The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4124-4129

Predictive Value of Monocyte/ HDL-Cholesterol Ratio for Coronary Artery Disease Severity in Patients Presenting with Non-ST Elevation Acute Coronary Syndrome

Islam Ghanem*, Ayman Tantawy, Ahmed Shaker
Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Islam Ghanem Ahmed Ghanem, **Mobile:** (+20) 01062829880,
E-Mail: dr.islam_2010@yahoo.com, **ORCID ID:** 0000-0001-5512-2978

ABSTRACT

Background: Despite the fact that the monocyte count/HDL-C ratio (MHR) has been studied extensively in patients with chronic kidney disease as an independent predictor of both fatal and composite cardiovascular events. Only a few studies have looked at the MHR in patients with non-ST elevation acute coronary syndrome (NST-ACS).

Objective: Using the SYNTAX score (SX score) in patients with non-NST-ACS, we will undertake this study to examine MHR as an independent predictor of the complexity and severity of coronary atherosclerosis.

Subjects and methods: This study was a cohort analytical retrospective study conducted on 156 patients presented with NST-ACS admitted for coronary angiography, collected from Zagazig Catheterization Laboratory Database. All patients had the following: Cardiac enzymes, complete blood count, lipid profile and serum creatinine. The SX score was determined with baseline coronary angiography

Results: Patients were divided into two groups based on their Syntax score: Group 1 (score < 23) and group 2 (Score > 23). There was significant positive correlation between monocyte/HDL-C ratio and SYNTAX score (p=0.001) with correlation coefficient 0.768. Receiver operating characteristic (ROC) curve showed that the best cutoff value for monocyte/HDL-C ratio for prediction of the severity of coronary artery disease assessed by SYNTAX score in the studied population was 22.25 with area under the curve (AUC): 0.975, sensitivity of 95% and specificity of 75%, (p value 0.0001). In-hospital non-fatal MI was higher among patients with high MHR (P: 0.029), but no statistically significant difference between both groups of MHR regarding in-hospital, 3 months CV mortality and 3 months non-fatal MI was revealed.

Conclusion: MHR as a novel inflammatory marker is indicated to be an independent predictor of severity of coronary artery disease among patients presenting with NST-ACS.

Keywords: MHR, NST-ACS, SYNTAX score.

INTRODUCTION

Innate immunity, which swiftly and effectively begins defence against pathogens, is mostly influenced by monocytes. In atherosclerotic plaques, these cells play a key role in the inflammatory process. In the initial phase of acute myocardial infarction (AMI), plaque growth has been associated with an increase in monocyte count [1], and monocytosis has been recognised as a distinct marker for both coronary artery disease (CAD) and AMI [2].

Although it has been demonstrated that a high monocyte count in healthy, middle-aged males might predict coronary events, a greater monocyte count may also hasten the onset of atherosclerosis [3]. It has been shown that large amounts of low density lipoprotein (LDL) that contains triglycerides and cholesterol encourage primary human monocyte adhesion to artery endothelial cells [4].

Atherogenesis is the process through which monocytes enter the subendothelial region, take up lipoproteins, and develop into macrophages or foam cells. The formation of atherosclerotic lesions depends on monocytes' capacity to move through the endothelium. The results demonstrate that circulating monocytes behave differently under conditions of elevated blood cholesterol, and it appears that monocytes move significantly better under hypercholesterolemic settings [5].

Several investigations [6, 7] have revealed the protective function of serum HDL cholesterol (HDL-C) levels in the general population. The HDL molecule's function in reverse cholesterol transport has been primarily identified as the cause of its anti-atherosclerotic capabilities. In individuals with chronic renal disease, a recent study showed that both fatal and composite cardiovascular events may be accurately predicted by the monocyte count/HDL-C ratio (MHR)[8].

Finding a correlation between MHR value and coronary atherosclerosis severity as measured by SYNTAX score in patients with ACS and follow-up after three months for significant adverse cardiac events was the goal of the study.

PATIENTS AND METHODS

This Cohort analytical retrospective study had been conducted in Cardiology Department; Zagazig University during the period from April 2022 to December 2022. The study included 156 patients suffering from NST-ACS admitted to Cath. Lab. for coronary angiography.

Inclusion criteria: All patients with NST-ACS and admitted to Zagazig University Catheterization Laboratory for coronary angiography and possible revascularization from April 2022 to December 2022.

Received: 02/11/2022
Accepted: 04/01/2023

Exclusion criteria: 1) An intolerance to contrast. 2) Factors that are well-known to affect inflammatory and immunological indicators.

All patients underwent the following:

1- A thorough medical history should be taken, taking into account factors such as age, sex, smoking, hypertension, dyslipidemia, family history, diabetes mellitus, and any other conditions that may be present.

2- Complete clinical examination and cardiac evaluation: peripheral pulse, heart rate, blood pressure, and cardiac auscultation.

3- Electrocardiogram (ECG): Each patient was given a 12-lead surface ECG at arrival.

4- Laboratory experimentation at the time of admission, peripheral venous blood samples were taken from the patients. Complete blood counts were measured using an automated blood cell counter (Beckman Coulter analyzer, California, USA) (monocyte count). Lipid profile utilising the Cobas Integra equipment and spectrophotometry method: HDL-C, LDL-C, Triglycerides, and Total Cholesterol. Moreover, cardiac enzymes were gathered. The same sample was used to assess serum creatinine as well. The MHR was estimated using the ratio of monocytes to HDL-C levels, both of which were measured during the first blood sample.

5- Coronary angiography: With the use of baseline coronary angiography, the SXscore was calculated.

Informed consent:

The study was authorised by the Zagazig University Faculty of Medicine's Research Ethical Committee after receiving signed informed permission from each participant (ZU-IRB#10532/19-3-2023). The Declaration of Helsinki, the International Medical Association's code of ethics for research involving human people, served as the guide for the study's conduct.

Statistical Analysis

Using SPSS version 24, all data were gathered, processed, and statistically examined. The Kolmogorov-Smirnov test was used to examine the normality of the data distribution. The mean and standard deviation were used to show numerical data having a normal distribution, whereas the median and interquartile range were used to display variables lacking a normal distribution. For categorical variables, frequencies (number of cases) and relative frequencies (percentages) were determined. The sensitivity and specificity of MHR as well as the ideal cutoff value for foretelling a high SX score were displayed using the ROC curve. Unpaired t-tests were used to compare two groups when comparing quantitative variables with normally distributed data and non-parametric Mann-Whitney tests were employed when comparing quantitative variables with non-normally distributed data. To compare categorical data, a Chi square (X2) test analysis was used. An exact test was used in its stead when the expected frequency was less than 5. Quantitative data correlations were found using the Spearman correlation coefficient. In order to uncover independent predictors of high syntax score, components with an uncorrected p-value of 0.10 were recognised as prospective risk markers and included in the complete model of multivariate logistic regression investigation. $P \leq 0.05$ were regarded as significant in statistics.

RESULTS

Regarding demographic data this study included 156 patients, mean age was 58.94 ± 7.9 year, 108 patients were males (69.2%), 48 patients were females (30.8%), 29 patients were hypertensive (55.8%) and 60 patients were diabetic (38.4%). Regarding lab tests of the studied population mean neutrophil count was 6.10 ± 4.40 (×103/µl), mean monocyte count was 0.61± 0.13mg /dl (×103/µl), mean HDL c was 41.66 ± 9.25 mg/dl , mean LDL c was 103.35 ± 24.13 mg/dl and mean creatinine was 1.02 ± 0.26 mg/dl . While, mean monocyte/HDL-C ratio was 33.16 ± 7.54 (Table 1).

Table (1): Laboratory data of the studied population

Laboratory data	(N=156) Mean ± SD
Neutrophil count (×10^3/µl)	6.10± 1.40
Monocyte count(×10^3/µl)	0.61± 0.13
HDL (mg/dl)	41.66± 9.25
LDL (mg/dl)	103.35± 24.13
Creatinine (mg/dl)	1.02± 0.26
MHR	33.16± 7.54

Regarding SYNTAX score of the studied population: Syntax score of 120 patients was < 23 (76.9%) and 36 patients had syntax score > 23 (23.1%).

Table (2) SYNTAX score of the studied population

		Count	%
SYNTAX	<23	120	76.9%
	>=23	36	23.1%

There was significant positive correlation between monocyte/HDL-C ratio and SYNTAX score (p=0.001) with correlation coefficient 0.768, as shown in figure (1).

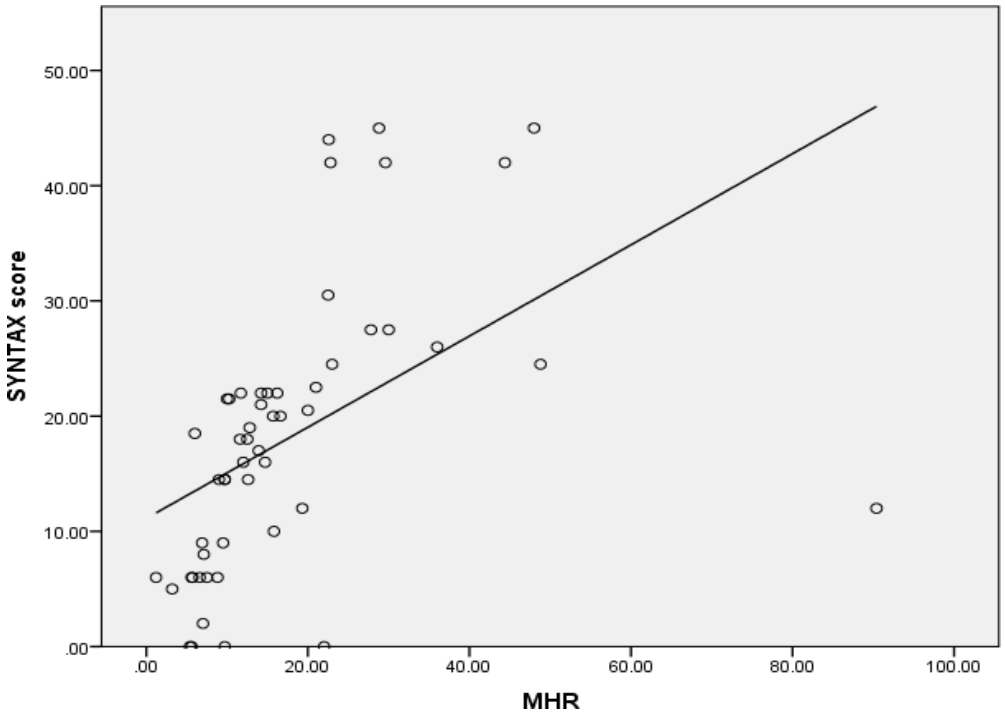

Figure (1): Correlation between MHR and SYNTAX score

As shown in figure (2), ROC curve showed that the best cutoff value for monocyte/HDL-C ratio for prediction of the severity of CAD assessed by syntax score in the studied population was 22.25 with area under the curve (AUC): 0.975, sensitivity of 95% and specificity of 75%, (p value 0.0001).

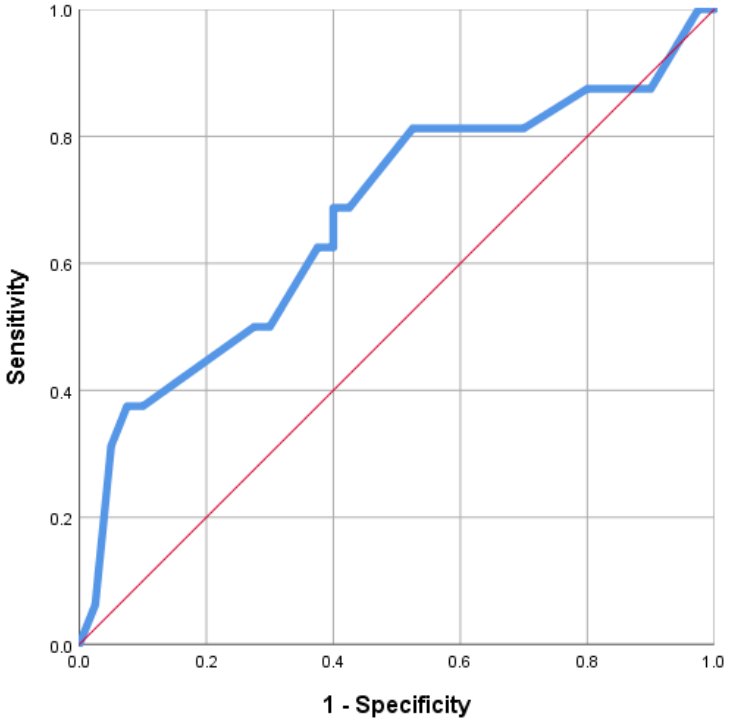

Figure (2): Receiver operating characteristic curve for the optimal cut-off value of monocyte/HDL C ratio (MHR) and it is correlation with syntax score in the studied population

We have 117 patients (75%) with a low MHR (as per cut-off value detected previously) and 39 patients (25%) with a high MHR. In hospital non-fatal MI was significantly higher in patients with the higher MHR (12 patients (30.8%) with an MHR > 22.25 compared to 6 patients with MHR < 22.25) (P: 0.029), but no statistically significant difference between both groups of MHR regarding in-hospital, 3 months CV mortality and 3 months non-fatal MI was revealed.

Table (3): Compares MACE (major cardiovascular events) both in hospital and in 3months follow-up according to MHR cutoff value

		MHR				P value
		<22.25 (N=117)		≥22.25 (N= 39)		
		Count	%	Count	%	
In hospital non-fatal myocardial infarction	**Yes**	6	5.1%	12	30.8%	**0.029**
	No	111	94.9%	27	69.2%	
In-hospital CV mortality	**No**	117	100.0%	39	100.0%	---
3months CV mortality	**No**	117	100.0%	39	100.0%	---
3 months Non-fatal myocardial infarction	**Yes**	30	25.6%	21	53.8%	0.089
	No	87	74.4%	18	46.2%	

DISCUSSION

Inflammatory and pro-thrombotic pathways are aggravated by a number of cytokines and chemicals generated by circulating monocytes, which typically interact with platelets and endothelial cells [9]. On the other hand, HDL-C blocks macrophage recruitment, oxidises LDL, and boosts cholesterol outflow to offset the pro-inflammatory and pro-oxidant actions of monocytes [10].

HDL-C particles have recently been associated with a suppressive effect in restricting monocyte activation and the proliferation-differentiation of monocyte progenitor cells, in addition to their well-known anti-inflammatory and antioxidant capabilities [11]. Thus, clinically significant risk stratification for potential cardiovascular events in CAD patients.

The goal of the study was to determine if the monocyte/HDL-C ratio (MHR) and the degree of coronary atherosclerosis are related in ACS patients who experienced a major adverse cardiac event and were under three months of observation (MACE).

In the current investigation, we discovered that MHR was a reliable predictor of more complicated coronary artery lesions in individuals with acute coronary syndrome (SXscore 23). The SXscore is a coronary angiography-based anatomical rating system. It measures the complexity and severity of the lesion and forecasts poor cardiovascular outcomes, including death, in CAD patients [12]. Increased levels of inflammatory mediators or indicators indicate the prevalence of atherosclerotic cardiovascular disease in the general population [14], which has been related to the development of atherosclerosis and future cardiovascular disease [13].

One of the main cell types for the production of atherosclerotic plaques are monocytes that have undergone transformation into circulating macrophages. As a result, circulating monocyte counts have drawn interest in elucidating the pathophysiology of atherosclerosis. Monocyte activation is a crucial step in the early stages of atherosclerosis. During the formation of atherosclerotic plaques, blood monocytes are pushed into the intima where they suck up oxidised LDL-C and other lipids before differentiating into foam cells. The circulating monocyte count, which is the source of tissue macrophages and foam cells, was found to be able to predict the development of new plaques [15]. **Bath *et al.*** [5] comparison of the migratory properties of monocytes generated from hypercholesterolemic patients with those from healthy individuals revealed that the hypercholesterolemic patients' monocytes migrated far more effectively.

HDL-C molecules prevent macrophage migration and eliminate cholesterol from those cells [16]. The monocyte chemotaxis experiment uses the HDL-C inflammatory index in the presence or absence of HDL to assess HDL-capacity C's to diminish LDL oxidation and monocyte chemoattractant protein 1 expression [17]. Moreover, the HDL-C molecule has the ability to inhibit active monocytes and stop them from activation and spreading [18].

In light of this, we hypothesise that MHR may be more accurate than individual monocyte counts or HDL-C levels, and that a greater MHR may be a predictor for the development and progression of atherosclerosis and, consequently, of cardiovascular events. Just a few studies have examined the relationship between it and cardiovascular problems. Significant cardiovascular events during follow-up in people with chronic renal illness were independently predicted by increased MHR and were associated with a worse cardiovascular profile, according to **Kanbay *et al.*** [19]**.**

MHR significantly and independently correlates with the existence of slow coronary flow, and it is a predictor of atrial fibrillation recurrence after cryoballoon-based catheter ablation, according to **Canpolat *et al.*** [20]**.** In a recent study [21], it was discovered that the presence and severity of isolated coronary artery ectasia were highly and independently linked with MHR. Its utility in predicting the complexity and severity of coronary atherosclerosis in people with acute coronary syndrome has not yet been studied. Those with stable CAD had a statistically

significant correlation between MHR and SX scores in the current study. Patients with high SX scores had significantly higher MHR (p 0.001), and a high SX score could be predicted with 100% sensitivity and 75% specificity using an MHR threshold value of 22.25 at admission (area under the curve: 0.975, p 0.001). In addition to being closely related to SX score. MHR, a recently discovered marker of inflammation, can be used to predict the degree of coronary atherosclerosis in people with acute coronary syndrome. Inflammation and oxidative stress, which are linked, have been recognised as the main elements of the pathophysiology of atherosclerosis. Pro-inflammatory and pro-oxidant states at baseline have been demonstrated to be important predictors of worse clinical outcomes in ACS. Monocytes and differentiated macrophages can govern the inflammatory response not only inside the arterial wall but also in the circulation, where monocyte activation is involved in the inflammatory process and cardiovascular disease [22, 23].

Circulating monocytes, a significant source of many proinflammatory and prooxidant chemicals, interact with platelets and endothelial cells to promote inflammation, thrombosis, and endothelial dysfunction[24].

The stent implantation procedure dramatically boosted the expression of monocyte tissue factor, according to **Canpolat *et al.*** [25]**.** Also, they discovered that, in comparison to the control group, when monocytes are removed from the environment, fibrin deposition is reduced by around 45% and the tissue factor level of thrombus is increased by 83%.

Monocytes may be essential in recurrent thrombotic events in ACS since they are the primary source of tissue factor in thrombosis. The advantages of HDL-cholesterol, in contrast, have been connected to both the quantity and quality of HDL-C [26]. HDL-cholesterol is recognised for its anti-inflammatory, antioxidant, and antithrombotic capabilities.

Moreover, HDL cholesterol has a strong relationship with monocytes, inhibiting their growth into macrophages and lowering their activity, which results in a milder form of inflammation [27].

Current study focuses on a different component of HDL's anti-inflammatory properties with recently discovered haematological consequences. An increase in HDL particles affects the haematopoietic system and lowers inflammation by inhibiting the growth of monocytes, stem cells, and multipotent progenitor cells[28].

Kurtul *et al.* [29] found that monocytes have a limited tissue half-life, but extramedullary monocytepoiesis, which continuously generates new monocytes from the spleen, assures monocyte survival for days after the onset of inflammation. It was found that the spleen is a prominent source of monocytes in ACS. Excessive extramedullary monocyte poiesis slows the shift to an anti-inflammatory repair phase, which also has an impact on heart function [26].

A variety of chemokines, including granulocyte-CSF and IL-23, as well as the extramedullary haematopoiesis process of generating monocytes and differentiating them are inhibited by elevated HDL levels or reconstituted HDL infusion [28]. MHR has been discovered to be a predictor of stent thrombosis, in-hospital MACE, as well as mortality in patients with STEMI [27]. In all studies, MHR has been suggested to be linked to systemic inflammation and endothelial dysfunction as a novel inflammation-based prognostic factor in cardiovascular diseases.

In the present study a statistically significant difference was found between the two groups regarding in-hospital non-fatal MIs. 12 patients (33%) of group 2 encountered an in-hospital MI compared to 6 patients (5%) in group 1. We also found a statistically significant difference between the two groups regarding three months occurrence of non-fatal AMI (p=0.042). 21 patients in group 2 (58%) encountered an AMI within the first three months compared to 30 patients (25%) in group 1. In hospital non-fatal MI was significantly higher in patients with the higher MHR (12 patients (30.8%) with an MHR $\geq$22.25 compared to 6 patients with MHR <22.25).

CONCLUSION

Patients with acute coronary syndrome and high SX scores had substantially increased MHR. We think MHR may be employed as a rapid, easy, and affordable criterion in routine clinical practise to predict a high SX score in patients with acute coronary syndrome and to predict MACE. Further prospective studies would help determine the clinical importance of MHR in CAD patients.

RECOMMENDATION

In patients with ACS, MHR, a new inflammation-based measure, appears to be a reliable predictor of the degree of coronary artery disease and subsequent cardiovascular events. This metric was shown to have a strong correlation with indicators of the severity of coronary artery disease and well-known inflammatory markers. The individualization of targeted treatment and the identification of individuals who are more likely to develop MACE may be used in MHR.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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