Monocyte to high-density lipoprotein ratio was associated with the severity of coronary artery disease: results from a large cohort study

Hao-Yu Wu1*, Li-Jun Wang1,2,3*, Jian-Hua Huo1, Hua Qiang1, Chen Wang1, Zu-Yi Yuan1,2,3, Shan-Shan Gao1,2,3

1 Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
2 Key Laboratory of Molecular Cardiology Xi'an Jiaotong University, Xi'an 710061, China
3 Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University Ministry of Education, Xi'an 710061, China

*Hao-Yu Wu and Li-Jun Wang contributed equally to this work.

Corresponding author to Zu-Yi Yuan at: Department of Cardiovascular Medicine, First Affiliated Hospital of Medical School, Xi'an Jiaotong University, 277 West Yanta Road, Xi'an, Shaanxi 710061, China
E-mail: zuiyuan@mail.xjtu.edu.cn

Corresponding and requests for materials should be addressed to Shan-Shan Gao at: Department of Cardiovascular Medicine, First Affiliated Hospital of Medical School, Xi'an Jiaotong University, 277 West Yanta Road, Xi'an, Shaanxi 710061, China
E-mail: gaoshanshi@163.com
Abstract

Background: Monocyte to high-density lipoprotein ratio (MHR) was a recently emerged lipid biomarker, might reflect the inflammation level and the lipid profile in a quantitative manner. We aimed to investigate the association of MHR with the severity of coronary artery disease (CAD), and the ability of MHR in predicting severe CAD and acute atherothrombosis events.

Methods: A total of 3930 CAD patients and 1020 non-CAD patients presented consecutively to our hospital for coronary angiography. The CAD patients were classified into four groups according to the quartile of the MHR (≤0.28, N=1218; 0.28-0.39, N=1262; 0.39-0.53, N=1209; >0.53, N=1261). CAD severity was quantified according to the Gensini score. A receiver operating characteristic (ROC) curve analysis was also performed to predict severe CAD and acute coronary thrombotic events.

Results: MHR was significantly higher in the CAD group than in the non-CAD group (0.45 ± 0.22 vs. 0.35 ± 0.17, p<0.001) and had a significant positive correlation with Gensini score. Compared with lower MHR value, a MHR in the fourth quartile was strongly associated with severe CAD and acute coronary thrombotic event after adjusting for baseline factors. Receiver-operating characteristic (ROC) curve analysis showed that combination of MHR and traditional risk predictors could better predict severe CAD especially acute coronary thrombosis events such as non-ST-elevation myocardial infarction (NSTEMI) and acute ST-segment elevation myocardial infarction (ASTEMI).

Conclusions: MHR was positive associated with the prevalence and severity of CAD.
Moreover, MHR may be a prognostic marker for acute atherothrombosis events.

Keywords:
Monocyte, High-density lipoprotein, Coronary artery disease severity, Gensini score, Major adverse cardiovascular events, Acute coronary thrombotic events
Introduction

Atherosclerosis (AS) is the pathophysiological basis of coronary artery disease (CAD) with inflammation and cholesterol metabolism disorder as its two basic hallmarks\(^1,2\). Monocytes in the circulation are the main cells secreting various pro-inflammatory factors, and play an extremely important role in the initiation of coronary AS, plaque formation and stability. Studies have shown that vulnerable plaques exhibit significant monocyte infiltration, and monocytes in the peripheral blood of patients are mostly activated\(^3,4\). High-density lipoprotein cholesterol (HDL-C) is a lipid component that exerts anti-AS effects, by promoting cholesterol efflux and preventing monocyte activation, proliferation and adhesion to endothelium\(^5,6\). Increased monocyte counts and decreased HDL-C levels have been reported to be associated with inflammatory disorders. Recently, monocyte to HDL-C ratio (MHR) has emerged as a novel and useful marker in different disease models, such as CAD, diabetes mellitus (DM), saphenous vein graft disease (SVGD) and acute ischemic stroke (AIS)\(^7\).

In a cross-sectional study on 1229 CAD patients, Akboga et al found that MHR is significantly correlated with the burden of AS\(^8\). Another study also found that MHR was obviously higher in 428 stable CAD patients with SYNTAX score of \(\geq 23\) than those with SYNTAX score of \(< 23\). However, the abovementioned studies usually had relatively small sample size, and few study has ever investigated the association of MHR with the severity of CAD assessed by Gensini score in a large scale population.
Therefore, in this study, we evaluated the association of MHR with the severity and complexity of CAD using the Genisi score and determined the ability of MHR in predicting severe CAD and acute atherothrombosis events.

Methods

Study population. A total of 4950 patients who presented to the Department of Cardiovascular Medicine of the First Affiliated Hospital of Xi’an Jiao University for angiography between 2017 January and 2018 July were recruited. The exclusion criteria were: current infection, autoimmune diseases, malignant tumors, surgery within 2 weeks, severe renal and liver insufficiency, non-coronary vascular inflammatory and embolic diseases (vasculitis, aortic dissection, abdominal aortic aneurysm, and transient ischemic attack), currently taking immunosuppressive agents. Written informed consent was obtained from all the participants. The present study complied with the Declaration of Helsinki and the research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University.

CAD patients in this study were defined had >50% stenosis in at least 1 major coronary artery, and then the CAD patients were further divided into 4 groups: stable angina pectoris (SAP), unstable angina pectoris (UAP), non-ST-elevation myocardial infarction (NSTEMI), and acute ST-segment elevation myocardial infarction (ASTEMI). Acute atherothrombosis events refer to NSTEMI/ASTEMI. Furthermore, to evaluate the relationship between the severity of CAD and MHR, patients were divided into 4 groups based on the quartiles of MHR (≤0.28, 0.28-0.39, 0.39-
Biochemical measurements. Blood samples were collected from each patient after fasting for 12 h. The WBC and differential leukocyte counts were measured using an automated hematology analyzer (Sysmex 2100, Japan). The lipid profile as well as the creatinine, uric acid, glycosylated hemoglobin (HbA1c), high-sensitive C reaction protein (hs-CRP), and homocysteine (HCY) levels were measured using standard methods in the local laboratory of the First Affiliated Hospital of Xi’an Jiao University.

Coronary angiography and Gensini score determination. The coronary angiography was performed in multiple projections. The coronary angiogram was reviewed by two experienced cardiologists who were blinded to the patients’ clinical information. The severity of CAD was quantified based on the Gensini score. The two cardiologists evaluated the severity of coronary lesion and calculated the Gensini score independently. The Gensini score is performed as follows: regarding the lumen of the coronary arteries, 1 for 1% to 25% stenosis, 2 for 26% to 50%, 4 for 51% to 75%, 8 for 76% to 90%, 16 for 91% to 99%, and 32 for total occlusion. The score is then multiplied by a factor representing the importance of the lesion’s location in the coronary artery system. For the location scores, 5 points are given for left main lesion; 2.5 for the proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for the mid-segment of the LAD and LCX; 1 for the distal segment of the LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and
intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches\textsuperscript{10,11}.

For patients who have previously received stent implantation, the Gensini score was calculated if there was restenosis in treated vessels or other vessels. Treated vessels were not scored if no restenosis was observed.

Severe CAD refer to the highest tertile of the Gensini score.

**Statistical analysis.** All data were statistically analyzed using SPSS for Windows (version 20.0, SPSS Inc., Chicago, Ill., USA). All continuous data were tested for normality. Continuous data were presented as mean ± standard deviation, and categorical data were expressed as quantity (or frequency) and percentage. The comparison between two groups was performed using the independent sample $t$-test (consistent with normality) or Mann-Whitney U test (not conforming to normality). The comparison between multiple groups was based on one-way ANOVA (consistent with normality) or Kruskal-Wallis H test (not conforming to normality). Analysis of categorical variables were performed using the chi-square test or Fisher's exact test. Multivariate logistic regression analysis was used to access the relationship between MHR and the severity of the coronary artery was assessed after correcting baseline confounders. The receiver-operating characteristics (ROC) curve analyses were used to assess the ability of different models in predicting severe CAD. A $p$-value <0.05 was considered statistically significant.
Results

Baseline clinical characteristics. A total of 3354 men and 1596 women with average age of 60.93 ± 10.17 years were included in this study. After receiving coronary angiography, 1020 patients were diagnosed with non-CAD, whereas the other 3930 were CAD patients (SAP, 260, 6.6%; UAP, 2726, 69.3%; NSTEMI, 224, 6.0%; ASTEMI, 720, 18.3%). The baseline clinical characteristics are summarized in Table 1.

In terms of demographical parameters, white blood cell count, monocyte count, and MHR were significantly different between non-CAD group and subtypes of CAD group (p<0.001). HDL-C was significantly lower in the NSTEMI/ASTEMI group than in the non-CAD and SAP/UAP group. The average Gensini score was much higher in the CAD group than in the non-CAD group (39.36 ± 31.88 vs. 4.40 ± 3.34, p<0.001). Moreover, a significant difference of Gensini score was also observed among the subtypes of CAD groups.

The CAD group had more males and elderly and had higher percentage of current smokers and those with a history of CAD, hypertension, and DM than in the non-CAD group. We also observed that CAD patients had higher levels of LDL-C, HbA1C, HCY, Creatinine, uric acid and hs-CRP. For concomitant therapy, CAD patients received statins, β-blocker, ACEI/ARB more frequently than non-CAD patients. Moreover, left ventricular ejection fraction (LVEF) was significantly lower in the CAD group than in the non-CAD group.

Association between MHR and CAD. All patients were divided into four groups
according to the quartiles of MHR (≤0.28, 0.28-0.39, 0.39-0.53, >0.53). Characteristics of groups according to MHR quartiles are summarized in Table 2. Data showed that the higher the MHR, the higher the Gensini score, suggesting that these two indicators are significantly positively correlated (25.09 ± 18.88, 28.47 ± 18.69, 33.94 ± 22.74, 40.99 ± 24.14, p<0.001).

As shown in Table 2, higher MHR was positively related to male sexes, current smokers, DM history, and family history of CAD but negatively associated with age (p<0.001). In addition, MHR was positively associated with TC, TG, LDL-C, creatinine, HCY and hs-CRP (p<0.001) but significantly negatively related to HDL-C and LVEF (p<0.001). Multivariable logistic regression analysis was performed to eliminate the impact of residual confounding factors. As shown in Table 3, after adjusting for baseline factors such as age, sex, current smoking, family history of CAD, hypertension and DM history, MHR was still strongly associated with severe CAD (2.251, 95% CI: 1.612-3.319, p<0.001) and NSTEMI/ASTEMI (6.653, 95% CI: 4.442-9.963, p<0.001), indicating that MHR was an independent indicator for severe CAD and NSTEMI/ASTEMI.

**Receiver operating characteristic (ROC) curve analysis.** We performed the ROC curve analysis to evaluate the contribution of MHR in discriminating CAD or NSTEMI/ASTEMI. As shown in Figure 1 and Table 4, ROC analysis for severe CAD showed that AUC was 0.651 (95% CI: 0.635-0.667, p<0.001) when the traditional factors were calculated alone, whereas AUC improved to 0.662 (95% CI: 0.646-0.678, p<0.001) when the combined model was calculated (Figure 1A). As for
NSTEMI/ASTEMI, ROC analysis showed that the AUC was 0.676 (95% CI: 0.657-0.696, p<0.001) when the traditional factors were calculated alone and the AUC significantly improved to 0.700 (95% CI: 0.682-0.717, p<0.001) when the combined model was calculated (Figure 1B). These results indicate that the combination of MHR and traditional risk indicators could better predict severe CAD especially acute coronary thrombosis events such as NSTEMI and ASTEMI.

Discussion

To the best of our knowledge, this is so far the largest single-center cohort study that has evaluated the relationship between MHR and the severity of CAD assessed by Gensini score. The results of the present study demonstrated that MHR in the CAD group is much higher than that in non-CAD group. In addition, this study revealed a positive correlation between MHR and the subtypes and severity of CAD. Moreover, MHR, combined with traditional risk factors, could better predict severe CAD and acute coronary thrombosis events.

Monocytes play a pivotal role in the initiation and progression of AS. Monocytes bind to activated endothelium, migrate into the intimal layer and take up lipoproteins to become macrophages. Monocyte/macrophages can induce the release of inflammatory factors, promote AS formation and induce plaque rupture, leading to the occurrence of acute coronary syndrome (ACS)\textsuperscript{9,12-15}. Previous study showed that monocytes are functionally different in hyperlipidemia\textsuperscript{16}. HDL-C, known as the anti-atherogenic lipoprotein, can inhibit the activation of CD11b in monocytes to exert anti-
inflammatory effects as well as the expression of monocyte chemoattractant protein-1 (MCP-1) to inhibit the chemotaxis of monocytes\textsuperscript{6,17,18}. Therefore, we hypothesize that the combination of increased monocyte count and decreased HDL-C was superior to individual monocyte count or HDL-C level in predicting atherosclerosis, and hence cardiovascular events. This initial model was first confirmed by Tani et al in predicting coronary atherosclerotic regression in the plaque volume after pravastatin therapy. The study also showed that change of coronary plaque volume was associated with a simultaneous elevation in serum HDL-C (\(\beta = -0.56\)) and a decrease in blood monocyte count (\(\beta = 0.23\))\textsuperscript{19}.

MHR, a newly introduced inflammatory marker, has been found to be associated with cardiovascular events in several studies. Kundi et al. reported that MHR was significantly associated with SYNTAX score in 428 patients with stable angina pectoris undergoing coronary angiography. Similar results were also obtained from Akboga and colleagues\textsuperscript{8,9}. In a study including 315 STEMI patients who underwent PCI, Çağdaş et al. found that MHR was better than neutrophil to lymphocyte ratio (NLR) and C-reactive protein in predicting severity of CAD\textsuperscript{20}. Kanbay et al. demonstrated that high MHR was an independent predictor for worse cardiovascular prognosis in patients with chronic kidney disease\textsuperscript{21}. Cetin and colleagues reported that ACS patients with high MHR value had 1.4-fold higher occurrence of in-hospital and long-term major adverse cardiovascular events (MACE) compared with those with a lower MHR value after median 31.6 months of follow-up\textsuperscript{22}.

MHR was also used as a novel inflammation-based marker in other inflammatory-
related diseases besides cardiovascular disorders. You et al. found that in patients with acute intracerebral hemorrhage (ICH), higher MHR was associated with 3.87-fold and 3.08-fold increased risk of disability or death at discharge and at 3 months post-ICH, respectively. In another study that enrolled 466 acute ischemia stroke (AIS) patients, Bolayir et al. demonstrated that MHR values were higher in the AIS group than in the control group. In addition, high MHR was found to be significantly related to the 30-day-mortality in patients with AIS. Metabolic syndrome (MS) is characterized by chronic systemic low-grade inflammation. Researchers investigated the relevance of MHR with MS severity in clinical practice and found that high MHR was an independent predictor in evaluating MS severity.

Gensini score is a convenient and widely used scoring tool for assessing the severity of coronary artery and complexity of lesions. In recent years, many researchers have begun to use the Gensini score to assess coronary severity. Cetin and colleagues reported in their study which recruited 2661 patients a significant positive correlation between MHR and Gensini score. In this study which included 4980 patients, we also found that MHR was positively associated with Gensini score, indicating that MHR could be an independent indicator to predict the prevalence and severity of CAD, which was consistent with previous studies. In addition, this study presents a number of important strengths. We used ROC analysis to demonstrate that MHR had great value in predicting severe CAD especially acute coronary thrombosis events such as NSTEMI and ASTEMI, which has important clinical significance but has not received enough attention from researchers.
Conclusion. We demonstrated in this study that MHR is positively associated with the severity of CAD and MHR is an independent indicator to predict severe CAD and acute coronary thrombosis events.

Abbreviations

CAD: Coronary artery disease; MHR: Monocyte to high-density lipoprotein cholesterol ratio; ROC: Receiver operating characteristic; NSTEMI: Non-ST-elevation myocardial infarction; ASTEMI: Acute ST-segment elevation myocardial infarction; AS: Atherosclerosis; HDL-C: High-density lipoprotein cholesterol; DM: Diabetes mellitus; SVGD: Saphenous vein graft disease; AIS: Acute ischemic stroke; SYNTAX:Synergy between PCI with TAXUS drug-eluting stent and Cardiac Surgery; SAP: Stable angina pectoris; UAP: Unstable angina pectoris; HbA1c: Glycosylated hemoglobin; hs-CRP:High-sensitive C reaction protein; HCY:homocysteine; LAD:Left anterior descending artery; LCX:Left circumflex artery; LVEF: Left ventricular ejection fraction; AUC: Area under the curve; ACS: Acute coronary syndrome; MCP-1: Monocyte chemoattractant protein-1; PCI: Percutaneous coronary intervention; NLR:Neutrophil to lymphocyte ratio; MACE:Major adverse cardiovascular events; ICH:Intracerebral hemorrhage; MS:Metabolic syndrome; OR: odds ratio; CI: Confidence interval
Acknowledgments

We acknowledge the volunteers who assisted with our study design, data collection and analysis, and participate in the manuscript writing or reviewing.

Author Contributions

Shan-Shan Gao devised and conducted the experiments and wrote the manuscript. Hao-Yu Wu, Li-Jun Wang and Chen Wang performed clinical data collection and analysis of data. Jian-Hua Huo and Hua Qiang participated in analysis and interpretation of clinical data. Zu-Yi Yuan and Shan-Shan Gao conceived the project, wrote the manuscript and approved the final version of this manuscript to be submitted. All the authors also agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (81700447 to S.-S.G., 81500389 to L.-J.W., 91639301 to Z.-Y.Y.); Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF-CRF-2018-010); Natural Science Foundation of Shaanxi Province, China (2019JQ-955 to S.-S.G., 2018JM7106 to L.-J.W.); and the Key Research and Development Program of Shaanxi Province, China (2017ZDCXL-SF-02-04-01).
Availability of data and materials

The data analyzed in the current study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University according to the principles of Declaration of Helsinki of 1975. Verbal information for all the participants was conducted.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

1 Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China

2 Key Laboratory of Molecular Cardiology Xi'an Jiaotong University, Xi'an 710061, China

3 Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University Ministry of Education, Xi'an 710061, China
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Figure Legends

Figure 1. The receiver-operating characteristic curve of MHR for the prediction of severe CAD or NSTEMI/ASTEMI.
### Table 1. Basic clinical characteristics for patients with or without CAD.

| Variable                | Non-CAD group (N=1020) | CAD group (N=3930) | p value |
|-------------------------|-------------------------|--------------------|---------|
|                         | SAP (N=260)             | UAP (N=2726)       | NSTEMI (N=224) | ASTEMI (N=720) |
| Age(yr)                 | 59.56 ± 10.10           | 62.97 ± 10.00      | 61.90 ± 9.60  | 60.95 ± 11.21  | 58.64 ± 11.64 | <0.001 |
| Male, n (%)             | 524(51.4)               | 178(68.8)          | 1908(70.0)    | 166(74.3)      | 578(80.3)     | <0.001 |
| Hypertension, n (%)     | 502(49.3)               | 154(59.5)          | 1654(60.7)    | 140(62.6)      | 368(51.2)     | <0.001 |
| DM, n (%)               | 234(23.0)               | 89(34.2)           | 905(33.2)     | 75(33.4)       | 265(36.9)     | <0.001 |
| Current smoker, n (%)   | 331(32.5)               | 122(47.0)          | 1365(50.1)    | 129(57.8)      | 440(61.2)     | <0.001 |
| Family history, n (%)   | 154(15.1)               | 41(15.9)           | 471(17.3)     | 50(22.6)       | 238(33.1)     | <0.001 |
| Previous PCI, n (%)     | 4(0.4)                  | 50(19.4)           | 861(31.6)     | 80(35.6)       | 185(25.7)     | <0.001 |
| Gensini score           | 4.40 ± 3.34             | 23.89 ± 20.75      | 37.84 ± 31.62 | 51.00 ± 34.35  | 49.22 ± 32.65 | <0.001 |
| LVEF, %                 | 66.71 ± 10.35           | 65.35 ± 9.50       | 64.17 ± 9.33  | 57.75 ± 9.78   | 51.83 ± 9.74  | <0.001 |
| Laboratory parameters        | 3.90 ± 0.92 | 3.78 ± 0.99 | 3.69 ± 0.97 | 4.00 ± 1.00 | 4.04 ± 0.94 | <0.001 |
|-----------------------------|-------------|-------------|-------------|-------------|-------------|--------|
| TC, mol/L                   | 2.24 ± 0.78 | 2.19 ± 0.85 | 2.11 ± 0.80 | 2.41 ± 0.81 | 2.48 ± 0.80 | <0.001 |
| LDL-C, mmol/L               | 1.54 ± 1.27 | 1.51 ± 1.08 | 1.54 ± 1.01 | 1.72 ± 1.50 | 1.67 ± 1.07 | 0.010  |
| TG, mmol/L                  | 5.54 ± 1.24 | 5.81 ± 1.68 | 5.89 ± 1.79 | 6.08 ± 1.35 | 6.15 ± 1.51 | <0.001 |
| HbA1C(%)                    | 61.23 ± 16.21 | 69.82 ± 57.99 | 65.76 ± 28.56 | 68.16 ± 28.45 | 66.92 ± 20.00 | <0.001 |
| Creatinine, μmol/L          | 307.98 ± 80.29 | 321.85 ± 86.79 | 318.52 ± 81.38 | 313.69 ± 79.66 | 322.78 ± 90.49 | 0.002  |
| Uric acid, μmol/L           | 18.43 ± 10.98 | 19.08 ± 9.32 | 20.52 ± 12.90 | 21.39 ± 12.47 | 23.61 ± 17.17 | <0.001 |
| HCY, μmol/L                 | 1.85 ± 2.39 | 2.38 ± 3.01 | 2.38 ± 2.78 | 4.53 ± 3.69 | 4.83 ± 3.73 | <0.001 |
| hs-CRP, mg/L                | 1.03 ± 0.26 | 1.00 ± 0.26 | 0.95 ± 0.23 | 0.93 ± 0.23 | 0.93 ± 0.21 | <0.001 |
| HDL-C, mmol/L               | 6.31 ± 2.35 | 6.52 ± 1.74 | 6.78 ± 1.97 | 8.00 ± 2.10 | 9.19 ± 3.15 | <0.001 |
| White blood cell, 10⁹/L     | 0.34 ± 0.13 | 0.37 ± 0.12 | 0.38 ± 0.14 | 0.45 ± 0.17 | 0.50 ± 0.22 | <0.001 |
| Monocyte count, 10⁹/L       | 0.35 ± 0.17 | 0.39 ± 0.17 | 0.42 ± 0.19 | 0.50 ± 0.23 | 0.56 ± 0.27 | <0.001 |
|                | n (%)            | 971 (95.1%) | 237 (91.1%) | 2630 (96.4%) | 220 (98.2%) | 713 (99.0%) | <0.001 |
|----------------|------------------|-------------|-------------|--------------|-------------|-------------|--------|
| Aspirin, n (%) |                  |             |             |              |             |             |        |
| Clopidogrel/Ticagrelor, n (%) |         |             |             |              |             |             | <0.001 |
| Statins, n (%) |                  |             |             |              |             |             | <0.001 |
| β-blocker, n (%) |                |             |             |              |             |             | <0.001 |
| ACEI/ARB, n (%) |                 |             |             |              |             |             | <0.001 |

DM, diabetes mellitus; TC, Total cholesterol; TG, Triglycerides; HCY, homocysteine; hs-CRP, high-sensitive C reaction protein; LVEF, left ventricular ejection fraction. Data presented are mean ± SEM or n(%).
| Variable               | MHR ≤0.28 (N=1218) | MHR 0.28-0.39 (N=1262) | MHR 0.39-0.53 (N=1209) | MHR >0.53 (N=1261) | p value |
|------------------------|---------------------|-------------------------|-------------------------|---------------------|---------|
| Age (yr)               | 62.14 ± 9.52        | 61.55 ± 10.19           | 60.38 ± 10.28           | 59.74 ± 10.22       | <0.001  |
| Male, n (%)            | 644 (53.3)          | 785 (64.5)              | 913 (74.5)              | 975 (79.3)          | <0.001  |
| Hypertension, n (%)    | 700 (57.9)          | 683 (56.1)              | 695 (56.7)              | 703 (57.2)          | 0.837   |
| Current smoker, n (%)  | 451 (37.3)          | 550 (45.2)              | 660 (53.8)              | 703 (57.2)          | <0.001  |
| DM, n (%)              | 352 (29.1)          | 363 (29.8)              | 391 (31.9)              | 447 (36.4)          | <0.001  |
| Family history, n (%)  | 235 (19.4)          | 215 (17.6)              | 251 (20.4)              | 247 (20.1)          | 0.305   |
| Previous PCI, n (%)    | 231 (19.1)          | 283 (23.2)              | 299 (24.4)              | 358 (29.1)          | <0.001  |
| TC, mmol/L             | 4.13 ± 0.95         | 3.88 ± 1.03             | 3.68 ± 0.90             | 3.54 ± 0.89         | <0.001  |
| LDL-C, mmol/L          | 2.38 ± 0.85         | 2.26 ± 0.83             | 2.15 ± 0.77             | 2.05 ± 0.74         | <0.001  |
| HDL-C, mmol/L          | 1.16 ± 0.25         | 1.00 ± 0.20             | 0.91 ± 0.17             | 0.81 ± 0.16         | <0.001  |
|                      | Mean ± Standard Error | Mean ± Standard Error | Mean ± Standard Error | Mean ± Standard Error | p-Value   |
|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------|
| TG, mmol/L           | 1.39 ± 0.76           | 1.55 ± 1.09           | 1.59 ± 1.00           | 1.74 ± 1.43           | <0.001    |
| HbA1C, %             | 5.73 ± 1.52           | 5.80 ± 1.64           | 5.95 ± 1.65           | 5.98 ± 1.72           | 0.001     |
| Creatinine, μmol/L   | 62.60 ± 18.89         | 64.88 ± 30.70         | 66.07 ± 28.69         | 67.78 ± 31.26         | <0.001    |
| Uric acid, μmol/L    | 302.75 ± 79.18        | 314.32 ± 83.78        | 321.93 ± 83.79        | 328.73 ± 82.72        | <0.001    |
| HCY, μmol/L          | 19.34 ± 12.27         | 19.95 ± 12.79         | 21.34 ± 13.69         | 21.94 ± 14.49         | <0.001    |
| hs-CRP, mg/L         | 2.60 ± 2.09           | 2.81 ± 2.89           | 2.89 ± 2.21           | 3.08 ± 2.27           | 0.012     |
| White blood cell, 10^9/L | 6.86 ± 2.33          | 7.04 ± 2.73           | 7.16 ± 2.32           | 7.31 ± 2.38           | <0.001    |
| Monocyte count, 10^9/L | 0.38 ± 0.16           | 0.39 ± 0.17           | 0.40 ± 0.15           | 0.41 ± 0.16           | <0.001    |
| Gensini score        | 25.09 ± 18.88         | 28.47 ± 18.69         | 33.94 ± 22.74         | 40.99 ± 24.14         | <0.001    |
| LVEF, %              | 65.13 ± 8.71          | 63.68 ± 9.52          | 62.23 ± 10.60         | 59.62 ± 11.43         | <0.001    |

DM, diabetes mellitus; TC, Total cholesterol; TG, Triglycerides; HCY, homocysteine; hs-CRP, high-sensitive C reaction protein; LVEF, left ventricular ejection fraction. Data presented are mean ± SEM or n(%).
Table 3. Multivariable logistic regression analysis predicts severe CAD and NSTEMI/ASTEMI.

|                         | Severe CAD          | NSTEMI/ASTEMI        |
|-------------------------|---------------------|---------------------|
|                         | OR      | 95% C.I. | p value | OR      | 95% C.I. | p value |
| Gender                  | 1.391   | 1.152-1.680 | 0.001   | 1.305   | 1.013-1.682 | 0.040   |
| Age                     | 1.017   | 0.010-1.023 | <0.001  | 0.993   | 0.984-1.001 | 0.080   |
| Hypertension history    | 1.161   | 1.020-1.321 | 0.024   | 0.874   | 0.744-1.032 | 0.112   |
| Current smoker          | 1.216   | 1.040-1.422 | 0.014   | 1.088   | 0.888-1.333 | 0.417   |
| Family history          | 0.985   | 0.837-1.159 | 0.852   | 2.073   | 1.709-2.516 | <0.001  |
| DM history              | 1.279   | 1.107-1.477 | 0.001   | 1.265   | 1.085-1.475 | 0.003   |
| Previous PCI history    | 1.401   | 1.214-1.616 | <0.001  | 1.274   | 1.058-1.533 | 0.110   |
| apoA1                   | 0.417   | 0.278-0.626 | <0.001  | 0.469   | 0.276-0.797 | 0.005   |
| LDL-C                   | 1.315   | 1.214-1.424 | <0.001  | 1.715   | 1.549-1.898 | <0.001  |
|            | Mean | 95% CI          | Standard Deviation | 99% CI          | 99.9% CI         | p-value |
|------------|------|-----------------|--------------------|-----------------|------------------|---------|
| Creatinine | 1.001| 0.999-1.003     | 0.348              | 0.998           | 0.995-1.001      | 0.273   |
| Uric acid  | 1.000| 0.999-1.000     | 0.251              | 0.998           | 0.997-1.000      | 0.044   |
| hs-CRP     | 1.084| 1.061-1.107     | <0.001             | 1.215           | 1.186-1.245      | <0.001  |
| HCY        | 1.006| 1.002-1.026     | 0.003              | 1.018           | 1.012-1.023      | <0.001  |
| HbA1C      | 1.057| 1.026-1.089     | 0.000              | 1.131           | 1.084-1.179      | <0.001  |
| MHR        | 2.251| 1.612-3.319     | <0.001             | 6.653           | 4.442-9.963      | <0.001  |

TC and HDL-C were not included in the model due to the existence of multicollinearity problems (TC vs. LDL-C; HDL-C vs. apoA1).

DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; HCY, homocysteine; hs-CRP, high sensitive C reactive protein; apoA1, apolipoprotein A1.
Table 4. ROC curve analyses of different predictive models.

| Variables          | AUC   | 95% CI    | p-value |
|--------------------|-------|-----------|---------|
| **For severe CAD** |       |           |         |
| MHR                | 0.610 | 0.593-0.627 | <0.001 |
| Traditional factors| 0.651 | 0.635-0.667 | <0.001 |
| Combined           | 0.662 | 0.646-0.678 | <0.001 |
| **For NSTEMI/ASTEMI** |       |           |         |
| MHR                | 0.676 | 0.657-0.696 | <0.001 |
| Traditional factors| 0.665 | 0.647-0.683 | <0.001 |
| Combined           | 0.700 | 0.682-0.717 | <0.001 |
Figure 1.