MHR and NHR but not LHR were associated with coronary artery disease in patients with chest pain with controlled LDL-C

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ABSTRACT

Several leukocyte to high-density lipoprotein cholesterol (HDL-C) ratios, including monocyte to HDL-C ratio (MHR), neutrophil to HDL-C ratio (NHR) and lymphocyte to HDL-C ratio (LHR), have been proposed as novel inflammatory indicators. We performed a cross-sectional study to investigate the relationships between these leukocyte to HDL-C ratios and coronary artery disease (CAD) in patients with chest pain with controlled low-density lipoprotein cholesterol (LDL-C). A total of 3482 patients with chest pain with LDL-C <1.8 mmol/L were enrolled. We evaluated the relationships between MHR, NHR, LHR and HDL-C and the occurrence of CAD as well as severe stenosis. We found that in patients with chest pain, higher MHR (adjusted OR=2.83, 95% CI 1.61 to 4.99, p<0.001) and NHR (adjusted OR=1.08, 95% CI 1.04 to 1.13, p<0.001), as well as lower HDL-C (adjusted OR=0.53, 95% CI 0.36 to 0.78, p=0.001), but not higher LHR (adjusted OR=1.06, 95% CI 0.94 to 1.20, p=0.341), had a stronger association with the occurrence of CAD. Moreover, unlike LHR (adjusted OR=1.02, 95% CI 0.93 to 1.13, p=0.654), higher MHR (adjusted OR=2.10, 95% CI 1.43 to 3.07, p<0.001) and NHR (adjusted OR=1.06, 95% CI 1.04 to 1.09, p<0.001) and lower HDL-C (adjusted OR=0.38, 95% CI 0.26 to 0.56, p<0.001) were risk factors for severe stenosis. A receiver operating characteristic curve analysis exhibited comparable abilities between MHR and NHR in predicting the presence and severity of CAD. In conclusion, even though patients with chest pain have achieved LDL-C <1.8 mmol/L, the inflammatory indicators MHR and NHR maintained their predictive abilities and remained associated with the occurrence and severity of CAD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Elevated low-density lipoprotein cholesterol (LDL-C) level is a risk factor for progression of atherosclerosis, while a remnant risk for adverse prognosis remains even if the LDL-C level of patients with coronary artery disease (CAD) has been controlled after statin treatment.
⇒ Chronic inflammation is another risk factor that accelerates the development of atherosclerosis.
⇒ Monocyte to high-density lipoprotein cholesterol ratio (MHR), neutrophil to high-density lipoprotein cholesterol ratio (NHR) and lymphocyte to high-density lipoprotein cholesterol ratio (LHR) are novel inflammatory biomarkers.
⇒ Few studies have explored the relationships between MHR, NHR and LHR and the severity of coronary lesions in patients with controlled LDL-C and whether there are differences in the associations.

WHAT THIS STUDY ADDS

⇒ In our enrolled patients with chest pain with LDL-C <1.8mmol/L, Spearman correlation analysis found that MHR, NHR and high-density lipoprotein cholesterol (HDL-C), but not LHR, were all associated with Gensini score.
⇒ Logistic regression analysis showed that, except for LHR, higher MHR and NHR and lower HDL-C all had correlations with the occurrence of CAD and severe stenosis even though patients with chest pain had achieved LDL-C <1.8mmol/L.
⇒ Receiver operating characteristic curve analysis exhibited comparable abilities between MHR and NHR in predicting CAD and severe stenosis in patients with chest pain with LDL-C <1.8mmol/L.

INTRODUCTION

The morbidity and mortality of coronary artery disease (CAD) have increased markedly in the last few decades around the world.[1 2] It is well documented that increased low-density lipoprotein cholesterol (LDL-C) level is a risk factor for progression of atherosclerosis lesion. Aggressive therapy using statins to reduce the LDL-C below 1.8 mmol/L has been recommended in recent years to prevent the progression and improve the prognosis of CAD.[3] However, several studies have shown that adverse clinical outcomes still existed even if the LDL-C level of patients with CAD

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The present study indicates that higher MHR and NHR are both promising predictors of the presence of CAD and severe stenosis in patients with chest pain with LDL-C <1.8mmol/L, which might help physicians optimize treatment therapy to some extent in clinical practice.

has been controlled.[4–6] To further prevent the progression of coronary lesions, it is necessary to explore other risk factors that accelerate the development of atherosclerosis in patients with controlled LDL-C.

Chronic inflammation plays an important role in the occurrence and development of CAD.[7 8] High-density lipoprotein cholesterol (HDL-C) plays important anti-inflammatory and antioxidant roles in protecting against atherosclerosis progression.[9] Several studies have found that monocyte to HDL-C ratio (MHR), neutrophil to HDL-C ratio (NHR) and lymphocyte to HDL-C ratio (LHR) are novel indicators comprehensively reflecting inflammation and dyslipidemia in patients,[10–12] and are more economical and available compared with other inflammatory cytokines and can be obtained from routine blood tests. Acikgoz *et al*[13] found that elevated MHR could reflect impaired endothelial function and increased systemic inflammation, which are a crucial pathophysiology for progression of atherosclerosis. Moreover, it has been found that MHR and NHR are risk factors for severe stenosis and poor prognosis in patients with CAD.[11 14–18] In addition, a general population from the USA showed that NHR is a predictor of all-cause and cardiovascular mortality.[19] LHR was proposed by Chen *et al*[12] as a novel inflammatory indicator. Consistent with the results from Chen *et al*,[12] other studies have confirmed the role of LHR in predicting the presence and severity of metabolic syndrome.[20 21] Considering the close relationship between metabolic syndrome and atherosclerosis, it is reasonable to wonder on the effect of LHR on the development of CAD. However, there is lack of data on the role of LHR in the CAD process. Moreover, there has been no previous study elucidating the impact of MHR, NHR and LHR on coronary lesions in patients with chest pain with controlled LDL-C. Furthermore, it is obscure whether there are differences in the associations between these leukocyte to HDL-C ratios and the severity of coronary lesions in patients with controlled LDL-C. Therefore, this study aimed to explore if MHR, NHR and LHR are related to coronary stenosis in patients with chest pain with controlled LDL-C and the differences in the associations.

MATERIALS AND METHODS

Study population

This is a single-center, cross-sectional study. The subjects are patients with suspected CAD with chest pain as their main symptom admitted for coronary angiography (CAG) at the Department of Cardiovascular Medicine of our hospital from March 2017 to March 2019. The exclusion criteria were as follows: age <18 years old, left ventricular ejection fraction <40%, pregnancy, tumor, severe liver function damage, severe renal function damage, history of autoimmune disease, rheumatic heart disease and blood system disease, current acute or chronic infection, missing LDL-C, monocyte, lymphocyte, neutrophil, leukocyte count or HDL-C test values, and LDL-C ≥1.8 mmol/L. A total of 3482 patients were enrolled in the present study (online supplemental figure 1). All study subjects signed the informed consent form.

CAG and Gensini score

CAG was performed by at least two experienced cardiovascular physicians who were blinded to the MHR, NHR and LHR status of the patients. CAD was diagnosed when at least one major coronary artery stenosis was >50%. The Gensini score was calculated according to the segment and degree of stenosis: 1 for 1%–25% stenosis, 2 for 26%–50%, 4 for 51%–75%, 8 for 76%–90%, 16 for 91%–99% and 32 for complete occlusion. The score was then multiplied by the following coefficient according to the segment of the lesion: main left coronary artery ×5; proximal left anterior descending (LAD) and proximal left circumflex artery (LCX) ×2.5; mid-segment of LAD ×1.5; distal segment of LAD, distal segment of LCX, right coronary artery, D1 diagonal branch and posterior descending branch ×1; and D2 diagonal branch and other small branches ×0.5. The final score is the sum of the scores for all lesions.[22] A Gensini score in the highest tertile was defined as a high Gensini score in all enrolled patients and indicated severe coronary stenosis.[23 24]

Laboratory measurements and left ventricular ejection fraction

All blood samples were collected from patients under an overnight fasting condition on the morning after admission. Baseline monocyte, lymphocyte, neutrophil and leukocyte count, total cholesterol, triglyceride (TG), HDL-C, LDL-C, albumin (ALB), glycated hemoglobin A_1c (HbA_1c), total bilirubin, alanine transaminase (ALT), aspartate aminotransferase, creatinine, uric acid, creatine kinase isoenzymes MB (CK-MB), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were measured by standard methods at the biochemical center of our hospital. MHR, NHR and LHR were calculated by monocyte count ($\times 10^9$/L)/HDL-C (mmol/L), neutrophil count ($\times 10^9$/L)/HDL-C (mmol/L) and lymphocyte count ($\times 10^9$/L)/HDL-C (mmol/L), respectively.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as median (with 25th and 75th percentiles). χ^2 test was used for categorical variables and Mann-Whitney U test was used for continuous variables. Spearman correlation was conducted to analyze the correlation between MHR, NHR, LHR, as well as HDL-C, and Gensini score. Logistic regression analysis was used to assess the association between MHR, NHR, LHR, HDL-C and CAD, as well as severe stenosis, respectively. Multivariate logistic regression analysis adjusted for age, sex, smoking, hypertension, ALT, HbA_1c, TG, LDL-C, CK-MB and uric acid.

Table 1 Baseline characteristics of all enrolled patients

	All N=3482	Non-CAD n=680	CAD n=2802	P value
Male	2543 (73.0)	409 (60.1)	2135 (76.2)	<0.001
Age, years	63 (56–70)	62 (55–69)	64 (56–70)	0.001
Hypertension	2087 (59.9)	366 (53.8)	1721 (61.4)	<0.001
Diabetes	960 (27.6)	111 (16.3)	849 (30.3)	<0.001
Smoking	1592 (45.7)	222 (32.6)	1370 (48.9)	<0.001
ALT, U/L	23 (16–35)	22 (15–32)	24 (16–35)	<0.001
AST, U/L	23 (19–31)	23 (19–28)	24 (19–32)	0.121
TBIL, µmol/L	12.75 (9.50–17.10)	12.80 (9.50–16.80)	12.70 (9.50–17.10)	0.732
ALB, g/L	39.3 (37.0–42.0)	39.6 (37.6–42.5)	39.2 (36.9–41.8)	0.023
Creatinine, µmol/L	64 (54–75)	61 (52–73)	64 (55–75)	0.007
Uric acid, µmol/L	319 (271–373)	311 (259–370)	321 (274–373)	0.068
CK-MB, U/L	12 (9–17)	11 (8–15)	12 (9–17)	0.001
Lg(NT-proBNP), pg/mL	2.21 (1.82–2.72)	2.00 (1.65–2.38)	2.27 (1.88–2.78)	<0.001
HbA_1c, %	5.7 (5.4–6.3)	5.6 (5.3–6.0)	5.8 (5.4–6.5)	0.001
Aspirin	3372 (96.8)	650 (95.6)	2722 (97.1)	0.037
P2Y12 inhibitors	3380 (97.1)	649 (95.4)	2731 (97.5)	0.005
Statins	3401 (97.7)	655 (96.3)	2746 (98.0)	0.009
Gensini score	29 (12–60)	5 (2–7)	40 (20–69)	<0.001

Data are presented as number (percentage) for categorical variables and as median (with 25th and 75th percentiles) for continuous variables.
ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; CAD, coronary artery disease; CK-MB, creatine kinase isoenzymes MB; HbA_1c, glycated hemoglobin A_1c; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TBIL, total bilirubin.

Subgroup analyses were then performed based on sex, age (young age in men <55 years old and in women <65 years old), smoking, hypertension and diabetes, adjusting for the same confounding factors in the overall multivariate logistic model except for the stratified variable. We conducted area under the receiver operating characteristic (ROC) curve analysis to evaluate the abilities of different parameters in predicting the presence and severity of CAD. We used the non-parametric approach of DeLong *et al*[25] (MedCalc) to evaluate for the differences between the different parameters on the ROC curves. All p values were two-sided and $p<0.05$ was considered significant. Statistical analyses were performed by SPSS V.20.0.

RESULTS

Baseline characteristics of the study population

The baseline characteristics of all patients are shown in table 1. There were 680 patients without CAD and 2802 patients with CAD in the current study. Compared with patients without CAD, patients with CAD were older and had higher prevalence of hypertension, diabetes and smoking history. Patients with CAD also had higher ALT, creatinine, CK-MB, NT-proBNP, HbA_1c and Gensini score, but lower ALB. In addition, patients with CAD had higher possibilities of getting aspirin, P2Y12 inhibitor and statin medications. With regard to hematological and lipid

Table 2 Clinical characteristics of leukocyte counts and serum lipids in all enrolled patients

	All N=3482	Non-CAD n=680	CAD n=2802	P value
Leukocytes, $\times10^9$/L	6.19 (5.14–7.48)	5.90 (4.93–7.01)	6.25 (5.19–7.60)	<0.001
Monocytes, $\times10^9$/L	0.34 (0.27–0.43)	0.31 (0.24–0.40)	0.34 (0.27–0.43)	<0.001
Neutrophils, $\times10^9$/L	4.11 (3.28–5.21)	3.84 (3.09–4.86)	4.18 (3.34–5.32)	<0.001
Lymphocytes, $\times10^9$/L	1.43 (1.11–1.82)	1.44 (1.12–1.84)	1.43 (1.10–1.81)	0.705
TC, mmol/L	2.93 (2.63–3.20)	2.95 (2.67–3.23)	2.93 (2.63–3.19)	0.558
TG, mmol/L	1.05 (0.79–1.42)	1.03 (0.78–1.41)	1.05 (0.80–1.43)	0.539
LDL-C, mmol/L	1.44 (1.22–1.63)	1.43 (1.21–1.60)	1.44 (1.22–1.63)	0.634
HDL-C, mmol/L	0.89 (0.76–1.05)	0.95 (0.80–1.12)	0.88 (0.76–1.03)	<0.001
MHR	0.38 (0.27–0.51)	0.34 (0.24–0.45)	0.40 (0.29–0.53)	<0.001
NHR	4.64 (3.41–6.33)	4.06 (3.05–5.36)	4.81 (3.53–6.50)	<0.001
LHR	1.59 (1.16–2.15)	1.53 (1.12–2.08)	1.61 (1.17–2.17)	0.015

Data are presented as median (with 25th and 75th percentiles) for continuous variables.
CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LHR, lymphocyte to high-density lipoprotein cholesterol ratio; MHR, monocyte to high-density lipoprotein cholesterol ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio; TC, total cholesterol; TG, triglyceride.

Table 3 Logistic regression analysis of the relationship between different parameters and the presence and severity of CAD

	CAD		Severe stenosis	
	OR (95% CI)	P value	OR (95% CI)	P value
Univariate analysis				
MHR	7.78 (4.66 to 13.01)	<0.001	3.48 (2.46 to 4.90)	<0.001
NHR	1.18 (1.13 to 1.23)	<0.001	1.10 (1.07 to 1.12)	<0.001
LHR	1.14 (1.02 to 1.27)	0.017	1.09 (1.01 to 1.19)	0.036
HDL-C	0.34 (0.24 to 0.48)	<0.001	0.31 (0.22 to 0.43)	<0.001
Multivariate analysis				
MHR	2.83 (1.61 to 4.99)	<0.001	2.10 (1.43 to 3.07)	<0.001
NHR	1.08 (1.04 to 1.13)	<0.001	1.06 (1.04 to 1.09)	<0.001
LHR	1.06 (0.94 to 1.20)	0.341	1.02 (0.93 to 1.13)	0.654
HDL-C	0.53 (0.36 to 0.78)	0.001	0.38 (0.26 to 0.56)	<0.001

Adjusted for age, sex, smoking, hypertension, ALT, HbA_1c, TG, LDL-C, CK-MB and uric acid.
ALT, alanine transaminase; CAD, coronary artery disease; CK-MB, creatine kinase isoenzymes MB; HbA_1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LHR, lymphocyte to high-density lipoprotein cholesterol ratio; MHR, monocyte to high-density lipoprotein cholesterol ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio; TG, triglyceride.

parameters, as shown in table 2, leukocyte, monocyte and neutrophil counts were higher in patients with CAD compared with those without. With regard to lipid metabolism, patients in the CAD group had lower HDL-C than those in the non-CAD group. Therefore, patients with CAD had higher MHR, NHR and LHR than patients without CAD.

Associations between different leukocyte to HDL-C ratios and the occurrence and severity of CAD in patients with controlled LDL-C

In order to explore the correlation between MHR, NHR, LHR and HDL-C and the severity of stenosis, respectively, we conducted Spearman correlation analysis. As shown in online supplemental table 1, except for LHR (r=0.032, p=0.103), MHR (r=0.210, p<0.001), NHR (r=0.208, p<0.001) and HDL-C (r=−0.152, p<0.001) were all significantly correlated with Gensini score. To further ascertain the relationships between leukocyte to HDL-C ratios and severity of coronary lesion, we conducted a logistic regression analysis. As shown in table 3, the univariate logistic regression analysis showed that MHR, NHR, LHR and HDL-C were all associated with CAD and severe stenosis, respectively. After adjusting for age, sex, smoking, hypertension, ALT, HbA_1c, TG, LDL-C, CK-MB and uric acid, except for LHR (adjusted OR=1.06, 95% CI 0.94 to 1.20, p=0.341), MHR, NHR and HDL-C remained associated with the presence of CAD, with an adjusted OR of 2.83 (95% CI 1.61 to 4.99, p<0.001), 1.08 (95% CI 1.04 to 1.13, p<0.001) and 0.53 (95% CI 0.36 to 0.78, p=0.001). Moreover, rather than LHR (adjusted OR=1.02, 95% CI 0.93 to 1.13, p=0.654), MHR (adjusted OR=2.10, 95% CI 1.43 to 3.07, p<0.001), NHR (adjusted OR=1.06, 95% CI 1.04 to 1.09, p<0.001) and HDL-C (adjusted OR=0.38, 95% CI 0.26 to 0.56, p<0.001) also showed persistent relationship with severe stenosis. We also conducted a logistic regression analysis in patients diagnosed with CAD to further ascertain the relationships between these different leukocyte to HDL-C ratios and the severity of coronary lesion. As shown in online supplemental table 2, similar to the results found in all patients with chest pain, except for LHR, higher MHR and NHR and lower HDL-C were all associated with the presence of severe stenosis in patients diagnosed with CAD. These results indicate that MHR, NHR and HDL-C are associated with the occurrence and severity of CAD, rather than LHR, even if the LDL-C level of these patients with chest pain has been low.

Moreover, we conducted a subgroup analysis to evaluate the relationships between different leukocyte to HDL-C ratios and the presence and severity of CAD based on sex, age (young age in men <55 years old and in women <65 years old), smoking, hypertension and diabetes. As shown in online supplemental figures 2-6, sex and smoking history interacted with MHR and NHR in predicting severe stenosis. In addition, age and smoking history interacted with HDL-C in predicting severe stenosis.

MHR and NHR had predictive abilities in the occurrence and severity of CAD in patients with controlled LDL-C

In order to evaluate the predictive values of the different leukocyte to HDL-C ratios for the presence and severity of CAD, we conducted an ROC curve analysis. As shown in figure 1 and table 4, MHR and NHR had comparable predictive values for the presence of CAD (z=0.240, p=0.810), which was higher than LHR (MHR vs LHR, z=6.569, p<0.001; NHR vs LHR, z=5.583, p<0.001) and HDL-C (MHR vs HDL-C, z=2.183, p=0.029; NHR vs HDL-C, z=1.993, p=0.046). In addition, MHR (sensitivity 54.3%, specificity 62.4%) and NHR (sensitivity 53.8%, specificity 62.8%) had similar sensitivities and specificities in predicting CAD. Moreover, significant and comparable predictive values for MHR, NHR and HDL-C were found in predicting severe stenosis in patients with chest pain with controlled LDL-C (MHR vs NHR, z=1.057, p=0.291; MHR vs HDL-C, z=0.859, p=0.390; NHR vs HDL-C, z=1.762, p=0.078). MHR (sensitivity 68.6%, specificity 45.6%) and HDL-C (sensitivity 64.6%, specificity 48.2%) had better sensitivity while NHR (sensitivity 54.6%, specificity 61.0%) had better specificity in predicting severe stenosis. We further evaluated the predictive value of MHR, NHR and HDL-C after combining with traditional risk factors, including age, hypertension, HbA_1c, TG and LDL-C, for the presence and severity of coronary stenosis. As shown in online supplemental table 3, combining MHR,

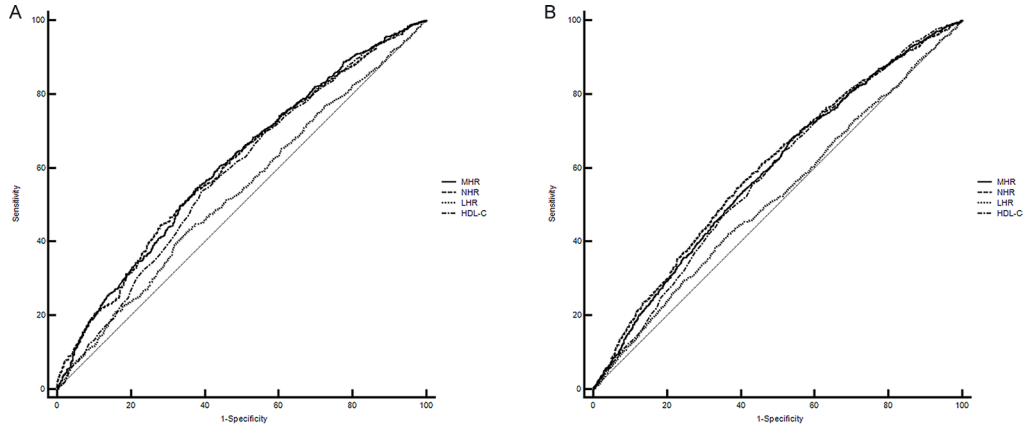

Figure 1 Receiver operating characteristic curve analysis of MHR, NHR, LHR and HDL-C in predicting coronary artery disease (A) and severe stenosis (B) in patients with chest pain with LDL-C <1.8 mmol/L. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LHR, lymphocyte to high-density lipoprotein cholesterol ratio; MHR, monocyte to high-density lipoprotein cholesterol ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio.

NHR and HDL-C with the traditional risk factors all improved the area under the curve of traditional risk factors for CAD and severe stenosis (all p values for z test <0.001). These results indicate that MHR, NHR and HDL-C have additional potential abilities to predict the presence and severity of CAD, as supplementary parameters to the traditional risk factors, even though these patients with chest pain had controlled LDL-C.

DISCUSSION

Control of cholesterol level is one of the most effective strategies to prevent cardiovascular disease.[26] Reduction of LDL-C level plays a crucial role in preventing adverse clinical events in patients with cardiovascular disease. However, clinical studies have shown that a number of patients still have a residual risk for cardiovascular disease even after achieving the targeted cholesterol level.[27] It has been documented that inflammation indicators play a dominant role in the poor prognosis of CAD in patients with a targeted LDL-C level.[28 29] Therefore, residual inflammatory risk has gained much interest in patients with controlled cholesterol.[30] In the present cross-sectional study, we found that even if LDL-C was <1.8 mmol/L, the novel inflammatory indicators MHR and NHR as well as HDL-C were still associated with the presence and severity of CAD, respectively, in patients with chest pain.

Lowering the serum level of LDL-C plays a predominant role in slowing the progression of CAD. PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors could further reduce the level of LDL-C on the basis of statins. However, even though PCSK9 inhibitors combined with statins could reduce LDL-C to a median of 0.78 mmol/L, it cannot be ignored that there were still respectable residual risks for adverse cardiovascular events in patients with extremely low levels of LDL-C.[31] The SPIRE-1 and SPIRE-2 (Studies of PCSK9 Inhibition and the Reduction in Vascular Events) cardiovascular outcomes trials demonstrated that patients with low LDL-C but elevated high sensitivity C-reactive protein (hs-CRP) had a persistent risk of future cardiovascular events.[32] The CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) confirmed that suppression of interleukin 1β in patients with cardiovascular disease with high hs-CRP levels could improve patients' prognosis, and this benefit was independent of cholesterol control.[33] These clinical trials indicated that control of inflammation was as important as control of cholesterol in the prevention and treatment of CAD. For patients whose cholesterol level has been controlled, additional anti-inflammatory therapy might provide additional benefits.[30]

Monocytes/macrophages play determinative roles in the development of atherosclerosis. Activated monocytes interact with damaged endothelial cells and induce the secretion of proinflammatory cytokines and adhesion molecules.[34] Macrophages engulf oxidized LDL-C, forming foam cells, and then facilitate inflammatory cascade reactions.[35 36] Neutrophils could be primed by hyperlipidemia and release superoxide, accelerating atherogenesis.[37] HDL-C protects

Table 4 Receiver operating characteristic curve analysis of the leukocyte to HDL-C ratio and their predictive value for coronary artery disease and severe stenosis in patients with chest pain with LDL-C <1.8 mmol/L

	AUC (95% CI)	P value	Sensitivity (%)	Specificity (%)
Coronary artery disease				
MHR	0.61 (0.58 to 0.63)	<0.001	54.3	62.4
NHR	0.61 (0.58 to 0.63)	<0.001	53.8	62.8
LHR	0.53 (0.51 to 0.56)	0.009	41.9	65.7
HDL-C	0.58 (0.56 to 0.61)	<0.001	53.7	60.9
Severe stenosis				
MHR	0.59 (0.57 to 0.61)	<0.001	68.6	45.6
NHR	0.60 (0.58 to 0.62)	<0.001	54.6	61.0
LHR	0.52 (0.50 to 0.54)	0.063	40.6	64.8
HDL-C	0.58 (0.56 to 0.60)	<0.001	64.6	48.2

AUC, area under the curve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LHR, lymphocyte to high-density lipoprotein cholesterol ratio; MHR, monocyte to high-density lipoprotein cholesterol ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio.

against atherosclerosis via reverse transport of macrophage cholesterol, amelioration of endothelial dysfunction, suppression of expression of adhesion molecules and inhibition of oxidation of LDL-C.[38] In addition, HDL-C could regulate the activation of neutrophils and monocytes.[18 37 39] Moreover, myeloperoxidase secretion by neutrophils and monocytes impairs the ability of HDL-C in protecting against atherosclerosis progression.[40] Previous studies have proposed that the novel indicators MHR and NHR, which comprehensively reflect inflammation and dyslipidemia status, are associated with worse clinical prognosis and more severe stenosis in patients with CAD.[11 17 18 41] Our study further found that even though LDL-C was of low level, higher MHR and NHR and lower HDL-C in patients with chest pain were still associated with the presence and severity of CAD (table 3), although these were not found for LHR. In addition, the ROC curve analysis exhibited no difference in the predictive values of MHR and NHR for the presence and severity of CAD. Our study suggests that, compared with LHR, higher MHR and NHR are better indicators of the presence and severity of CAD in patients with controlled LDL-C. It indicates that patients with chest pain with higher MHR or NHR might need to be treated timely and aggressively to improve prognosis, even with LDL-C level below 1.8 mmol/L.

It has been found that LHR as a novel inflammatory indicator correlated with the presence and severity of metabolic syndrome, which is one of the risk factors for CAD.[12] In addition, Zhao *et al*[42] reported that decreased lymphocyte count was a risk factor for adverse prognosis in patients with CAD. However, data in our present study did not show a significant association between LHR and the presence and severity of CAD in patients with chest pain with controlled LDL-C. The baseline characteristics in our study showed that there was no significant difference in the lymphocyte count between the non-CAD and the CAD group. Moreover, the logistic regression analysis showed that decreased HDL-C level was a strong predictor of CAD and severe stenosis. Due to the anti-inflammatory role of both HDL-C and lymphocytes, it is possible that the effect of LHR in predicting CAD and severe stenosis in our data was eliminated by HDL-C to some extent. Second, we enrolled patients with LDL-C <1.8 mmol/L; thus, the remnant inflammation in these patients might be improved by the low LDL-C level and the statin treatment, which might further influence the relationships between LHR and the presence and severity of CAD. However, further studies are necessary to elucidate the role of LHR in the progression of CAD.

There were some limitations to the current study. First, this was a single-center, observational study. Majority of the subjects were from Northwest China and only patients with chest pain who were admitted for CAG were enrolled, which may cause some inevitable selection biases. Second, this was a cross-sectional study and we cannot make a conclusion on causal relationship. Third, our results lacked follow-up data to assess the impact of these leukocyte to HDL-C ratios on the prognosis of patients with chest pain with controlled LDL-C. Fourth, we did not collect data on obesity or body mass index, which might influence the relationships between MHR, NHR and LHR and the presence and severity of CAD. Future studies are necessary to collect these data and further evaluate the effects of obesity on our findings. Finally, we enrolled patients with baseline LDL-C <1.8 mmol/L regardless of their prehospital medication, and the MHR, NHR, LHR and HDL-C values might be influenced by prehospital treatment.

CONCLUSIONS

MHR, NHR and HDL-C, but not LHR, were independently associated with CAD and severe stenosis in patients with chest pain with controlled LDL-C. Moreover, the predictive values between MHR and NHR for CAD and severe stenosis are comparable. Therefore, higher MHR and NHR and lower HDL-C might be promising indicators of the severity of coronary lesions.

Contributors ZY and JZ conceived and designed the study. ML, ZW, RH, XH and YH collected the data. ML, XL and ZW analyzed the data. ML, XL and JZ interpreted and revised the results. ML and JZ wrote the paper. ML submitted the manuscript for publication. ML acts as a guarantor for the overall content. All authors reviewed and revised the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and all procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Xi'an Jiao Tong University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This was an observational study and was not provided a reference number. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Zhao D, Liu J, Wang M, *et al*. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol* 2019;16:203–12.
2 Roth GA, Forouzanfar MH, Moran AE, *et al*. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;372:1333–41.
3 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *Circulation* 2019;139:e1082–143.
4 Guedeney P, Claessen BE, Kalkman DN, *et al*. Residual Inflammatory Risk in Patients With Low LDL Cholesterol Levels Undergoing Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2019;73:2401–9.
5 Ridker PM, Danielson E, Fonseca FA, *et al*. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the Jupiter trial. *Lancet* 2009;373:1175–82.

6 Bohula EA, Giugliano RP, Cannon CP, *et al*. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation* 2015;132:1224–33.
7 Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. *Nat Med* 2011;17:1410–22.
8 Tousoulis D, Papageorgiou N, Androulakis E, *et al*. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. *J Am Coll Cardiol* 2013;62:667–76.
9 Krentz AJ. Lipoprotein abnormalities and their consequences for patients with type 2 diabetes. *Diabetes Obes Metab* 2003;5 Suppl 1:s19–27.
10 Chen JW, Li C, Liu ZH, *et al*. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima-media thickness in patients with type 2 diabetes. *Front Endocrinol* 2019;10:191.
11 Kou T, Luo H, Yin L. Relationship between neutrophils to HDL-C ratio and severity of coronary stenosis. *BMC Cardiovasc Disord* 2021;21:127.
12 Chen H, Xiong C, Shao X, *et al*. Lymphocyte to high-density lipoprotein ratio as a new indicator of inflammation and metabolic syndrome. *Diabetes Metab Syndr Obes* 2019;12:2117–23.
13 Acikgoz N, Kurtoğlu E, Yagmur J, *et al*. Elevated monocyte to high-density lipoprotein cholesterol ratio and endothelial dysfunction in Behçet disease. *Angiology* 2018;69:65–70.
14 Çağdaş M, Karakoyun S, Yesin M, *et al*. The association between monocyte HDL-C ratio and SYNTAX score and SYNTAX score II in STEMI patients treated with primary PCI. *Acta Cardiol Sin* 2018;34:23–30.
15 Akboga MK, Balci KG, Maden O, *et al*. Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease. *Biomark Med* 2016;10:375–83.
16 Cetin EHO, Cetin MS, Canpolat U, *et al*. Monocyte/HDL-cholesterol ratio predicts the definite stent thrombosis after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Biomark Med* 2015;9:967–77.
17 Açıkgöz SK, Açıkgöz E, Şensoy B, *et al*. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. *Cardiol J* 2016;23:505–12.
18 Huang J-B, Chen Y-S, Ji H-Y, *et al*. Neutrophil to high-density lipoprotein ratio has a superior prognostic value in elderly patients with acute myocardial infarction: a comparison study. *Lipids Health Dis* 2020;19:59.
19 Jiang M, Sun J, Zou H, *et al*. Prognostic role of neutrophil to high-density lipoprotein cholesterol ratio for all-cause and cardiovascular mortality in the general population. *Front Cardiovasc Med* 2022;9:807339.
20 Yu S, Guo X, Li G, *et al*. Lymphocyte to high-density lipoprotein ratio but not platelet to lymphocyte ratio effectively predicts metabolic syndrome among subjects from rural China. *Front Cardiovasc Med* 2021;8:583320.
21 Chen T, Chen H, Xiao H, *et al*. Comparison of the value of neutrophil to high-density lipoprotein cholesterol ratio and lymphocyte to high-density lipoprotein cholesterol ratio for predicting metabolic syndrome among a population in the southern coast of China. *Diabetes Metab Syndr Obes* 2020;13:597–605.
22 Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983;51:606.
23 Zhang H-W, Zhao X, Guo Y-L, *et al*. Elevated lipoprotein (a) levels are associated with the presence and severity of coronary artery disease in patients with type 2 diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2018;28:980–6.
24 Gao W, Li J, Ni H, *et al*. Tenascin C: a potential biomarker for predicting the severity of coronary atherosclerosis. *J Atheroscler Thromb* 2019;26:31–8.
25 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
26 Breathett K, Sims M, Gross M, *et al*. Cardiovascular health in American Indians and Alaska natives: a scientific statement from the American heart association. *Circulation* 2020;141:e948–59.
27 Koenig W. Low-Grade inflammation modifies cardiovascular risk even at very low LDL-C levels: are we aiming for a dual target concept? *Circulation* 2018;138:150–3.
28 Takahashi N, Dohi T, Endo H, *et al*. Residual inflammation indicated by high-sensitivity C-reactive protein predicts worse long-term clinical outcomes in Japanese patients after percutaneous coronary intervention. *J Clin Med* 2020;9:1033.
29 Peikert A, Kaier K, Merz J, *et al*. Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort. *Clin Res Cardiol* 2020;109:315–23.
30 Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. *Eur Heart J* 2016;37:1720–2.
31 Sabatine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–22.
32 Pradhan AD, Aday AW, Rose LM, *et al*. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation* 2018;138:141–9.
33 Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.
34 Ghattas A, Griffiths HR, Devitt A, *et al*. Monocytes in coronary artery disease and atherosclerosis: where are we now? *J Am Coll Cardiol* 2013;62:1541–51.
35 Chen M-Q, Shi W-R, Shi C-N, *et al*. Impact of monocyte to high-density lipoprotein ratio on prevalent hyperuricemia: findings from a rural Chinese population. *Lipids Health Dis* 2020;19:48.
36 Koelwyn GJ, Corr EM, Erbay E, *et al*. Regulation of macrophage immunometabolism in atherosclerosis. *Nat Immunol* 2018;19:526–37.
37 Murphy AJ, Woollard KJ, Suhartoyo A, *et al*. Neutrophil activation is attenuated by high-density lipoprotein and apolipoprotein A-I in in vitro and in vivo models of inflammation. *Arterioscler Thromb Vasc Biol* 2011;31:1333–41.
38 Rosenson RS, Brewer HB, Ansell BJ, *et al*. Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat Rev Cardiol* 2016;13:48–60.
39 Yılmaz M, Kayançiçek H. A new inflammatory marker: elevated monocyte to HDL cholesterol ratio associated with smoking. *J Clin Med* 2018;7:76.
40 Shao B, Oda MN, Oram JF, *et al*. Myeloperoxidase: an oxidative pathway for generating dysfunctional high-density lipoprotein. *Chem Res Toxicol* 2010;23:447–54.
41 Cetin MS, Ozcan Cetin EH, Kalender E, *et al*. Monocyte to HDL cholesterol ratio predicts coronary artery disease severity and future major cardiovascular adverse events in acute coronary syndrome. *Heart Lung Circ* 2016;25:1077–86.
42 Zhao X, Jiang L, Xu L, *et al*. Predictive value of in-hospital white blood cell count in Chinese patients with triple-vessel coronary disease. *Eur J Prev Cardiol* 2019;26:872–82.