

# Variability In Non-HDL-C and Lp(a) Affect The Neutrophil To Lymphocyte Ratio In Patients Undergoing Elective Percutaneous Coronary Intervention

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## Research Article

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## Abstract

**Objective:** To evaluate the influence of the variability of Lipoprotein a (Lp(a)) and Non-high-density lipoprotein cholesterol (non-HDL-C) on the neutrophil to lymphocyte ratio (NLR) during the follow-up period in patients with coronary heart disease (CHD) after elective coronary intervention.

**Methods:** A total of 3320 consecutive patients with CHD after percutaneous coronary intervention (PCI) in a multi-center from January 2010 to January 2019 were enrolled. The baseline demographic data were Analyzed, and the NLR levels in tertile groups according to the baseline Lp(a) and non-HDL-C levels were compared. Linear regression is used to analyze the association of the variation rate of Lp(a) and non-HDL-C with NLR; and subgroup analysis of the relevant factors were found. All verifications are verified by SD, CV, and VIM triple methods.

**Results:** The NLR is significantly different among tertile Lp(a) variation groups in SD, CV and VIM methods, which is consistent in non-HDL-C variation rate except SD method. Multiple linear regression indicated that Lp(a) variability, age, gender, BMI, hypertension, eGFR were related to NLR, which was verified in age, gender, hypertension and non-diabetic subgroups. Non-HDL-C variability, age, gender, BMI, eGFR, statins, follow-up HDL-C and non-HDL-C were also related to NLR, and established in the above subgroups.

**Conclusion:** The variation rate of Lp(a) and non-HDL-C are independent positive predictors of NLR after elective PCI.

## Background

Coronary atherosclerotic heart disease (CHD), which is characterized by lipid deposition in the coronary arterial intima and chronic inflammation in the coronary artery wall[1], seriously threaten people's safety and quality of life. Lipid and inflammation theory are the two main basic theory of atherosclerosis.

Although many clinical studies have confirmed that decreasing levels of low-density lipoprotein cholesterol (LDL-C) can reduce atherosclerotic lesions, thereby significantly reducing the risk of atherosclerotic-cardiovascular disease (ASCVD) [2–4]. Meta-analysis showed that a certain number of patients with CHD still have a higher risk of ASCVD despite LDL-C levels reached the target after treatment[5], suggesting that LDL-C is not the only risk factor for ASCVD. Non-high-density lipoprotein cholesterol (non-HDL-C), as the sum of all cholesterol except HDL-C, has gradually become a research hotspot in recent years[6]. A meta-analysis of patients who have received statin therapy shows that the use of non-HDL-C levels is better than LDL-C levels in predicting the risk of major cardiovascular events in the future[7]. Many guidelines also recommend the use of non-HDL-C as the secondary intervention target in the prevention and treatment of ASCVD [7]. Except non-HDL-C, Lipoprotein a (Lp(a)) has also received great attention in the atherosclerotic blood lipid research. Lp(a) not only possesses all the harmful atherogenic properties of LDL-C units, but also has pro-thrombotic effect. It is an independent risk factor for CHD and is related to the severity of CHD[8].

In the development of CHD, the inflammatory response runs through the entire process of atherosclerosis. Although C-reactive protein (CRP) is a classic indicator of inflammation, the status of neutrophil to lymphocyte ratio (NLR) in clinical research is constantly involved. Peripheral blood NLR, as an important inflammatory indicator, represents the relative balance of neutrophils and lymphocytes. In the process of atherosclerosis, neutrophils reflect the nonspecific inflammatory process, while lymphocytes reflect the immune regulation pathway. The decreasing levels of lymphocytes are associated with the progression of atherosclerosis[9]. More importantly, the increase in NLR levels has been shown to be a predictor of the prognosis, severity and mortality of atherosclerosis and cardiovascular diseases [10].

At present, many studies have confirmed the correlation between abnormal lipid metabolism and inflammation[11, 12], but most of them are based on the absolute lipid levels and inflammation markers. The stability index of lipid level may be another intuitive reflection of the individual's own lipid metabolism level. Our previous study has found that the variation rate of serum LDL-C and HDL-C levels are predictors of inflammation index NLR [13]. However, few studies concern the variability of non-HDL-C and Lp(a). Although Marcovina SM et al reported that only a very minimal number of patients may have Lp(a) variation more than 25% from the baseline during the half-year follow-up period of Lp(a) [14], the increased Lp(a) variability often indicates that the body may have events related to inflammation and plaque instability[15].

In the current study, we aimed to explore the association of the variability of non-HDL-C and Lp(a) with NLR during the follow-up period in the elective percutaneous coronary intervention (PCI) population, which will provide theoretical basis and research direction for patients with CHD to control the chronic low-grade inflammation after interventional therapy.

# Methods

## Population and procedures

This study is a multicenter, retrospective, observational study. All consecutive eligible patients with CHD underwent elective PCI were enrolled from January 2010 to January 2019 at Sir Run Run Shaw Hospital and its medical consortium hospitals. The inclusion criteria were listed as follows: (1) Diagnosed with CHD and received elective PCI; (2) At least 3 follow-up visits within 1 year after PCI and completion of follow-up related inspections; (3) Complete hospitalization and follow-up data can be obtained. Exclusion criteria: (1) Congenital heart disease; (2) Complicated with severe valvular heart disease; (3) Complicated with heart failure, and the New York heart function class IV; (4) Peripheral artery disease; (5) Severe liver and kidney insufficiency; (6) Combined with blood system disease; (7) Combined with malignant tumor; (8) Combined with immune system disease; (9) Combined with severe acute/chronic infection.

All PCI procedures were performed by experienced interventional cardiologists in accordance with the recommendations of the current guidelines [16], using femoral or radial artery approach. Blood samples were collected 24 hours before PCI as baseline information. Patients undergoing PCI will be followed up 3 or more times within 1 year. After a one-night fast, blood samples were taken by anterior elbow vein puncture, and laboratory evaluations were routinely measured. Use an automatic blood cell counter to analyze the total number of white blood cells and their subtypes, including neutrophils and lymphocytes. Use Hitachi 747 (*Tokyo, Japan*) blood chemistry analyzer to measure total cholesterol (TC), triglycerides (TG), LDL-C, HDL-C, Lp(a), very low-density lipoprotein cholesterol (VLDL) and other lipid values. This study was approved by the Ethics Committee of the Sir Run Run Shaw Hospital of Zhejiang University (NO.20201217-36).

## Grouping

According to the level of Lp(a) variation rate and non-HDL-C variation rate during the follow-up period, all patients were equally divided into low-variation group, medium-variation group, and high-variability group. SD, CV and VIM were used to represent the rate of variation for one-way analysis of variance, and make comparisons between groups.

## Definitions

The patients' demographic data (including gender, age, body mass index (BMI), smoking history, diabetes, hypertension, previous myocardial infarction (MI), previous PCI history), serological indicators (including NLR, Lp(a), uric acid, estimated glomerular filtration rate (eGFR) HDL-C), TC, non-HDL-C) were collected from Health Information System (HIS). Data during the follow-up period were collected to calculate the variation rate of non-HDL-C and Lp(a), and the mean value of NLR. Smoking history is defined as subjects who currently have smoking habit or have quit smoking for less than 3 months. Hypertension is defined as three times with systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg without using antihypertensive drugs, and these three times are not within the same day. Diabetes is defined as those with typical diabetic symptoms (polydipsia, polyuria, and unexplained weight loss) with random blood glucose  $\geq 11.1$  mmol/L or fasting blood glucose  $\geq 7.0$  mmol/L.

The definition of variation rate in this study uses the following three methods at the same time: 1) SD Method: Standard deviation is used to describe the variation rate of a univariate during the follow-up period, that is, the arithmetic square root of the square of the difference between the three observations and the mean. 2) CV method:  $CV = (SD / \text{mean}) \times 100(\%)$  (standard deviation of the observed values measured at each node during the follow-up period / average Number)  $\times 100(\%)$ . 3) VIM method:  $VIM = (SD / \text{mean}^\beta) \times 100(\%)$  (standard deviation of the observed values measured at each node during the follow-up period /  $\text{mean}^\beta$ )  $\times 100(\%)$ ;  $\beta$  comes from curve fitting, which is based on SD The regression coefficient of natural logarithm and mean natural logarithm [17].

## Statistical analysis

SPSS18.0 software package (*IBM, USA*) was used for statistical analysis of the data. Without special instructions,  $p < 0.05$  was considered statistically significant. If the measurement data obey the normal distribution and the homogeneity of variance, it was expressed by the mean  $\pm$  standard deviation ( $X \pm SD$ ); otherwise, it was expressed by the quartile method. The comparison between groups is based on whether the variance is homogeneous or not, using one-way analysis of variance or the non-parametric Kruskal-Wallis method. Through the univariate analysis, variables with  $p$  value  $< 0.1$  were screened out for the test of multiple analyses. Multivariate linear regression analysis was performed to construct the prediction model between Lp(a) variation rate, non-HDL-C variation rate and NLR. In the subgroup analysis, according to age ( $\geq 65$  years old /  $< 65$  years old), gender, presence or absence of diabetes, presence or absence of hypertension, patients were divided into subgroups, and the association of Lp(a) variation rate and non-HDL-C variation rate with NLR in each subgroup was analyzed as above.

# Results

## Baseline characteristics

A total 3320 patients with CHD underwent elective PCI were enrolled in the study. The mean age was 64.99 years old, 72.4% were male, 26.8% with smoking history, 24.9% with diabetes, and 64.1% with hypertension. The baseline non-HDL-C, Lp(a) and NLR level were  $3.29 \pm 1.19$  mmol/L,  $23.63 \pm 25.56$  mg/dl and  $3.65 \pm 3.75$ , respectively; and the average non-HDL-C, Lp(a) and NLR level during the follow-up period were  $2.59 \pm 0.74$  mmol/L,  $25.09 \pm 26.59$  mg/dl and  $3.67 \pm 2.79$ , respectively. The baseline demographic data, laboratory tests, and medications were shown in Table 1.

**Table 1** Baseline and follow-up data of patients included

	Sample size (n=3320)
<b>Demographic information</b>	
Age (years)	64.99±11.04
Male, N (%)	2403 (72.4)
BMI	24.48±3.03
Current smoking, N (%)	890 (26.8)
Diabetes, N (%)	826 (24.9)
Hypertension, N (%)	2129 (64.1)
Previous myocardial infarction, N (%)	100 (3.0)
Previous PCI surgery, N (%)	214 (6.4)
<b>Laboratory Indicators</b>	
Baseline NLR	3.65±3.75
Average follow-up NLR	3.67±2.79
Baseline Lp(a) (mg/dl)	23.63±25.56
Average follow-up Lp(a) (mg/dl)	25.09±26.59
Lp(a) variation SD (mg/dl)	5.77±6.37
Lp(a) variationCV	0.27±0.19
Lp(a) variationVIM	0.20±0.10
Baseline non-HDL-C (mmol/L)	3.29±1.19
Average follow-up non-HDL-C (mmol/L)	2.59±0.74
non-HDL-Cvariation SD (mmol/L)	0.50±0.35
non-HDL-CvariationCV	0.19±0.11
non-HDL-CvariationVIM	0.02±0.01
Baseline eGFR ml/(min×1.73 m <sup>2</sup> )	97.79±33.26
<b>Drug treatment during the follow-up</b>	
ACEI, N (%)	988 (29.8)
ARB, N (%)	1140 (34.3)
β- blockers, N (%)	1966 (59.2)
CCB, N (%)	1006 (30.3)
Statins, N (%)	3250 (97.9)
Ezetimibe, N (%)	487 (14.7)
Intensive statins, N (%)	504 (15.2)

Data are presented as mean ± SD, absolute n (%), or median (inter quartile range). BMI, Body Mass Index; PCI, percutaneous coronary intervention; NLR, neutrophil to lymphocyte ratio; Lp(a), Lipoprotein a; eGFR, estimated glomerular filtration rate; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

#### Comparison of NLR levels among Lp(a) and non-HDL-C groups during follow-up

According to the level of Lp(a) variation rate during the follow-up period, all patients were equally divided into three groups, named low-variation group (group 1), medium-variation group (group 2) and high-variability group (group 3). SD method: The NLR levels of Group 1,

2, and 3 were  $3.32 \pm 2.12$  vs.  $3.70 \pm 2.87$  vs.  $4.03 \pm 3.20$  ( $p < 0.001$ ). CV method: The NLR levels of Group 1, 2, 3 were  $3.34 \pm 1.89$  vs.  $3.55 \pm 2.51$  vs.  $4.16 \pm 3.66$  ( $p < 0.001$ ). VIM method: The NLR levels of Group 1, 2, and 3 were  $3.34 \pm 1.89$  vs.  $3.55 \pm 2.51$  vs.  $4.16 \pm 3.66$  ( $p < 0.001$ ). In pairwise comparisons between groups, three methods showed significant difference between Group 1 and Group 3, and Group 2 and Group 3, but the difference between Group 1 and Group 2 was only significant in SD method ( $p = 0.008$ ). (Fig. 1)

According to the level of non-HDL-C variation rate during the follow-up period, all patients were equally divided into three groups, named low-variability group (group 1), medium-variation group (group 2) and high-variability group (group 3). SD method: The NLR levels of Group 1, 2, and 3 were  $3.55 \pm 2.65$  vs.  $3.67 \pm 2.44$  vs.  $3.79 \pm 2.86$  ( $p = 0.147$ ). The difference is not significant. CV method: The NLR levels of Group 1, 2, and 3 were  $3.45 \pm 2.41$  vs.  $3.63 \pm 2.43$  vs.  $3.94 \pm 3.05$  ( $p < 0.001$ ). Pairwise comparison found that compared with Group 1 ( $p < 0.001$ ) and Group 2 ( $p = 0.037$ ), Group 3 has a higher level of NLR. There was no significant difference between Group 1 and Group 2 ( $p = 0.412$ ). VIM method: The NLR levels of Group 1, 2, and 3 were  $3.45 \pm 2.41$  vs.  $3.63 \pm 2.43$  vs.  $3.94 \pm 3.05$  ( $p < 0.001$ ), and the results of the pairwise comparison were close to the CV method. (Fig. 2).

### Regression analysis of Lp(a) variation rate to NLR level during follow-up

Univariate regression analysis was performed, and found Lp(a) variability, age, sex, BMI, diabetes, hypertension, uric acid, eGFR, Ezetimibe, statins and follow-up TC were significantly related to NLR ( $p < 0.1$ ), and included in the multiple linear regression. The results indicate that the Lp(a) variation rate is a significant risk factor for increased NLR levels in SD, CV and VIM methods (SD:  $\beta = 0.045$ , 95%CI [0.016,0.074],  $p = 0.002$ ; CV:  $\beta = 1.678$ , 95%CI [0.791,2.564],  $p < 0.001$ ; VIM:  $\beta = 2.840$ , 95%CI [1.298,4.382],  $p < 0.001$ ) (Table 2). In addition, the result was further verified in the subgroup analysis by age, gender, hypertension and non-diabetic population (Fig. 3).

Table 2 LP (a): Univariate and multivariate linear regression of NLR level

	Univariate regression			Multivariate regression											
	$\beta$	95%CI	P value	SD			CV			VIM					
				$\beta$	95%CI	P value	$\beta$	95%CI	P value	$\beta$	95%CI	P value			
lp(a) (SD)	0.042	[0.026 to 0.058]	< 0.001	0.045	[0.016 to 0.074]	<b>0.002</b>									
lp(a) (CV)	2.162	[1.635 to 2.689]	< 0.001				1.678	[0.791 to 2.564]	<b>&lt; 0.001</b>						
lp(a) (VIM)	4.023	[3.052 to 4.994]	< 0.001							2.840	[1.298 to 4.382]	<b>&lt; 0.001</b>			
Age(y)	0.044	[0.035 to 0.053]	< 0.001	0.017	[0.002 to 0.032]	0.025	0.017	[0.002 to 0.032]	0.028	0.017	[0.002 to 0.032]	0.028	0.017	[0.002 to 0.032]	0.028
male	0.348	[0.126 to 0.570]	0.002	0.424	[0.110 to 0.738]	0.008	0.423	[0.110 to 0.736]	0.008	0.419	[0.106 to 0.732]	0.009	0.419	[0.106 to 0.732]	0.009
BMI	-0.081	[-0.113 to -0.048]	< 0.001	-0.047	[-0.090 to -0.003]	0.035	-0.047	[-0.090 to -0.004]	0.032	-0.048	[-0.091 to -0.004]	0.031	-0.048	[-0.091 to -0.004]	0.031
Current smoking	-0.060	[-0.174 to 0.055]	0.306												
Diabetes	0.227	[-0.002 to 0.455]	0.052	0.149	[-0.148 to 0.446]	0.324	0.170	[-0.125 to 0.465]	0.259	0.171	[-0.125 to 0.466]	0.257	0.171	[-0.125 to 0.466]	0.257
Hypertension	0.215	[0.008 to 0.423]	0.042	0.389	[0.100 to 0.679]	0.008	0.376	[0.088 to 0.665]	0.011	0.378	[0.089 to 0.666]	0.010	0.378	[0.089 to 0.666]	0.010
Uric acid	0.002	[0.001 to 0.003]	< 0.001	-0.001	[-0.002 to 0.001]	0.349	-0.001	[-0.002 to 0.001]	0.321	-0.001	[-0.002 to 0.001]	0.321	-0.001	[-0.002 to 0.001]	0.321

Values are expressed as mean  $\pm$  SD or n (%) unless otherwise indicated. CI, confidence interval. Other abbreviations as in Table 1.

### Regression analysis of non-HDL-C variation rate to NLR level during follow-up

Univariate regression analysis was performed, and found non-HDL-C variability, age, sex, BMI, diabetes, hypertension, uric acid, eGFR, Ezetimibe, statins, follow-up HDL-C and follow-up non-HDL-C were significantly related to NLR ( $p < 0.1$ ), and included in the multiple linear regression. The results suggested that the variation rate of non-HDL-C was a significant risk factor for increased NLR levels in SD, CV and VIM methods. (SD:  $\beta = 0.724$ , 95% CI [0.393 to 1.055],  $p < 0.001$ ; CV:  $\beta = 2.430$ , 95%CI [1.529 to 3.33],  $p < 0.001$ ; VIM:  $\beta = 17.676$ , 95%CI [10.839 to 24.513],  $p < 0.001$ ) (Table 3). In addition, this result was further verified in the subgroup analysis by age, sex, hypertension, and diabetes (Fig. 4).

Table 3 Univariate and multivariate linear regression of non-HDL-C to NLR level

Values are expressed as mean  $\pm$  SD or n (%) unless otherwise indicated. CI, confidence interval. Other abbreviations as in Table 1.

	Univariate regression			Multivariate regression								
				SD			CV			VIM		
	$\beta$	95%CI	P value	$\beta$	95%CI	P value	$\beta$	95%CI	P value	$\beta$	95%CI	P value
nonHDL-C (SD)	0.173	[-0.114 to 0.460]	0.237	0.724	[0.393 to 1.055]	<b>0.001</b>						
nonHDL-C (CV)	1.788	[0.873 to 2.702]	<b>0.001</b>				2.43	[1.529 to 3.33]	<b>0.001</b>			
nonHDL-C (VIM)	13.045	[6.106 to 19.985]	<b>0.001</b>							17.676	[10.839 to 24.513]	<b>0.001</b>
Age(y)	0.044	[0.035 to 0.053]	<b>0.001</b>	0.043	[0.033 to 0.053]	<b>0.001</b>	0.044	[0.034 to 0.054]	<b>0.001</b>	0.044	[0.034 to 0.054]	<b>0.001</b>
male	0.348	[0.126 to 0.570]	0.002	0.369	[0.139 to 0.599]	0.002	0.406	[0.178 to 0.633]	<b>0.001</b>	0.406	[0.179 to 0.634]	<b>0.001</b>
BMI	-0.081	[-0.113 to -0.048]	<b>0.001</b>	-0.115	[-0.149 to -0.081]	<b>0.001</b>	-0.117	[-0.151 to -0.084]	<b>0.001</b>	-0.118	[-0.151 to -0.084]	<b>0.001</b>
Current smoking	-0.060	[-0.174 to 0.055]	0.306									
Diabetes	0.227	[-0.002 to 0.455]	0.052	0.125	[-0.1 to 0.351]	0.276	0.128	[-0.097 to 0.353]	0.263	0.130	[-0.095 to 0.355]	0.259
Hypertension	0.215	[0.008 to 0.423]	0.042	0.132	[-0.08 to 0.343]	0.222	0.142	[-0.069 to 0.354]	0.186	0.141	[-0.07 to 0.352]	0.191
Uric acid	0.002	[0.001 to 0.003]	<b>0.001</b>	<b>0.001</b>	[-0.001 to 0.001]	0.744	<b>0.001</b>	[-0.001 to 0.001]	0.867	<b>0.001</b>	[-0.001 to 0.001]	0.866
eGFR	-0.012	[-0.015 to -0.009]	<b>0.001</b>	-0.007	[-0.01 to -0.004]	<b>0.001</b>	-0.007	[-0.01 to -0.004]	<b>0.001</b>	-0.007	[-0.01 to -0.004]	<b>0.001</b>
Ezetimibe	-0.284	[-0.563 to -0.004]	0.047	-0.048	[-0.319 to 0.223]	0.726	-0.108	[-0.378 to 0.161]	0.429	-0.103	[-0.373 to 0.166]	0.452
Intensive statins	-0.203	[-0.475 to 0.069]	0.143									
Statins	-3.385	[-4.078 to -2.693]	<b>0.001</b>	-3.458	[-4.179 to -2.737]	<b>0.001</b>	-3.401	[-4.121 to -2.682]	<b>0.001</b>	-3.412	[-4.131 to -2.692]	<b>0.001</b>
Follow-up HDL-C	-2.040	[-2.423 to -1.656]	<b>0.001</b>	-2.286	[-2.688 to -1.885]	<b>0.001</b>	-2.275	[-2.676 to -1.875]	<b>0.001</b>	-2.272	[-2.673 to -1.872]	<b>0.001</b>
Follow-up non-HDL-C	-0.202	[-0.337 to -0.067]	0.003	-0.261	[-0.414 to -0.108]	0.001						

## Discussion

The current study found that the variation rate of Lp(a) and non-HDL-C could significantly affect the average level of NLR during follow-up in the elective PCI population, and was further verified in the subgroup of age (over 65 years old), genders, hypertension and diabetes.

Blood lipid levels play a key role in the process of atherosclerosis[18]. The levels of Lp(a), non-HDL-C and LDL-C are related to the occurrence and development of chronic inflammation, atherosclerosis, and adverse cardiovascular outcomes[1, 19, 20]. Lp(a) is minimally affected by factors such as diet, lifestyle, statins therapy, etc., and its level is relatively stable compared to LDL-C; however, the increased Lp(a) variability often indicates that the body may have events related to inflammation and plaque instability[15]. Compared with LDL-C, non-HDL-C can more directly and accurately reflect the total number of all atherogenic lipoprotein particles. In the Bypass Angioplasty Revascularization Investigation (BARI) study, a 5-year follow-up of 1514 patients with coronary artery disease followed up by coronary angiography revealed that non-HDL-C is the most predictive lipid index, while LDL-C, HDL-C showed a negative result: for every 10% increase in non-HDL-C, the incidence of non-fatal myocardial infarction and angina pectoris increased by 5% and 10%, respectively [21]. In addition, in patients with hypertriglyceridemia, LDL-C levels may be reduced due to enhanced exchange and may underestimate the risk of atherosclerosis, while non-HDL-C levels will not be affected, and the risk can be estimated continuously [22]. Therefore, using these two lipid metabolism indicators (Lp(a) and non-HDL-C) as research variables can better reflect the specific conditions of atherosclerotic lipid indicators during the follow-up process, and can also reflect the total lipids level.

At present, most researches pay attention to the absolute value of lipid metabolism index, but pay less attention to variability and stability. In recent years, in addition to the average level of blood lipids, the stability of lipid metabolism has also been considered critical. In our previous studies, it was found that the variation rate of LDL-C is significantly related to inflammation[13]. The study of Clark.D et al. also found that the variation rate of LDL-C was an important indicator related to the progression of coronary atherosclerosis [23]. Meanwhile, the variation rate of other lipid molecules, such as VLDL, TG, Lp(a) and other atherosclerotic blood lipids, has a significant effect on patients with CHD after PCI. The current research focuses on non-HDL-C and Lp(a), both of which are used as indicators to comprehensively reflect the level of lipid metabolism, which can better reflect the stability of overall blood lipids and the relationship between atherosclerotic cholesterol and inflammation. The current study found that the variation rate of non-HDL-C and Lp(a) during the follow-up period was significantly correlated with the level of NLR, and they were independent risk factors for NLR, which indicated that non-HDL-C and Lp(a) variability rate can reflect and predict the chronic low-grade inflammation level in patients with CHD after elective PCI. Previous studies have found that compared with the low blood lipid variation rate group, the high blood lipid variation rate group has higher inflammatory cell infiltration around the fibrous cap of the vascular artery plaque [24], which is consistent with the results of current study, and provides important basic research evidence. Although the mechanism by which the increased variation rate of non-HDL-C and Lp(a) promotes inflammation is still unclear, controlling blood lipid variability can affect NLR level, thereby improving the prognosis of patients undergoing PCI, and has good application value.

In our opinion, it may be that the circulating LDL, VLDL, and Lp(a) particles can penetrate the endothelium of the arterial wall and be oxidized, thereby promoting inflammation, and causing endothelial damage. Firstly, the high variability of non-HDL-C and Lp(a) may damage the cholesterol-dependent plaque stability mechanism, leading to plaque vulnerability and even rupture, releasing inflammatory factors, and promoting inflammation. Secondly, the higher variability may reflect the proportion of time that the lipid profile is not within the therapeutic target range, which will cause the worse prognosis. Furthermore, Lipid-related metabolic and genetic factors such as LDL-C receptor, VLDL receptor or HMG-CoA(3-hydroxy-3-methylglutaryl-coenzyme A )reductase polymorphism, and LP (a) gene expression and variation may also lead to increase lipid variation [25–28]. In addition, the higher blood lipid variability may reflect the body's accompanying diseases or changes in the internal environment, which in turn is related to inflammation. Finally, high variability may reflect poor compliance and tolerance to lipid-lowering drugs, including statins.

In the current study, it has found that in the subgroups such as age, gender, hypertension, and diabetes, the impact of non-HDL-C variant rate on the NLR of patients with CHD after PCI has significant significance. There is good agreement among the three analysis methods of variation rate. This reflects that non-HDL-C has a good and stable inflammatory feedback effect in most people, and is not affected by factors such as age, gender, hypertension, and diabetes. In the subgroup analysis of the effect of Lp(a) variation rate on NLR in patients with CHD after PCI, it has found that the correlation analysis results of the three variation rate description methods still had good consistency. Moreover, the three methods all suggested that there was no significant correlation between Lp(a) variation rate and NLR in diabetic population. Previous studies have shown that the level of Lp(a) is affected by genetic factors and is relatively stable within an individual with a small variation rate[29]. Therefore, in this study, it was also shown that the variation rate of Lp(a) is relatively small, and the diabetic subgroup itself has long-term chronic low-grade inflammation, which makes the variation of Lp(a) in this subgroup relatively small. The influence of the level of inflammation is interfered by the inflammatory factors of diabetes, which weakens the correlation between the two. Conversely, the variability of non-HDL-C during the follow-up period is much greater, and its correlation with NLR is relatively less covered by diabetes to inflammatory factors. Therefore, it still shows a significant correlation in the diabetic population□

The current study still has several limitations: (1) It was a retrospective study, inclusion bias is inevitable, and the follow-up times of the samples in this study is not completely consistent, so the results may be biased. (2) This study focuses more on the assessment of the

inflammation level after PCI in patients with CHD, and does not make further follow-up on the outcome of the end-point event. (3) NLR, as an indicator reflecting the level of inflammation in patients after PCI, may not be comprehensive. If the patients' serum samples can be collected, and molecular biology techniques can be used to further evaluate tumor necrosis factor, interleukins, etc., it may better reflect the degree of inflammation in the patients' body. (4) The follow-up time is not long enough, and the long-term effects of the interaction between lipid metabolism and inflammation may require further follow-up observation. Therefore, in order to avoid the above shortcomings, we believe that further prospective randomized controlled trials are needed in the future, and the sample size should be expanded.

## In Conclusion

The variation rate of non-HDL-C and Lp(a) are independent positively predictors of systemic inflammation in patients after elective PCI, better control of its variability may improve the the low grade inflammation of CHD patients with elective PCI.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Sir Run Run Shaw Hospital of Zhejiang University (NO.20201217-36). No informed consent was available due to the retrospective design.

### Consent for publication

All authors confirmed and approved to publication.

### Availability of data and material

Definitely, the corresponding author would like to provide data for proper requests.

### Competing interests

The authors declare no competing interests.

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### Authors' contributions

The study was designed by Sisi Zhang, Duanbin Li, Wenbin Zhang and Zhaoyang Chen; Sisi Zhang, Daqi Xie and Tian Xu performed the statistical analysis; Sisi Zhang, Duanbin Li, Wenyi Hu, Maoning Lin and Ya Li drafted the manuscript. All authors gave comments and suggestions, and approved publication.

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## Figures

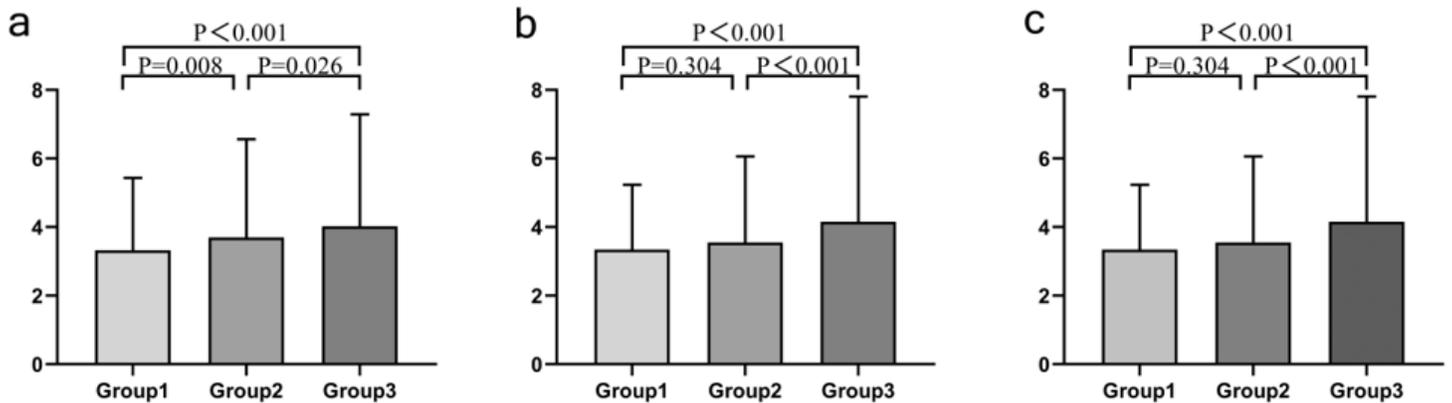


Figure 1

The average follow-up NLR of trisection grouping by Lp(a) variation

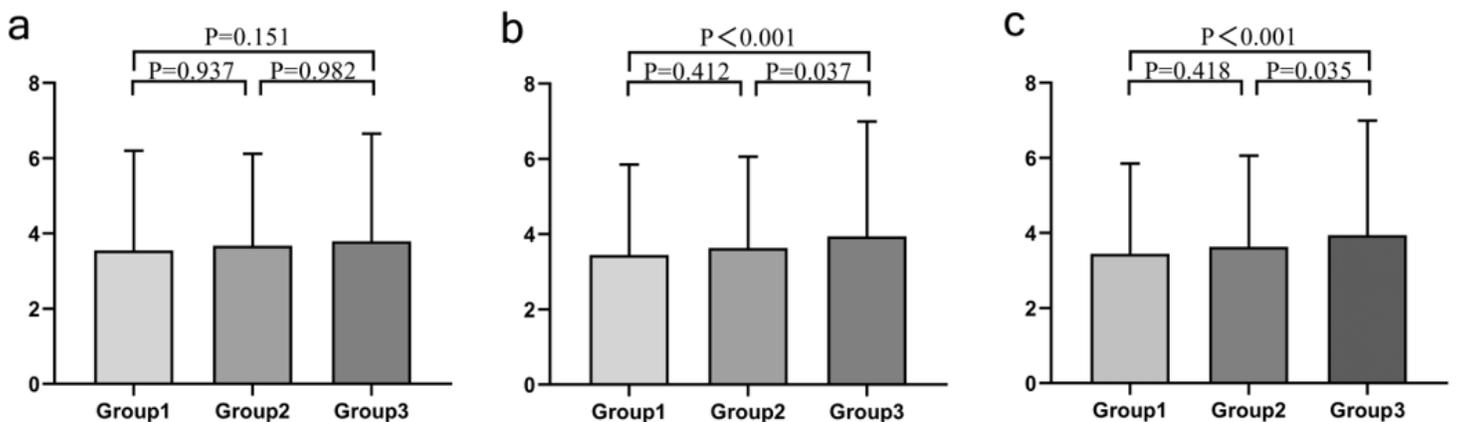


Figure 2

The average follow-up NLR of trisection grouping by non-HDL-C variation

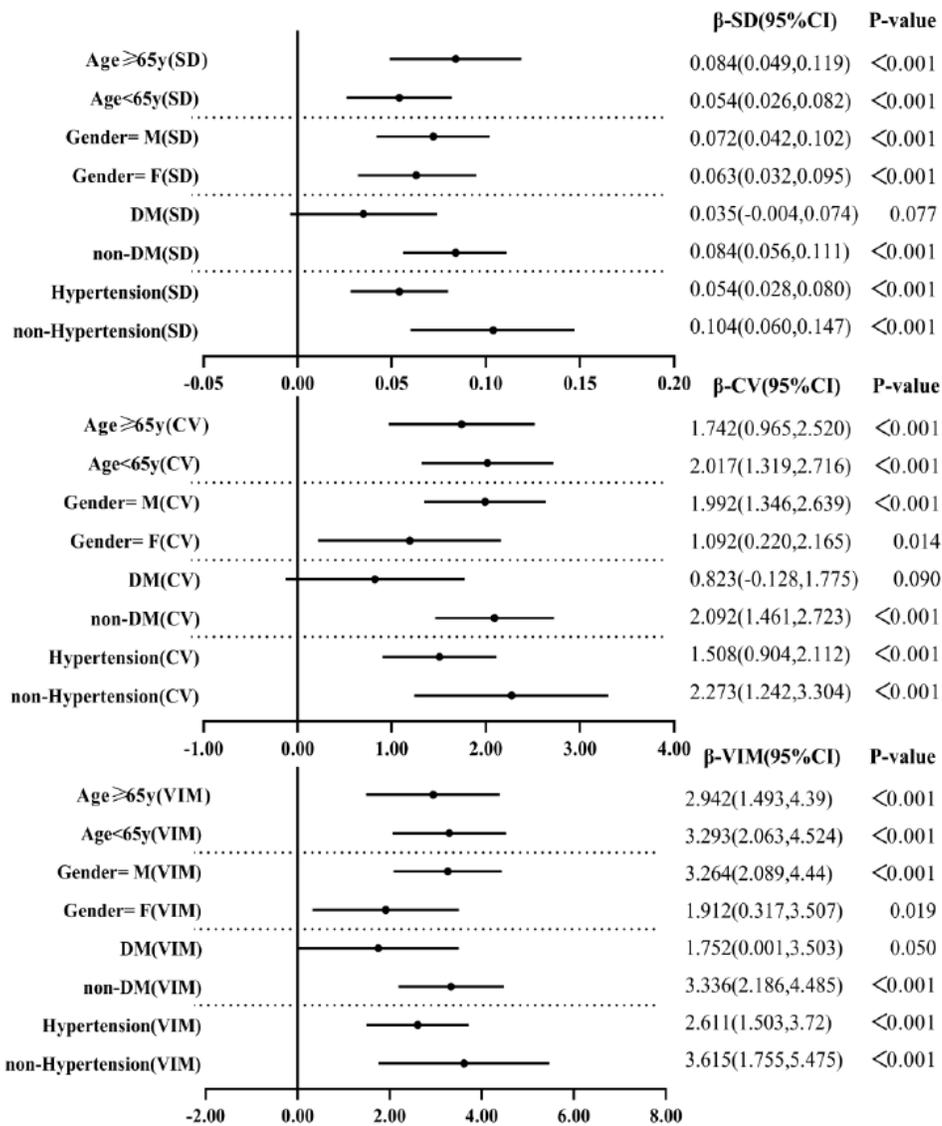


Figure 3

Subgroup analysis of the effect of LP(a) variation on average NLR during follow-up

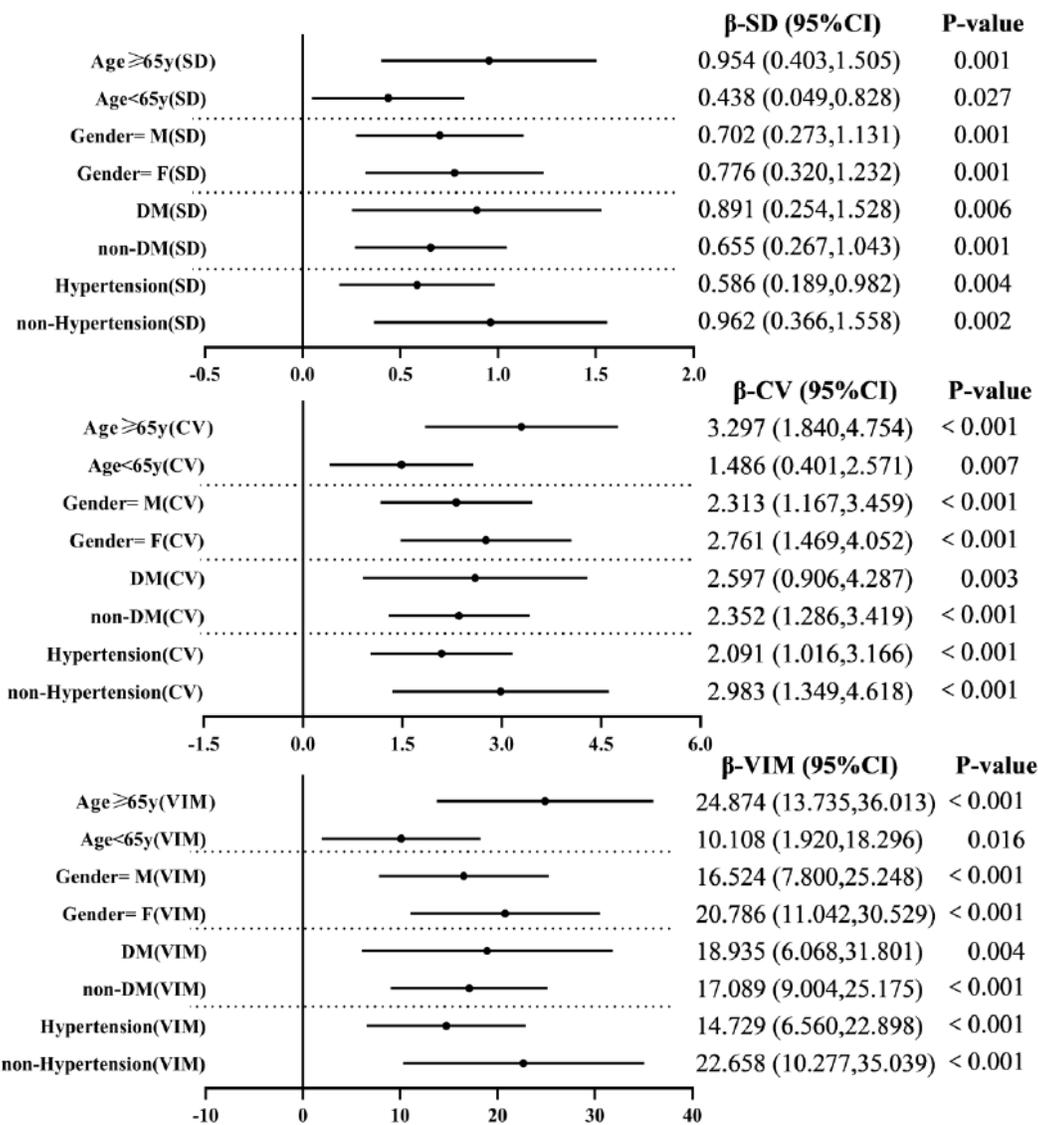


Figure 4

Subgroup analysis of the effect of non-HDL-C variation on average NLR during follow-up