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Predictive values of novel high-density lipoprotein-related inflammatory indices in in-stent restenosis among patients undergoing elective percutaneous coronary intervention

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Abstract. Inflammation and disorders in lipid metabolism play pivotal roles in the development and progression of in-stent restenosis (ISR). The present study aimed to investigate the association between the high-density lipoprotein (HDL)-related inflammatory indices and the risk of developing ISR among patients undergoing elective percutaneous coronary intervention (PCI). A sum of 1,471 patients undergoing elective PCI were retrospectively included and classified by tertiles of HDL-related inflammatory indices. The study endpoint was ISR. The multivariable Cox proportional hazards regression analysis with restricted cubic splines (RCS) was used to assess the associations. During a median follow-up of 62.27 months, 251 (17.06%) patients experienced ISR. The incidence of ISR increased with the increasing white blood cell-to-HDL ratio (WHR) tertiles (log-rank test, overall P=0.0082). After full adjustment, the highest tertile of WHR was significantly associated with a 1.603-fold risk of ISR (hazard ratio, 1.603; 95% confidence interval, 1.152-2.231; P=0.005) in contrast to the lowest tertile of the WHR. Results of RCS further indicated that the association between WHR and ISR was in a non-linear and dose-dependent manner (non-linear P=0.034; P overall=0.019). The lymphocyte-to-HDL ratio (LHR) and neutrophil-to-HDL ratio (NHR) were also significantly and positively associated with the risk of ISR, of which the third tertiles were at increased risk of 41.2 and 44.7% after full adjustment, respectively. Overall, lipid metabolism disorders and inflammation were interconnected in the development of ISR; therefore, HDL-related inflammatory indices, including WHR, LHR and NHR, might be potential predictors in the prognosis of elective PCI.

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Abbreviations: ACS, acute coronary syndrome; AIC, Akaike information criterion; ANOVA, one-way analysis of variance; BMI, body mass index; CCS, chronic coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; CCTA, coronary CT angiography; CI, confidence interval; CEC, cholesterol efflux capacity; CHR, CRP-to-HDL ratio; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; hs-CRP, high-sensitive C-reactive protein; HbA1c, glycated hemoglobin; HR, hazard ratio; ISR, in-stent restenosis; IQR, interquartile range; LHR, lymphocyte-to-HDL ratio; MI, myocardial infarction; MHR, monocyte-to-HDL ratio; NHR, neutrophil-to-HDL ratio; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; RCS, restricted cubic splines; RCT, reverse cholesterol transport; WBC, white blood cell; WHR, WBC-to-HDL ratio

Key words: coronary artery disease, in-stent restenosis, elective PCI, high-density lipoprotein, inflammatory mediators

Introduction

Elective percutaneous coronary intervention (PCI) is a widely used revascularization strategy in the treatment of patients with chronic coronary syndrome (CCS) (1). Evidence from a clinical trial has demonstrated that elective PCI, compared with medical therapy, can provide symptom relief and survival benefits in lowering the risk of adverse events such as cardiac death and myocardial infarction (MI) (2). In-stent restenosis (ISR) is a progressive re-narrowing of the coronary lesion after stent implantation in PCI. Clinically, ISR commonly presents as unstable angina pectoris and is associated with an increased risk for acute coronary syndrome (ACS) (3). While the advance of the drug-eluting stent (DES) has reduced the prevalence of ISR, ISR remains a significant clinical problem and accounts for ~10% of coronary revascularization, with associated mortality and morbidity (4). Considering that >1,000,000 PCIs are performed in China annually among the CCS population, identifying prognostic factors for ISR is important in informing the disease burden and risk stratification (5).

Inflammatory responses to implanted stents are the driving force and primary pathophysiology mechanism of ISR (6). Previous studies have established that systemic inflammation, indicated by the count of white blood cell (WBC) and its subsets, is closely associated with the risk of ISR (7,8). In addition, WBC and its subsets are positively related to adverse clinical endpoints in patients undergoing elective PCI (9). Recently, apolipoprotein A-I, a major protein component of high-density lipoprotein (HDL), has been revealed to improve the predictive value of WBC for coronary artery disease (CAD) (10). Given that HDL is directly involved in immunoregulation by altering the membrane lipid contents of immune cells, the combined effects of HDL with WBC and its subsets have been explored to assess the inflammatory risk (11). It has been revealed that the HDL-related inflammatory indices, including monocyte-to-HDL ratio (MHR), neutrophil-to-HDL ratio (NHR), WBC-to-HDL ratio (WHR) and C-reactive peptide-to-HDL ratio (CHR), can independently predict the risk of adverse cardiac events both in the short term and long-term (12,13). Moreover, the MHR has been identified to be an independent predictor in the ISR of DES and bare-mental stents (BMS) among patients with different CAD manifestations (14). However, data regarding the association of HDL-related inflammatory indices with ISR among the CCS population undergoing elective PCI with DES implantation is currently limited.

To address this, the present study aimed to investigate the associations between HDL-related inflammatory indices and ISR after elective PCI in patients with CCS, which might provide significant prognostic information in this population.

Materials and methods

Ethics statement. The present retrospective, single-center and observational study conformed to the Declaration of Helsinki and was authorized by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (Beijing, China; approval no. 2016-786). All participants provided written/oral informed consent.

Study population. The present study followed the methods of Guo *et al* (15). A total of 25,776 patients admitted with suspected CAD were retrospectively screened in Fuwai Hospital, Chinese Academy of Medical Sciences, from January 2017 to December 2017. The inclusion criteria were: i) Age >18 years; ii) significant coronary stenosis (≥50%) in baseline coronary angiography (CAG); iii) successful DES implantation at baseline; iv) no history of coronary artery bypass grafting (CABG); v) receiving follow-up coronary evaluation, including CAG and coronary CT angiography (CCTA). The exclusion criteria were: i) Patients presenting with ACS; ii) patients with missing measurements for HDL-related inflammatory indices; iii) considering the high specificity but relatively lower sensitivity of CCTA, patients with suspected ISR on CCTA but absence of CAG confirmation; and iv) patients with concurrent inflammatory diseases. Finally, 1,471 patients were included in the analysis. All participants were divided into three groups according to the tertiles of the HDL-related inflammatory indices (Fig. 1).

Endpoints and follow-up. The follow-up period lasted until October 2022. The primary endpoint was ISR and was assessed as enrolled time to the first event or until October 2022. ISR was defined as ≥50% re-narrowing over the entire length of the stent or involving its 5-mm edges. After the baseline successful PCI, all participants underwent follow-up CAG or CCTA in Fuwai Hospital, Chinese Academy of Medical Sciences. The outpatient and emergency records were reviewed during the follow-up to exclude patients with symptoms of ISR who declined coronary evaluation. To avoid counting endpoints in patients with early stent thrombosis, ISR within 30 days was excluded. Of note, CAG and CCTA were interpreted by experienced radiologists and interventional cardiologists. All participants received guideline-directed medical therapy.

Measurements and definitions. Data on sociodemographic characteristics, clinical history and laboratory tests were collected from medical records or interviews with the participants. The sociodemographic characteristics included age, sex, height, weight and smoking status. Clinical history of diabetes, hypertension, dyslipidemia, leukemia, inflammatory disease, previous PCI and peripheral artery disease (PAD) were recorded. The laboratory tests consisting of WBC, neutrophil, lymphocyte, monocyte, total cholesterol, triglyceride, low-density lipoprotein cholesterol, HDL-cholesterol (HDL-C), high-sensitive CRP (hs-CRP), fasting blood glucose and glycated hemoglobin (HbA1c), were performed under standardized instructions and assaying system in the laboratory of Fuwai Hospital, Chinese Academy of Medical Sciences. To ensure the parameters of each participant were at the same temporal window, all blood samples were obtained after overnight fasting before the elective PCI.

The diagnosis of CCS was based on the current guidelines of the European Society of Cardiology (16). Body mass index (BMI) was calculated as weight/height squared (kg/m^2). The estimated glomerular filtration rate (eGFR) was evaluated according to the modified Modification of Diet in Renal Disease equation: 186x Plasma creatine -1.154x age -0.203x0.742 (if female) x1.233 (if Chinese) (17). WHR was calculated as WBC/HDL-C. MHR was calculated as monocyte/HDL-C. Lymphocyte-to-HDL ratio (LHR) was calculated as lymphocyte/HDL-C. NHR was calculated as neutrophil/HDL-C. CHR was calculated as hs-CRP/HDL-C.

Statistical analysis. The random forest method was used to impute the missing data (18). The normality of the continuous variables was tested by the Kolmogorov-Smirnov test, in which data with normal distribution were described as mean ± standard deviation, otherwise as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. The one-way analysis of variance (ANOVA) was performed to assess the data with normal distribution, while the Kruskal-Wallis ANOVA on ranks was used for categorical variables and variables following skew distribution. Post-hoc analyses were implemented when appropriate with the

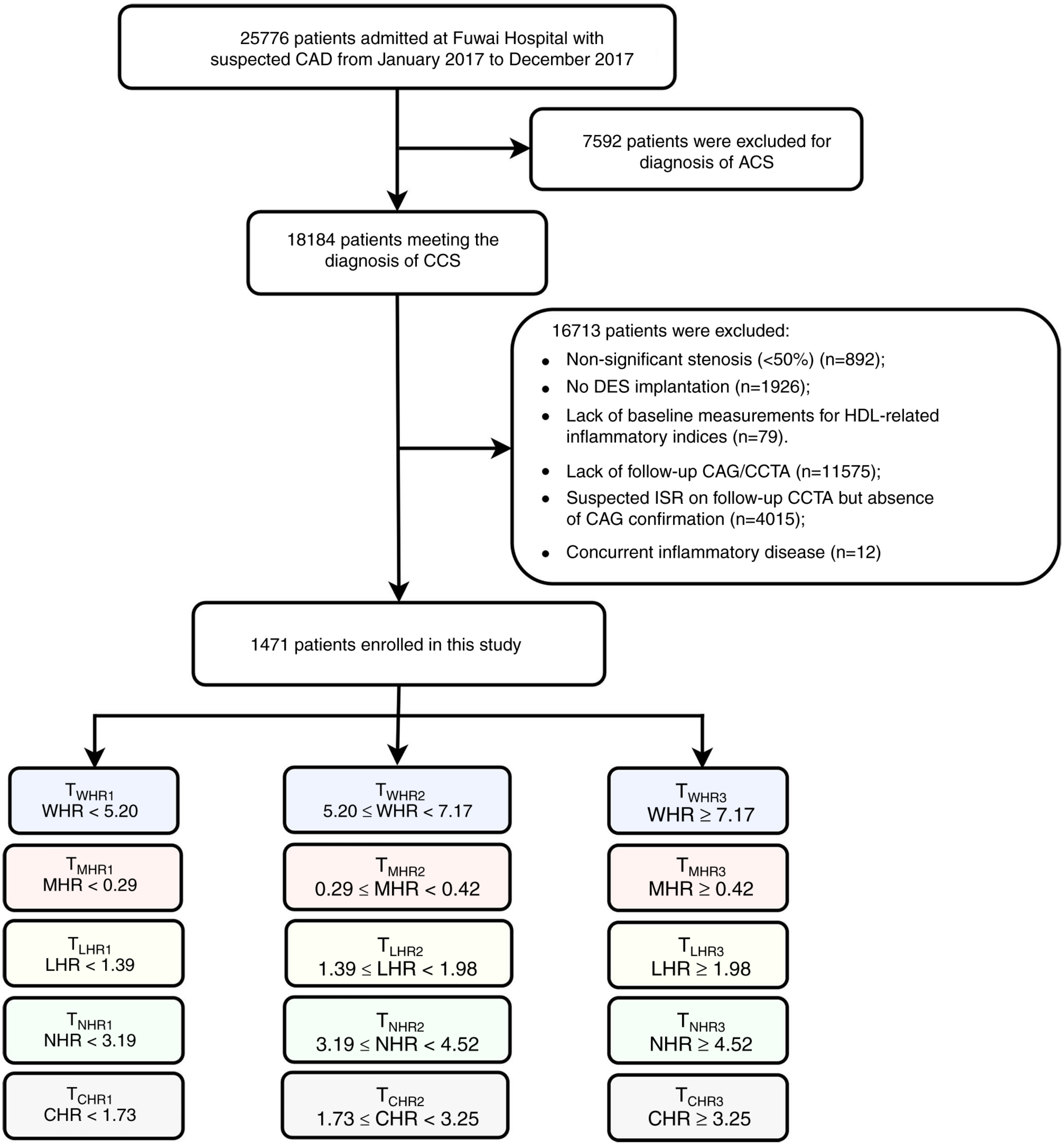

Figure 1. Flowchart of study participants. ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; CAG, coronary angiography; CCTA, coronary computed tomography angiography; CHR, C-reactive protein-to-high-density lipoprotein ratio; DES, drug-eluting stent; ISR, in-stent restenosis; LHR, lymphocyte-to-high-density lipoprotein ratio; MHR, monocyte-to-high-density lipoprotein ratio; NHR, neutrophil-to-high-density lipoprotein ratio; WHR, white blood cell-to-high-density lipoprotein ratio.

Tukey-Kramer post-hoc test (homoscedasticity) or Dunnett's T3 post-hoc test (heteroscedasticity).

The incidence of ISR among the groups was shown by Kaplan-Meier (KM) method and compared by log-rank tests. To control the false discovery rate at the level of 5%, the Benjamin-Hochberg procedure was used to correct the P-values in the pairwise comparisons. The multivariable Cox proportional hazards regression analysis was further utilized to estimate the hazard ratio (HR) and the 95% confidence interval (CI) of the HDL-related inflammatory indices in developing ISR. According to the clinical significance and findings from previous studies, the following covariates were included in the multivariable Cox regression model: Age (continuous), sex, BMI (continuous), prior PCI, presence of PAD, presence of multivessel CAD, eGFR (continuous), hs-CRP (continuous), presence of lesion's length ≥20 mm, stent length (continuous), presence of restenotic lesions and stent number (continuous). Proportionality of hazards was assessed for each variable, and Schoenfeld residuals were visually inspected for potential time-variant biases. The Schoenfeld residual test showed

Table I. Baseline characteristics according to the primary endpoint.

Variable	Total (n=1471)	Non-ISR (n=1220)	ISR (n=251)	P-value
Demographics				
Age, years (mean ± SD)	58.10±9.31	58.08±9.31	58.22±9.34	0.836
Male sex, n (%)	1151 (78.25)	951 (77.95)	200 (79.68)	0.602
Median BMI, kg/m^2 (IQR)	25.78 (23.89, 27.78)	25.80 (23.89, 27.78)	25.69 (23.90, 27.71)	0.551
Risk factors, n (%)				
Cigarette smoking	898 (61.05)	740 (60.66)	158 (62.95)	0.544
Diabetes	613 (41.67)	506 (41.48)	107 (42.63)	0.789
Hypertension	955 (64.92)	782 (64.10)	173 (68.92)	0.166
Dyslipidemia	1458 (99.12)	1211 (99.26)	247 (98.41)	0.343
Prior PCI	440 (29.91)	342 (28.03)	98 (39.04)	<0.001
PAD	200 (13.60)	154 (12.62)	46 (18.33)	0.022
Clinical presentations				
Multi-vessel CAD, n (%)	1189 (80.83)	972 (79.67)	217 (86.45)	0.017
Median LVEF, % (IQR)	64 (60, 66)	64 (60, 66)	63 (60, 66)	0.010
Laboratory measurements				
WBC, 10^9/l (mean ± SD)	6.70±1.69	6.64±1.67	6.98±1.78	0.003
Neutrophil, 10^9/l (mean ± SD)	4.28±1.38	4.24±1.34	4.46±1.51	0.025
Lymphocyte, 10^9/l (mean ± SD)	1.86±0.60	1.84±0.60	1.93±0.64	0.033
Monocyte, 10^9/l (mean ± SD)	0.39±0.13	0.39±0.13	0.40±0.15	0.093
TC, mmol/l (mean ± SD)	4.06±1.04	4.03±1.04	4.17±1.04	0.063
LDL-C, mmol/l (mean ± SD)	2.41±0.85	2.39±0.84	2.50±0.87	0.079
HDL-C, mmol/l (mean ± SD)	1.10±0.31	1.11±0.32	1.06±0.27	0.045
Triglycerides, mmol/l (mean ± SD)	1.76±1.22	1.73±1.23	1.91±1.20	0.041
HbA1c, % (mean ± SD)	6.38±1.20	6.31±1.14	6.70±1.43	<0.001
Median eGFR, ml/min per 1.73 m^2 (IQR)	110.99 (97.27, 125.57)	110.46 (97.07, 124.54)	114.18 (98.54, 129.67)	0.088
hs-CRP, mg/l (mean ± SD)	4.03±5.87	4.03±5.81	4.03±6.18	0.994
Medications at discharge, n (%)				
DAPT	1468 (99.80)	1217 (99.75)	251 (100.00)	0.985
Statins	1441 (97.96)	1195 (97.95)	246 (98.01)	1.000
ACEI/ARBs	736 (50.03)	598 (49.02)	138 (54.98)	0.099
β-blockers	1236 (84.02)	1009 (82.70)	227 (90.44)	0.003
Angiographic findings				
Target vessel territory				
LM, n (%)	44 (2.99)	38 (3.11)	6 (2.39)	0.682
LAD, n (%)	824 (56.02)	704 (57.70)	120 (47.81)	0.005
LCX, n (%)	368 (25.02)	301 (24.67)	67 (26.69)	0.553
RCA, n (%)	564 (38.34)	452 (37.05)	112 (44.62)	0.030
Restenotic lesions, n (%)	80 (5.44)	38 (3.11)	42 (16.73)	<0.001
Trifurcation/bifurcation lesions, n (%)	801 (54.45)	667 (54.67)	134 (53.39)	0.762
Lesions ≥20 mm long, n (%)	1038 (70.56)	846 (69.34)	192 (76.49)	0.029
Median number of stents (IQR)	2 (1, 2)	2 (1, 2)	2 (1, 3)	0.195
Median length of stent, mm (IQR)	30 (21, 48)	30 (20, 45)	33 (23, 54)	0.014
TIMI grade 0/1, n (%)	263 (17.88)	206 (16.89)	57 (22.71)	0.036
Median WHR (IQR)	6.16 (4.79, 7.93)	6.08 (4.75, 7.86)	6.54 (5.21, 8.25)	0.003
WHR tertiles, n (%)				0.006
T_1	484 (32.90)	423 (34.67)	61 (24.30)	
T_2	486 (33.04)	395 (32.38)	91 (36.25)	
T_3	501 (34.06)	402 (32.95)	99 (39.44)	
Median MHR (IQR)	0.35 (0.26, 0.46)	0.35 (0.26, 0.45)	0.36 (0.28, 0.51)	0.035

Table I. Continued.

Variable	Total (n=1471)	Non-ISR (n=1220)	ISR (n=251)	P-value
MHR tertiles, n (%)				0.097
T_1	458 (31.14)	389 (31.89)	69 (27.49)	
T_2	512 (34.81)	430 (35.25)	82 (32.67)	
T_3	501 (34.06)	401 (32.87)	100 (39.84)	
Median LHR (IQR)	1.67 (1.24, 2.21)	1.65 (1.22, 2.18)	1.74 (1.35, 2.31)	0.008
LHR tertiles, n (%)				0.046
T_1	485 (32.97)	417 (34.18)	68 (27.09)	
T_2	485 (32.97)	402 (32.95)	83 (33.07)	
T_3	501 (34.06)	401 (32.87)	100 (39.84)	
Median NHR (IQR)	3.87 (2.92, 5.10)	3.82 (2.88, 5.05)	4.08 (3.14, 5.32)	0.014
NHR tertiles, n (%)				0.064
T_1	482 (32.77)	414 (33.93)	68 (27.09)	
T_2	487 (33.11)	403 (33.03)	84 (33.47)	
T_3	502 (34.13)	403 (33.03)	99 (39.44)	
Median CHR (IQR)	2.37 (1.48, 4.17)	2.36 (1.48, 4.11)	2.44 (1.50, 4.34)	0.742
CHR tertiles, n (%)				0.773
T_1	481 (32.70)	400 (32.79)	81 (32.27)	
T_2	490 (33.31)	410 (33.61)	80 (31.87)	
T_3	500 (33.99)	410 (33.61)	90 (35.86)	

ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CHR, CRP-to-HDL ratio; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; hs-CRP, hypersensitive C-reactive protein; IQR, interquartile range; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein-cholesterol; LM, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex branch; LHR, lymphocyte-to-HDL ratio; MHR, monocyte-to-HDL ratio; NHR, neutrophil-to-HDL ratio; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; RCA, right coronary artery; TC, total cholesterol; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell; WHR, WBC-to-HDL ratio.

that none were significant based on a P-value threshold 0.05. Moreover, the trend analysis was conducted by entering the tertiles of the HDL-related inflammatory indices as a continuous variable and rerunning the corresponding regression models. The potential non-linear relationship was further explored through the multivariable Cox proportional hazards model with restricted cubic splines (RCS) (19). To balance the effects of best fitting and overfitting in the RCS, the Akaike information criterion (AIC) was used, and the median of the HDL-related inflammatory indices was assigned as the reference value (20).

All statistical analyses were performed using R software (version 4.2.2) (21). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. The baseline characteristics of the study population according to the development of ISR were displayed in Table I. The average age was 58.10±9.31 years (age range, 25-86 years), and 1,151 (78.25%) were men. It was shown that in comparison with patients without ISR, patients experiencing ISR were more likely to have a history of prior PCI, concurrent PAD, multivessel CAD and use of β-blockers (all P<0.05). For the angiographic details, the presence of restenotic lesions, lesions ≥20 mm and TIMI grade 0/1 were more frequent in patients with ISR (all P<0.05). Moreover, patients with ISR had higher proportions of target vessel territory in the right coronary artery but lower proportions the in left anterior descending coronary artery (all P<0.05). Decreased HDL-C and elevated levels of WBC, neutrophils, lymphocytes, triglycerides and HbA1c were exhibited in patients who developed ISR (all P<0.05). Of note, the values of WHR, LHR and NHR were significantly higher in the ISR group, in which greater proportions of patients were observed in T2 and T3 tertiles. The characteristics of participants by the HDL-related inflammatory indices were presented in Tables SI-SV.

Association between WHR and ISR. A total of 251 (17.06%) patients experienced ISR during the median follow-up time of 62.27 months (IQR, 58.78-65.67 months). In the KM survival analyses, the incidence of ISR was significantly higher in the T2 and T3 groups of WHR (overall P=0.0082, adjusted pairwise P between T1 and T2=0.0150; T1 and T3=0.0098) (Fig. 2A).

The risk estimates for the associations between HDL-related inflammatory indices and ISR in the multivariable Cox regression analyses were presented in Table II. By classifying the patients into WHR tertiles, the T2 (HR, 1.524; 95% CI

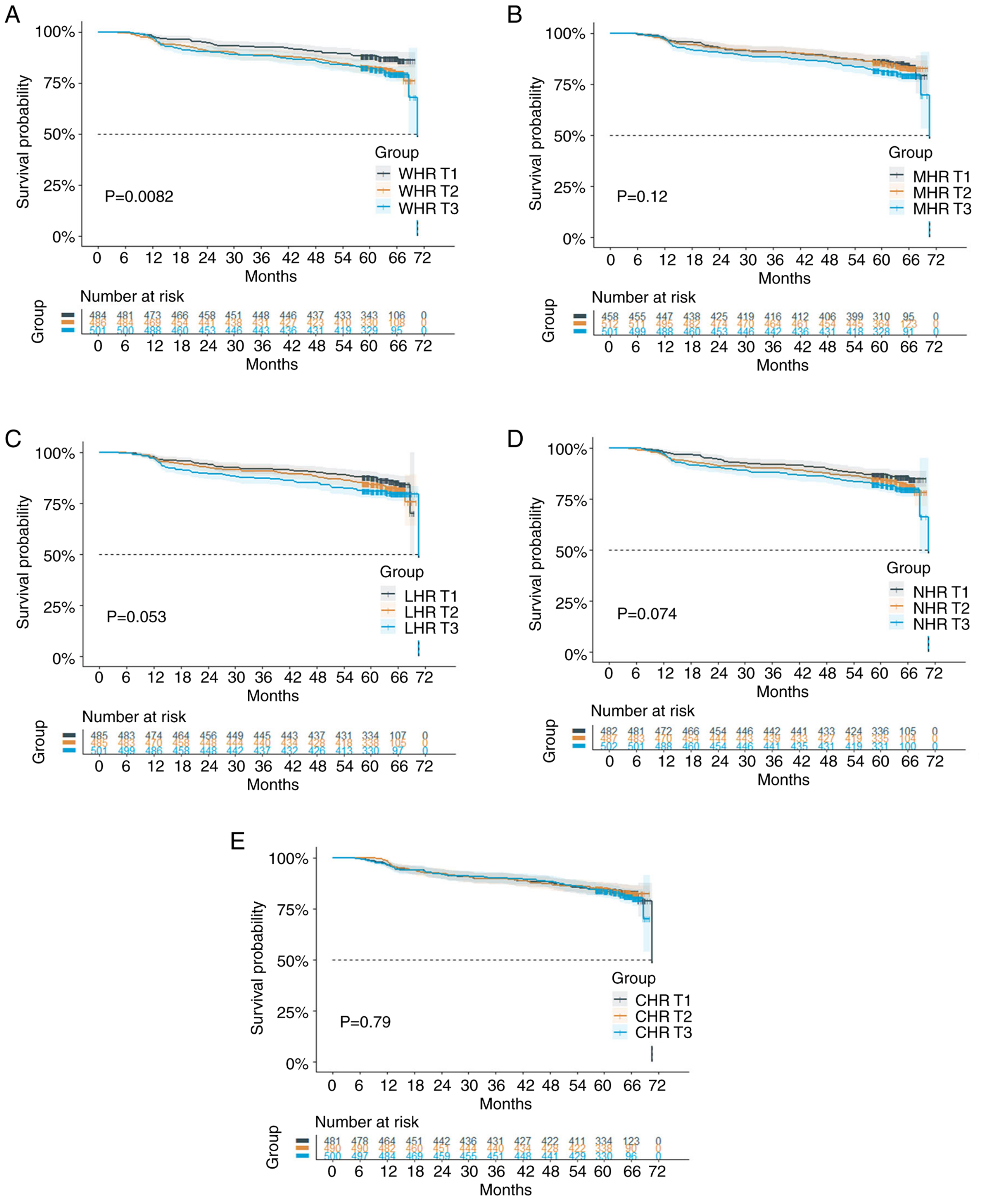

Figure 2. Kaplan-Meier analyses for the incidences of ISR. (A) ISR in WHR tertiles; (B) ISR in MHR tertiles; (C) ISR in LHR tertiles; (D) ISR in NHR tertiles; (E) ISR in CHR tertiles. CHR, C-reactive protein-to-high-density lipoprotein ratio; ISR, in-stent restenosis; LHR, lymphocyte-to-high-density lipoprotein ratio; MHR, monocyte-to-high-density lipoprotein ratio; NHR, neutrophil-to-high-density lipoprotein ratio; WHR, white blood cell-to-high-density lipoprotein ratio; HR, hazard ratio; CI, confidence intervals.

1.102-2.108; P=0.011) and T3 (HR, 1.608; 95% CI 1.168-2.214; P=0.004) groups of WHR were found at increased risk of ISR in the unadjusted model 1. After adjusting for demographic characteristics (age, sex, BMI), clinical presentations (prior PCI, concurrent PAD, multivessel CAD), laboratory measures (hs-CRP, eGFR) and angiographic presentations (lesion's length ≥20 mm, stent length) in model 2, the risk of the ISR remained increased in T2 (HR, 1.514; 95% CI, 1.090-2.102;

Table II. Associations between the HDL-related inflammatory indices and ISR.

	Model 1			Model 2			Model 3		
Variable	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
WHR	1.03	1.004-1.057	0.026	1.029	1.001-1.058	0.045	1.03	1.002-1.060	0.037
WHR tertiles									
T_1	Reference			Reference			Reference		
T_2	1.524	1.102-2.108	0.011	1.514	1.090-2.102	0.013	1.547	1.114-2.148	0.009
T_3	1.608	1.168-2.214	0.004	1.567	1.127-2.179	0.008	1.603	1.152-2.231	0.005
P for trend			0.004			0.01			0.006
MHR	1.301	0.862-1.964	0.21	1.248	0.796-1.956	0.335	1.24	0.777-1.979	0.366
MHR tertiles									
T1	Reference			Reference			Reference		
T2	1.055	0.766-1.454	0.742	1.051	0.755-1.461	0.769	0.992	0.711-1.383	0.96
T3	1.341	0.986-1.823	0.061	1.329	0.962-1.835	0.084	1.295	0.937-1.791	0.118
P for trend			0.054			0.071			0.091
LHR	1.051	0.982-1.126	0.153	1.052	0.980-1.129	0.164	1.051	0.977-1.132	0.181
LHR tertiles									
T1	Reference			Reference			Reference		
T2	1.231	0.893-1.696	0.204	1.202	0.870-1.661	0.265	1.188	0.861-1.641	0.295
T3	1.462	1.074-1.991	0.016	1.455	1.062-1.995	0.02	1.412	1.031-1.933	0.032
P for trend			0.016			0.019			0.031
NHR	1.061	1.009-1.115	0.022	1.056	1.001-1.114	0.045	1.061	1.006-1.120	0.029
NHR tertiles									
T1	Reference			Reference			Reference		
T2	1.241	0.902-1.709	0.185	1.241	0.898-1.713	0.19	1.192	0.862-1.649	0.288
T_3	1.431	1.050-1.950	0.023	1.394	1.016-1.914	0.04	1.447	1.053-1.988	0.023
P for trend			0.023			0.041			0.022
CHR	1.003	0.984-1.022	0.753	1.018	0.953-1.086	0.6	1.009	0.955-1.066	0.75
CHR tertiles									
T_1	Reference			Reference			Reference		
T_2	0.993	0.728-1.354	0.965	0.969	0.710-1.324	0.845	0.97	0.710-1.325	0.848
T_3	1.09	0.805-1.473	0.575	1.078	0.763-1.522	0.669	1.186	0.844-1.666	0.325
P for trend			0.57			0.696			0.357

Model 1: Unadjusted. Model 2: Adjusted for age, sex, BMI, prior PCI, presence of PAD, presence of multivessel CAD, hs-CRP, eGFR, presence of ≥20 mm lesion length and stent length. Model 3: Adjusted for age, sex, BMI, prior PCI, presence of PAD, presence of multivessel CAD, hs-CRP, eGFR, presence of ≥20 mm lesion length, stent length, presence of restenotic lesions and stent number. BMI, body mass index; CI, confidence interval; CAD, coronary artery disease; hs-CRP, hypersensitive C-reactive protein; CHR, CRP-to-HDL ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LHR, lymphocyte-to-HDL ratio; MHR, monocyte-to-HDL ratio; NHR, neutrophil-to-HDL ratio; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; WHR, white blood cell to high-density lipoprotein ratio.

P=0.013) and T3 (HR, 1.567; 95% CI, 1.127-2.179; P=0.008) in contrast to the T1 group. Specifically, after additionally adjusting the presence of restenotic lesions and stent number in model 3, it was found that the risk for ISR increased by 54.7% in T2 (HR, 1.547; 95% CI 1.114-2.148; P=0.009) and 60.3% in T3 (HR, 1.603; 95% CI 1.152-2.231; P=0.005) compared with T1 of WHR. The trend analyses for the three models were all statistically significant (all P for trend <0.05).

Similarly, the WHR as a continuous variable was shown to be significantly associated with the ISR (HR, 1.030; 95% CI, 1.004-1.057; P=0.026) in the unadjusted model 1 and could serve as an independent predictor of ISR after adjusting the potential confounders in model 2 (HR, 1.029; 95% CI, 1.001-1.058; P=0.045) and model 3 (HR, 1.030; 95% CI, 1.002-1.060; P=0.037).

To further identify the associations between the HDL-related inflammatory indices with the risk of ISR, the RCS based on the multivariable-adjusted Cox regression model 3 with three knots at the 10, 50 and 90th centiles according to AIC was performed. It was identified that the WHR was associated with the risk of ISR in a non-linear and dose-dependent manner (non-linear P=0.034; P overall=0.019). As illustrated in Fig. 3A, the risk of developing ISR increased rapidly before WHR of 6.16 and turned

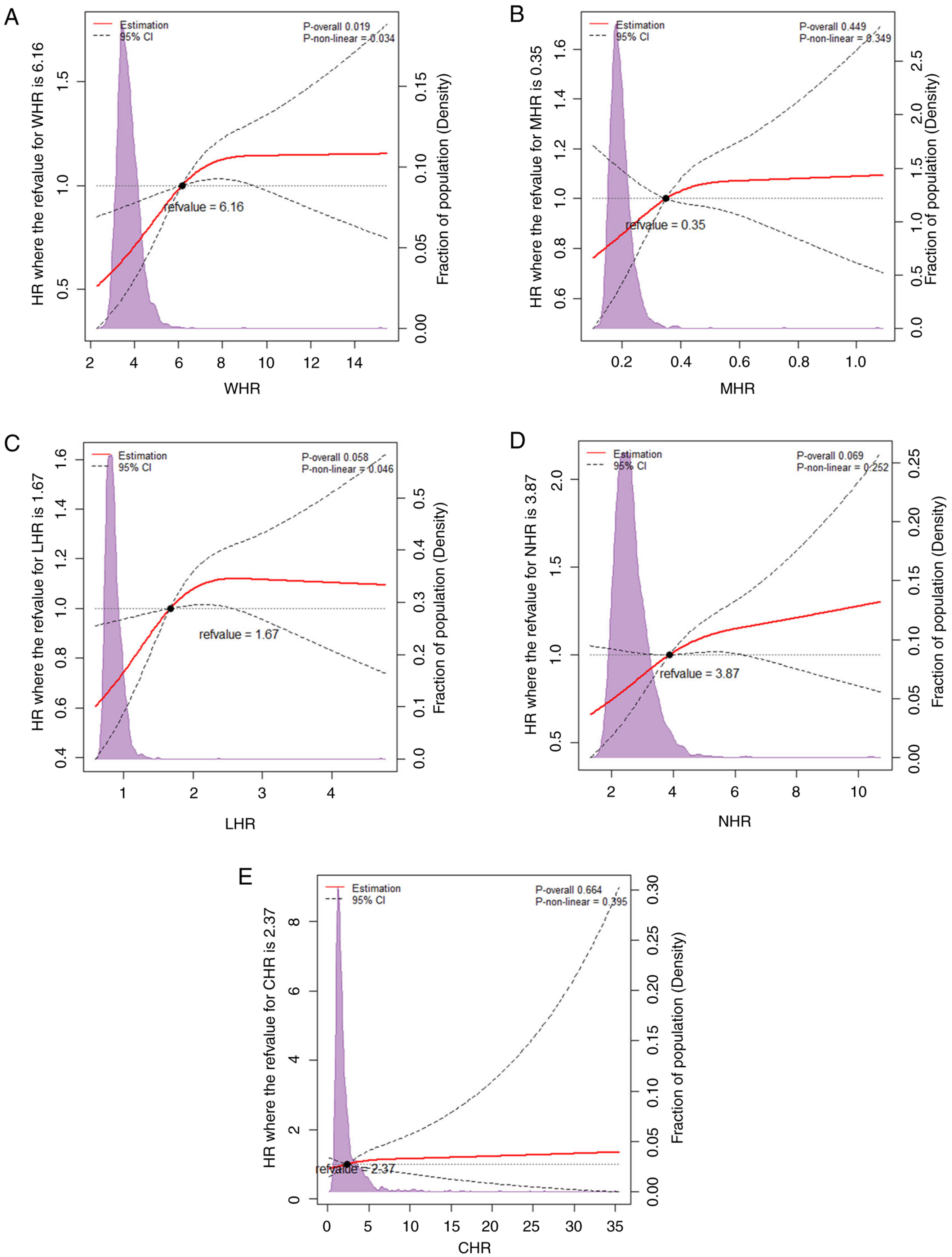

Figure 3. Restricted cubic splines for the adjusted dose-response associations between the HDL-related inflammatory indices and ISR. All data were fitted with a linear regression model using restricted cubic spines with three knots at the 5, 50 and 95th percentiles. Y-axis represents the odds ratio, and the dashed lines are 95% confidence intervals. (A) Association between WHR and ISR; (B) association between MHR and ISR; (C) association between LHR and ISR; (D) association between NHR and ISR; (E) association between CHR and ISR. CI, confidence interval; CHR, C-reactive peptide-to-HDL ratio; HDL, high-density lipoprotein cholesterol; HR, hazards ratio; LHR, lymphocyte-to-HDL ratio; MHR, monocyte-to-HDL ratio; NHR, neutrophil-to-HDL ratio; ISR, in-stent restenosis; WHR, white blood cell-to-HDL ratio.

to a flat trend afterward. Taking the WHR of 6.16 as the cut-off point, the HR per unit increase in WHR was 0.857 (95% CI, 0.744-0.988; P=0.034) below the point and 1.206 (95% CI, 1.045-1.392; P=0.010) above the point.

Association between LHR and ISR. After classifying the participants according to the tertiles of LHR, no significant differences were demonstrated across the tertiles of LHR in the KM analyses (overall P≥0.05) (Fig. 2C).

Notably, in the multivariable Cox regression analyses, participants in the T3 group of LHR were identified to have an increased risk of 46.2% in developing ISR in model 1 (HR, 1.462; 95% CI 1.074-1.991; P=0.016) in contrast to participants of T1. After adjusting for potential confounders in model 2 and model 3, the risk of ISR remained at 1.455-fold (HR, 1.455; 95% CI 1.062-1.995; P=0.020) and 1.412-fold (HR, 1.412; 95% CI 1.031-1.933; P=0.032) in T3, respectively. The trend analyses were all statistically significant (all P<0.05).

The potential non-linear relationship between LHR and ISR was also investigated in the RCS. However, the present study failed to demonstrate a significant association between them (P overall ≥0.05) (Fig. 3C).

Association between NHR and ISR. The KM analysis showed non-significant differences across the tertiles of NHR for the ISR incidence (overall P≥0.05) (Fig. 2D).

In the multivariable Cox regression analyses, as a continuous scale, NHR was associated with ISR with an adjusted HR of 1.056 (HR, 1.056; 95% CI 1.001-1.114; P=0.045) in model 2 and 1.061 (HR, 1.061; 95% CI 1.006-1.120; P=0.029) in model 3. For the risk of ISR across the NHR tertiles, the T3 was at elevated risk in all three models (model 1: HR, 1.431; 95% CI 1.050-1.950; P=0.023; model 2: HR, 1.394; 95% CI 1.016-1.914; P=0.040; model 3: HR, 1.447; 95% CI 1.053-1.988; P=0.023). The trend analyses for the three models were all statistically significant in NHR (all P<0.05).

Additionally, the possible non-linear relationships of NHR with ISR failed to demonstrate significance (P overall ≥0.05) (Fig. 3D).

Discussion

To the best of our knowledge, the present study is the first to investigate the associations between HDL-related inflammatory indices and the risk of ISR in patients with elective PCI. The main findings of this study are as follows: i) The WHR and NHR, as a continuous or categorical variable, were significantly associated with ISR; ii) patients with higher values of WHR, NHR and LHR were more likely to develop ISR after the baseline elective PCI; and iii) the HDL-related inflammatory indices could act as independent predictors in the prognosis of elective PCI which might provide clinical significance in the risk stratification of ISR at an early stage.

Vascular inflammation of stented lesions is the primary contributor to ISR (6). In the early stage following PCI (6-12 months), balloon expansion and stent implantation cause endothelial injury and activation of inflammatory cells, resulting in stimulation and proliferation of vascular smooth muscle cells, eventually neointima hyperplasia (22). In the late stage (>12 months), chronic inflammation within the neointima could cause neoatherogenesis and consequent ISR (22). The inflammatory infiltration of ISR has been confirmed in *in vivo* coronary imaging and human-derived restenotic samples (23). By altering the content and structure of membrane lipids and functional proteins in immune cells through reverse cholesterol transport (RCT), HDL is recently recognized to modulate the inflammatory response. Additionally, components of HDL have been identified to have direct immunological roles independent of RCT (24). The anti-inflammatory property of HDL has been verified in clinical studies in which decreased levels of HDL are inversely correlated with amplified systemic inflammation and autoimmune disorders (25,26). Therefore, combining HDL with inflammatory biomarkers is of great significance in assessing the residual inflammatory risk under the guideline of PCI management. To date, the HDL-related inflammatory indices have been found to contribute to the increased risk of ISR in diverse CAD cohorts. Specifically, the MHR is positively associated with ISR in patients with ST-elevation MI undergoing BMS stenting and in patients with CAD after successful BMS implantation (27,28). Additionally, the MHR is significantly correlated with the risk of ISR in non-ST-elevation MI patients with DES (29). Among participants presented with angina pectoris receiving BMS, the MHR has been found to positively predict the risk of ISR as well (30).

In line with the previous findings, the present study further revealed that WHR, LHR and NHR were independently associated with the risk of ISR among patients receiving elective PCI. After adjusting for potential confounders involving clinical presentation, laboratory measures and angiographic manifestation, WHR values above the second and third tertiles were related to an increased ISR risk of 60.3 and 54.7%, respectively. Besides, participants in the third tertiles of LHR and NHR were also at greater risk of having ISR. Notably, the WHR was associated with ISR in a non-linear way in which the value of 6.16 might serve as a cut-off point for the increasing trend in ISR risk. In this context, the present study extended the association between HDL-related inflammatory indices and ISR, indicating the potential for improved risk stratification among CCS patients undergoing elective PCI. However, different from previous studies, the present study failed to demonstrate significant associations between MHR and ISR. Given that the present study focused on patients clinically presented with CCS and DES implantation, we hypothesized that the differences in study population, implanted stents and duration of follow-up might account for the inconsistent findings. Moreover, experimental data has suggested different modes of monocyte trafficking between acute and chronic inflammation and the inflammatory response of monocytes varies in relation to type of stents (31,32). Therefore, the present study might provide preliminary evidence for the associations between HDL-related inflammatory indices and the risk of ISR in patients with CCS undergoing DES stenting.

Notably, although HDL is generally considered an atherosclerosis protective factor for its cholesterol efflux capacity (CEC), results from extensive epidemiological studies do not support the cardiovascular benefits of HDL in patients with CAD (33,34). It was found that inflammatory cytokines in particular circumstances, such as ACS and DM, can affect the role of RCT in HDL by impairing lipid constituents and structure (35,36). Furthermore, HDL has been revealed to promote the inflammatory process in atherosclerosis with a gain of dysfunction (37). Therefore, increasing attention has been focused on functional measurements of HDL instead of concentrations (38). Evaluated by radioisotopic or fluorimetric bioassays, the CEC is currently used to estimate the RCT efficiency of HDL (39). Accumulating data from clinical studies has demonstrated that higher HDL CEC is inversely associated with the risk of cardiac outcomes (40,41). Considering this, the prognostic significance of WHR might be further improved with HDL CEC.

There are several limitations to the present study. First, this was a retrospective and single-center study which might affect the generalizability of the findings. Second, there might be information bias as the patients without follow-up coronary imaging were excluded. Third, potential confounding factors affecting the inflammatory condition and activity of HDL, such as food intake and training habits, were not recorded and included in the analysis. Lastly, the laboratory parameters were measured only once at the baseline, leaving a potential bias due to measurement mistakes.

In conclusion, the present study first demonstrated that higher HDL-related inflammatory indices, including WHR, LHR and NHR, were significantly and independently associated with an increased risk of ISR among patients receiving elective PCI. In addition, a non-linear relationship with a cut-off point being 6.16 was identified between the WHR and the risk of developing ISR. The current study indicated that the interplay between lipid metabolism disorder and inflammation contributed to the development of ISR. Furthermore, the assessment of HDL-related lipoprotein indices might potentially aid in identifying patients with high risk for ISR. To validate the present findings, prospective, multi-center studies are required.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LM and XG conceptualised the study. XG and PL designed the methodology. XG and RS performed the statistical analyses. RS collected the data, interpreted the data and wrote the original draft. PL reviewed the manuscript. LM acquired funding. XG and RS confirm the authenticity of all the raw data. All authors contributed important intellectual content to this study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was performed in line with the Declaration of Helsinki and was authorized by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (approval no. 2016-786). All participants provided written/oral informed consent for participating.

Patient consent for publication

All participants provided written/oral informed consent for publication, which the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences has approved.

Competing interests

The authors declare that they have no competing interests.

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