Novel Risk Biomarker for Infective Endocarditis Patients With Normal Left Ventricular Ejection Fraction — Monocyte to High-Density Lipoprotein Cholesterol Ratio —

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Background: The monocyte to high-density lipoprotein cholesterol ratio (MHR) appears to be a newly emerging inflammatory marker. However, its prognostic value in patients with infective endocarditis (IE) and normal left ventricular ejection fraction (LVEF) has been unclear.

Methods and Results: We enrolled consecutive patients with IE and normal LVEF and divided into 3 groups based on the tertiles of MHR. Of 698 included patients, 44 (6.3%) died while in hospital. The occurrence of in-hospital death (3.9%, 4.3%, and 10.8%, P=0.003) and of major adverse clinical events (MACEs) (15.6%, 20.9%, and 30.6%, P<0.001) increased from the lowest to the highest MHR tertiles, respectively. Receiver-operating characteristic analysis demonstrated that MHR had good predictive value for in-hospital death (area under the curve [AUC] 0.670, 95% confidence interval [CI] 0.58–0.76, P<0.001) and was similar to C-reactive protein (AUC 0.670 vs. 0.702, P=0.444). Furthermore, MHR >21.3 had a sensitivity of 74.4% and specificity of 57.6% for predicting in-hospital death. Multiple analysis showed that MHR >21.3 was an independent predictor of both in-hospital (odds ratio 3.98, 95% CI 1.91–8.30, P<0.001) and long-term death (hazard ratio 2.29, 95% CI 1.44–3.64, P<0.001) after adjusting for age, female, diabetes mellitus, estimated glomerular filtration rate <90 mL/min/1.73 m², and surgical treatment. Kaplan-Meier survival curves showed that patients with MHR >21.3 had an increased rate of long-term death compared to those without (P<0.002).

Conclusions: Elevated MHR was independently associated with in-hospital and long-term death in patients with IE and normal LVEF.

Key Words: High-density lipoprotein; Infective endocarditis; Monocytes; Outcomes

Despite earlier diagnosis and more intensive therapeutic approaches, the mortality rate for infective endocarditis (IE) remains high and is approximately 10% at initial admission and reaches approximately 20% in the first year. Early and quick identification of patients at high risk of poor outcome is necessary and urgent in order to make accurate clinical decisions for improving patient prognosis.

Monocyte activation plays an important role in chronic inflammation and cardiovascular disease (e.g., heart failure and atherosclerosis). Monocytes and macrophages are essential components in innate immunity and can modulate the secretion of inflammatory cytokines, which play an important role in IE development. In addition, high-density lipoprotein cholesterol (HDL-C) has been proven to exert anti-inflammatory, antioxidant, and antithrombotic effects. Low levels of HDL-C also increase the risk of poor prognosis for IE patients. Therefore, monocytes exert a proinflammatory and pro-oxidant effect, but HDL-C functions as a reversal factor. The monocyte to HDL-C ratio (MHR), which combines 2 opposite processes, would be helpful to identify IE patients at high risk of poor outcome. However, to the best of our knowledge, no study has evaluated...
the prognostic role of MHR in IE patients.

In addition, reduced left ventricular ejection fraction (LVEF) is an important prognostic factor for IE patients. However, most IE patients have a normal LVEF and evaluating such patients for poor outcomes would be helpful for clinicians. Nevertheless, few studies have investigated this issue. The present study aimed to evaluate the predictive value of MHR for the clinical outcomes of IE patients with normal LVEF.

Methods

Patient Enrolment and Data Collection

Between January 2009 and July 2015, patients at Guangdong General Hospital with a definite IE diagnosis according to the modified Duke criteria were enrolled. Patients with autoimmune or hematological diseases other than anemia, chronic liver disease, or those who had received lipid-lowering therapy before admission were excluded. Furthermore, we also excluded patients who did not have serum hematological and biochemical indices that included monocyte and HDL-C values on admission. Of 1,293 patients with IE, 228 were <18 years or had multiple hospital admissions. For 280 patients, either admission blood tests or lipid levels were not measured before surgery, and 2 patients were excluded, and only 46 patients had LVEF <50%. We also excluded 10 patients with estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m². Thus, 698 patients comprised the final enrolment (Figure 1). The current study was approved by the Ethical Committee of Guangdong General Hospital and written informed consent was given by each patient before the procedure.

Patients’ demographic, clinical, laboratory, and echocardiographic data were collected from electronic case report forms and then randomly checked by another researcher. All participants underwent transthoracic M-mode and 2D and Doppler ultrasound echocardiography within 24h of admission. LVEF was acquired by the biplane Simpson’s method. At least 3 different venipuncture sites were used for blood sampling. Blood culture results obtained before admission were accepted. Blood parameters and other variables such as renal and liver function, creatine kinase MB, and electrolyte levels were measured at hospital admission. HDL-C and other standard clinical parameters were measured on the morning of the first day after admission. HDL was measured by catalase assay using an automatic biochemical analyzing system (UniCel DxC 800 Synchron, Beckman Coulter, Brea, CA, USA) and monocytes by impedance method using an automated blood cell counter (XE-5000, Sysmex, Japan). MHR was calculated by monocyte counts (*10⁶/L)/HDL-C (mg/dL).

Follow-up and Endpoints

The primary endpoint was in-hospital death, and the secondary endpoints were major adverse in-hospital clinical events (MACEs) and long-term all-cause death. MACEs were composite endpoints including renal dialysis, embolic events, acute heart failure, or death during hospitalization. Each patient was followed for at least half of a year via telephone interviews. Long-term mortality was defined as all-cause death after IE diagnosis.

Statistical Analysis

Continuous data are presented as mean±SD and compared by variance analysis when the data were normally distributed; otherwise data were compared by the Wilcoxon rank-sum test and shown as median and interquartile range. Categorical data are presented as a percentage and compared by χ² or Fisher’s exact test. Variables with P value less than 0.05 in the univariate logistic regression analysis were included in the multivariable analysis. Factors of clinical importance based on previous study were also included. The thresholds were analyzed by a receiver-operating characteristic (ROC) curve. Areas under the curve (AUC) were compared using z statistics. Statistical analyses were performed using SPSS® software version 19.0 (SPSS Inc., Chicago, IL, USA). A value of P<0.05 was considered significant.

Results

Baseline Clinical Characteristics

Of the 698 patients (70.1% men; age 45±15 years) included in this study, 44 (6.3%) died, 55 (7.9%) suffered acute heart failure, 32 (4.6%) underwent renal dialysis, and 86 (12.3%) had embolic events during hospitalization. Patients were divided into 3 groups according to the tertiles of MHR: (1) Tertile 1 (<14.7); (2) Tertile 2 (14.7–25.2) and (3) Tertile 3 (>25.2) (Table 1). Patients with higher MHR were more likely to be male and have a history of IE. The rate of coronary artery disease was not significantly different among the different tertiles of MHR. Higher white blood cell (WBC), neutrophil and monocyte counts, C-reactive protein (CRP), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels; and erythrocyte
A ROC curve analysis demonstrated that MHR >21.3 had a sensitivity of 74.4% and specificity of 57.6% for predicting in-hospital death (AUC 0.670, 95% confidence interval [CI] 0.58–0.76, P<0.001). Compared with CRP and WBC, MHR had a similar predictive value for in-hospital death (AUC: 0.670 vs. 0.702, P=0.444 and 0.670 vs. 0.637, P=0.488, respectively, Figure 2). Univariate logistic regression analysis showed that MHR >21.3, age, diabetes mellitus, eGFR <90 mL/min/1.73 m², surgical treatment, lgCRP, WBC, neutrophil, lymphocyte and monocyte counts, TC, LDL-C, HDL-C and Staphylococcus infection were associated with in-hospital death. Multiple logistic regression analysis showed that MHR >21.3 independently predicted in-hospital death (odds ratio [OR] 3.98, 95% CI 1.91–8.30, P<0.001; Table 2, Model 1) after adjusting for age, female sex, diabetes mellitus, eGFR <90 mL/min/1.73 m², and surgie-
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Similar results were seen even after additionally adjusting for *Staphylococcus* infection, and neutrophil and lymphocyte counts (Table 2, Model 2); IgCRP and WBC (Table 2, Model 3); or TC and LDL-C (Table 2, Model 4). In addition, when we performed the adjusted models including model 1 plus monocyte count or HDL-C concentration, MHR remained an independent value for in-hospital death (OR 3.58, 95% CI 1.58–8.11, P=0.002; OR 2.55, 95% CI 1.03–6.28, P=0.042, respectively).

After a median 28.8-month period post-diagnosis of IE, 80 (11.5%) patients had died. Additionally, 82 (11.7%) subjects were lost to follow-up. Results of multivariate Cox regression analysis showed that MHR >21.3 was an independent predictor of long-term death (hazard ratio 2.29, 95% CI 1.44–3.64, P<0.001, Figure 3) after adjusting for age, female sex, diabetes mellitus, eGFR <90 mL/min/1.73 m², and surgical treatment. Kaplan-Meier survival curves revealed that patients with MHR >21.3 had an increased long-term mortality rate compared with those with MHR ≤21.3 (17.5% vs. 9.2%, log-rank test 9.91, P=0.002) (Figure 4).

**Discussion**

The present study demonstrated the possible predictive value of MHR in IE patients. The results demonstrated that MHR was independently associated with in-hospital death. Similar results were seen even after additionally adjusting for *Staphylococcus* infection, and neutrophil and lymphocyte counts (Table 2, Model 2); IgCRP and WBC (Table 2, Model 3); or TC and LDL-C (Table 2, Model 4). In addition, when we performed the adjusted models including model 1 plus monocyte count or HDL-C concentration, MHR remained an independent value for in-hospital death (OR 3.58, 95% CI 1.58–8.11, P=0.002; OR 2.55, 95% CI 1.03–6.28, P=0.042, respectively).

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**Table 2. Multivariable Logistic Regression Analysis for In-Hospital Death of Infective Endocarditis Patients**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Model 1</td>
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<td></td>
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<tr>
<td>MHR &gt;21.3</td>
<td>3.98</td>
<td>1.91, 8.30</td>
<td>&lt;0.001</td>
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<tr>
<td>Model 2</td>
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<tr>
<td>MHR &gt;21.3</td>
<td>3.42</td>
<td>1.59, 7.33</td>
<td>0.002</td>
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<td>Model 3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MHR &gt;21.3</td>
<td>3.00</td>
<td>1.27, 7.07</td>
<td>0.012</td>
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<tr>
<td>Model 4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MHR &gt;21.3</td>
<td>3.40</td>
<td>1.58, 7.34</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Model 1 adjusted for age, female sex, diabetes mellitus, eGFR <90 mL/min/1.73 m², and surgical treatment. Model 2 adjusted for model 1 plus *Staphylococcus* infection, neutrophil and lymphocyte counts. Model 3 adjusted for model 1 plus IgCRP, WBC. Model 4 adjusted for model 1 plus TC and LDL-C. CI, confidence interval; MHR, monocyte to high-density lipoprotein cholesterol ratio; OR, odds ratio. Other abbreviations as in Table 1.

**Figure 2.** Receiver-operating characteristic (ROC) curves for predictive ability of monocyte to high-density lipoprotein cholesterol ratio (MHR), C-reactive protein (CRP) and white blood cell count (WBC) for in-hospital death of patients with infective endocarditis.

**Figure 3.** Multivariate Cox proportional hazard analysis for long-term death after diagnosis of infective endocarditis (IE). eGFR, estimated glomerular filtration rate; MHR, monocyte to high-density lipoprotein cholesterol ratio.

**Figure 4.** Cumulative rate of long-term mortality in infective endocarditis patients with and without a monocyte to high-density lipoprotein cholesterol ratio (MHR) >21.3.
or long-term death. Furthermore, MHR >21.3 was a significantly good predictor of in-hospital or long-term death. Many factors associated with mortality and morbidity risk have been identified and used for risk stratification in IE patients. For example, baseline CRP levels have been shown to be associated with short-term and 1-year mortality. Heiro et al reported that normalization of CRP and WBC was a good predictor of a favorable IE outcome. However, the in-hospital and long-term follow-up mortality rates of IE remain high. Therefore, it is urgent and important to find a new and exact biomarker to identify patients at high risk of a poor outcome.

MHR, as a newly emerging inflammatory marker, has been associated with adverse outcomes in various clinical conditions. Kanbay et al indicated that MHR was an independent predictor of major cardiovascular events in chronic kidney disease patients. Canpolat et al also reported that increased MHR was associated with an increased recurrence of atrial fibrillation after cryoballoon-based catheter ablation and was independently related to the existence of slow flow and systemic inflammation. Subsequently, Karataş et al performed a study in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention and found that the MHR at admission correlated with in-hospital MACES and death after the procedure. MHR has also been used in the field of contrast-induced nephropathy and coronary artery ectasia. However, to the best of our knowledge, the relationship between MHR and prognosis in IE patients remains unclear.

The current study showed that elevated MHR was independently associated with in-hospital and long-term death. In addition, MHR >21.3 had a sensitivity of 74.4% and specificity of 57.6% for predicting in-hospital death. MHR had a linear correlation with CRP and WBC, which proved its effective value in predicting systemic inflammation. Although the pathophysiological mechanism(s) of high MHR levels and poor outcomes in IE patients remain unclear, multiple important mechanisms may be involved. Monocytes and macrophages play an essential role in the immune system. At the site of inflammation, monocytes are activated and then migrate to the vascular wall and damaged endothelial tissue, which induces the secretion of proinflammatory and pro-oxidant cytokines. In addition, macrophages transform to promote inflammation.

HDL-C has anti-inflammatory, antioxidant, and anti-thrombotic effects, which decrease in infectious states. Previous studies have demonstrated an inverse relationship between HDL-C levels and sepsis severity. Low HDL-C levels have been related to an increase in adverse clinical events. Recent studies have also reported that decreased HDL-C may result in worse prognosis in left-sided IE. It has been speculated that a high level of proinflammatory cytokines suppresses lipoprotein production, which is the reason for low HDL-C levels during infection. Importantly, IE is an inflammatory entity, which is characterized by elevation of multiple inflammatory markers such as CRP, WBC, and the neutrophil to lymphocyte ratio. These mechanisms encouraged us to combine monocytes and HDL-C into a new index for patients with IE. The MHR combines 2 opposite processes, pro-inflammatory and anti-inflammatory, and appears to be a suitable and novel biomarker for IE patients. It may be helpful for identifying a high risk of poor outcome among IE patients in future studies or clinical practice.

Clinical Implications

Although there are multiple risk predictors for evaluating the clinical outcomes of IE patients, MHR, by combining 2 detrimental processes, may be a novel biomarker for IE patients. In addition, MHR is an easily available and relatively cheap test and accurate for identifying IE patients at high risk of poor outcomes. Therefore, patients with high MHR could be managed with early, additional specific management (e.g., surgical treatment and antibiotic adjustment).

Study Limitations

First, this study was a retrospective analysis based on prospectively collected data, and the number of enrolled patients was relatively low and all from a single center. Second, our study only included IE patients with relatively normal LVEF, and the conclusions cannot be used for IE patients with decreased LVEF. However, the incidence of such patients was low. Third, MHR was not dynamically monitored, so it is unknown whether analyte changes are associated with prognosis. Future randomized trials are warranted to investigate whether decreasing the MHR below the cutoff point as indicated in our study would lead to a better outcome.

Conclusions

The present study showed that in patients with IE and normal LVEF, an elevated MHR was independently associated with in-hospital and long-term death. MHR may be another useful screening tool for identifying IE patients with a high risk of poor outcome who may need additional therapeutic measures.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References


