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RESEARCH ARTICLE

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Correlation of pre-operative circulating inflammatory cytokines with restenosis and rapid angiographic stenotic progression risk in coronary artery disease patients underwent percutaneous coronary intervention with drug-eluting stents

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Abstract

Background: This study aimed to explore the associations of common inflammatory cytokine levels with restenosis and rapid angiographic stenotic progression (RASP) risk in coronary artery disease (CAD) patients underwent percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods: Two hundred and ten CAD patients underwent PCI with DES were consecutively recruited, then pre-operative serum levels of TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17A, IL-21, and IL-23 were determined by ELISA. The 12-month in-stent restenosis and RASP of non-intervened lesion were assessed by quantitative coronary angiography analysis.

Results: The pre-operative TNF-α, IL-6, IL-17A, and IL-23 expressions were increased while IL-4 expression was decreased in restenosis patients compared with non-restenosis patients. Further analysis revealed that IL-6, IL-8, hypercholesteremia, diabetes mellitus, and HsCRP could independently predict restenosis risk, and subsequent ROC curve revealed that their combination was able to differentiate restenosis patients from non-restenosis patients with an AUC of 0.951 (95%CI: 0.925-0.978). Meanwhile, the pre-operative TNF-α, IL-6, IL-17A, IL-21, and IL-23 expressions were increased whereas IL-4 level was decreased in RASP patients compared with non-RASP patients. Further analysis revealed that TNF-α, IL-6, IL-23, hypercholesteremia, SUA, HsCRP, and multivessel artery lesions could independently predict RASP risk, and subsequent ROC curve disclosed that their combination could discriminate RASP patients from non-RASP patients with an AUC of 0.886 (95%CI: 0.841-0.931).

Conclusions: This study unveils the potentiality of pre-operative circulating inflammatory cytokines as markers for predicting restenosis and RASP risk in CAD patients underwent PCI with DES.

Sun and Yu contributed equally to this work.

KEYWORDS
Coronary artery disease, drug-eluting stents, percutaneous coronary intervention, rapid angiographic stenotic progression, restenosis

1 | INTRODUCTION

Coronary artery disease (CAD) is a global health concern that accounts for approximately one-third of all deaths in individuals older than 35 years.[1-3] In order to decrease the mortality of CAD, various treatment approaches have been raised, such as calcium channel blockers, β-receptor blocks, antithrombotic treatment, percutaneous coronary intervention (PCI), and coronary artery bypass graft.[1] Among these treatment approaches, PCI with drug-eluting stents (DES) is one of the most widely performed procedures for the treatment of CAD, which obviously reduces the acute vascular closure and the risk of repeat revascularization.[4] However, a number of CAD patients still occur in-stent restenosis of target artery and rapid angiographic stenotic progression (RASP) of non-intervened lesion after underwent PCI with DES, which pronouncedly decrease the long-term outcomes of these patients.[5,6] Therefore, investigating valuable biomarkers for predicting restenosis and RASP is of great importance to optimize the treatment schedule and improve the prognosis of CAD patients underwent PCI with DES.

Accumulating evidences suggest that inflammatory reactions play important roles in the development and progression of restenosis; however, seldom studies investigate the predictive value of specific inflammatory factors for risk of restenosis or RASP, only a study discovers that HsCRP is able to predict the increased risk of restenosis and RASP in CAD patients underwent PCI with DES.[7,8] As the most common inflammatory factors, inflammatory cytokines (including TNF-α, IL-1, IL-6, and so on) exert multiple functions (such as promote leukocyte recruitment, monocyte chemotaxis, and oxidative stress) in endothelial cells, thereby mediate the inflammation reactions and induce the neointimal hyperplasia (such as smooth muscle proliferation/migration, extracellular matrix deposition) and vessel remodeling in CAD patients.[2,9] In addition, several inflammatory cytokines (such as IL-6 and IL-18) are also discovered to be associated with elevated risk of CAD.[2,10,11] Considering all the evidences above, we hypothesized that some inflammatory cytokines might be able to predict restenosis and RASP risk in CAD patients underwent PCI with DES. Therefore, this study aimed to explore the associations of nine common pre-operative inflammatory cytokine expressions with restenosis and RASP risk in CAD patients underwent PCI with DES.

2 | MATERIALS AND METHODS

2.1 | Patients

Two hundred and ten CAD patients underwent PCI treatment with sirolimus-eluting stent at our hospital were consecutively recruited as study subjects, between January 2015 and May 2018. The patients were enrolled if they met the following inclusion criteria: (a) diagnosed as CAD according to angiographic demonstration; (b) about to undergo PCI with DES implantation; (c) no clinical contraindications to PCI and no anaphylaxis to sirolimus-eluting stents; and (d) age ≥18 years old. The exclusion criteria were as follows: (a) history of cardiovascular surgery (such as PCI, revascularization, or coronary artery bypass grafting); (b) complicated with inflammatory diseases, autoimmune diseases, or hematologic malignancies; (c) history of severe infection or malignant tumors; (d) treatment with anti-inflammatory drugs or immunosuppressive drugs within 3 months before enrollment; (e) unable to be followed up regularly; and (f) pregnant or lactating women. The study was approved by the Institutional Review Board of ZiBo Central Hospital. All patients provided written informed consents at the time of enrollment.

2.2 | Data collection

After enrollment, the clinical data of patients were recorded, which included (a) demographic characteristics: age, gender and body mass index (BMI); (b) CAD risk factors: current smoke status, hypertension, diabetes mellitus, hypercholesteremia, hyperuricemia, and family history of CAD; (c) cardiac function index: left ventricular ejection fraction (LVEF); (d) laboratory indexes: mean arterial pressure (MAP), fasting blood-glucose (FBG), glycated hemoglobin, serum creatinine (Scr), serum uric acid (SUA), cardiac troponin I (cTnI), N-terminal probrain natriuretic peptide (NT-proBNP), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (HsCRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC), and neutrophil; (e) lesion features: number of artery lesion, location of artery lesion, number of target lesion, stenosis degree of target lesion, and length of target lesion; (f) operation procedures: length of stent, diameter of stent, time of stent dilation, and balloon dilation pre-stent; and (g) drugs used after PCI: aspirin, clopidogrel, nitrates, statins, β-receptor blockers, angiotensin-converting enzymes inhibitors/angiotensin receptor blockers (ACEIs/ARBs), and calcium channel blockers.

2.3 | Sample collection and detection

Peripheral blood samples of patients were collected in the coagulation tube before PCI treatment, and then, the serum was centrifuged at the condition of 2500 g, 15 minutes (4°C). After separation, the serum was stored at −80°C until determination. The levels of inflammatory cytokines in serum including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-4, IL-6, IL-8, IL-10, IL-17A, IL-21, and IL-23 were determined by enzyme-linked immunosorbent assay (ELISA) using commercial human ELISA Kits (eBioscience) following the manufacturer's protocol.

2.4 | Assessment of in-stent restenosis and RASP

The PCI procedures, the implantation of sirolimus-eluting stent (Lepu (Beijing) Medical Devices Co., Ltd) as well as the pre-operative and postoperative management (eg, the management of aspirin, clopidogrel, and so on) were performed as recommended by the PCI guideline.[12] Coronary angiography was conducted before PCI, immediately post PCI and at 12-month follow-up (or earlier if clinically indicated), and the in-stent restenosis and RASP of non-intervened lesion were assessed by the quantitative coronary angiography (QCA) analysis. The QCA analysis was performed on the computer-based system Cardiovascular Angiographic Analysis System (CAAS) II (Pie Medical, Maastricht, the Netherlands), which was used as previously described.[13,14] The diameter function of the coronary artery lumen was determined by computing the shortest distance between the edge points of the right and left boundaries. The minimum in-stent lumen diameter was determined on an end-diastolic frame of CAAS. The interpolated diameter was based on a computer estimation of the original lumen diameter, determined at the site of the minimum lumen diameter by taking into account the diameter function of the proximal and distal references. The percent diameter stenosis (PDS) was derived from the measured minimum lumen diameter and the interpolated reference diameter. According to the previous study,[7] in-stent restenosis was defined as follows: the PDS of stent-implanted segment at 12-month follow-up ≥50%. The RASP of non-intervened lesion was defined as the occurrence of at least one of the following conditions[7]: (a) the increase of PDS ≥10% at 12-month follow-up if the original PDS was ≥50% before PCI; (b) the increase of PDS ≥ 30% at 12-month follow-up if the original PDS was <50% before PCI; (c) newly developed stenosis ≥30% at 12-month follow-up if no original stenosis existed before PCI; and (d) the stenosis aggravated and turned to complete occlusion lesion at 12-month follow-up.

2.5 | Sample size calculation

In this study, sample size calculation was based on the level of TNF-α between patients with restenosis and patients without restenosis in our pilot study, using PASS V11.0 software (NCSS). In the pilot study, a total of 10 eligible patients were recruited, including five patients developed restenosis after PCI with sirolimus-eluting stent and five patients without restenosis after PCI with sirolimus-eluting stent. The TNF-α mean level of 10 patients was restenosis patients: 50.7 ± 30.9 pg/mL and patients without restenosis: 34.0 ± 20.7 pg/mL. As reported in the previous study,[7] the restenosis occurrence was 21.0%. Hence, the hypothetical sample ratio of restenosis patients and non-restenosis patients was 1:4. Using the TNF-α mean level of restenosis patients (50.7 ± 30.9) and patients without restenosis (34.0 ± 20.7), a sample ratio of 1:4, a power of 85%, a two-sided 5% level of significance (α), and a two-sample t test, the required sample size was 180. In order to ensure the analysis power, the minimum sample size should be 180, meanwhile, taking a 15% attrition rate into account, the sample size was increased to 210 finally.

2.6 | Statistical analysis

Continuous variables were checked for normality by using the Kolmogorov-Smirnov test, and the normally distributed continuous variables were presented as mean ± standard deviation (SD); the non-normal distributed continuous variables were presented as median and interquartile range (IQR). Categorical variables were presented as count (percentage). Comparison of inflammatory cytokine level between restenosis and non-restenosis patients, RASP and non-RASP patients was determined by Wilcoxon's rank sum test, and the comparison of characteristics between restenosis and non-restenosis patients, RASP and non-RASP patients was determined by Student's *t* test, Wilcoxon's rank sum test, or chi-square test. Univariate logistic regression and forward stepwise multivariate logistic regressions were used to analyze the inflammatory cytokines predicting the restenosis risk and the RASP risk, while due to the limited sample size, only the inflammatory cytokines and the discrepant characteristics (between restenosis and non-restenosis patients, RASP and non-RASP patients) were included in the logistic regression analyses. The predicting performances of independent predictors in the logistic regression were further assessed by plotting receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC) with 95% confidence interval (CI). All the statistical analyses were performed with the use of SPSS 24.0 statistical software (SPSS Inc), and figures were made using GraphPad Prism 7.00 software (GraphPad Software Inc, San Diego, USA). *P* value <0.05 was considered significant.

3 | RESULTS

3.1 | Characteristics of CAD patients

Among the 210 CAD patients, there were 11 patients who lost follow-up and did not have restenosis assessment. Thus, we regarded these 11 patients as patients without restenosis and RASP. In this study, 54 were restenosis patients and 156 were non-restenosis patients; meanwhile, 88 were RASP patients and the other 122 were non-RASP patients (Detailed characteristics were shown in Table 1). For the comparison between restenosis patients and non-restenosis patients, the percentages of patients with hypertension ($P = 0.016$), diabetes mellitus ($P = 0.028$), and multivessel artery lesions ($P = 0.049$) were higher in restenosis patients compared with non-restenosis patients. Also, the SUA level ($P = 0.002$), HsCRP level ($P < 0.001$), the length of target lesion ($P = 0.011$), and the length of stent ($P = 0.013$) were elevated in restenosis patients compared with non-restenosis patients. Referring to demographic (all $P > 0.05$) and other clinical characteristics (all $P > 0.05$), there was no difference between restenosis patients and non-restenosis patients (Table 1). For the characteristics between RASP and non-RASP patients, the percentages of patients with hypercholesteremia ($P = 0.009$) and multivessel artery lesions ($P < 0.001$) were higher in RASP patients compared with non-RASP patients. Meanwhile, the SUA level

TABLE 1 Comparison of characteristics between restenosis and non-restenosis patients, RASP and non-RASP patients

Items	CAD patients (N = 210)	Restenosis patients (n = 54)	Non-restenosis patients (n = 156)	*P* value	RASP patients (n = 88)	Non-RASP patients (n = 122)	*P* value
Demographic characteristics							
Age (y)	63.1 ± 10.3	63.1 ± 10.9	63.1 ± 10.1		64.5 ± 10.8	62.1 ± 9.8	0.099
Gender							
Male	169 (80.5)	45 (83.3)	124 (79.5)	0.539	68 (77.3)	101 (82.8)	0.320
Female	41 (19.5)	9 (16.7)	32 (20.5)		20 (22.7)	21 (17.2)	
BMI (kg/m^2)	25.9 ± 3.5	26.1 ± 3.3	25.8 ± 3.6	0.547	26.4 ± 3.5	25.5 ± 3.5	0.068
CAD risk factors							
Current smoker	58 (27.6)	27 (30.7)	31 (25.4)	0.399	17 (31.5)	41 (26.3)	0.461
Hypertension	157 (74.8)	47 (87.0)	110 (70.5)	**0.016**	70 (79.5)	87 (71.3)	0.175
Diabetes mellitus	61 (29.0)	22 (40.7)	39 (25.0)	**0.028**	31 (35.2)	30 (24.6)	0.094
Hypercholesteremia	126 (60.0)	31 (57.4)	95 (60.9)	0.652	62 (70.5)	64 (52.5)	**0.009**
Hyperuricemia	87 (41.4)	20 (37.0)	67 (42.9)	0.447	36 (40.9)	51 (41.8)	0.897
Family history of CAD	37 (17.6)	10 (18.5)	27 (17.3)	0.840	16 (18.2)	21 (17.2)	0.856
Cardiac function index							
LVEF (%)	64.9 ± 6.8	64.1 ± 6.6	65.2 ± 6.8	0.274	65.0 ± 5.9	64.9 ± 7.3	0.886
Laboratory indexes							
MAP (mm Hg)	104.2 ± 17.8	101.3 ± 17.8	105.3 ± 17.7	0.157	104.3 ± 18.1	104.3 ± 17.6	0.999
FBG (mmol/L)	5.7 (5.2-6.6)	5.64 (5.28-6.51)	5.80 (5.05-6.58)	0.863	5.74 (5.29-6.65)	5.73 (5.05-6.47)	0.398
Glycated hemoglobin (%)	6.20 (4.90-7.60)	6.40 (5.00-7.72)	6.05 (4.90-7.40)	0.366	6.30 (5.25-7.92)	5.90 (4.80-7.52)	0.145
Scr (umol/L)	79.7 ± 16.5	76.4 ± 20.1	80.0 ± 15.0	0.092	78.5 ± 17.8	80.6 ± 15.6	0.379
SUA (umol/L)	346.2 ± 79.2	343.7 ± 87.5	336.4 ± 73.9	**0.002**	368.8 ± 76.0	330.0 ± 77.7	**<0.001**
cTnI (ng/mL)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.876	0.03 (0.02-0.05)	0.02 (0.01-0.04)	**0.045**
NT-proBNP (ng/mL)	0.08 (0.04-0.12)	0.08 (0.04-0.13)	0.08 (0.04-0.12)	0.652	0.09 (0.05-0.12)	0.07 (0.03-0.13)	0.073
TG (mmol/L)	1.83 (1.00-2.53)	1.94 (1.07-2.63)	1.80 (0.94-2.50)	0.140	1.94 (1.07-2.53)	1.75 (0.96-2.52)	0.188
TC (mmol/L)	4.6 ± 1.0	4.7 ± 1.1	4.6 ± 1.0	0.501	4.5 ± 1.1	4.7 ± 1.0	0.133
LDL-C (mmol/L)	2.8 ± 0.7	2.9 ± 0.7	2.7 ± 0.6	0.111	2.8 ± 0.7	2.8 ± 0.6	0.542
HDL-C (mmol/L)	1.01 (0.81-1.15)	1.04 (0.82-1.15)	0.97 (0.80-1.14)	0.316	0.96 (0.75-1.09)	1.04 (0.87-1.17)	**0.029**
HsCRP (mg/L)	6.40 (2.43-10.45)	13.23 (9.41-16.53)	4.03 (1.79-7.71)	**<0.001**	9.38 (3.28-15.02)	4.59 (2.05-7.93)	**<0.001**
ESR (mm/h)	16.92 (8.96-24.22)	19.98 (8.85-24.85)	16.19 (8.98-23.61)	.649	16.36 (8.87-24.46)	16.97 (9.35-24.05)	.229
WBC ($x10^9/L$)	6.0 ± 1.4	5.8 ± 1.3	6.1 ± 1.4	0.220	6.1 ± 1.4	6.0 ± 1.4	0.698
Neutrophil ($10^9/L$)	3.41 (2.88-4.08)	3.46 (2.98-4.29)	3.41 (2.85-4.07)	0.429	3.56 (3.01-4.41)	3.33 (2.80-3.92)	0.057

(Continues)

TABLE 1 (Continued)

Items	CAD patients (N = 210)	Restenosis patients (n = 54)	Non-restenosis patients (n = 156)	*P* value	RASP patients (n = 88)	Non-RASP patients (n = 122)	*P* value
Lesion features							
Multivessel artery lesions	158 (75.2)	46 (85.2)	112 (71.8)	**0.049**	79 (89.8)	79 (64.8)	**<0.001**
Target lesion at LAD	119 (56.7)	33 (61.1)	86 (55.1)	0.444	48 (54.5)	71 (58.2)	0.598
Target lesion at LCX	74 (35.2)	21 (38.9)	53 (34.0)	0.515	27 (30.7)	47 (38.5)	0.240
Target lesion at RCA	77 (36.7)	17 (31.5)	60 (38.5)	0.359	36 (40.9)	41 (33.6)	0.279
Patients with two target lesions	60 (28.6)	17 (31.5)	43 (27.6)	0.583	23 (26.1)	37 (30.3)	0.507
Stenosis degree of target lesion (%)	88.00 (85.00-92.00)	86.50 (84.00-92.00)	88.00 (85.00-92.00)	0.277	86.50 (84.00-92.00)	88.00 (85.75-92.00)	0.231
Length of target lesion (mm)	35.00 (27.00-41.00)	33.75 (29.25-44.25)	33.50 (26.25-40.00)	**0.011**	37.50 (27.00-44.0)	34.00 (27.00-40.00)	0.074
Operation procedures							
Length of stent (mm)	38.00 (31.00-44.25)	41.50 (32.75-47.00)	37.00 (30.00-43.00)	**0.013**	41.00 (31.00-47.00)	37.00 (31.00-43.00)	0.113
Diameter of stent (mm)	3.30 (3.00-3.40)	3.20 (3.10-3.42)	3.30 (3.00-3.40)	0.513	3.30 (3.02-3.47)	3.20 (3.00-3.40)	0.213
Time of stent dilation (s)	15.00 (12.00-18.00)	14.50 (12.00-18.00)	15.00 (12.25-18.00)	0.187	15.00 (12.00-17.00)	15.50 (12.75-18.00)	0.122
Balloon dilation pre-stent	66 (31.4)	16 (29.6)	50 (32.1)	0.741	26 (29.5)	40 (32.8)	0.618
Drugs used after PCI							
Aspirin	210 (100.0)	54 (100.0)	156 (100.0)	1.000	88 (100.0)	122 (100.0)	1.000
Clopidogrel	210 (100.0)	54 (100.0)	156 (100.0)	1.000	88 (100.0)	122 (100.0)	1.000
Nitrates	200 (95.2)	50 (92.6)	150 (96.2)	0.290	85 (96.6)	115 (94.3)	0.434
Statins	205 (97.6)	52 (96.3)	153 (98.1)	0.459	86 (97.7)	119 (97.5)	0.930
β-receptor blockers	193 (91.9)	49 (90.7)	144 (92.3)	0.716	79 (89.8)	114 (93.4)	0.336
ACEIs/ARBs	143 (68.1)	39 (72.2)	104 (66.7)	0.450	61 (69.3)	82 (67.2)	0.747
Calcium channel blockers	72 (34.3)	20 (37.0)	52 (33.3)	0.621	29 (33.0)	43 (35.2)	0.730

Note: The boldface values stand for values with statistical significance.

Data were presented as mean ± standard deviation, median (25th-75th quantiles), or count (percentage).

Comparison between two groups was determined by Student's *t* test, Wilcoxon's rank sum test, or chi-square test.

Abbreviations: ACEIs/ARBs, angiotensin-converting enzymes inhibitors/angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; ESR, erythrocyte sedimentation rate; FBG, fasting blood-glucose; HDL-C, high-density lipoprotein cholesterol; HsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LAD, left anterior descending branch; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; PCI, percutaneous coronary intervention; RASP, rapid angiographic stenotic progression; RCA, right coronary artery; Scr, serum creatinine; SD, standard deviation; SUA, serum uric acid; cTnI, cardiac troponin I; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

($P < 0.001$), cTnI level ($P = 0.045$), and HsCRP level ($P < 0.001$) were elevated whereas the HDL-C level ($P = 0.029$) was declined in RASP patients compared with non-RASP patients. As to demographic (all $P > 0.05$) and other clinical characteristics (all $P > 0.05$), they were similar between RASP patients and non-RASP patients (Table 1).

3.2 | Comparison of pre-operative inflammatory cytokine expressions between restenosis and non-restenosis patients

The pre-operative expressions of TNF-α ($P = 0.002$, Figure 1A), IL-6 ($P < .001$, Figure 1D), IL-17A ($P < 0.001$, Figure 1G), and IL-23 ($P = 0.004$, Figure 1I) were increased, while the pre-operative IL-4 ($P = 0.013$, Figure 1C) expression was decreased in restenosis patients compared with non-restenosis patients. As for pre-operative IL-1β ($P = 0.369$, Figure 1B), IL-8 ($P = 0.079$, Figure 1E), IL-10 ($P = 0.362$, Figure 1F), and IL-21 ($P = 0.127$, Figure 1H) expressions, they were similar between restenosis patients and non-restenosis patients.

3.3 | Analysis of inflammatory cytokines affecting restenosis risk

Univariate logistic regression analysis was conducted to investigate the inflammatory cytokines affecting restenosis risk, which disclosed that pre-operative TNF-α ($P = 0.001$), IL-6 ($P < 0.001$), IL-8 ($P = 0.048$), IL-17A ($P = 0.002$), and IL-23 ($P = .009$) were correlated with increased restenosis risk, while pre-operative IL-4 ($P = .033$) expression was associated with decreased restenosis risk. In addition, hypertension ($P = 0.019$), diabetes mellitus ($P = 0.030$), SUA ($P = 0.003$), HsCRP ($P < 0.001$), length of target lesion ($P = 0.014$), and length of stent ($P = 0.016$) were correlated with increased restenosis risk. Forward stepwise multivariate logistic regression analysis was further conducted, which revealed that pre-operative IL-6

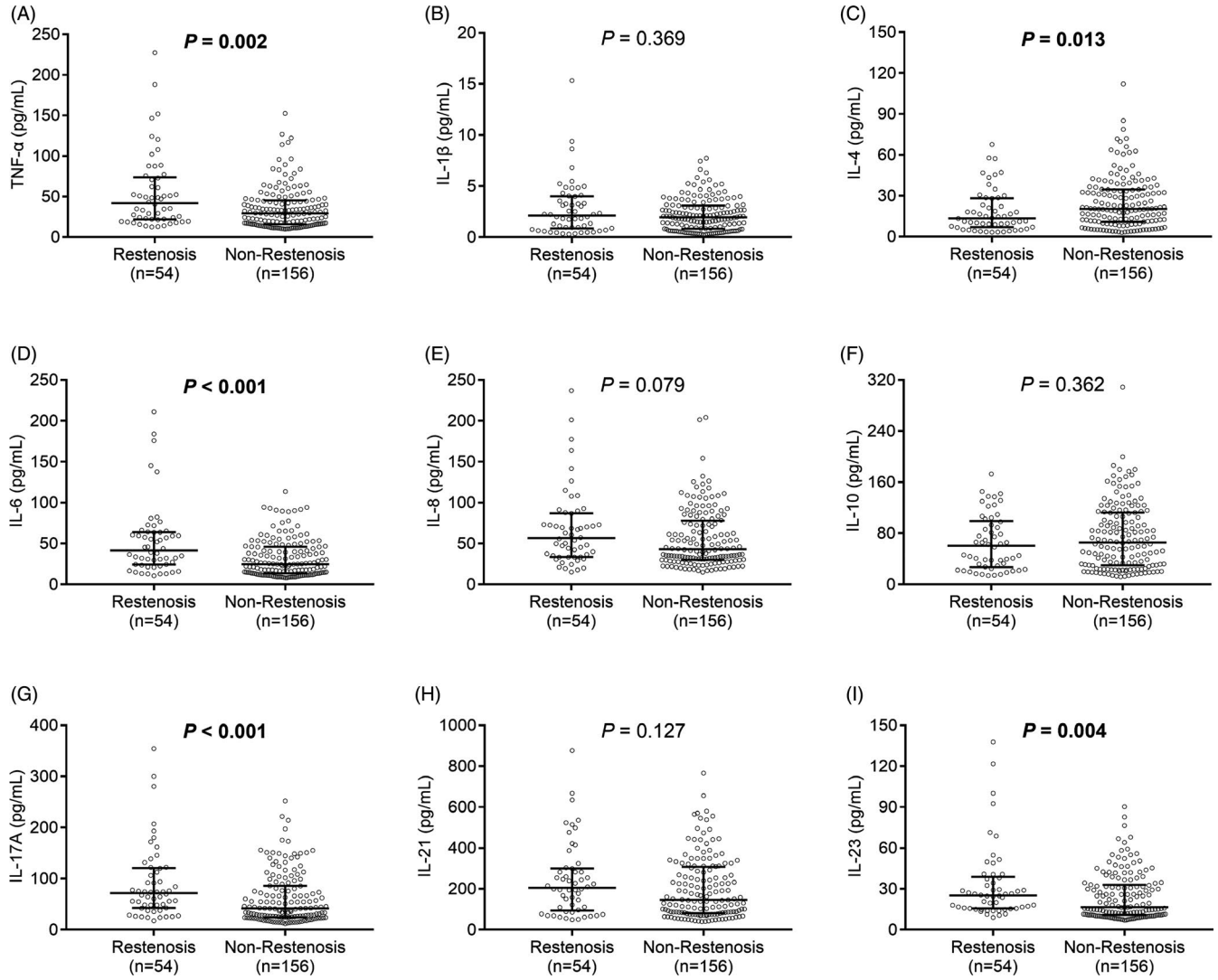

FIGURE 1 Pre-operative inflammatory cytokine expressions in restenosis patients and non-restenosis patients. Comparison of pre-operative TNF-α (A), IL-1β (B), IL-4 (C), IL-6 (D), IL-8 (E), IL-10 (F), IL-17A (G), IL-21 (H), and IL-23 (I) expressions between restenosis patients and non-restenosis patients. Comparison between two groups was determined by the Wilcoxon rank sum test. $P < 0.05$ was considered as significant. IL, interleukin; TNF-α, tumor necrosis factor-α

TABLE 2 Logistic regression analysis of factors predicting restenosis risk

Items	Logistic regression model			
			95%CI	
	P value	OR	Lower	Higher
Univariate logistic regression				
Demographic characteristics				
Age	0.964	0.999	0.970	1.030
Gender	0.540	1.290	0.572	2.913
BMI	0.545	1.027	0.941	1.121
CAD risk factors				
Current smoker	0.462	1.289	0.656	2.533
Hypertension	**0.019**	2.808	1.182	6.671
Diabetes mellitus	**0.030**	2.063	1.074	3.961
Hypercholesteremia	0.652	0.865	0.462	1.622
Hyperuricemia	0.448	0.781	0.413	1.477
Family history of CAD	0.840	1.086	0.487	2.422
Cardiac function index				
LVEF	0.273	0.974	0.930	1.021
Laboratory indexes				
MAP	0.157	0.987	0.970	1.005
FBG	0.900	0.983	0.748	1.291
Glycated hemoglobin	0.319	1.089	0.921	1.289
Scr	0.094	0.984	0.965	1.003
SUA	**0.003**	1.006	1.002	1.010
cTnI	0.850	0.229	<0.001	>999.99
NT-proBNP	0.803	1.845	0.015	226.263
TG	0.127	1.294	0.929	1.801
TC	0.499	1.109	0.821	1.498
LDL-C	0.112	1.469	0.914	2.359
HDL-C	0.424	1.587	0.512	4.916
HsCRP	**<0.001**	1.407	1.275	1.553
ESR	0.248	1.018	0.988	1.049
WBC	0.220	0.868	0.692	1.088
Neutrophil	0.258	1.200	0.875	1.647
Lesion features				
Multivessel artery lesions	0.054	2.259	0.987	5.169
Target lesion at LAD	0.445	1.279	0.680	2.405
Target lesion at LCX	0.515	1.237	0.652	2.344
Target lesion at RCA	0.360	0.735	0.380	1.420
Patients with two target lesions	0.583	1.207	0.616	2.367
Stenosis degree of target lesion	0.416	0.978	0.927	1.032
Length of target lesion	**0.014**	1.047	1.009	1.085
Operation procedures				
Length of stent	**0.016**	1.045	1.008	1.083
Diameter of stent	0.364	1.560	0.597	4.078
Time of stent dilation	0.256	0.956	0.885	1.033
Balloon dilation pre-stent	0.741	0.893	0.455	1.751
Drugs used after PCI				
Nitrates	0.298	0.500	0.136	1.844
Statins	0.467	0.510	0.083	3.136
β-receptor blockers	0.716	0.817	0.274	2.435
ACEIs/ARBs	0.451	1.300	0.657	2.572
Calcium channel blockers	0.621	1.176	0.617	2.242
Inflammatory cytokines				
TNF-α	**0.001**	1.016	1.007	1.026
IL-1β	0.068	1.153	0.989	1.343
IL-4	**0.033**	0.978	0.959	0.998
IL-6	**<0.001**	1.021	1.010	1.033
IL-8	**0.048**	1.008	1.000	1.015
IL-10	0.247	0.996	0.990	1.003
IL-17A	**0.002**	1.008	1.003	1.014
IL-21	0.094	1.002	1.000	1.003
IL-23	**0.009**	1.019	1.005	1.034
Forward stepwise multivariate logistic regression				
IL-6	**0.014**	1.026	1.005	1.046
IL-8	**0.040**	1.014	1.001	1.029
Hypertension	**0.002**	10.395	2.292	47.144
Diabetes mellitus	**0.001**	7.215	2.328	22.356
HsCRP	**<0.001**	1.522	1.332	1.740

Note: The boldface values stand for values with statistical significance. Factors predicting restenosis risk were analyzed by the univariate logistic regression, and the independent predicting factors of restenosis risk were screened by forward stepwise multivariate logistic regression from variables with *P* value <0.1 in univariate logistic regression.

The restenosis risk prediction model was as follows: $P = Exp[(-11.264 + 0.025(IL\text{-}6) + 0.014(IL\text{-}8) + 2.341(hypertension) + 1.976(diabetes\ mellitus) + 0.420(HsCRP))]/1 + Exp[(-11.264 + 0.025(IL\text{-}6) + 0.014(IL\text{-}8) + 2.341(hypertension) + 1.976(diabetes\ mellitus) + 0.420(HsCRP))]$, −2ln(likelihood ratio)=109.519.

Abbreviations: ACEIs/ARBs, angiotensin-converting enzymes inhibitors/angiotensin receptor blockers; BMI, body mass index; CI: confidence interval; ESR, erythrocyte sedimentation rate; FBG, fasting blood-glucose; HDL-C, high-density lipoprotein cholesterol; HsCRP, high-sensitivity C-reactive protein; IL, interleukin; LAD, left anterior descending branch; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; OR: odds ratio; PCI, percutaneous coronary intervention; RCA, right coronary artery; Scr, serum creatinine; SUA, serum uric acid; cTnI, cardiac troponin I; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; WBC, white blood cell.

(P = 0.014) and IL-8 (P = 0.040) expressions were independent risk factors for restenosis. Hypercholesteremia (P = 0.002), diabetes mellitus (P = 0.001), and HsCRP (P < 0.001) could also independently predict restenosis risk (Table 2).

3.4 | Predicting values of potential factors for restenosis risk

To further explore the predicting values of IL-6, IL-8, HsCRP, hypercholesteremia, and diabetes mellitus for restenosis risk, ROC curves were drawn, which showed that the AUCs were 0.679 (95%CI: 0.599-0.759), 0.580 (95%CI: 0.492-0.668), 0.902 (95%CI: 0.860-0.944), 0.583 (95%CI: 0.499-0.667), 0.579 (95%CI: 0.488-0.669), and 0.951 (95%CI: 0.925-0.978) for IL-6, IL-8, HsCRP, hypercholesteremia, diabetes mellitus, and the combination of these five factors, respectively (Figure 2).

3.5 | Comparison of pre-operative inflammatory cytokine levels between RASP and non-RASP patients

Pre-operative expressions of TNF-α (P < 0.001, Figure 3A), IL-6 (P < 0.001, Figure 3D), IL-17A (P < 0.001, Figure 3G), IL-21 (P = 0.006, Figure 3H), and IL-23 (P < 0.001, Figure 3I) were increased, whereas pre-operative IL-4 (P = 0.005, Figure 3C) expression was decreased in RASP patients compared with non-RASP patients. As for pre-operative IL-1β (P = 0.773, Figure 3B), IL-8 (P = 0.300, Figure 3E), and IL-10 (P = 0.466, Figure 3F) expressions, there was no difference between RASP patients and non-RASP patients.

3.6 | Analysis of inflammatory cytokines affecting RASP risk

Univariate logistic regression analysis was conducted to investigate the inflammatory cytokines affecting RASP risk, which disclosed that pre-operative TNF-α (P < 0.001), IL-6 (P < 0.001), IL-17A (P = 0.008), IL-21 (P = 0.015), and IL-23 (P < 0.001) were correlated with increased RASP risk, while pre-operative IL-4 (P = 0.017) expression was associated with declined RASP risk. In addition, hypertension (P = 0.009), SUA (P = 0.001), HsCRP (P < 0.001), neutrophil (P = 0.036), and multivessel artery lesions (P < 0.001) were correlated with increased RASP risk, Forward stepwise multivariate logistic regression analysis was further performed, which showed that pre-operative TNF-α (P = 0.003), IL-6 (P < 0.001), and IL-23 (P = 0.001) expressions were independent risk factors for RASP (Table 3). Hypercholesteremia (P = 0.021), SUA (P = 0.011), HsCRP (P < 0.001), and multivessel artery lesions (P = 0.006) could also independently predict RASP risk (Table 3).

3.7 | Predicting values of pre-operative TNF-α, IL-6, IL-21, and IL-23 expressions for RASP risk

To further explore the predicting values of TNF-α, IL-6, IL-23, hypercholesteremia, SUA, HsCRP, and multivessel artery lesions for RASP risk,

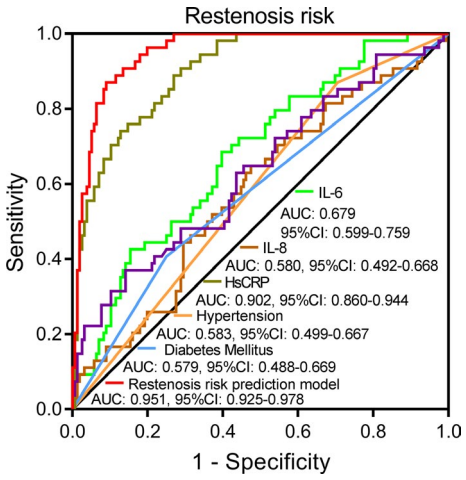

FIGURE 2 Receiver operating characteristic curves for predicting restenosis risk of IL-6, IL-8, hypercholesteremia, diabetes mellitus and HsCRP for restenosis risk. The predicting performance of IL-6, IL-8, hypercholesteremia, diabetes mellitus, HsCRP, and their combination were assessed by plotting ROC curves and calculating the AUCs with 95%CI. AUC, area under the curve; CI, confidence interval; HsCRP, high-sensitivity C-reactive protein; IL, interleukin; ROC, receiver operating characteristic

ROC curves were drawn, which revealed that the AUCs were 0.706 (95%CI: 0.636-0.755), 0.738 (95%CI: 0.671-0.804), 0.726 (95%CI: 0.659-0.793), 0.590 (95%CI: 0.512-0.667), 0.637 (95%CI: 0.562-0.713), 0.696 (95%CI: 0.618-0.774), 0.625 (95%CI: 0.550-0.700), and 0.886 (95%CI: 0.841-0.931) for TNF-α, IL-6, IL-23, hypercholesteremia, SUA, HsCRP, multivessel artery lesion, and the combination of these seven factors, respectively (Figure 4).

4 | DISCUSSION

Restenosis is characterized by the gradual re-narrowing of a stented coronary artery lesion owing to the arterial damage and the neointimal tissue proliferation.[5,15] According to a previous study, restenosis occurs in about 30% of CAD patients underwent PCI with bare-metal stents.[5,6] In recent years, DES has been invented and become more and more popular due to the better treatment efficacy and the lower the complication rate compared with bare-metal stents.[16] However, about 20% of CAD patients still occur restenosis after 2 years of PCI with DES.[17] In addition, a meta-analysis of 11 randomized clinical trials displays that the angiographic restenosis rate is 8.9% for drug-eluting stents within 1 year, while the restenosis rate was about 25% in this study, which was relatively higher compared with these previous studies.[18] The possible reasons were that (a) CAD patients enrolled in these 11 randomized clinical trials were less severe, and their disease severity (such as the length of target lesion) was lighter compared with our study. For instance, the length of target lesion ranged from 9.6 to 14.9 mm in these previous studies, while it was nearly 35.00 mm in this study. Considering relatively longer length of target lesion meant worse disease conditions, the restenosis rate was relatively high in CAD

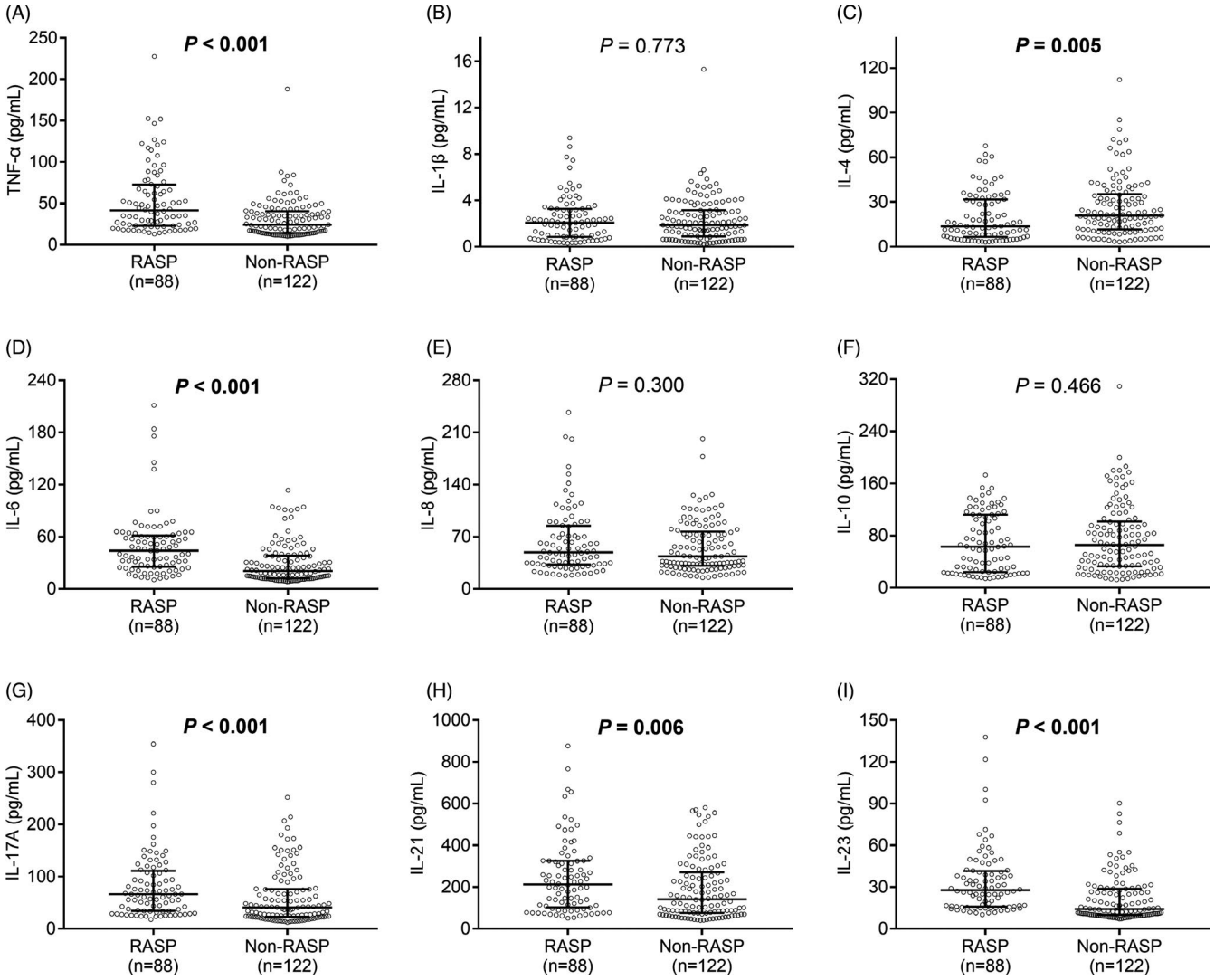

FIGURE 3 Pre-operative inflammatory cytokine expressions in RASP patients and non-RASP patients. Comparison of pre-operative TNF-α (A), IL-1β (B), IL-4 (C), IL-6 (D), IL-8 (E), IL-10 (F), IL-17A (G), IL-21 (H), and IL-23 (I) expressions between RASP patients and non-RASP patients. Comparison between two groups was determined by the Wilcoxon rank sum test. $P < 0.05$ was considered as significant. IL, interleukin; RASP, rapid angiographic stenotic progression; TNF-α, tumor necrosis factor-α

patients enrolled in this study. (b) CAD patients enrolled in these 11 randomized clinical trials might be relatively young with the mean age of fluctuated around 60 years old, while the mean age was about 63.1 years in CAD patients enrolled in this study. Due to that the slightly larger age might be related to worse resilience and weak immunity, the restenosis rate was relatively high in CAD patients enrolled in this study. To sum up, restenosis remains to be a challenge in clinical practices, and in order to reduce the incidence of restenosis, exploring the potential biomarkers for predicting restenosis risk is paramount.

The development and progression of restenosis is reported to be closely correlated with inflammatory activities in endothelial cells, while the predictive value of specific inflammatory factors for risk of restenosis is poorly understood.[2,7] Just a previous study discloses that HsCRP could predict the elevated restenosis risk in CAD patients underwent PCI with DES.[2,7] For inflammatory cytokines (the most common inflammatory proteins), they have been discovered to promote the formation of coronary artery lesion and the proliferation of neointimal tissue in CAD patients via multiple functions (such as recruit leukocytes to intima, facilitate the transformation of macrophages to foam cells, and promote the proliferation/migration of smooth muscle cells to the intima).[2,19,20] Besides, a few previous studies also observe that several inflammatory cytokines (such as IL-6 and TNF-α) are associated with increased CAD risk.[21,22] Considering all the aforementioned evidences, we hypothesized that some specific inflammatory cytokines might also be associated with risk of restenosis in CAD patients underwent PCI with DES.[7] In addition, based on accumulating evidence, TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17A, IL-21, and IL-23 are the most common inflammatory cytokines in CAD patients, which play important roles in the pathological processes of CAD.[23-25] Therefore, we enrolled 210 CAD patients underwent PCI with DES to compare the expressions of nine common inflammatory cytokines between restenosis patients

TABLE 3 Logistic regression analysis of factors predicting RASP risk

Items	Logistic regression model			
			95%CI	
	P value	OR	Lower	Higher
Univariate logistic regression				
Demographic characteristics				
Age	0.100	1.023	0.996	1.051
Gender	0.321	0.707	0.356	1.403
BMI	0.070	1.076	0.994	1.165
CAD risk factors				
Current smoker	0.400	1.299	0.706	2.390
Hypertension	0.177	1.564	0.817	2.996
Diabetes mellitus	0.095	1.668	0.914	3.042
Hypercholesteremia	0.009	2.161	1.210	3.858
Hyperuricemia	0.897	0.964	0.552	1.682
Family history of CAD	0.856	1.069	0.522	2.190
Cardiac function index				
LVEF	0.889	1.003	0.963	1.045
Laboratory indexes				
MAP	0.999	1.000	0.985	1.016
FBG	0.359	1.120	0.879	1.428
Glycated hemoglobin	0.181	1.108	0.953	1.289
Scr	0.377	0.992	0.976	1.009
SUA	0.001	1.007	1.003	1.010
cTnI	0.234	3444.185	0.005	>999.999
NT-proBNP	0.472	4.829	0.066	351.200
TG	0.156	1.238	0.922	1.662
TC	0.134	0.812	0.619	1.066
LDL-C	0.528	0.874	0.575	1.328
HDL-C	0.069	0.379	0.133	1.080
HsCRP	<0.001	1.184	1.114	1.260
ESR	0.485	1.010	0.983	1.038
WBC	0.697	1.040	0.855	1.264
Neutrophil	0.036	1.359	1.021	1.810
Lesion features				
Multivessel artery lesions	<0.001	4.478	2.183	10.456
Target lesion at LAD	0.598	0.862	0.496	1.498
Target lesion at LCX	0.241	0.706	0.395	1.263
Target lesion at RCA	0.279	1.368	0.776	2.412
Patients with two target lesions	0.507	0.813	0.441	1.500
Stenosis degree of target lesion	0.450	0.982	0.936	1.030
Length of target lesion	0.076	1.029	0.997	1.062
Operation procedures				
Length of stent	0.102	1.026	0.995	1.059
Diameter of stent	0.272	1.613	0.688	3.782
Time of stent dilation	0.165	0.952	0.888	1.020
Balloon dilation pre-stent	0.618	0.860	0.475	1.557
Drugs used after PCI				
Nitrates	0.439	1.725	0.433	6.864
Statins	0.930	1.084	0.177	6.628
β-receptor blockers	0.340	0.616	0.228	1.665
ACEIs/ARBs	0.747	1.102	0.611	1.988
Calcium channel blockers	0.730	0.903	0.506	1.612
Inflammatory cytokines				
TNF-α	<0.001	1.026	1.015	1.038
IL-1β	0.757	1.022	0.888	1.177
IL-4	0.017	0.980	0.964	0.996
IL-6	<0.001	1.029	1.016	1.042
IL-8	0.166	1.005	0.998	1.012
IL-10	0.353	0.997	0.992	1.003
IL-17A	0.008	1.007	1.002	1.012
IL-21	0.015	1.002	1.000	1.004
IL-23	<0.001	1.035	1.017	1.053
Forward stepwise multivariate logistic regression				
TNF-α	0.003	1.021	1.007	1.035
IL-6	<0.001	1.032	1.014	1.049
IL-23	0.001	1.037	1.014	1.061
Hypercholesteremia	0.021	2.650	1.161	6.048
SUA	0.011	1.007	1.002	1.012
HsCRP	<0.001	1.197	1.104	1.298
Multivessel artery lesions	0.006	3.774	1.454	9.797

Note: The boldface values stand for values with statistical significance. Factors predicting RASP risk were analyzed by the univariate logistic regression, and the independent predicting factors of RASP risk were screened by forward stepwise multivariate logistic regression from variables with *P* value < 0.1 in univariate logistic regression. The restenosis risk prediction model was as follows:

$$P = Exp[(-8.500 + 0.021(TNF\text{-}\alpha) + 0.031(IL\text{-}6) + 0.037(IL\text{-}23) + 0.975(hypercholesteremia) + 0.007(SUA) + 0.180(HsCRP) + 1.328(multivessel\ artery\ lesions)]/1 + Exp[(-8.500 + 0.021(TNF\text{-}\alpha) + 0.031(IL\text{-}6) + 0.037(IL\text{-}23) + 0.975(hypercholesteremia) + 0.007(SUA) + 0.180(HsCRP) + 1.328(multivessel\ artery\ lesions)],$$

−2ln(likelihood ratio)=173.198

Abbreviations: ACEIs/ARBs, angiotensin-converting enzymes inhibitors/angiotensin receptor blockers; BMI, body mass index; cTnI, cardiac troponin I; CI: confidence interval; ESR, erythrocyte sedimentation rate; FBG, fasting blood-glucose; Scr, serum creatinine; HDL-C, high-density lipoprotein cholesterol; HsCRP, high-sensitivity C-reactive protein; IL, interleukin; LAD, left anterior descending branch; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NT-proBNP, N-terminal probrain natriuretic peptide; OR: odds ratio; PCI, percutaneous coronary intervention; RASP: rapid angiographic stenotic progression; RCA, right coronary artery; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; WBC, white blood cell.

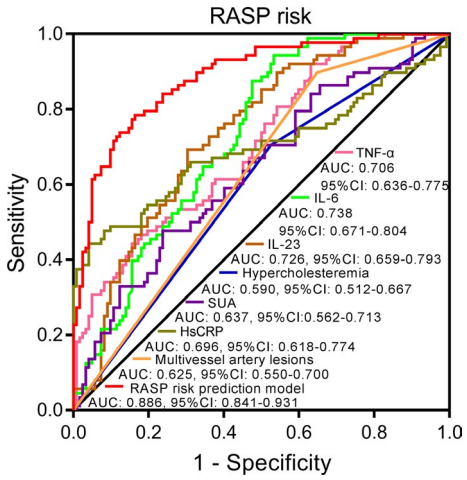

FIGURE 4 Receiver operating characteristic curves for predicting RASP risk of TNF-α, IL-6, IL-23, hypercholesteremia, SUA, HsCRP, and multivessel artery lesions. The predicting performance of TNF-α, IL-6, IL-23, hypercholesteremia, SUA, HsCRP, multivessel artery lesions, and their combination were assessed by plotting ROC curves and calculating the AUCs with 95%CI. AUC, area under the curve; CI, confidence interval; HsCRP, high-sensitivity C-reactive protein; IL, interleukin; RASP, rapid angiographic stenotic progression; ROC, receiver operating characteristic; SUA, serum uric acid; TNF-α, tumor necrosis factor-α

and non-restenosis patients, and we discovered that pre-operative TNF-α, IL-6, IL-17A, and IL-23 expressions were increased, while pre-operative IL-4 expression was decreased in restenosis patients compared with non-restenosis patients, indicating that pre-operative TNF-α, IL-6, IL-17A, and IL-23 expressions might be associated with increased restenosis risk and pre-operative IL-4 expression might be associated with decreased restenosis risk. To further explore the predicting values of these inflammatory cytokine expressions for restenosis risk, logistic regression analysis was performed and then ROC curves were drawn. These analyses revealed that pre-operative IL-6 and IL-8 expressions were independent risk factors for restenosis, and they disclosed predicting values for restenosis risk with AUCs more than 0.6; more importantly, when combining IL-6, IL-8, hypercholesteremia, diabetes mellitus, and HsCRP, the AUC for predicting restenosis risk was more than 0.9. The possible reasons for the results might be as follows: IL-6 and IL-8 were able to deteriorate disease conditions of CAD patients underwent PCI with DES via multiple effects (such as increased endothelial cell expression of adhesion molecules, activated the macrophages, increased metalloprotease expressions, and mediated the detrimental effects of angiotensin II to the vessels); therefore, the higher pre-operative expressions of IL-6 and IL-8 predicted the increased risk of restenosis in CAD patients underwent PCI with DES.[2,26,27]

Rapid angiographic stenotic progression is another common complication in CAD patients underwent PCI with DES, which strikingly affects the treatment efficacy of PCI with DES.[7,28] Therefore, it is also crucial to investigate the biomarkers for predicting RASP risk. Considering the predicting values of some inflammatory cytokines for cardiovascular disease risk including restenosis as aforementioned, we hypothesized that a series of inflammatory cytokines might also be associated with increased RASP risk. However, the relevant information is limited. Therefore, we also compared the expressions of inflammatory cytokines between RASP patients and non-RASP patients and found that pre-operative TNF-α, IL-6, IL-17A, IL-21, and IL-23 expressions were increased, whereas pre-operative IL-4 expression was decreased in RASP patients compared with non-RASP patients, implying that the pre-operative TNF-α, IL-6, IL-17A, IL-21, and IL-23 expressions might be associated with elevated RASP risk while pre-operative IL-4 expression might be correlated with reduced RASP risk. In addition, we also observed that pre-operative TNF-α, IL-6, and IL-23 expressions were independent risk factors for RASP, and they predicted RASP risk with AUCs more than 0.6; more interestingly, when combining TNF-α, IL-6, IL-23 hypercholesteremia, SUA, HsCRP, and multivessel artery lesions, the AUC for predicting RASP risk was over 0.8. In brief, our study facilitated the discovery of novel and convincing biomarkers for predicting restenosis and RASP risk in CAD patients underwent PCI with DES.

There remained some limitations in this study. Firstly, the sample size of restenosis patients was not matched with that of non-restenosis patients (due to the relatively low incidence of restenosis in CAD patients underwent PCI with DES), which might decrease the statistical power. Secondly, we compared the pre-operative expressions of nine common inflammatory cytokines between restenosis patients and non-restenosis patients, and between RASP patients and non-RASP patients, while the comparisons of other inflammatory cytokines between these patients needed additional investigations. Finally, the molecular mechanisms of these inflammatory cytokines in regulating restenosis and RASP were also required further explorations.

In summary, pre-operative IL-6 and IL-8 present with acceptable value for predicting restenosis risk; meanwhile, pre-operative TNF-α, IL-6, and IL-23 exhibit favorable value for predicting RASP risk in CAD patients underwent PCI with DES.

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REFERENCES

1. Hanson MA, Fareed MT, Argenio SL, Agunwamba AO, Hanson TR. Coronary artery disease. *Prim Care*. 2013;40(1):1-16.
2. Christodoulidis G, Vittorio TJ, Fudim M, Lerakis S, Kosmas CE. Inflammation in coronary artery disease. *Cardiol Rev*. 2014;22(6):279-288.
3. Roberts R. Genetics of coronary artery disease. *Circ Res*. 2014;114(12):1890-1903.
4. Ding Y, Zhou M, Wang Y, Cai L, Shi Z. Comparison of Drug-Eluting Stent with Bare-Metal Stent Implantation in Femoropopliteal

Artery Disease: A Systematic Review and Meta-Analysis. *Ann Vasc Surg*. 2018;50:96-105.
5. Her AY, Shin ES. Current management of in-stent restenosis. *Korean Circ J*. 2018;48(5):337-349.
6. Li TD, Zeng ZH. Adiponectin as a potential therapeutic target for the treatment of restenosis. *Biomed Pharmacother*. 2018;101:798-804.
7. Wu Y, Fu X. Comprehensive analysis of predictive factors for rapid angiographic stenotic progression and restenosis risk in coronary artery disease patients underwent percutaneous coronary intervention with drug-eluting stents implantation. *J Clin Lab Anal*. 2019;33(2):e22666.
8. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. *Circulation*. 2005;111(17):2257-2273.
9. Shaw DM, Merien F, Braakhuis A, Dulson D. T-cells and their cytokine production: The anti-inflammatory and immunosuppressive effects of strenuous exercise. *Cytokine*. 2018;104:136-142.
10. Anrather J, Iadecola C. Inflammation and Stroke: An Overview. *Neurotherapeutics*. 2016;13(4):661-670.
11. Mechmeche R, Zaroui A, Aloui S, et al. Late mitral restenosis after percutaneous commissurotomy: Predictive value of inflammation and extracellular matrix remodeling biomarkers. *Heart Lung*. 2017;46(4):258-264.
12. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2013;82(4):E266-355.
13. Bruining N, Sabate M, de Feyter PJ, et al. Quantitative measurements of in-stent restenosis: A comparison between quantitative coronary ultrasound and quantitative coronary angiography. *Catheter Cardiovasc Interv*. 1999;48(2):133-142.
14. Haase J, Escaned J, van Swijndregt EM, et al. Experimental validation of geometric and densitometric coronary measurements on the new generation Cardiovascular Angiography Analysis System (CAAS II). *Cathet Cardiovasc Diagn*. 1993;30(2):104-114.
15. Texakalidis P, Tzoumas A, Giannopoulos S, et al. Risk factors for restenosis following carotid revascularization: a meta-analysis of hazard ratios. *World Neurosurg*. 2019.
16. Liu L, Liu B, Ren J, Hui G, Qi C, Wang J. Comparison of drug-eluting balloon versus drug-eluting stent for treatment of coronary artery disease: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2018;18(1):46.
17. Mehilli J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2009;53(19):1760-1768.
18. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364(9434):583-591.
19. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. *Circ Res*. 2019;124(2):315-327.
20. Scott L Jr, Li N, Dobrev D. Role of inflammatory signaling in atrial fibrillation. *Int J Cardiol*. 2019;287:195-200.
21. Kaptoge S, Seshasai SR, Gao P, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J*. 2014;35(9):578-589.
22. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000;101(15):1767-1772.
23. Lubrano V, Balzan S. Consolidated and emerging inflammatory markers in coronary artery disease. *World J Exp Med*. 2015;5(1):21-32.
24. Khojasteh-Fard M, Abolhalaj M, Amiri P, et al. IL-23 gene expression in PBMCs of patients with coronary artery disease. *Dis Markers*. 2012;33(6):289-293.
25. Ding R, Gao W, He Z, et al. Effect of serum interleukin 21 on the development of coronary artery disease. *APMIS*. 2014;122(9):842-847.
26. Moshapa FT, Riches-Suman K, Palmer TM. Therapeutic targeting of the proinflammatory IL-6-JAK/STAT signalling pathways responsible for vascular restenosis in type 2 diabetes mellitus. *Cardiol Res Pract*. 2019;2019:9846312.
27. Wang H, Zhong D, Chen H, Jin J, Liu Q, Li G. NLRP3 inflammasome activates interleukin-23/interleukin-17 axis during ischaemia-reperfusion injury in cerebral ischaemia in mice. *Life Sci*. 2019;227:101-113.
28. Floria M, Guedes A, Schroeder E. Rapid progression of coronary artery stenosis revealed by stress echocardiography. *Acta Cardiol*. 2013;68(2):216-218.

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