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ORIGINAL RESEARCH

Monocyte to High-Density Lipoprotein Ratio Is Associated With Carotid Plaque: A Retrospective Cohort Study

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BACKGROUND: The level of monocyte to high-density lipoprotein ratio (MHR) is associated with cardiovascular diseases. Carotid plaque (CP) is an independent risk factor for cardiovascular diseases. However, evidence for association of MHR with risk of CP is scarce.

METHODS AND RESULTS: This study involved 5260 participants aged >18 years old from the Dalian health management cohort in 2014 to 2022. The subjects were stratified into 4 groups based on the quartile of the MHR at baseline. Multivariable-adjusted Cox regression models were used to calculate the MHR-associated risk of incident CP. The mean age of the population was 46.14 years and 58.8% (n=3093) of the participants were male. Seven hundred fifty-nine (14.4%) of participants developed new-onset CP. During the follow-up of 9725 person-years, the MHR at quartile 4 group experienced a significantly higher incidence of CP than the MHR at quartile 1 group (56.9 versus 101.5 per 1000 person-years; log-rank P <0.001). Compared with the MHR at quartile 1 group, the MHR at quartile 4 group had the highest CP risk (hazard ratio. 1.389 [95% CI, 1.059–1.823]) and 10-year cardiovascular risk (China-PAR Project score: odds ratio, 1.975 [95% CI, 1441–2.708 in men]; odds ratio, 6.015 [95% CI, 1.949–18.564 in women) (P <0.001). Meanwhile, similar results were observed in multiple sensitivity analyses.

CONCLUSIONS: Elevated MHR was associated with the risk of CP. The assessment and management of MHR is helpful for the early detection of patients with CP and the primary prevention of cardiovascular diseases.

Key Words: atherosclerosis ■ carotid plaque ■ cohort study ■ monocyte to high-density lipoprotein ratio

Carotid plaque (CP), as a manifestation of carotid atherosclerosis, is associated with increased incidence of stroke, coronary heart disease, and myocardial infarction.[1,2] A recent multicenter study across 31 provinces in China suggests that nearly one-quarter of Chinese adults have increased carotid intima-media thickness (CIMT) or CP.[3] The large number of people living with CP or carotid stenosis might be indicative of a future considerable burden of cardiovascular diseases and is a major public health concern worldwide.[4]

Inflammation and lipid accumulation are recognized as fundamental to the pathophysiology and progression of atherosclerosis.[5] The composite inflammatory indicator, monocyte to high-density lipoprotein ratio (MHR), is a novel type of parameter based on the traditional peripheral blood cell count,[6] and is considered a characterization of low-grade metabolic inflammation.[7] Recent studies have established that the MHR has emerged as a novel inflammatory biomarker of atherosclerotic cardiovascular disease (CVD).[8] CP is an important risk factor for CVD. It has been found that MHR

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CLINICAL PERSPECTIVE

What Is New?

- In this cohort study, we found that a new inflammatory marker, monocyte to high-density lipoprotein ratio, is associated with the onset of carotid plaque and increased cardiovascular risk over 10 years.

What Are the Clinical Implications?

- Compared with carotid color ultrasonography, monocyte to high-density lipoprotein ratio, a biomarker calculated by blood index, is more convenient and saves time and money.
- The discovery and application of a new marker, monocyte to high-density lipoprotein ratio, contributes to the early diagnosis and prevention of carotid plaque and cardiovascular disease, reducing the cost and time consumption; it has important application value and development potential.

Nonstandard Abbreviations and Acronyms

CIMT	carotid intima-media thickness
CP	carotid plaque
MHR	monocyte to high-density lipoprotein ratio

may be related to CP formation;[9,10] however, the data of these studies are limited and mostly cross-sectional, making it difficult to make causal inference.

Therefore, this study aimed to explore the association of MHR with the risk of CP and CVD through a cohort design.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request (dllengsong@163.com). In addition, dummy R/Stata code for some methods in this study is accessible in Data S1.

Study Population

We used data from the Dalian health management cohort, which is a large ongoing prospective real-life cohort study started in 2014 in Dalian, North China. It was initially designed to collect information from physical examinations from a population from the Second Affiliated Hospital of Dalian Medical University and evaluate the health status of people to conduct health management (trial registration number: ChiCTR2300073363). This current investigation was a subset analysis of the Dalian health management cohort, and it was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University (2023/146), which waived the requirement for patient informed consent.

We retrospectively recruited 10 116 participants, aged 18 to 92 years, who participated in 2 or more carotid ultrasound examinations from 2014 to 2022. We excluded 55 people with a history of CVD (including stroke, coronary heart disease, heart failure, myocardial infarction, and atrial fibrillation), and 49 participants with a history of malignant tumors, severe liver or kidney diseases at baseline. We also excluded 2387 participants in whom CP was detected at baseline. We further excluded 451 subjects with acute inflammation response or too low white blood cell (WBC) counts (defined as WBC counts $>10\times10^9$/L, or WBC counts $<4\times10^9$/L) to avoid the effects of the acute phase of infection on the inflammatory status. We also excluded those with incomplete data on monocyte counts or high-density lipoprotein cholesterol (HDL-C) at baseline (n=1914). Finally, a total of 5260 participants were included in the final analysis (Figure 1). The earliest physical examination data of every participant were recorded as the baseline. The primary end point of this study was the incidence of CP. The follow-up ended at the date of CP onset, death, or the last follow-up before December 31, 2022, whichever came first.

Baseline Data Collection

Demographic characteristics (including age and sex), previous history (including family history, smoking history, drinking history, and diseases history), bilateral carotid ultrasound information, and laboratory indicators data were acquired through the electronic information system. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2). Systolic blood pressure and diastolic blood pressure were calculated as the mean of 2 measurements on the brachial artery in the right upper arm using a sphygmomanometer after resting quietly for at least 5 minutes. Laboratory tests used blood samples from those who had been fasting for at least 8 hours including assays for routine blood tests (including WBC, platelet, neutrophil, lymphocyte, and monocyte counts, and hemoglobin), fasting blood glucose, total cholesterol, triglycerides, HDL-C, and low-density lipoprotein cholesterol. All laboratory tests accomplished the standardization.

Exposure

The exposure factor in this study was MHR, which was calculated by the following: MHR=monocyte count (10^9/L)/HDL-C (mmol/L).[6]

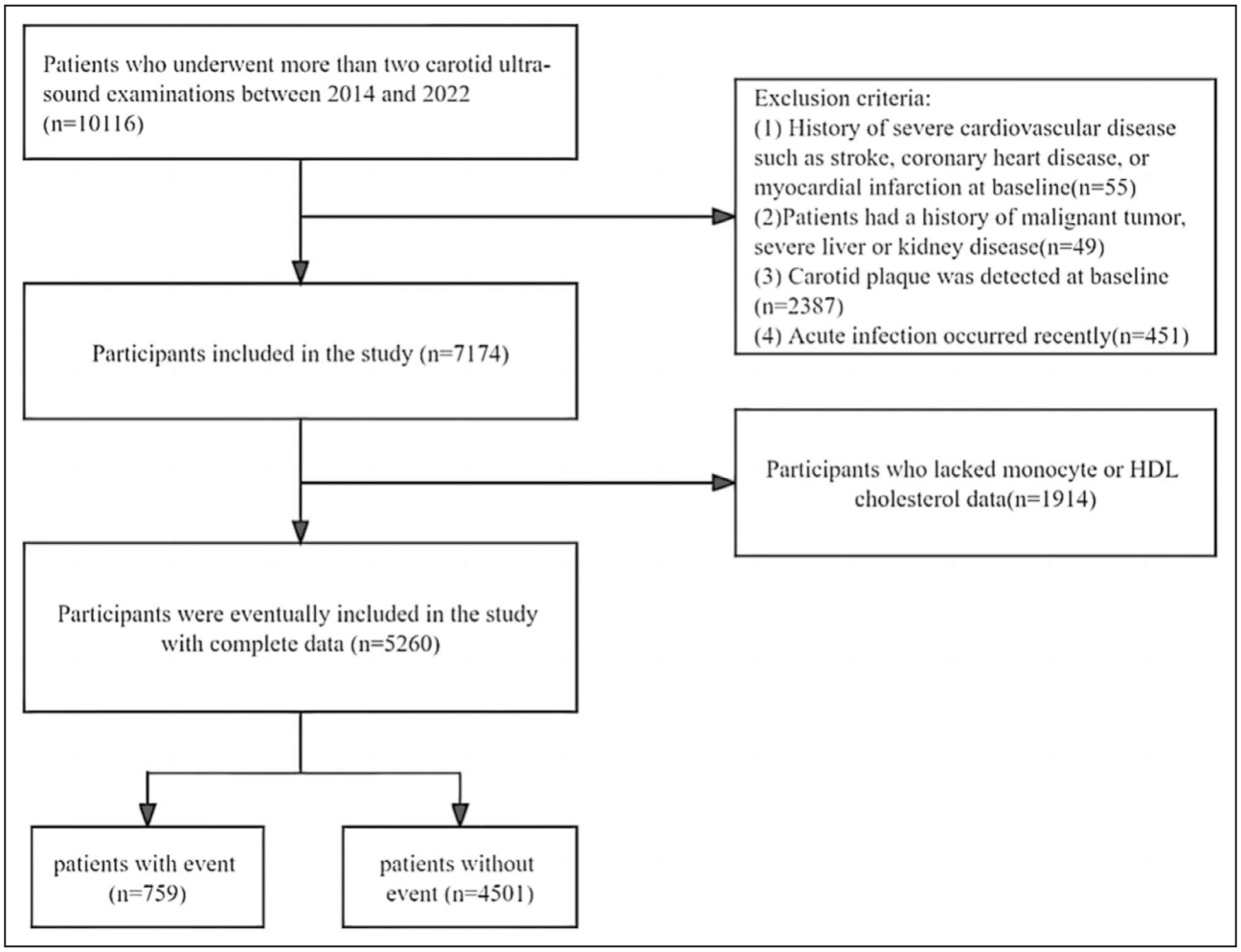

Figure 1. Flow diagram of study population.
HDL indicates high-density lipoprotein.

Ascertainment of Outcome

The outcome of this study was CP measured by Doppler color ultrasound. The unified trained ultrasound specialist examined 3 carotid artery areas with carotid ultrasonography on the subjects (internal carotid artery, bifurcating carotid artery, and common carotid artery). CPs were defined as IMT ≥1.5 mm or focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value. An increased CIMT was defined as IMT ≥1.0 mm in either the right or the left carotid artery.[11] Participants with increased CIMT or plaques were defined as having carotid atherosclerosis.[10]

We evaluated the 10-year risk of cardiovascular events to analyze the association between MHR and cardiovascular risk. We used the Framingham Heart Study score[12] and the China-PAR Project score[13] to assess the relationship between MHR levels and 10-year cardiovascular risk. The Framingham Heart Study score including age, sex, total cholesterol, HDL-C, diastolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status in the primary model for individuals from 30 to 74 years of age and without cardiovascular disease history. Also, the China-PAR Project score was constructed in a large Chinese cohort study.

Covariates

A smoker was defined as smoking continuously or cumulatively for >1 year and smoking at least 1 cigarette per day.[14] An alcohol drinker was defined as drinking for >1 year and drinks on average ≥100 mL/d.[14] Hypertension was defined if a person had systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a self-declared history of hypertension.[15] Diabetes was defined as fasting blood glucose levels ≥7.0 mmol/L or any self-declared history of diabetes or current drug use for diabetes.[16] Dyslipidemia was defined as those taking oral antidyslipidemic drugs, having any self-declared history, or any one of the following outcomes: triglycerides levels ≥1.70 mmol/L, total cholesterol levels ≥5.18 mmol/L, low-density lipoprotein cholesterol levels

≥3.37 mmol/L, or HDL-C level ≤1.04 mmol/L.[17] Other complex inflammatory indicators were the following: neutrophil to high-density lipoprotein ratio=neutrophil count (10^9/L)/HDL-C (mmol/L)[18]; systemic inflammation response index=neutrophil count (10^9/L)×monocyte count (10^9/L)/lymphocyte count (10^9/L).[6]

Statistical Analysis

The population was, respectively, divided into 4 groups (Q1, Q2, Q3, Q4) according to their baseline MHR levels. Missing values of potential covariates were imputed by multivariate chained imputation (Figure S1). For baseline descriptions, continuous variables were represented by the median and interquartile range for skew distribution, and were compared among groups with the Kruskal–Wallis test. Categorical variables were described as percentage (%) and were compared using the χ^2 test.

The incidence rates of CP were calculated. Kaplan–Meier plots were generated with the log-rank test to compare the relationship between MHR quartile and cumulative incidence of CP. After confirming that the proportional hazards assumption was satisfied (Figure S2), Cox proportional hazard regression models were used to compare the hazard ratios (HR) with 95% CI for CP across the MHR subgroups. We screened confounding factors and adjusted by mapping causal pathways through Directed Acyclic Graph (Table S1; Figure S3). Three Cox models using robust SEs were applied: Model 1 was adjusted for age and sex; Model 2 adjusted the variables in Model 1 plus increased CIMT. Model 3 was adjusted for covariates in Model 2 plus BMI, platelet, hemoglobin, neutrophil, lymphocyte, smoking, drinking, family history of hypertension, family history of diabetes, diabetes, hyperlipidemia, hypertension, taking hypoglycemic drugs, and taking anti-hypertension drugs. We further used the restricted cubic spline regression model, with 4 knots, to more thoroughly assess the dose–response relationship between the MHR and new-onset CP. Subgroup analyses were also utilized to examine the robustness of the MHR's relationship to CP. The interactions between the MHR and hypertension, diabetes, dyslipidemia, family history of hypertension, and obesity statuses were tested by the likelihood test with the fully adjusted Cox proportional hazard regression model.

In addition, to examine the robustness of our findings, after excluding some potentially problematic participants, we performed other subgroup analyses based on Model 3. First, the study end points recorded at the first years of follow-up visit were excluded in order to address potential reverse causation (n=5018). Second, to minimize the influence of increased CIMT, participants with preexisting increased CIMT were excluded (n=4677). Third, to reduce the difference between all quartile groups, we conducted propensity score matching (n=3915). Finally, maximally selected rank statistics, facilitated by the "maxstat" package, were used to discern the optimal cutoff point for MHR, which segregated participants into lower and higher MHR groups.

Finally, the logistic regression was used to assess the relationship between MHR levels and 10-year cardiovascular risk.

Statistical analysis was carried out using R version 4.3.0 software, Stata 15.1 software, and DAGitty (http://www.dagitty.net/development/dags.html). All *P* values were taken bilaterally for statistical inference, and $P < 0.05$ was considered a statistically significant difference.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of the participants. A total of 5260 participants were included in the final analysis, and 58.8% (n=3093) of them were male. The mean age was 46.14±9.85 years. After 9725.5 person-years of follow-up, 759 subjects (571 men and 188 women) were detected with newly formed CP. Participants with an elevated MHR were more prone to be male, have diabetes, hypertension, increased CIMT, and a family history of hypertension and dyslipidemia. Participants in higher MHR quartiles had the high level of BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol, WBC, platelet, neutrophil, lymphocyte, and monocyte counts, hemoglobin, neutrophil to high-density lipoprotein ratio, and systemic inflammation response index. In contrast, the HDL-C level was significantly lower than those with a lower MHR ($P < 0.05$). People who developed plaque after follow-up had a high level of MHR compared with people who did not develop plaque (Table S2). Baseline information for participants grouped according to different blood glucose, blood pressure, and lipid profiles is presented in Tables S3 through S5.

Incidence Density of CP

The incidence density of CP was 78.04 per 1000 person-years, and in the quartile were 56.93, 77.47, 78.84, and 101.52 per 1000 person-years, respectively. In addition, older male subjects were more vulnerable to acquiring CP, and stratified analyses disclosed that subjects had a significantly higher probability of developing CP if they had diabetes, hypertension, dyslipidemia, increased CIMT, and obesity (Table S6).

Table 1. Baseline Characteristics of the Participants

Variables	Overall (n=5260)	MHR Quartile				*P* value
		Quartile 1 (n=1323)	Quartile 2 (n=1325)	Quartile 3 (n=1307)	Quartile 4 (n=1305)	
Male, n (%)	3093 (58.8)	442 (33.4)	737 (55.6)	850 (65.0)	1064 (81.5)	<0.001*
Age, y	47 (38–53)	47 (38–53)	47 (38–52)	47 (38–52)	46 (38–53)	0.922
BMI, kg/m^2	24.61 (22.34–27.08)	23.05 (21.10–25.18)	24.34 (21.95–26.73)	24.86 (22.92–27.20)	26.17 (24.01–28.41)	<0.001*
Diabetes, n (%)	406 (7.7)	55 (4.2)	86 (6.5)	102 (7.8)	163 (12.5)	<0.001*
Hypertension, n (%)	1244 (23.7)	226 (17.1)	317 (23.9)	319 (24.4)	382 (29.3)	<0.001*
Dyslipidemia, n (%)	3397 (64.6)	703 (53.1)	768 (58.0)	872 (66.7)	1054 (80.8)	<0.001*
Taking hypoglycemic drugs, n (%)	110 (27.1)	15 (27.2)	20 (23.3)	19 (18.6)	56 (34.4)	<0.001*
Taking antihypertension drugs, n (%)	368 (29.6)	43 (19.0)	87 (27.4)	95 (29.7)	143 (37.4)	<0.001*
Increased CIMT, n (%)	583 (11.1)	111 (8.4)	154 (11.6)	148 (11.3)	170 (13.0)	0.002*
Smoking history, n (%)	116 (2.2)	21 (1.6)	28 (2.1)	27 (2.1)	40 (3.1)	0.072
Drinking history, n (%)	117 (2.2)	22 (1.7)	28 (2.1)	27 (2.1)	40 (3.1)	0.094
Family history of diabetes, n (%)	51 (1.0)	11 (0.8)	10 (0.8)	12 (0.9)	18 (1.4)	0.359
Family history of hypertension, n (%)	237 (4.5)	40 (3.0)	63 (4.8)	64 (4.9)	70 (5.4)	0.022*
SBP, mm Hg	126 (115–136)	122 (112–134)	126.0 (115–136)	126 (116–136)	128 (118–137)	<0.001*
DBP, mm Hg	78 (70–85)	75 (68–83)	77 (70–85)	78 (71–86)	80 (73–87)	<0.001*
TC, mmol/L	4.93 (4.38–5.57)	5.02 (4.44–5.70)	4.99 (4.40–5.57)	4.91 (4.35–5.51)	4.85 (4.32–5.45)	<0.001*
TG, mmol/L	1.55 (1.12–2.13)	1.23 (0.91–1.65)	1.46 (1.08–1.94)	1.65 (1.21–2.21)	1.97 (1.41–2.76)	<0.001*
HDL-C, mmol/L	1.28 (1.09–1.51)	1.57 (1.37–1.77)	1.33 (1.18–1.52)	1.22 (1.08–1.38)	1.06 (0.93–1.19)	<0.001*
LDL-C, mmol/L	2.69 (2.23–3.19)	2.62 (2.16–3.15)	2.68 (2.26–3.18)	2.73 (2.28–3.23)	2.70 (2.23–3.20)	0.008*
FBG, mmol/L	5.53 (5.23–5.92)	5.42 (5.15–5.79)	5.51 (5.23–5.86)	5.53 (5.22–5.92)	5.65 (5.35–6.13)	<0.001*
Leukocytes, 10^9/L	5.19 (5.06–6.81)	5.12 (4.58–5.86)	5.63 (4.99–6.33)	6.06 (5.36–6.84)	6.83 (6.00–7.77)	<0.001*
Neutrophils, 10^9/L	3.41 (2.84–4.14)	2.98 (2.57–3.58)	3.26 (2.77–3.83)	3.51 (2.97–4.20)	4.02 (3.31–4.77)	<0.001*
Lymphocytes, 10^9/L	1.94 (1.63–2.29)	1.77 (1.51–2.10)	1.89 (1.60–2.22)	1.99 (1.69–2.33)	2.11 (1.79–2.49)	<0.001*
Monocytes, 10^9/L	0.30 (0.24–0.38)	0.21 (0.18–0.25)	0.27 (0.24–0.31)	0.33 (0.29–0.38)	0.43 (0.38–0.50)	<0.001*
Platelets, 10^9/L	233 (201–269)	230 (198–263)	230 (199–267)	236 (200–274)	236 (206–275)	<0.001*
Hemoglobin, g/L	149 (136–159)	138 (130–150)	147 (136–157)	151 (139–160)	156 (146–164)	<0.001*
MHR	0.24 (0.17–0.32)	0.14 (0.12–0.16)	0.21 (0.19–0.22)	0.27 (0.25–0.29)	0.40 (0.35–0.47)	<0.001*
NHR	2.67 (2.03–3.51)	1.94 (1.58–2.42)	2.44 (2.00–3.03)	2.88 (2.35–3.53)	3.83 (3.00–4.78)	<0.001*
SIRI	0.53 (0.38–0.75)	0.35 (0.27–0.47)	0.47 (0.36–0.62)	0.59 (0.46–0.77)	0.80 (0.61–1.09)	<0.001*

BMI indicates body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MHR, monocyte to high-density lipoprotein ratio; NHR, neutrophil to high-density lipoprotein cholesterol ratio; SBP, systolic blood pressure; SIRI, systemic inflammation response index; TC, total cholesterol; and TG, triglyceride.

*P<0.05, the difference was statistically significant.

Association Between MHR and Risk of CP

Kaplan–Meier curves showed that the cumulative incidence of CP was consistently higher in the Q4 group than that in the Q1 group (Figure 2). A significant difference was observed among groups (log-rank test: P <0.001). The results of Cox proportional hazard regression models after multivariate adjustment were shown that compared with Q1, subjects with MHR at Q4 groups had HR (95% CI) of 1.389 (1.059–1.823) (P <0.05). Similar findings were shown when MHR was used as a continuous variable (Table 2). The incidence of CPs was increasing with the elevated level of MHR. Restricted cubic spline results showed a nonlinear relationship between MHR and CP risk. When the baseline MHR level was <0.4, the risk of CP gradually increased with the increase of MHR, but when the MHR level was >0.4, the risk of CP slowly decreased (Figure S4). In addition, we found that higher MHR levels were associated with an increased risk of carotid intima-media thickening and carotid atherosclerosis (Table S7).

Stratified Analysis

Sex, age, BMI, diabetes, and dyslipidemia had no significant interaction in the association between MHR and CP (P >0.05). Notably, a significant interaction between hypertension and MHR was observed and was

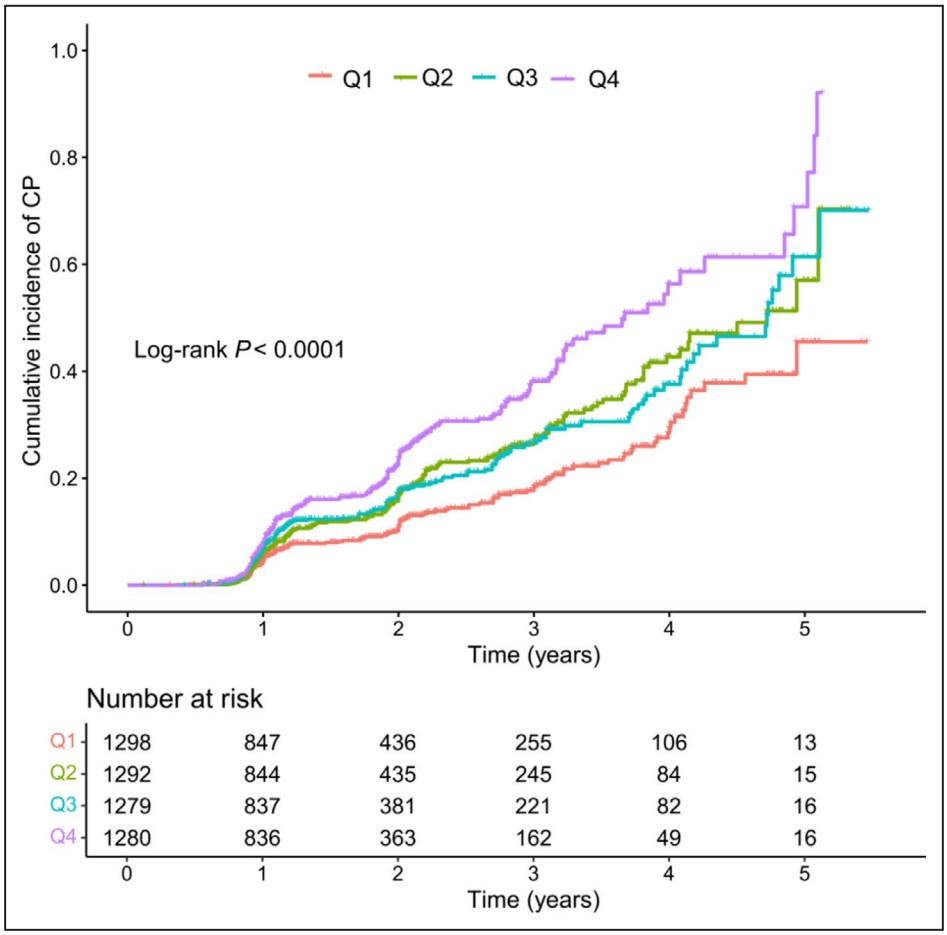

Figure 2. Comparison on cumulative incidence of carotid plaque between different MHR status groups.
CP indicates carotid plaque; MHR, monocyte to high-density lipoprotein ratio.

associated with incident CP (*P*-interaction=0.006). Although the CP incidence rates tended to consistently increase with increases in blood pressure, the MHR-associated CP risks attenuated greatly with elevation in blood pressure levels, with adjusted HRs (95% CIs) of 0.582 (0.203–1.670) and 2.985 (1.492–5.971), respectively, for those with and without hypertension (Table 3; Table S8).

Effect of MHR on 10-Year Cardiovascular Risk

We calculated the 10-year cardiovascular risk for 5007 individuals between 30 and 74 years old without CVD history by the Framingham Heart Study score. The calculations were repeated for all participants using the China-PAR Project score. The highest cardiovascular risk was found in the subjects with MHR at quartile 4, and the odds ratio was 6.661 (95% CI, 4.453–9.964) in the Framingham Heart Study and 4.782 (95% CI, 3.570–6.404) in the China-PAR Project. Of note, men with MHR in quartile 2 and 3 groups were also both associated with an increased 10-year cardiovascular risk, regardless of which cardiovascular risk score was used (Table 4).

Other Subgroup Analysis

Four other subgroup analyses were performed, and the results were consistent. First, after excluding participants who developed CP within the first year of the follow-up, the highest MHR quartile had a significant risk of CP (HR=1.501 [95% CI, 1.072–2.102]) (Table S9). Moreover, excluding the participants who were diagnosed with increased CIMT at the baseline did not lead to substantial changes in the results. MHR was independent potential risk factors of CP (HR=1.464 [95% CI, 1.069–2.006]) (Table S9). Also, using data disposed by propensity score matching, similar results were obtained (HR=1.270 [95% CI, 1.079–1.493]) (Figure S5; Table S10). After using the “maxstat” package to identify the optimal cutoff point of the MHR, we found that individuals in the higher MHR group had a 1.25 times (HR=1.251 [95% CI, 1.049–1.491]) greater

Table 2. Risk of Carotid Plaque According to Baseline MHR Categories

	Model 3, HR (95% CI)	*P* value
MHR quartile		
Quartile 1	Reference	
Quartile 2	1.175 (0.925–1.492)	0.186
Quartile 3	1.220 (0.947–1.572)	0.125
Quartile 4	1.389 (1.059–1.823)	0.017*
Continuous MHR	1.666 (0.941–2951)	0.080
P for trend		0.020*

Model 3 was adjusted for age, sex, increased CIMT, BMI, platelets, hemoglobin, neutrophils, lymphocytes, smoking, drinking, family history of hypertension, family history of diabetes, hyperlipidemia, hypertension, diabetes, take hypoglycemic drugs, take antihypertension drugs. BMI indicates body mass index; CIMT, carotid intima-media thickness; HR, hazard ratio; and MHR, monocyte to high-density lipoprotein ratio.

*$P<0.05$, the difference was statistically significant.

risk of developing CP than those with low MHR levels (Figure S6; Table S11).

DISCUSSION

Our study showed that population high MHR levels are significantly associated with the increased risk of CP and 10-year increased cardiovascular risk. The restricted cubic spline regression model showed a nonlinear relationship between MHR and CP, with the greatest risk of future CP occurring when baseline MHR levels reached 0.4. Our study also found a higher incidence of CP in men, older people, people with diabetes, hypertension, a family history of hypertension, dyslipidemia, and obesity, which further validates the influence of these traditional risk factors on CP. In addition, MHR interacted with hypertension on CP. Collectively, our findings illustrated the significance of evaluating the value of MHR in the primary prevention of CP and even CVD.

Table 3. Subgroup Analysis of MHR as a Continuous Variable

Variables	Model 3 HR (95% CI)	*P* for interaction
Sex		0.907
Female	6.080 (1.082–34.181)	
Male	1.410 (0.748–2.659)	
Age, y		0.573
<45	3.459 (0.638–18.768)	
≥45	1.535 (0.825–2.854)	
Body mass index		0.223
<24	2.776 (1.225–6.291)	
≥24	1.178 (0.509–2.724)	
Diabetes		0.075
Yes	1.424 (0.351–5.774)	
No	2.004 (1.034–3.884)	
Hypertension		0.006*
Yes	0.582 (0.203–1.670)	
No	2.985 (1.492–5.971)	
Dyslipidemia		0.541
Yes	1.635 (0.879–3.044)	
No	2.871 (0.489–16.453)	

Model 3 was adjusted for age, sex, increased CIMT, BMI, platelets, hemoglobin, neutrophils, lymphocytes, smoking, drinking, family history of hypertension, family history of diabetes, hyperlipidemia, hypertension, diabetes, take hypoglycemic drugs, take antihypertension drugs. BMI indicates body mass index; CIMT, carotid intima-media thickness; HR, hazard ratio; and MHR, monocyte to high-density lipoprotein ratio.

*$P<0.05$, the difference was statistically significant.

A convincing body of experimental and clinical data now indicates that inflammation participates fundamentally in atherogenesis and in the pathophysiology of ischemic events.[19] The pathogenesis of CP has been associated with inflammation.[20] Moreover, blood counts are more frequently used to reflect inflammatory states in clinical or large population screening than inflammatory factors commonly used in molecular studies such as interleukin-1/6 and tumor necrosis factor α. In addition, studies have shown that MHR is an important marker for predicting ischemic stroke.[21] Approximately 18% to 25% of all ischemic strokes are attributable to thromboembolism caused by carotid atherosclerotic disease.[5] A cross-sectional study showed that the MHR could be used as a possible marker for plaque formation and severity.[9] Another study found that MHR is a convenient and effective indicator for predicting the presence and progression of subclinical carotid atherosclerosis.[22] Our findings are consistent with those of the previous studies, and once again confirm the role of MHR in new-onset CP. Furthermore, we also found a nonlinear relationship between MHR and CP through restricted cubic spline regression model, although the risk of CP decreased slowly when MHR level exceeded 0.4 in our study. This may be related to drug use and should be verified in subsequent studies. The previous research results showed that monocytes play a key role in the atherosclerosis-associated inflammatory response, involved in all stages of atherosclerosis.[23] In addition, other studies have shown that monocytes are associated with CIMT, carotid artery stenosis, and neovascularization of CP.[10,24,25] These principles all explain that changes in MHR induce the occurrence of CP. On the other hand, monocyte-dominated leukocytes pass through endothelial cells and are activated in the intima, mediating endothelial damage and atherosclerosis.[26] HDL-C exhibits anti-atherosclerotic effects by neutralizing the proinflammatory and prooxidant effects of monocyte via inhibiting the migration of macrophages and low-density lipoprotein oxidation in addition to the efflux of cholesterol from these cells.[27] Monocytosis and specific HDL deficiency can exacerbate the deterioration of the inflammatory state.

Table 4. Association of MHR with 10-Year Cardiovascular Risk

MHR quartile	Total	*P* value	Men	*P* value	Women	*P* value
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
China-PAR Project score						
Quartile 1	Reference		Reference		Reference	
Quartile 2	2.503 (1.836–3.413)	<0.001*	1.518 (1.083–2.127)	0.015*	2.725 (0.860–8.637)	0.088
Quartile 3	3.031 (2.236–4.107)	<0.001*	1.598 (1.150–2.221)	0.005*	3.301 (1.031–8.916)	0.044
Quartile 4	4.782 (3.570–6.404)	<0.001*	1.975 (1.441–2.708)	<0.001*	6.015 (1.949–18.564)	0.002*
Framingham score						
Quartile 1	Reference		Reference		Reference	
Quartile 2	2.848 (1.846–4.395)	<0.001*	1.954 (1.199–3.185)	0.007*	2.262 (0.801–6.392)	0.123
Quartile 3	2.924 (1.897–4.505)	<0.001*	1.732 (1.067–2.811)	0.026*	2.243 (0.749–6.715)	0.149
Quartile 4	6.661 (4.453–9.964)	<0.001*	3.253 (2.068–5.118)	<0.001*	5.045 (1.732–14.694)	0.003*

The general cardiovascular risk is calculated using the Framingham Heart Study 10-year risk score. The score includes age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status in the primary model. HDL indicates high-density lipoprotein; MHR, monocyte to high-density lipoprotein ratio; and OR, odds ratio.

*P<0.05, the difference was statistically significant.

Therefore, higher MHR, which indicates an enhanced inflammation and oxidative stress, was significant.[28] The critical role of monocytes in atherogenesis, and the beneficial anti-inflammatory and anti-atherogenic properties of HDL-C, both explain the greater risk of developing CP in people with high levels of MHR found in this study. Therefore, MHR, as an inexpensive and readily available biomarker, has practical value in predicting the occurrence of CP.

CVD has become an important public health problem as a disease that seriously endangers people's health. With rapid urbanization and population aging, it is expected that CVD morbidity and mortality will keep rising in the next decade in China.[29] Given that prevention and remission of CVD represent unmet, high-priority targets to alleviate the health and economic burden, it is essential to identify potential risk factors and promote primary, even primordial prevention against its occurrence. There is some compelling evidence that MHR is significantly associated with all-cause mortality and CVD mortality, and it can be used as a risk stratification tool.[30] Furthermore, studies have found that reducing mononucleosis can improve CVD outcomes, highlighting the compelling benefits of controlling MHR levels.[31] In addition, inflammatory markers can predict the risk of CVD in a wide range of individuals with or without manifest CVD independently of all traditional risk factors.[32] Our study showed that high MHR levels in the population are significantly associated with 10-year increased cardiovascular risk, especially in men. This result further illustrates the value of MHR in the primary prevention of CVD.

We also observed the strength of the association of MHR and CP risk in the stratified analysis. Although the results of the interaction test showed that sex, age, BMI, diabetes, and dyslipidemia had no significant interaction with MHR (P >0.05), this does not mean that these indicators do not influence the association between MHR and CP. Possible reasons for this result are the smaller number of people in the subgroup, lipid-lowering medication, or lifestyle effects that we failed to adjust. There is no doubt that older people, men, those with thickened carotid intima-media at baseline, and those with diabetes, hypertension, dyslipidemia, and obesity have a higher incidence of CP accumulation. Currently, many studies have shown that inflammatory response is closely related to traditional risk factors leading to atherosclerosis. For example, a large amount of evidence shows that inflammation is related to hypertension, diabetes, obesity and other metabolic diseases.[33–36] These studies further illustrate the importance of the effects of inflammation on CP. However, the complex association between these traditional risk factors and inflammation and CP needs to be further explored in future studies. In this study, we also observed a significant epidemiological interaction between the MHR with hypertension. This finding may provide directions for further in-depth exploration to disentangle the intertwined association of monocyte proliferation, HDL-C, and blood pressure in chronic metabolic inflammatory diseases.

The dual advantages of wide availability and cost-effectiveness of MHR in clinical settings warrant further attention to the potential use of MHR for determining the inflammatory risk for CP. Our findings suggested that the MHR may be used as a tool for early diagnosis of CPs and even CVD conditions. We can further prevent CP and CVD by reducing MHR through moderate exercise, adequate sleep, and proper diet.

Strengths and Limitations

This prospective study extended the investigation to determine the time sequence between the MHR and

the probability of CP. Moreover, the follow-up procedures for incident CP were accurate, the information was obtained with advanced diagnostic techniques, and the population-based sample size was relatively large. We also avoided a large amount of possible bias through a series of inclusion–exclusion criteria and performed multiple sensitivity analyses to verify the robustness of the results.

However, several limitations in the current study also need to be considered. First, we only assessed the presence or absence of plaque components, not CP stability. The stability of CP can be further explored in the future. Second, although the influence of major confounders such as sex, age, blood pressure, lipids, and blood glucose was controlled, there are still unknown confounding components that may have influenced the results. Third, even though we excluded patients with stroke, coronary artery disease, or CP at baseline, we may have underestimated the effect of MHR on CP due to our lack of detailed information on lipid-lowering drugs. Finally, due to our lack of mortality data to analyze the competing risk of death for CP, and our data from the physical examination population rather than the general population, we may have underestimated the incidence of CP.

CONCLUSIONS

To summarize, our research revealed that a higher MHR was associated with an elevated onset risk of CP and 10-year CVD in the Chinese population. It provides longitudinal epidemiological insights into the association between MHR and developing CP. Thus, MHR could be used as a possible marker for plaque formation. Focusing on MHR levels during a health checkup is a promising way to prevent CP and CVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S11
Figures S1–S6

REFERENCES

1. Ihle-Hansen H, Vigen T, Berge T, Walle-Hansen MM, Hagberg G, Ihle-Hansen H, Thommessen B, Ariansen I, Røsjø H, Rønning OM, et al. Carotid plaque score for stroke and cardiovascular risk prediction in a middle-aged cohort from the general population. *J Am Heart Assoc*. 2023;12:e030739. doi: 10.1161/jaha.123.030739
2. Bos D, Arshi B, van den Bouwhuijsen QJA, Ikram MK, Selwaness M, Vernooij MW, Kavousi M, van der Lugt A. Atherosclerotic carotid plaque composition and incident stroke and coronary events. *J Am Coll Cardiol*. 2021;77:1426–1435. doi: 10.1016/j.jacc.2021.01.038
3. Fu J, Deng Y, Ma Y, Man S, Yang X, Yu C, Lv J, Wang B, Li L. National and provincial-level prevalence and risk factors of carotid atherosclerosis in Chinese adults. *JAMA Netw Open*. 2024;7:e2351225. doi: 10.1001/jamanetworkopen.2023.51225
4. Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, Fowkes FGR, Fowkes FJI, Rudan I. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health*. 2020;8:e721–e729. doi: 10.1016/s2214-109x(20)30117-0
5. Saba L, Saam T, Jäger HR, Yuan C, Hatsukami TS, Saloner D, Wasserman BA, Bonati LH, Wintermark M. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol*. 2019;18:559–572. doi: 10.1016/s1474-4422(19)30035-3
6. Wang P, Guo X, Zhou Y, Li Z, Yu S, Sun Y, Hua Y. Monocyte-to-high-density lipoprotein ratio and systemic inflammation response index are associated with the risk of metabolic disorders and cardiovascular diseases in general rural population. *Front Endocrinol (Lausanne)*. 2022;13:944991. doi: 10.3389/fendo.2022.944991
7. Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, Cetinkaya H, Karaman M, Oguz Y, Eyileten T, Vural A, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. *Int Urol Nephrol*. 2014;46:1619–1625. doi: 10.1007/s11255-014-0730-1
8. Wang HY, Shi WR, Yi X, Zhou YP, Wang ZQ, Sun YX. Assessing the performance of monocyte to high-density lipoprotein ratio for predicting ischemic stroke: insights from a population-based Chinese cohort. *Lipids Health Dis*. 2019;18:127. doi: 10.1186/s12944-019-1076-6
9. Xi J, Men S, Nan J, Yang Q, Dong J. The blood monocyte to high density lipoprotein cholesterol ratio (MHR) is a possible marker of carotid artery plaque. *Lipids Health Dis*. 2022;21:130. doi: 10.1186/s12944-022-01741-8
10. Zhang Z, Gao Y, Li Z, Li B, Gao S, Sun J, Tu J, Ning X, Zhang W, Wang J. Association of carotid atherosclerotic plaque and intima-media thickness with the monocyte to high-density lipoprotein cholesterol ratio among low-income residents of rural China: a population-based cross-sectional study. *BMC Public Health*. 2023;23:2541. doi: 10.1186/s12889-023-17447-0
11. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid intima-media thickness task force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189–190. doi: 10.1016/j.echo.2007.11.011
12. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation*. 2008;117:743–753. doi: 10.1161/circulationaha.107.699579
13. Yang X, Li J, Hu D, Chen J, Li Y, Huang J, Liu X, Liu F, Cao J, Shen C, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR project (prediction for ASCVD risk in China). *Circulation*. 2016;134:1430–1440. doi: 10.1161/circulationaha.116.022367
14. Huang Z, Ding X, Yue Q, Wang X, Chen Z, Cai Z, Li W, Cai Z, Chen G, Lan Y, et al. Triglyceride-glucose index trajectory and stroke incidence

in patients with hypertension: a prospective cohort study. *Cardiovasc Diabetol*. 2022;21:141. doi: 10.1186/s12933-022-01577-7
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, et al. The seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572. doi: 10.1001/jama.289.19.2560
16. Standards of medical Care in Diabetes-2020 abridged for primary care providers. *Clin Diabetes*. 2020;38:10–38. doi: 10.2337/cd20-as01
17. 2016 Chinese guidelines for the management of dyslipidemia in adults. *J Geriatr Cardiol*. 2018;15:1–29. doi: 10.11909/j.issn.1671-5411.2018.01.011
18. Wang L, Zhang Y, Yu B, Zhao J, Zhang W, Fan H, Ren Z, Liang B. The monocyte-to-high-density lipoprotein ratio is associated with the occurrence of atrial fibrillation among NAFLD patients: a propensity-matched analysis. *Front Endocrinol (Lausanne)*. 2023;14:1127425. doi: 10.3389/fendo.2023.1127425
19. Libby P, Hansson GK. From focal lipid storage to systemic inflammation: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:1594–1607. doi: 10.1016/j.jacc.2019.07.061
20. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*. 1999;340:115–126. doi: 10.1056/nejm199901143400207
21. López P, Rodríguez-Carrio J, Martínez-Zapico A, Pérez-Álvarez ÁI, Suárez-Díaz S, Mozo L, Benavente L, Caminal-Montero L, Suárez A. Low-density granulocytes and monocytes as biomarkers of cardiovascular risk in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2020;59:1752–1764. doi: 10.1093/rheumatology/keaa016
22. Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, Zhang RY, Shen WF, Lu L, Wang XQ. 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. doi: 10.3389/fendo.2019.00191
23. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47:C7–C12. doi: 10.1016/j.jacc.2005.09.068
24. Liu Z, Fan Q, Wu S, Lei Y. Associations of monocytes and the monocyte/high-density lipoprotein ratio with extracranial and intracranial atherosclerotic stenosis. *Front Neurol*. 2021;12:756496. doi: 10.3389/fneur.2021.756496
25. Jaipersad AS, Shantsila A, Lip GY, Shantsila E. Expression of monocyte subsets and angiogenic markers in relation to carotid plaque neovascularization in patients with pre-existing coronary artery disease and carotid stenosis. *Ann Med*. 2014;46:530–538. doi: 10.3109/07853890.2014.931101
26. Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. *J Am Coll Cardiol*. 2004;44:1945–1956. doi: 10.1016/j.jacc.2004.07.056
27. Ganjali S, Gotto AM Jr, Ruscica M, Atkin SL, Butler AE, Banach M, Sahebkar A. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. *J Cell Physiol*. 2018;233:9237–9246. doi: 10.1002/jcp.27028
28. Canpolat U, Çetin EH, Cetin S, Aydin S, Akboga MK, Yayla C, Turak O, Aras D, Aydogdu S. Association of Monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. *Clin Appl Thromb Hemost*. 2016;22:476–482. doi: 10.1177/1076029615594002
29. Song P, Xia W, Zhu Y, Wang M, Chang X, Jin S, Wang J, An L. Prevalence of carotid atherosclerosis and carotid plaque in Chinese adults: a systematic review and meta-regression analysis. *Atherosclerosis*. 2018;276:67–73. doi: 10.1016/j.atherosclerosis.2018.07.020
30. Villanueva DLE, Tiongson MD, Ramos JD, Llanes EJ. Monocyte to high-density lipoprotein ratio (MHR) as a predictor of mortality and major adverse cardiovascular events (MACE) among ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention: a meta-analysis. *Lipids Health Dis*. 2020;19:55. doi: 10.1186/s12944-020-01242-6
31. Jordan S, Tung N, Casanova-Acebes M, Chang C, Cantoni C, Zhang D, Wirtz TH, Naik S, Rose SA, Brocker CN, et al. Dietary intake regulates the circulating inflammatory monocyte Pool. *Cell*. 2019;178:1102–1114.e1117. doi: 10.1016/j.cell.2019.07.050
32. Ridker PM, Koenig W, Kastelein JJ, Mach F, Lüscher TF. Has the time finally come to measure hsCRP universally in primary and secondary cardiovascular prevention? *Eur Heart J*. 2018;39:4109–4111. doi: 10.1093/eurheartj/ehy723
33. Xiao L, Harrison DG. Inflammation in hypertension. *Can J Cardiol*. 2020;36:635–647. doi: 10.1016/j.cjca.2020.01.013
34. Karam BS, Chavez-Moreno A, Koh W, Akar JG, Akar FG. Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. *Cardiovasc Diabetol*. 2017;16:120. doi: 10.1186/s12933-017-0604-9
35. Ménégaut L, Laubriet A, Crespy V, Leleu D, Pilot T, Van Dongen K, de Barros JP, Gautier T, Petit JM, Thomas C, et al. Inflammation and oxidative stress markers in type 2 diabetes patients with advanced carotid atherosclerosis. *Cardiovasc Diabetol*. 2023;22:248. doi: 10.1186/s12933-023-01979-1
36. Chawla A, Nguyen KD, Goh YP. Macrophage-mediated inflammation in metabolic disease. *Nat Rev Immunol*. 2011;11:738–749. doi: 10.1038/nri3071