification of biomolecules/tissues in the development of CIN. Moreover, the multivariate logistic regression analysis in this study revealed that age, hypertension, diabetes mellitus, old myocardial infarction and baseline WBC were also independent predictors of CIN in such patients in accordance with the literature.^{31,32} Patients with OMI often simultaneously suffer from a variety of other medical and cardiovascular diseases with the progress of ventricular remodeling after myocardial infarction; many patients have cardiac and renal insufficiency and the level of inflammatory cytokines increases significantly, which is often accompanied by the activation of inflammatory cells. Yamamoto et al found, through multivariate analysis, that high preoperative WBC count was a novel risk factor for developing CIN following mechanical thrombectomy.³³ Similar reports show an increase in inflammation-related molecules in CIN after PCI, including WBC counts (especially neutrophils).³⁴ Inflammatory

cells cause the release of oxygen free radicals, vasoconstrictors, leukotrienes and thromboxane, leading to kidney damage. If the white blood cell count is high before surgery, for various reasons, the increase of systemic inflammatory reaction may promote the pathological progress of CIN.

Limitations

This study has some limitations that should be considered. First, this is an observational study, the number of patients studied with CIN is relatively small, and all participants were recruited from a single center. Second, our data only detects the baseline MPO level; dynamic observations on the changes of MPO and SCr were not conducted. Third, the measurements of inflammatory markers and other relevant biomarkers,³⁵ such as neutrophil gelatinase-associated lipocalin, urinary interleukin 18 and kidney injury molecule-1, are not available, thus study of the inflammatory and oxidative stress mechanisms of CIN is not deep enough. Thus, we could not dig out the essential mechanisms between serum MPO levels and deteriorated renal injury.

Conclusion

In conclusion, our study demonstrates that a higher pre-procedural MPO level is a risk factor for the development of CIN in patients with AMI. However, larger sample and prospective randomized controlled trials are needed to evaluate and confirm whether high preoperative MPO levels affect CIN or lowering MPO treatment reduces the incidence of CIN.

Data Sharing Statement

Data related to this manuscript can be made available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Zhongda Hospital, Southeast University Medical School. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no competing interests concerning this paper.

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