Monocyte to high-density lipoprotein ratio predict long-term clinical outcomes in patients with coronary heart disease
A meta-analysis of 9 studies
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Abstract
Background: A novel inflammation-related biomarker, the monocyte to high-density lipoprotein cholesterol ratio (MHR), had a great relation to the development and prognosis of coronary atherosclerotic heart disease. Current study was to investigate whether the MHR was a potential tool in predicting the mortality and major adverse cardiac events (MACEs) in patients suffering coronary heart disease (CHD) by meta-analysis.

Methods: The Cochrane Library, PubMed, MEDLINE, Scopus, EMBASE, and Web of science were searched for relevant cohort studies published prior to February 10, 2022. The association between MHR and mortality/MACEs was analyzed in patients with CHD. Hazard ratios (HR) with 95% confidence interval (CI) were calculated to estimate the strength of association.

Results: In the meta-analysis, a total of 9 studies of 11,345 patients with CHD were included. Compared with the low level of MHR group, the high MHR value was associated with higher long-term MACEs (HR = 1.72 95% CI 1.36–2.18, \( P < .001 \)), long-term mortality (HR = 1.71, 95% CI 1.10–2.66, \( P = .017 \)), and in-hospital mortality/MACEs (HR = 2.82, 95% CI = 1.07–7.41, \( P = .036 \)).

Conclusions: This study suggested that increased MHR value might be associated with higher long-term mortality and long-term MACEs in CHD patients. MHR might serve as a potential prognostic indicator for risk stratification in patients with CHD.

Abbreviations: CAD = coronary artery disease, CHD = coronary heart disease, CI = confidence interval, HDL = High-density lipoprotein, HDL-C = HDL-cholesterol, HR = Hazard ratios, MACEs = major adverse cardiac events, MHR = monocyte to high-density lipoprotein cholesterol ratio, NOS = New Castle-Ottawa scale, PRISMA = preferred reporting items for systematic reviews and meta-analyses, STEMI = ST-segment elevation myocardial infarction.

Keywords: coronary heart disease, major adverse cardiac events, monocyte to high-density lipoprotein ratio, mortality

1. Introduction
Accumulating evidence suggests that coronary heart disease (CHD) is one of the most prevalent and chronic life-threatening disease.[1,2] Patients of CHD are frequently hospitalized and at high risk for death and major adverse cardiac events (MACEs), which would increase the medical burden.[3,4] The current dilemma for clinical physician is figuring out a simple and powerful prognostic biomarker to identify the high-risk CHD patients.[5,6]

Clinical and experimental evidences found that inflammation played a critical role in the development and progression of CHD.[7] Previous studies showed that some laboratory markers, such as white blood cells and its subtypes including monocyte, had been reported as prognostic indicators in patients with CHD.[8] Monocytes have been established as a predictor of coronary events.[9] Monocytes and their descendant macrophages were of great importance to the progression of atherosclerotic plaque.[10] Except functioning inside the arterial wall, the monocytes extended to the circulation contributed to the pathogenesis of CHD and its complications.[11]

High-density lipoprotein (HDL) represents a variety of lipoproteins and HDL-cholesterol (HDL-C) is the most widely used biomarker about HDL. Although the causal relationship

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The datasets generated during and/or analyzed during the current study are publicly available.

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between HDL and atherosclerosis was uncertain, previous studies from different racial and ethnic groups worldwide had showed that HDL-C and the risk of CHD were of negative correlation. What’s more, it was also reported that the HDL-C had a protective effect on the process of atherosclerosis.\textsuperscript{11,13}

Previous researches assessed the value of a novel biomarker, named as monocyte to HDL-C ratio (MHR), in predicting mortality and MACEs in patients with CHD.\textsuperscript{11–21} MHR has showed to be an inexpensive and convenient method for predicting the prognosis of CHD, but the outcomes were diverse. Therefore, we carried out a meta-analysis to evaluate the relationship between MHR and the risk of mortality and MACEs in CHD patients.

2. Material and Methods

2.1. Search strategy

This research was carried out according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for meta-analyses of observational studies.\textsuperscript{22} A systematic literature search for prospective cohort studies was conducted in the Cochrane Library, PubMed, MEDLINE, Scopus, EMBASE, and Web of science. The latest update was performed in February 10, 2022. We used the following terms: “coronary heart disease”, “acute coronary syndrome”, “myocardial infarction”, “monocyte to high-density lipoprotein ratio”, “monocyte count/HDL cholesterol ratio”, “monocyte to high-density lipoprotein ratio”, “monocyte/HDL ratio”. The reference list of all included articles was scrutinized to identify additional eligible studies.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (1) Prospective clinical studies with follow-up time. (2) Adults patients (over 18 years old) diagnosed as CHD, including acute coronary syndrome (ACS) and chronic coronary artery disease (CAD). (3) The outcomes were associated with mortality or MACEs. (4) peer-reviewed publications in English journals. The following 4 points were exclusion criteria: (1) Overlapping or duplicate publications. (2) Absence of available data or their corresponding 95% CI. (3) Nonhuman studies. (4) Absence of MHR or mortality/MACEs. If any of the above 4 characteristics were met, the study was excluded. If duplicate studies were from the same cohort, only the latest published study was included in our meta-analysis.

2.3. Data extraction and collection

Two investigators (Hong-Tao Liu, Zhong-Hui Jiang) independently extracted data from all of the included studies using a standardized data collection form for analysis. Disagreements were solved by discussion with other investigators (Xiao-Qing Quan, Zhong-Bin Yang). For each selected study, the following data were extracted: authors, year of publication, study region, sample size and gender of patients, the mean age, disease subtypes, duration of follow-up, HRs and 95% CIs, and end points. It should be noted that the MACEs was defined as cardiovascular death, acute left ventricular failure, ventricular arrhythmia, nonfatal myocardial infarction, cardiogenic shock and nonfatal ischemic stroke.

2.4. Quality analysis of study

The quality of each study was evaluated by the New Castle-Ottawa scale (NOS) system.\textsuperscript{23} If the score was >6, we considered the study to be of high quality.

2.5. Ethics

In this study, ethical approval was not necessary because the included data was based on previous published articles, and no original clinical data was collected or utilized.

2.6. Statistical analysis

All data analyses were performed with STATA 15.1 statistical software. For stabilizing the variances and normalizing the distributions, before pooling the data, adjusted HR from were converted to lnHR. The heterogeneity among studies was evaluated by using Cochran Q test and the I² statistic, whereby $I^2 > 50\%$, $P < .05$ indicated significant heterogeneity. The random-effects model was used to minimize inter-study heterogeneity when there was significant heterogeneity between various studies. The fixed effect model was used if there was no significant heterogeneity between studies. If not, the random effects model was used.

3. Results

3.1. Study identification and selection

The details of how the studies were selected were showed in the flow chart (Fig. 1). Initially, a total of 2302 potential articles were found in the electronic databases, of which 1715 duplicates were removed. The remaining 587 articles were reviewed in titles and abstracts, of which 549 were excluded. The remaining 38 articles were acquired for full article access. Of these, 29 articles were excluded and 9 studies were chosen for this meta-analysis.\textsuperscript{11–21} Details of study selection and the flowchart of the literature search were depicted in Figure 1.

3.2. Characteristics of included studies

The basic information of the 9 studies was shown in Table 1. A total of 11,345 patients with 8054 (70.99\%) males were included, and the mean ages of them were among 55.9–64.6 years old. All of the end points selected were analyzed by Cox proportional hazard model, and we chose the HR and 95% CI of the adjusted analyses. These studies were all observation researches and were conducted in China\textsuperscript{11,15–20} and Turkey\textsuperscript{13,14,16,21} One study included CAD patients,\textsuperscript{13} 3 studies included ST-segment elevation myocardial infarction (STEMI) patients,\textsuperscript{14,16,19} and 5 studies ACS patients.\textsuperscript{13,17,18,20,21}

3.3. Incidence of long-term mortality/MACEs

Six studies covering 9595 patients documented the relationship between MHR and long-term MACEs. Elevated MHR was associated with an increased risk of long-term MACEs in patients with CHD (HR = 1.72 95\% CI 1.36–2.18, $P < .001$, Fig. 2).\textsuperscript{11–13,15–20} Besides, the pooled result of 5 studies including 6270 patients found that the high MHR value was associated with higher long-term mortality (HR = 1.71, 95\% CI 1.10–2.66, $P = .017$, Fig. 3).\textsuperscript{13–16,21} These were 3 studies included the data of in-hospital mortality/MACEs. The meta-analysis analysis results show that compared with the low level of MHR group, the risk of in-hospital mortality/MACEs was 2.82-fold in high MHR patients (95\% CI 1.07–7.41, $P = .036$, Fig. 4).\textsuperscript{13,14,16}

3.4. Subgroup analyses

In the subgroup analysis, we grouped the studies by country, disease subtype, sample size, mean age, and follow-up. Analysis showed that the risk of long-term MACEs in high MHR group was significantly higher than patients with low MHR in population of Turkey (HR = 1.90, 95\% CI 1.27–2.85, $P = .002$)\textsuperscript{13,14} and age > 60
years (HR = 2.02, 95% CI 1.38–2.96, \( P < .001 \)).[18,20] Subgroup analysis according to sample size, and follow-up showed pooled HR estimates with similar results to that of the original analysis. Interestingly, STEMI patients (HR = 2.66, 95% CI 1.62–4.35, \( P < .001 \)) with high MHR tend to have a higher risk of developing long-term MACEs than ACS patients (HR = 1.41, 95% CI 1.15–1.73, \( P = .001 \)).[13,17,18,20] The subgroup analysis results of HR values for long-term MACEs were shown in Table 2.

### 4. Discussion

As one of the most widespread chronic diseases, CHD is associated with tremendous social and economic costs because of its high morbidity and mortality rate. Early assessment of the condition can provide better guidance for CHD patients. This was a meta-analysis drawn from 9 studies involving 11,345 patients reported that elevated MHR level was related to mortality and MACEs. The aggregated results showed that higher MHR had an increased risk of poor prognosis. MHR might be a potential biomarker of risk stratification in patients with CHD.

The present meta-analysis indicated that MHR might be a predictor for long-term MACEs and long-term mortality in patients with CHD. CHD patients with the high MHR respectively had 1.72-fold and 1.71-fold risk of long-term MACEs and long-term mortality. The exact mechanism underlying elevated\( ^{\text{a}} \)
MHR and poor clinical outcome in CHD are not fully understood. One possible explanation for these findings is that combination of monocyte and HDL-cholesterol may reflect the level of the systemic inflammation. CHD is related to atherosclerosis, which is accompanied with the infiltration of inflammatory/immunocompetent cells. It is known that inflammation has an essential role in the progression of atherosclerosis. Monocytes are pivotal immune cells and play an important role in inflammatory response and atherosclerosis development. Experimental and clinical data supports the notion that monocytes, representing the innate immune system, play a crucial role in the occurrence and development of atherosclerotic lesions. Activated by different factors, peripheral blood mononuclear cells cross the surface of endothelium and differentiate into macrophages. After that, macrophages in the arterial wall ingest oxidized low-density lipoprotein and assume a foamy appearance. Several kinds of pro-inflammatory cytokines, growth

### Long-term MACEs

| Study (year) | HR (95% CI) | Weight % |
|--------------|-------------|----------|
| Cetin MS (2016) | 1.30 (1.12, 1.52) | 24.63 |
| Zhang Y (2016) | 2.19 (1.39, 3.44) | 13.82 |
| Karata (2016) | 2.81 (1.48, 5.32) | 9.23 |
| Hu (2018) | 2.45 (1.13, 5.32) | 7.04 |
| Mao (2019) | 2.19 (1.08, 4.47) | 7.99 |
| Wu T (2019) | 2.39 (1.38, 4.14) | 11.17 |
| Chen (2021) | 1.21 (1.07, 1.37) | 25.62 |
| Overall, DL ($I^2 = 71.2\%, p = 0.002$) | 1.72 (1.36, 2.18) | 100.00 |

**Figure 2.** Pooled risk of MHR and long-term MACEs of the included studies. MACEs = major adverse cardiac events, MHR = monocyte to high-density lipoprotein ratio.

### Long-term mortality

| Study (year) | HR (95% CI) | Weight % |
|--------------|-------------|----------|
| Ackguz S (2016) | 2.05 (1.23, 4.09) | 20.04 |
| Cetin M (2016) | 1.53 (1.20, 1.96) | 30.88 |
| Karata M (2016) | 19.20 (2.26, 161.80) | 3.80 |
| Wu T (2019) | 3.65 (1.17, 11.42) | 10.43 |
| Oylumlu M (2020) | 1.03 (1.01, 1.04) | 34.08 |
| Overall, DL ($I^2 = 85.3\%, p = 0.000$) | 1.71 (1.10, 2.66) | 100.00 |

**Figure 3.** Pooled risk of MHR and long-term mortality of the included studies. MHR = monocyte to high-density lipoprotein ratio.

### In-hospital MACEs/mortality

| Study (year) | HR (95% CI) | Weight % |
|--------------|-------------|----------|
| Cetin MS (2016) | 1.41 (1.14, 1.73) | 44.89 |
| Ackguz (2016) | 3.74 (1.31, 5.65) | 35.77 |
| Chen (2021) | 8.36 (1.57, 44.47) | 19.34 |
| Overall, DL ($I^2 = 79.9\%, p = 0.007$) | 2.82 (1.07, 7.41) | 100.00 |

**Figure 4.** Pooled risk of MHR and in-hospital mortality/MACEs of the included studies. MACEs = major adverse cardiac events, MHR = monocyte to high-density lipoprotein.
Table 2
The subgroup analysis of the association of MHR and long-term MACEs for CHD patients.

| Subgroup               | Study (no.) | F(%) | P(F) | HR     | P(HR) |
|------------------------|-------------|------|------|--------|-------|
| Country                |             |      |      |        |       |
| China[15, 17–20]       | 5           | 80.9 | 0.022| 1.79   | 0.85–3.76| 0.123 |
| Turkey[13, 14]         | 2           | 74.2 | 0.004| 1.90   | 1.27–2.85| 0.002 |
| Disease subtype        |             |      |      |        |       |
| ACS[13, 17, 18, 20]    | 4           | 66.3 | 0.039| 1.41   | 1.15–1.73| 0.001 |
| STEMI[8, 19]           | 2           | 0.0  | 0.789| 2.66   | 1.62–4.35| <0.001 |
| CAD[7]                 | 1 NA        | NA   | NA   | 2.39   | 1.38–4.14| 0.046 |
| Sample size            |             |      |      |        |       |
| > 1000[13, 17, 18]    | 3           | 67.8 | 0.045| 1.36   | 1.11–1.65| 0.002 |
| ≤ 1000[14, 15, 19, 20]| 4           | 0.0  | 0.964| 2.46   | 1.77–3.41| <0.001 |
| Mean Age               |             |      |      |        |       |
| > 60 years[13–15, 17, 18] | 2   | 71.3 | 0.007| 2.02   | 1.38–2.96| <0.001 |
| ≤ 60 years[13–15, 17, 18] | 5  | 61.6 | 0.107| 1.46   | 0.85–2.51| 0.169 |
| Follow-up              |             |      |      |        |       |
| > 12 months[13, 17, 18]| 3           | 75.5 | 0.017| 1.79   | 1.15–2.78| 0.009 |
| ≤ 12 months[14, 18–20]| 4           | 73.9 | 0.009| 1.21   | 1.07–1.37| 0.013 |

CHD = coronary heart disease, CI = confidence interval, HR = hazard ratio, MACEs = major adverse cardiac events, MHR = monocyte to high-density lipoprotein cholesterol ratio.

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Author contributions
Hong-Tao Liu and Zhong-Hui Jiang: Design of the study, acquisition and interpretation of data, manuscript preparation and the initial draft, accountable for all aspects of the work. Zhong-Hui Jiang and Zhong-Bin Yang: statistical analysis, analysis and interpretation of data, accountable for all aspects of the work. Xiao-Qing Quan and Hong-Tao Liu: Design of the study, critical review of the draft and contribution to the writing of the manuscript, final approval of the version to be published, and accountable to the accuracy or integrity of the work.

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