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Associations of myeloperoxidase, interleukin-17A and heparin-binding EGF-like growth factor levels with in-stent restenosis after percutaneous coronary intervention: a single-centre case–control study in China

Hua Jiang,[1] Hongmei Zhang,[2] Ying Yang ,[3] Xuezhou Yang[4]

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HJ and HZ contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Ying Yang;
53472156@qq.com

ABSTRACT

Objectives To investigate the changes in serum myeloperoxidase (MPO), interleukin (IL)-17A and heparin-binding EGF-like growth factor (HB-EGF) levels before and after percutaneous coronary intervention (PCI), and to evaluate the associations of MPO, IL-17A and HB-EGF levels with the 1-year restenosis rate.

Design Case–control study.

Settings Xiangyang Central Hospital between January 2012 and December 2017.

Participants Patients with coronary heart disease who underwent PCI.

Interventions Not applicable.

Primary and secondary outcome measures Not applicable.

Results Finally, 407 and 132 patients were included in the control and in-stent restenosis (ISR) groups, respectively. The general clinical characteristics of the patients were not significantly different between the two groups. The MPO, IL-17A and HB-EGF levels were not significantly different between the two groups at baseline but significantly increased after PCI. The ISR group showed higher levels of MPO, IL-17A and HB-EGF compared with the control group at all postoperative time points. Multivariable analysis showed that MPO, IL-17A and HB-EGF were associated with increased ISR [MPO (OR=1.003; 95% CI: 1.001 to 1.005; p=0.002), IL-17A (OR=1.015; 95% CI: 1.009 to 1.020; p<0.0001) and HB-EGF (OR=2.256; 95% CI: 1.103 to 4.009; p=0.002)]. All three factors had sensitivity and specificity ≥68% for ISR.

Conclusions HB-EGF could be used for the detection of ISR after PCI and could be of use for the prediction of ISR, but the value of MPO and IL-17A might be more limited. This will have to be validated in future studies.

Strengths and limitations of this study

- This study evaluated the associations of myeloperoxidase (MPO), interleukin (IL)–17A and heparin-binding EGF-like growth factor (HB-EGF) levels with in-stent restenosis (ISR) following percutaneous coronary intervention (PCI).
- Patients with coronary heart disease (CHD) administered PCI for drug-eluting stent implantation in a Chinese hospital were analysed.
- The present trial provided novel insights into the inter-relationships among MPO, IL-17A, HB-EGF and ISR in this patient population.
- Major limitations include the single-centre case–control study design and a limited sample size.
- The precise molecular roles of MPO, IL-17A and HB-EGF in ISR deserve further investigation.

INTRODUCTION

Coronary heart disease (CHD) is caused by atherosclerosis and is among the leading causes of death worldwide.[1] The risk of CHD increases with age.[2] The prevalence of CHD is about 6.5% in persons>20 years of age.[3] The treatments for CHD include drugs and interventional therapies. Percutaneous coronary intervention (PCI) is one of the most effective treatments for CHD, rapidly increasing the patency of relevant arteries, restoring blood flow, improving the symptoms of ischaemia and reducing the incidence of adverse cardiovascular events.[4 5]

Unfortunately, postoperative in-stent restenosis (ISR) is still inevitable.[6] The incidence of ISR is as high as 10%–20% at 3–6 months after PCI. Despite numerous advances in stent technology, ISR still remains a tricky challenge.[6 7] ISR after PCI is a complex process.[8–10] The disruption of the integrity of the vascular endothelial cells triggers intimal hyperplasia, vascular remodelling and elastic recoil, and involves inflammatory responses. Because of this complexity, the preoperative prediction of ISR is very difficult.[6 11 12] Kornowski *et al*[13] investigated the underlying mechanisms of

restenosis in coronary artery in pig models and demonstrated the reciprocal causal relationship between vascular damages/inflammatory responses and in-stent neointimal formation. High severity of vascular damage is associated with more intense inflammatory responses, thicker neointima, smaller lumen diameter and a higher risk of restenosis.[14]

Myeloperoxidase (MPO) is secreted by activated neutrophils, monocytes and macrophages, and participates in oxidative stress. MPO is closely associated with unstable plaques in coronary arteries and promotes atherosclerosis through the oxidation of low-density lipoproteins, as well as by producing other bioactive molecules.[15] Inflammation in atherosclerotic plaques is accompanied by the invasion of large amounts of polymorphonuclear neutrophils, high MPO levels and oxidative metabolites.[16] Tiyerili *et al*[17] demonstrated that stenting could be associated with the release of MPO.

Interleukin (IL)-17A is secreted by Th17 cells and stimulates the release of adhesion molecules and proinflammatory cytokines from various cells, including intercellular adhesion molecule, tumour necrosis factor-α and IL-lβ. IL-17A plays an important role in various inflammatory diseases by participating in the regulation of chronic inflammation, the formation of atherosclerosis and thrombi.[18]

Heparin-binding EGF-like growth factor (HB-EGF) is a member of the epithelial growth factors, activating the proliferation of vascular smooth muscle cells, fibroblasts and keratinocytes, participating in atherosclerosis, tumour growth and smooth muscle hyperplasia.[19] HB-EGF protein and mRNA are highly expressed in atherosclerotic plaques and in the intima of arteries with restenosis.[20 21]

Nevertheless, the understanding of the exact interrelationships among MPO, IL-17A, HB-EGF and ISR still needs to be improved. Therefore, the aim of the present study was to investigate the changes in serum MPO, IL-17A and HB-EGF levels before and after PCI, and to evaluate the associations of MPO, IL-17A and HB-EGF levels with the 1 year restenosis rate.

PATIENTS AND METHODS

Study design and patients

In this case–control study, patients with CHD who underwent PCI for drug-eluting stent implantation at the Department of Cardiology of the Xiangyang Central Hospital between January 2012 and December 2017 were included. Written informed consent was obtained from all patients after informing them about the objectives and protocol of this study.

The exclusion criteria were: (1) patients taking anti-inflammatory drugs such as steroid anti-inflammatory analgesics and other steroid drugs and (2) patients with other disorders or conditions that could affect the results, such as severe cardiac or renal insufficiency, allergic diseases, myocarditis, autoimmune diseases that could induce the increase of MPO, IL-17A or HB-EGF, malignant tumours, severe infection, acute pulmonary embolism, pulmonary heart disease, psoriasis, pregnancy or fever.

ISR and grouping

ISR was diagnosed according to the results of coronary angiography (CAG). If CAG showed lumen loss of ≥50% in diameter over the full length of the stent or affecting 5 mm segments at both ends of the stent, the patients were diagnosed with ISR; otherwise, the patients were considered without ISR and were categorised in the control group.

Data collection

The general characteristics of the patients (age, gender, hypertension, diabetes, dyslipidaemia, smoking, drinking, family history of CHD and postoperative usage of anticoagulants), information about the stent implantation (number, length and diameter), information about the vascular lesion (number of blood vessels affected, lesions of the left main coronary artery, lesions of the left anterior descending branch, lesions of the intermediate branch, lesions of the left circumflex artery and lesions of the right coronary artery), time of the first coronary stent implantation, location of the vascular stenosis, severity, and type of the stenosis, location of the stent implantation, type of the stent, type of the balloon, blood flow grade (Thrombolysis In Myocardial Infarction (TIMI)), time of CAG, ISR, location of the restenosis, de novo stenosis and second stent implantation were collected. Patients in the restenosis group were classified according to their Gensini Score.[22]

PCI and angiography

Aspirin (oral administration, 100 mg/day) and clopidogrel (oral administration, 75 mg/day) were given routinely before elective PCI for at least 3 days. For patients undergoing emergency PCI, aspirin (oral administration, 300 mg/day) and clopidogrel (oral administration, 450–600 mg) were given after PCI. All patients were operated by the same three experienced cardiologists. Prestenting balloon dilatation was performed in all patients. Sirolimus-eluting stents (Firebird, Shanghai MicroPort Medical, China) were implanted using a conventional routine technique. The diameters of the stents were identical to the diameters of the affected arteries. The stents were 3–5 mm longer than the lengths of the affected segments. If residual stenosis was <20% and the TIMI flow grade was grade 3, stent implantation was considered successful. After the procedure, patients received clopidogrel (75 mg/day) for at least 12 months and life-long aspirin (100 mg/day).

Standard CAG was conducted with the Judkins technique using a digital subtraction angiography machine (Innova 4100, GE Healthcare, Waukesha, Wisconsin, USA). Two experienced interventional cardiologists with uniform training reviewed the CAG images independently

and in a blind manner. The quantitative analysis of the CAG images was conducted by a validated independent central laboratory.

Blood samples

Blood (5 mL) was obtained before and at 48 hours, 1 week, 1 month and 6 months after PCI. The blood samples were centrifuged at 1000 relative centrifugal force for 10 min to collect serum, which was stored at −80°C until use.

Biochemistry

Levels of HB-EGF (R&D Systems, USA), IL-17A (R&D Systems) and MPO (R&D Systems) were measured by ELISA, of which the reference ranges were 0–35 ng/L, 0–20 pg/mL and 0–3.4 µg/L, respectively. Blood routine examination was performed using a blood cell analysis workstation (XE-AlphaN, Sysmex Corp., Kobe, Japan).

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), serum uric acid, Cr, blood urea nitrogen (BUN) and triglycerides (TG) were measured using an automatic biochemical analyzer (Aeroset, Abbott Laboratories, Abbott Park, Illinois, USA).

Statistical analysis

Statistical analyses were performed using SPSS V.13.0. Categorical data are presented as n (%) and were analysed using the χ^2 test. Continuous data are presented as means±SD and were analysed using the Student's t-test (normal distribution) or the Mann-Whitney U test (skewed distribution). Cox logistic regression was used to identify the factors associated with restenosis; the results are presented as ORs and 95% CIs. Receiver operating characteristics (ROC) curves were used to determine the diagnostic value of identified factors for restenosis. Two-sided p values<0.05 were considered statistically significant.

Patient and public involvement

Patient and public involvement was sought after the methods, and outcome measures were identified. The protocol and study design were reviewed by a human research ethics committee. Patients and members of the public were not involved with the development of the research questions or study design.

RESULTS

General characteristics

A total of 554 patients met the inclusion criteria. Thirteen were excluded for incomplete data and two for autoimmune diseases. Therefore, 539 patients were included in this study. Among the 539 patients, 317 (58.8%) were males and 222 (41.2%) were females. The mean age was 64.2±9.8 years.

CAG at 1 year after PCI showed that 132 patients had ISR ≥50% (restenosis group), while the remaining 407 were without ISR (control group). The general characteristics of the patients are shown in table 1. The general baseline characteristics including age, sex distribution, history of hyperlipaemia, history of hypertension, history of diabetes, smoking, drinking, family history, history of drug application, perioperative conditions of the affected blood vessels, the severity of stenosis and types and number of stents were not significantly different between the two groups (all p>0.05) (table 1).

Table 1 Baseline characteristics of the study population

	In-stent restenosis (n=132)	Controls (n=407)	P value*
Sex (male/female)	76/56	241/166	0.885
Age (years)	65.5±9.5	62.8±10.2	0.842
Smoking, n (%)	69 (52.1)	188 (46.3)	0.162
Drinking, n (%)	35 (26.5)	98 (24.1)	0.635
Family history of CAD, n (%)	13 (9.8)	37 (9.1)	0.365
Hypertension, n (%)	86 (65.2)	281 (69.0)	0.426
Dyslipidaemia, n (%)	36 (27.3)	108 (26.5)	0.318
MI, n (%)	47 (35.6)	155 (38.1)	0.557
Diabetes, n (%)	23 (17.4)	67 (16.5)	0.603
LAD, n (%)	67 (50.8)	195 (47.9)	0.512
CX, n (%)	24 (18.2)	81 (19.9)	0.571
RCA, n (%)	41 (31.0)	131 (32.2)	0.384
Average number of stent (sticks)	2.1±1.1	2.0±1.1	0.302
Stent diameter (mm)	2.8±0.3	2.9±0.3	0.291
Stent length (mm)	23.5±6.9	23.6±6.8	0.375
Stent thickness (um)	108.9±22.7	107.8±20.6	0.764
Beta-blocker, n (%)	114 (86.4%)	367 (90.2%)	0.324
ACE inhibitor, n (%)	101 (76.5%)	294 (72.2%)	0.068
Statins, n (%)	127 (96.2%)	396 (97.3%)	0.726
Antiplatelet agents, n (%)	132 (100%)	407 (100%)	–
Uric acid (mmol/L)	341±99	329±88	0.765

*Unpaired t-test and χ^2 test.
CAD, coronary artery disease; CX, circumflex artery; LAD, left anterior descending artery; MI, myocardial infarction; ; RCA, right coronary artery.

MPO, IL-17A and HB-EGF levels between the two groups before and after PCI

The white blood cell count, red blood cell count, creatinine (Cr), BUN, TG, TC and HDL-C were not significantly different between the restenosis and control groups, whether before or at any time point after PCI. The levels of MPO, IL-17A and HB-EGF were significantly higher in the restenosis group than in the control group (all p<0.05) at all time points before and after PCI (table 2).

Table 2 Comparisons of blood routine, renal functions, blood lipid, MPO, IL-17A and HB-EGF levels before and after PCI between the two groups

	Time point	Restenosis	Control	P between groups
MPO (μg/L)	Pre PCI	29.81±8.25	13.76±4.32	0.003
	48 hours post PCI	46.28±11.46*	20.84±5.78*	0.002
	1 week post PCI	40.35±10.83*†	15.12±5.36	0.002
	6 months post PCI	30.65±9.83	14.03±4.34	0.002
IL-17A (pg/mL)	Pre PCI	63.51±8.24	33.45±5.32	0.001
	48 hours post PCI	108.15±13.64*	55.48±6.87*	0.001
	1 week post PCI	90.65±10.83*†	44.21±5.23*†	0.001
	6 months post PCI	70.65±9.83	34.03±5.44	0.001
HB-EGF (pg/mL)	Pre PCI	167.81±81.25	102.76±51.32	0.003
	48 hours post PCI	326.28±150.46*	285.84±120.78*	0.032
	1 week post PCI	281.65±123.83*†	241.03±99.34*†	0.045
	6 months post PCI	210.65±103.27*	140.03±81.65*	0.002
RBC ($\times 10^{12}$/L)	Pre PCI	5.14±0.46	5.13±0.42	0.554
	48 hours post PCI	5.12±0.45	5.11±0.43	0.562
	6 months post PCI	5.15±0.45	5.12±0.43	0.557
WBC ($\times 10^{9}$/L)	Pre PCI	6.36±1.26	6.34±1.30	0.478
	48 hours post PCI	7.12±1.24*	7.10±1.31*	0.442
	6 months post PCI	6.38±1.24	6.36±1.31	0.476
TG (mmol/L)	Pre PCI	1.75±1.39	1.73±1.25	0.781
	48 hours post PCI	1.76±1.34	1.70±1.26	0.765
	6 months post PCI	1.76±1.35	1.71±1.27	0.779
TC (mmol/L)	Pre PCI	4.50±1.05	4.23±0.87	0.768
	48 hours post PCI	4.50±1.05	4.23±0.86	0.766
	6 months post PCI	4.51±1.05	4.24±0.85	0.764
HDL-C (mmol/L)	Pre PCI	1.22±0.32	1.19±0.30	0.786
	48 hours post PCI	1.22±0.32	1.18±0.30	0.776
	6 months post PCI	1.23±0.31	1.18±0.31	0.784
Creatinine (mmol/L)	Pre PCI	76.20±19.86	80.45±20.14	0.658
	48 hours post PCI	76.30±19.51	80.46±20.12	0.678
	6 months post PCI	76.31±19.42	80.52±20.12	0.653
BUN (mmol/L)	Pre PCI	5.33±1.24	5.61±1.41	0.551
	48 hours post PCI	5.32±1.25	5.54±1.42	0.564
	6 months post PCI	5.31±1.25	5.52±1.42	0.553

*P<0.01 versus pre PCI in the same group.
†P<0.01 versus 48 hour post PCI in the same group.
BUN, blood urea nitrogen; HB-EGF, heparin-binding epidermal growth factor-like growth factor; HDL-C, high-density lipoprotein cholesterol; IL-17A, interleukin 17A; MPO, myeloperoxidase; RBC, red blood cells; TC, total cholesterol; TG, triglycerides; WBC, white blood cells.

The levels of MPO, IL-17A and HB-EGF all showed significant increases at 48 hours after PCI compared with baseline in both groups, while the other biomarkers remained stable (table 2).

In addition, the levels of MPO, IL-17A and HB-EGF peaked at 48 hours after PCI, and then gradually decreased. The levels of MPO and IL-17A at 6 months after PCI were almost returned to baseline, while HB-EGF remained high (table 2).

Logistic regression analysis of ISR

Logistic regression was conducted using restenosis as the dependent variable, while age, sex, hypertension, hyperlipidaemia, MPO, IL-17A and HB-EGF were entered as independent variables. The MPO, IL-17A and HB-EGF levels were those measured at 48 hours. Sex, age, hypertension and hyperlipidaemia were excluded from the regression model (all p>0.05). Regression was further conducted for MPO, IL-17A and HB-EGF (table 3), which showed that all these three indicators were significantly and independently associated with ISR (p<0.05).

Table 3 Results of the logistic regression for the factors associated with restenosis

	OR	95% CI	P value
Age	0.997	0.951 to 1.049	0.902
Male	1.125	0.298 to 4.274	0.861
Smoking	1.456	0.573 to 3.645	0.432
Diabetes	1.903	0.694 to 5.205	0.206
Hypertension	1.305	0.712 to 2.396	0.384
History of cardiovascular diseases	0.436	0.153 to 1.312	0.142
Single-vessel coronary artery disease	0.323	0.156 to 0.665	0.004
TG	0.608	0.312 to 1.127	0.134
TC	0.826	0.154 to 4.064	0.782
HDL-C	2.894	0.389 to 21.27	0.328
MPO	1.003	1.001 to 1.005	0.002*
IL-17A	1.015	1.009 to 1.020	<0.001*
HB-EGF	2.256	1.103 to 4.009	0.002*

*Adjusted for age, sex and other cardiovascular risk factors.
HB-EGF, heparin-binding epidermal growth factor-like growth factor; HDL-C, high-density lipoprotein cholesterol; IL-17A, interleukin 17A; MPO, myeloperoxidase; TC, total cholesterol; ; TG, triglycerides.

Correlation test

The Spearman's correlation test showed that HB-EGF was positively correlated with MPO and IL-17A, but not with age, white blood cell count and HDL-C (table 4).

Diagnostic value

The sensitivity and specificity of the indicators were assessed by ROC curve analysis. The sensitivity and specificity of HB-EGF >35 ng/L were 85% and 100%, respectively (area under the ROC (AUC)=0.913, 95% CI 0.820 to 0.972). The sensitivity and specificity of MPO>20 µg/mL were 68% and 87%, respectively (AUC=0.836, 95% CI 0.746 to 0.914). The sensitivity and specificity of IL-17A>3.4 pg/L were 85% and 81%, respectively (AUC=0.892, 95% CI 0.786 to 0.949) (figure 1).

Table 4 Results of the Spearman's correlation test (r values)

	HB-EGF	MPO	IL-17A	Age	White blood cell count	HDL-C
HB-EGF	–	0.685*	0.412*	0.065	0.036	0.020
MPO	0.685*	–	0.325*	0.034	0.055	0.063
IL-17A	0.412*	0.325*	–	0.102	0.062	0.035

*P<0.001.
HB-EGF, heparin-binding epidermal growth factor-like growth factor; HDL-C, high-density lipoprotein cholesterol; IL-17A, interleukin 17A; MPO, myeloperoxidase.

DISCUSSION

The understanding of the exact inter-relationships among MPO, IL-17A, HB-EGF and ISR still needs to be improved. Therefore, the aim of the present study was to investigate the changes in serum MPO, IL-17A and HB-EGF levels before and after PCI, and to evaluate the associations of MPO, IL-17A and HB-EGF levels with the 1-year restenosis rate. The results suggest that HB-EGF could be used for the detection of ISR after PCI, and could be of use for the prediction of ISR. MPO and IL-17A might also be used for the prediction of ISR, but their value was low and should be examined in future studies.

Because of the complexity of the process of restenosis, the preoperative prediction of ISR is very difficult.[9 10 13 14] Balloon dilation of the affected vascular wall is required before PCI, which may increase vascular wall damages and induce the aggregation of platelets. After stent implantation, the accumulation of activated platelets on the surface of the stent can induce the formation of minute thrombi. The consequent responses of the body can lead to the release of large amounts of tissue factors, which promote vascular remodelling and neointimal hyperplasia and finally result in ISR.[13]

The restenosis rate at 3–6 months was higher than the 20% reported in the literature.[6 7] We observed the patients treated between 2012 and 2017 and followed them for 1 year, and longer follow-up could lead to higher ISR rates. The relatively high (near 25%) restenosis rate might be related to ageing (average age: 65.5±9.5 years old). As the patients grow older, the occurrence of ISR gradually increases.[8–10] The risk factors of ISR include clinical factors such as male, older age, hypertension, PCI procedure, infectious factors, genetic factors and biochemical factors.[6–10] Therefore, the longer follow-up and the characteristics of the patients could explain, at least in part, the higher 10-year ISR rate.

Tiyerili *et al*[17] showed that stenting procedures were associated with MPO secretion. In the present study, not only MPO levels increased after PCI, but also it is the only marker that remained high at 6 months after PCI. Of note, the 6-month MPO levels in the control group gradually decreased back to baseline, while the MPO levels in the restenosis group remained higher than baseline. These results suggested that high MPO levels at 6 months after PCI could predict ISR. We speculated that the underlying mechanisms could be associated with the degradation of the endothelium-derived relaxing factor NO by MPO to reduce the bioactivity of NO, attenuate blood vessel dilation, and anti-inflammation abilities, leading to coronary vasospasm. In addition, MPO could also induce the expression of endothelial P-selectin and tissue factors, which promote the aggregation of platelets and thrombogenesis.[23–25] Therefore, as a biomarker of oxidative stress, MPO could be measured to help assess the effectiveness of revascularisation after PCI, and thus predicting the development of ISR. This is supported by Pleva *et al*[26] Claessen *et al*[27] showed that high MPO levels at 30 days were associated with ISR.

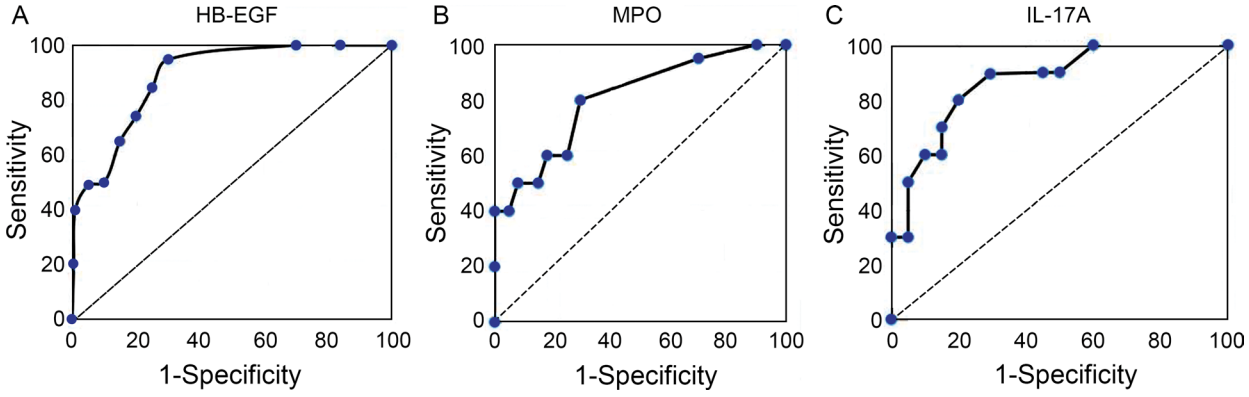

Figure 1 Receiver operating characteristics (ROC) curves of heparin-binding epidermal growth factor-like growth factor (HB-EGF), myeloperoxidase (MPO) and interleukin (IL)-17A. The sensitivity and specificity of HB-EGF>35 ng/L were 85% and 100%, respectively, (area under the ROC (AUC)=0.913, 95% CI 0.820 to 0.972). The sensitivity and specificity of MPO>20 µg/mL were 68% and 87%, respectively, (AUC=0.836, 95% CI 0.746 to 0.914). The sensitivity and specificity of IL-17A>3.4 pg/L were 85% and 81%, respectively, (AUC=0.892, 95% CI 0.786 to 0.949).

IL-17A plays an important role in various inflammatory diseases by participating in the regulation of chronic inflammation, the formation of atherosclerosis, thrombi and plaque instability.[28–30] In the present study, ISR was associated with IL-17A levels, independently from age, sex, hypertension and hyperlipidaemia. These findings demonstrate that serum IL-17A after PCI could be an inflammation biomarker for ISR. In addition, the dynamic changes of IL-17A before and after PCI also suggest that higher IL-17A levels indicate more severe inflammatory responses induced by the coronary arterial ISR, and demonstrated that inflammatory responses participated in the development and progression of ISR after PCI. This is supported by Alexandr *et al*[31] who showed that high IL-17 levels at baseline and at 7 days after PCI predicted ISR at 1 year.

As an endothelial growth factor, HB-EGF participates in intimal hyperplasia.[20] HB-EGF participated not only in the proliferation of vascular smooth muscle cells, but also in the migration of vascular smooth muscle, and therefore promoted the pathogenesis of restenosis.[32 33] The results of the present study showed that the serum levels of HB-EGF were higher in the restenosis group. This is supported by Jiang *et al*,[34] who showed that high levels of HB-EGF were independently associated with ISR.

The ROC curve analyses showed that MPO, IL-17A and HB-EGF levels could all three be used to predict the occurrence of ISR at 1 year, with high sensitivity and specificity. Studies about the predictive power of those markers for ISR are lacking. Only Alexandr *et al*[31] showed that high IL-17 levels at baseline and at 7 days after PCI predicted ISR at 1 year. Many other predictive markers were explored, including inflammation parameters. Indeed, Hajizadeh *et al*[35] showed that eosinophil counts at 6 weeks after PCI were independently associated with ISR. Of note,[36] eosinophils are major players in inflammation and may participate in the secretion of MPO and IL-17A. Nevertheless, additional studies are necessary to build predictive models that could include multiple parameters in addition to MPO, IL-17A and HB-EGF.

The PCI procedure might lead to increases in MPO, IL-17A and HB-EGF, so the levels of biomarkers at 48 hours post PCI might be affected by the PCI procedure. Therefore, we further tested the biomarkers at 1 week after PCI to rule out the possible influence of PCI procedure. Moreover, to minimise bias, all the PCI procedures were performed using a standard protocol. We observed that the same differences were observed between the two groups, irrespective of the time point after PCI. The measurement at 48 hours could be more clinically meaningful since it would allow the measurement to be done before the patient is discharged.

The present study has limitations. The included patients were all from a university hospital, limiting the generalisability of the results. This study is also limited by a relatively small sample size, and its results should be confirmed in a larger sample of patients. Further prospective studies are required to determine the role of increased MPO, IL-17A and HB-EGF levels in the clinical outcomes of patients with CAD. No analysis was made specifically in patients with and without diabetes. Nevertheless, there is already a wealth of literature about the close correlation between those biomarkers and diabetes[37–43] and between diabetes and ISR.[44–48] Additional studies are required to evaluate the precise molecular roles of MPO, IL-17A and HB-EGF in ISR.

CONCLUSIONS

This study strongly suggests that MPO, IL-17A and HB-EGF were associated with ISR, with higher levels of MPO, IL-17A and HB-EGF, indicating a higher risk of restenosis. Nevertheless, given the low magnitude of change in MPO and IL-17A in the ISR group, further studies should be conducted to determine their exact value for the prediction of ISR. These results further support the associations among arterial damages, inflammation and

vascular intimal hyperplasia, and therefore suggest that reducing arterial damages and inhibiting inflammatory responses could be valuable methods to manage intimal hyperplasia.

Author affiliations
[1]Department of Medical Examination, Xiangyang Central Hospital, Xiangyang, Hubei, China
[2]Department of Clinical Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3]Department of Endocrinology, Xiangyang Central Hospital, Xiangyang, Hubei, China
[4]Reproductive Medicine Center, Xiangyang Central Hospital, Xiangyang, Hubei, China

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The protocol was approved by the Medical Ethics Committee of Xiangyang Central Hospital. The study was conducted according to the ethical guidelines of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data are available.

ORCID iD
Ying Yang http://orcid.org/0000-0001-5556-5517

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