



# The monocyte to high-density lipoprotein cholesterol ratio and outcomes in type 2 diabetes mellitus patients with non-ST-segment elevation acute coronary syndrome

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**Background:** The monocyte to high-density lipoprotein cholesterol ratio (MHR) has been demonstrated as a new marker of inflammation. However, at present, the prognostic value of MHR in type 2 diabetes mellitus (T2DM) accompanied with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) is unclear.

**Methods:** T2DM patients with NSTE-ACS undergoing PCI were consecutively enrolled from January 1, 2010 to December 31, 2014 and divided according to MHR value tertiles. Baseline, procedural, and follow-up data were collected. The primary outcomes were in-hospital major adverse clinical events (MACE). The prespecified secondary outcomes included any bleeding [as indicated by Bleeding Academic Research Consortium definition (BARC) grades 1–5] and death during follow-up.

**Results:** Of the 1,405 enrolled patients, the rates of in-hospital MACE (0.2%, 0.2%, and 1.3%,  $P=0.043$ ) and bleeding (12.4%, 12.2%, and 17.1%,  $P=0.048$ ) increased significantly in high MHR tertiles. After 1 year of follow-up, the rates of bleeding (15.0%, 14.5%, and 22.2%,  $P=0.002$ ) and all-cause death (1.5%, 1.7%, and 4.3%,  $P=0.010$ ) were higher in higher MHR tertiles. Our results also suggested that MHR was an independent predictor of in-hospital MACE [adjusted odds ratio =8.36; 95% confidence interval (CI): 1.57–44.47;  $P=0.013$ ] and long-term bleeding (adjusted hazard ratio =1.21; 95% CI: 1.07–1.37;  $P=0.002$ ). Receiver-operating characteristic curve analysis indicated that MHR >0.022 had a sensitivity of 75.0% and specificity of 72.7% for predicting in-hospital MACE [area under the curve (AUC) =0.722; 95% CI: 0.51–0.933;  $P=0.040$ ]. Furthermore, Kaplan-Meier curves showed that a higher risk of all-cause death in long-term follow-up was prevalent in patients with high MHR ( $P=0.033$ ).

**Conclusions:** The increased level of MHR was related to in-hospital MACE and long-term bleeding events in T2DM patients with NSTE-ACS undergoing PCI.

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**Keywords:** Monocyte to high-density lipoprotein cholesterol ratio (MHR); non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS); type 2 diabetes mellitus (T2DM); outcomes

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## Introduction

Despite the significant improvements of reperfusion strategies and antithrombotic therapy in recent years, acute coronary syndrome (ACS) remains the primary cause of mortality and morbidity worldwide (1). Diabetes is reported to be an independent risk factor for cardiovascular disease (CVD) and led to a high incidence of repeated hospitalization and poor prognoses (2,3). A study of 1,612 patients with coronary heart disease followed up for 2.8 years undergoing PCI showed 6.4% patients died, and mortality risk increased with increasingly abnormal FG status (4). Diabetic suffering from ACS undergoing percutaneous coronary intervention (PCI) can have a high residual risk. Therefore, the early identification of high-risk patients is essential for better clinical strategies, in order to avoid cardiovascular events.

Previous studies have suggested that oxidative stress and inflammation are involved in the pathogenesis of all phases of atherosclerosis (5-7). It was reported that white blood cell (WBC) count and its subtypes are related to increased cardiovascular risk. For example, previous findings suggest that monocytes were particularly important in the pathogenesis of atherosclerosis owing to their ability to secrete pro-inflammatory and pro-oxidative cytokines (8,9).

The monocyte to high-density lipoprotein cholesterol ratio (MHR) has been known as a prognostic predictor and new marker of CVD (10,11). At present, the value of MHR in predicting the long-term prognosis of diabetic patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) has not been investigated. Our study aims to evaluate the association between MHR and clinical outcomes in NSTEMI-ACS patients with type 2 diabetes mellitus (T2DM) undergoing PCI. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-4876>).

## Methods

### *Experiment design and patients*

Our study was conducted based on a large cohort study that

included 8,197 adults undergoing PCI for NSTEMI-ACS (12). Data on the clinical history, demographic features, in-hospital management, physical examination, and outcomes of patients were fully described in our previous reports (12). In this study, of the 8,197 included patients, 243 patients were readmitted to the hospital. According to the exclusion criteria, 3,349 patients were excluded because of missing monocyte or high-density lipoprotein cholesterol (HDL-C) examination on admission. Furthermore, 90 patients with nosocomial infection, 45 patients with intra-aortic balloon pump, and 14 patients with PCI information incomplete were also excluded. A total of 3,051 patients were not diagnosed with T2DM. Finally, 1,405 patients were enrolled in this study (*Figure 1*).

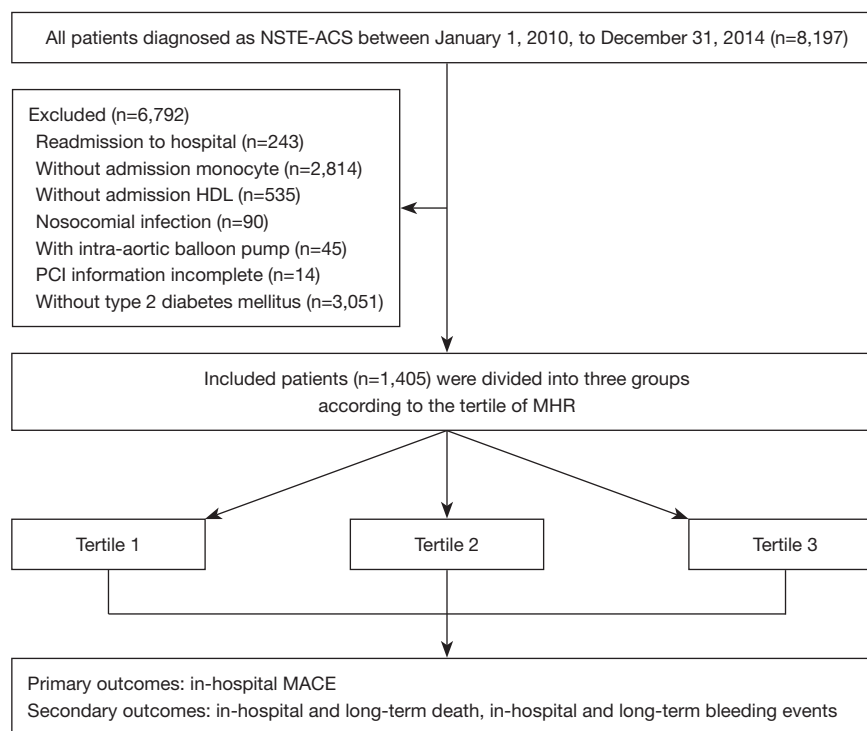
All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Guangdong Provincial People's Hospital of No. GDREC2016210H (R1).

### *Data collection and processing*

Blood samples obtained immediately from all patients on admission before PCI were collected in this study. An automated blood cell counter (Sysmex XE-5000) purchased from Japan was used to analyze the following indicators of hemoglobin content: WBC, lymphocytes, neutrophils, monocytes, and platelets. A catalase assay was applied to analyze the serum HDL-C and other biochemical parameters using an automatic biochemical analyzing system (Beckman Coulter, USA). The MHR was obtained by dividing the monocyte count by the HDL-C count. Data were collected from the hospital by trained study coordinators.

### *Clinical outcomes*

The primary outcomes were in-hospital major adverse clinical events (MACE). The prespecified secondary outcomes included any bleeding [as indicated by Bleeding



**Figure 1** The flowchart presents the selection criteria used in the study and the clinical layout of the study population. NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; MHR, monocyte to high-density lipoprotein cholesterol ratio.

Academic Research Consortium definition (BARC) grades 1–5] and death during follow-up (13). MACE was defined as a combination of non-fatal myocardial infarction (MI), stroke, all-cause death, and target vessel revascularization (TVR). Major bleeding was indicated by the BARC definition (grades 3–5) (13). Follow-up data was collected by trained nurses via telephone interview and outpatient visit.

### Statistical analysis

The level of MHR was modeled as a continuous variable and in tertiles. Data were shown as mean and standard deviation, interquartile range and median, or proportions. Continuous data were compared using the *t*-test. Categorical data were expressed as a percentage, and were compared using Fisher's exact test and the  $\chi^2$  test. Univariable and multivariable Cox proportional hazard regressions were conducted to obtain the odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI), and to identify the relationship between the MHR (as a categorical or continuous variable) and clinical outcomes. Survival

curves were constructed using the Kaplan-Meier method during follow-up for the MHR, and the log-rank test was used to perform statistical assessment. In the present study, SAS (version 9.4, SAS Institute, USA) was used to analyze the data based on existing cases without missing data. A two-sided *P* value <0.05 was considered to indicate statistical significance.

### Results

#### Baseline clinical characteristics

The baseline characteristics results of the patient group based on the MHR tertile groups are presented in *Table 1*. In total, 1,405 patients were included, with an average age of 64.2 (10.4) years. Of these patients, 972 (69.2%) were males. The differences between the groups in terms of gender, weight, smoking, and history of MI and atrial fibrillation were statistically significant. There were no significant differences in previous medications among the different triads of MHR. We found that increased WBC, neutrophil, lymphocyte, monocyte, and platelet (PLT), as

**Table 1** Baseline clinical characteristics of infective endocarditis patients according to the tertile of MHR

Variables	Tertile 1 (<0.014, n=468)	Tertile 2 (0.014–0.020, n=469)	Tertile 3 (>0.020, n=468)	P
Age, mean ± SD, years	66.20±9.37	64.62±10.53	64.49±9.66	0.013
Male gender, No. (%)	258 (55.1)	345 (73.6)	369 (78.8)	<0.001
Weight, No. (%), kg	64.14±11.73	68.01±11.18	67.81±13.03	<0.001
Heart rate, No. (%), bpm	74.52±11.14	74.41±10.92	75.67±10.89	0.153
Blood pressure, No. (%), mmHg				
Systolic	137.08±18.89	135.30±19.04	133.99±18.67	0.043
Diastolic	77.11±10.63	77.07±11.19	76.20±11.06	0.357
Heart failure, No. (%)	56 (12.0)	51 (10.9)	63 (13.5)	0.476
Medical history and risk factors, No. (%)				
Smoking	59 (12.6)	110 (23.5)	130 (27.8)	<0.001
Myocardial infarction	64 (13.7)	78 (16.6)	105 (22.4)	0.002
Percutaneous coronary intervention	108 (23.1)	111 (23.7)	103 (22.0)	0.829
Coronary artery bypass surgery	10 (2.1)	9 (1.9)	6 (1.3)	0.590
Stroke	29 (6.2)	29 (6.2)	35 (7.5)	0.658
Atrial fibrillation	7 (1.5)	17 (3.6)	22 (4.7)	0.020
Hypertension	361 (77.1)	364 (77.6)	354 (75.6)	0.757
Hyperlipemia	67 (14.3)	63 (13.4)	40 (8.5)	0.014
In-hospital medication, No. (%)				
Aspirin	452 (96.6)	459 (97.9)	455 (97.2)	0.488
P2Y12	463 (98.9)	467 (99.6)	465 (99.4)	0.493
Plataal	18 (3.8)	11 (2.3)	18 (3.8)	0.337
Dual antiplatelet therapy	449 (95.9)	457 (97.4)	452 (96.6)	0.439
Statin	455 (97.2)	460 (98.1)	462 (98.7)	0.259
Warfarin	1 (0.2)	4 (0.9)	7 (1.5)	0.103
ACE inhibitor or ARB	371 (79.3)	385 (82.1)	394 (84.2)	0.147
CCB	143 (30.6)	129 (27.5)	126 (26.9)	0.416
Nitroglycerin	239 (51.1)	232 (49.5)	259 (55.3)	0.177
Beta-blockers	380 (81.2)	394 (84.0)	400 (85.5)	0.200
Glycoprotein IIb/IIIa inhibitor	46 (9.8)	39 (8.3)	52 (11.1)	0.353
Laboratory parameters				
LVEF, mean ± SD, %	62.08±11.12	61.40±10.81	58.96±12.39	<0.001
WBC, mean ± SD, ×10 <sup>9</sup> /L	6.80±1.99	7.54±1.70	9.01±2.31	<0.001
Neutrophil, mean ± SD, ×10 <sup>9</sup> /L	4.35±1.80	4.72±1.52	5.82±2.10	<0.001
Lymphocyte, mean ± SD, ×10 <sup>9</sup> /L	1.78±0.57	1.99±0.68	2.09±0.71	<0.001
Monocyte, mean ± SD, ×10 <sup>9</sup> /L	0.43±0.12	0.59±0.11	0.83±0.23	<0.001

**Table 1** (continued)

Table 1 (continued)

Variables	Tertile 1 (<0.014, n=468)	Tertile 2 (0.014–0.020, n=469)	Tertile 3 (>0.020, n=468)	P
Hemoglobin, mean ± SD, g/L	128.58±17.30	131.14±17.33	128.88±18.88	0.056
PLT, mean ± SD, ×10 <sup>9</sup> /L	213.40±59.01	217.92±57.71	235.32±74.30	<0.001
PDW, mean ± SD, fL	15.49±2.17	15.45±2.20	15.44±2.21	0.944
TG, mean ± SD, mmol/L	2.01±2.02	1.85±1.37	1.89±1.35	0.275
TC, mean ± SD, mmol/L	4.77±1.38	4.34±1.17	4.14±1.05	<0.001
HDL-C, mean ± SD, mmol/L	1.11±0.32	0.93±0.17	0.79±0.16	<0.001
LDL-C, mean ± SD, mmol/L	2.74±0.98	2.60±0.94	2.47±0.86	<0.001
Serum creatinine, mean ± SD, μmol/L	97.12±87.65	99.74±87.39	108.21±77.52	0.110
eGFR, mean ± SD, mL/min/1.73 m <sup>2</sup>	80.45±28.42	81.53±29.51	75.18±29.81	0.002
GRACE score, mean ± SD	128.34±27.35	126.67±27.99	131.38±28.74	0.050

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; LVEF, left ventricular ejection fraction; WBC, white blood cell; PLT, platelet; PDW, platelet distribution width; TG, total triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; SD, standard deviation

well as decreased total cholesterol (TC), HDL-C, low-density lipoprotein (LDL), detected glomerular filtration rate, and left ventricular ejection fraction were more prevalent in the highest tertile group.

### Clinical outcomes

In this study, the incidence of MACE (0.2%, 0.2%, and 1.3%,  $P=0.043$ ) and any bleeding (12.4%, 12.2%, and 17.1%,  $P=0.048$ ) was increased in patients with the highest MHR tertiles. However, among the three groups, no significant difference was noted in the in-hospital all-cause deaths (0.0%, 0.0% and 0.4%,  $P=0.135$ ) and major bleeding (1.1%, 1.3% and 1.5%,  $P=0.845$ ) (Table 2). In the univariate analysis, increased MHR was associated with in-hospital MACE. Furthermore, multivariate analysis indicated that the MHR (adjusted OR: 8.36; 95% CI: 1.57–44.47;  $P=0.013$ ) was an independent predictor of in-hospital MACE, after adjusting for other variables (Table 3). The multivariate Cox proportional hazard regression model showed that the MHR (adjusted HR: 1.21; 95% CI: 1.07–1.37;  $P=0.002$ ) was an independent predictor of long-term bleeding, after adjusting for other factors (Table 4).

Receiver-operating characteristic curve analysis indicated that MHR >0.022 had a sensitivity of 75.0% and specificity of 72.7% for predicting in-hospital MACE [area under the curve (AUC) =0.722; 95% CI: 0.51–0.933;  $P=0.040$ ]

(Figure 2). Kaplan-Meier curves based on the cut-off values of MHR are shown in Figure 3. Patients with a high MHR were found to have a significantly higher long-term mortality rate (33.48% vs. 13.71%,  $P=0.003$ , Figure 3).

### Discussion

In the present study, our findings demonstrated the predictive value of MHR in T2DM patients undergoing PCI for NSTEMI-ACS. It was noted that the MHR was independently related to in-hospital MACE or long-term bleeding events. Furthermore, our study revealed that MHR >0.022 had good discrimination in predicting in-hospital MACE.

T2DM is a pro-inflammatory disease, and an enhanced inflammatory reaction at the site of implantation of stents after PCI. Compared with normal patients, DM patients have a higher incidence of composite clinical outcomes (14). Circulating monocytes, which function as a source of molecules and cytokines, lead to the activation of pro-thrombotic pathways and inflammation via interaction with platelets or endothelial cells. However, HDL-C can inhibit the migration and oxidation of macrophages and LDL molecules, respectively. Additionally, HDL-C promotes the outflow of cholesterol from these cells. HDL-C has been shown to inhibit the pro-inflammation and pro-oxidation of monocytes (15).

**Table 2** In-hospital and long-term clinical outcomes

Outcome	Tertile 1 (n=468)	Tertile 2 (n=469)	Tertile 3 (n=468)	P
In-hospital outcome, No. (%)				
MACE	1 (0.2)	1 (0.2)	6 (1.3)	0.043
Any bleeding	58 (12.4)	57 (12.2)	80 (17.1)	0.048
Major bleeding	5 (1.1)	6 (1.3)	7 (1.5)	0.845
Death	0 (0.0)	0 (0.0)	2 (0.4)	0.135
Long-term outcome, No. (%)				
30 days				
Any bleeding	58 (12.4)	58 (12.4)	81 (17.3)	0.043
Major bleeding	4 (0.9)	6 (1.3)	7 (1.5)	0.659
Death	0 (0.0)	1 (0.2)	3 (0.6)	0.173
6 months				
Any bleeding	62 (13.2)	63 (13.4)	87 (18.6)	0.035
Major bleeding	6 (1.3)	7 (1.5)	10 (2.1)	0.562
Death	3 (0.6)	2 (0.4)	10 (2.1)	0.021
1 year				
Any bleeding	70 (15.0)	68 (14.5)	104 (22.2)	0.002
Major bleeding	7 (1.5)	8 (1.7)	11 (2.4)	0.600
Death	7 (1.5)	8 (1.7)	20 (4.3)	0.010

MACE, major adverse cardiovascular event.

**Table 3** Significant predictors of in-hospital MACEs in univariate and multivariate analyses

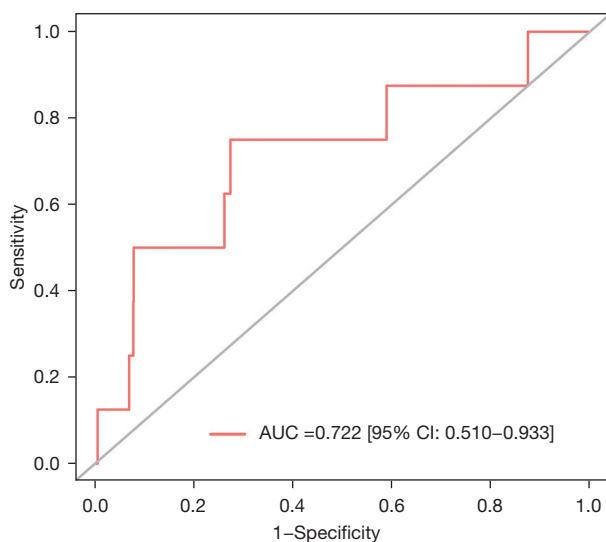
Factors	Univariate analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
MHR	7.97	1.60–39.67	0.011	8.36	1.57–44.47	0.013
CHF	4.42	1.05–18.66	0.043	4.11	0.82–20.51	0.085
Male gender	1.35	0.32–5.67	0.682	1.89	0.39–9.09	0.425
eGFR	0.99	0.97–1.02	0.484	1.00	0.98–1.03	0.937
Age	1.01	0.94–1.09	0.689	1.00	0.92–1.08	0.931
History of atrial fibrillation	4.29	0.52–35.62	0.177	2.34	0.25–22.00	0.457
History of myocardial infarction	1.57	0.31–7.81	0.583	0.97	0.17–5.41	0.971
History of stroke	2.03	0.25–16.65	0.511	2.39	0.28–20.68	0.428

MACE, major adverse cardiac event; MHR, monocyte to high-density lipoprotein cholesterol ratio; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval.

**Table 4** Significant predictors of any bleeding in univariable and multivariable Cox regression analyses

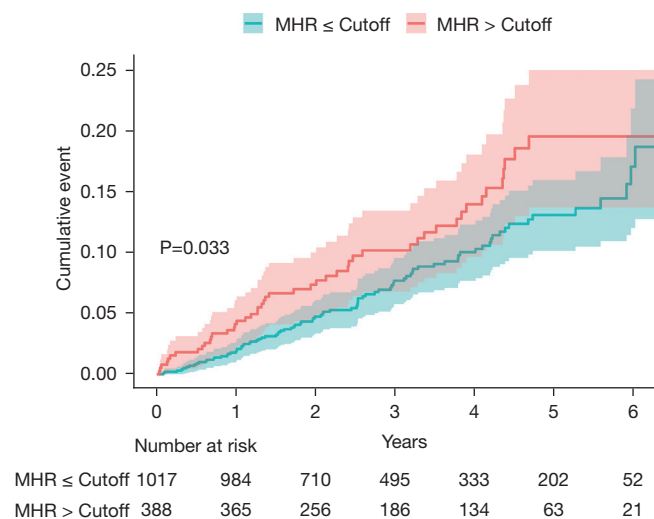
Factors	Univariate analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
MHR	1.21	1.08–1.36	0.001	1.21	1.07–1.37	0.002
CHF	1.15	0.83–1.60	0.389	0.87	0.62–1.23	0.432
Male gender	1.24	0.98–1.57	0.070	1.21	0.94–1.54	0.135
eGFR	0.99	0.99–0.99	<0.001	0.99	0.99–1.00	<0.001
Age	1.03	1.01–1.04	<0.001	1.02	1.00–1.03	0.009
History of atrial fibrillation	1.87	1.15–3.05	0.012	1.46	0.89–2.41	0.135
History of myocardial infarction	1.12	0.84–1.50	0.422	1.10	0.82–1.47	0.544
History of stroke	1.24	0.82–1.89	0.303	1.16	0.76–1.76	0.493

MHR, monocyte to high-density lipoprotein cholesterol ratio; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.



**Figure 2** ROC curves analysis showing the predictive cut-off value of MHR for in-hospital MACE. ROC, receiver-operating characteristic; MHR, monocyte to high-density lipoprotein cholesterol ratio; MACE, major adverse cardiac events.

Increased MHR is prevalent in a variety of cardiovascular conditions, which is thought to contribute to the pathogenesis and progression of these diseases. Moreover, increased MHR was also demonstrated as a powerful predictive marker for the early diagnosis of cardiovascular diseases. A previous study conducted in patients revealed that the MHR can be regarded as an independent predictor of major cardiovascular events (16). MHR was reported to be correlated with long-term mortality and in-hospital and



**Figure 3** Kaplan-Meier estimated rates of all-cause death. Cumulative rate of long-term mortality in NSTEMI-ACS patients with and without a MHR >0.022. NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; MHR, monocyte to high-density lipoprotein cholesterol ratio.

MACE in ST-Segment Elevation Myocardial Infarction (STEMI) (17). Cetin *et al.* claimed that the MHR, as a new inflammatory marker, was related to cardiovascular events in patients with ACS (18). Another previous study demonstrated that MHR plays a role in the increased recurrence of atrial fibrillation in patients undergoing cryoballoon-based catheter ablation (19). Chen *et al.* reveal that MHR is both associated with basal thickness and

progression of CIMT inpatients with T2DM, and log-transformed MHR was associated with elevated CIMT in diabetic but not non-diabetic patients (5). Although MHR is associated with multiple complications of diabetes, there was no difference with regard to MHR between patients with or without diabetic peripheral neuropathy in a study (20). MHR has also been used in the early diagnosis of acute ischemic stroke (21), contrast-induced nephropathy (22), hyperuricemia (23), and metabolic syndrome (24). Our study revealed the potential predictive value of MHR in T2DM patients undergoing PCI for NSTEMI-ACS. Our results illustrated that MHR was independently related to MACE and long-term bleeding events during hospitalization. Furthermore, MHR >0.022 was a notable predictor of in-hospital MACE and long-term death. Thus, we assumed that MHR is a predictor of abnormal lipid metabolism and inflammation status in patients with NSTEMI-ACS and T2DM. Additionally, our findings in the present study are consistent with the previous findings. The etiology of NSTEMI-ACS is complicated, and involves an inflammatory reaction, alternated lipid metabolism, oxidation injury, and other pathological processes (25-27). Some potential prognostic marker as neutrophil to high-density lipoprotein ratio (NHR), monocyte lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), and ischemia-modified albumin (IMA) have also been confirmed affect the prognosis of coronary artery disease (28-31).

In addition, it was noted that a high level of MHR was an independent risk factor of bleeding events. The precise role of high MHR in the increased bleeding risk of T2DM patients with NSTEMI-ACS is still unclear. A previous study has shown that higher monocyte counts in patients with atrial fibrillation are related to an increased risk of major bleeding. The underlying mechanism of this is excessive elevation in monocytes or abnormal function of monocytes may alter the strictly controlled local hemostasis towards a bleeding state. The ability of monocytes to produce matrix metalloproteinases may further amplify this process, thus overcoming the characteristics of procoagulant monocytes (32). Our findings support the idea that excessive monocytes may be associated with any bleeding events; however, no significant increase in major bleeding was observed in our study.

However, our study still has some limitations that should be noted. Firstly, there was no dynamic monitoring of MHR, so it was not clear whether the changes in MHR were related to the prognosis. Secondly, other oxidative

stress and inflammation markers, such as uric acid and C-reactive protein, were not compared with the MHR. To further improve the validity and predictive power of our model, the sample size should be increased as much as possible, and interference of numerous confounding factors should be eliminated through multi-factor correction. Therefore, the relationship between dynamic MHR and prognosis, and the comparison between the MHR and classical inflammatory markers should be explored in future studies.

## Conclusions

In summary, this study demonstrated that the MHR is an independent predictor of in-hospital MACE and long-term mortality in T2DM patients with NSTEMI-ACS undergoing PCI. Furthermore, it was revealed that increased levels of MHR were significantly related to bleeding events.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-4876>

*Data Sharing Statement:* Available at <https://dx.doi.org/10.21037/atm-21-4876>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-4876>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are 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 procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics



Committee of Guangdong Provincial People's Hospital of No. GDREC2016210H(R1) and informed consent was taken from all the patients.

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