European Review for Medical and Pharmacological Sciences 2019; 23: 2570-2575

# The association between the lymphocyte-to-monocyte ratio and coronary artery disease severity in patients with stable coronary artery disease

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**Abstract. – OBJECTIVE: Inflammation plays an important role in the pathogenesis of atherosclerosis. The lymphocyte-to-monocyte ratio (LMR) may reflect a systemic inflammatory status. We investigated the association between the LMR and coronary artery disease (CAD) in patients with stable angina pectoris.**

**PATIENTS AND METHODS: A total of 221 consecutive patients who had been routinely referred for coronary angiography, for stable angina pectoris and 72 patients with normal coronary arteries were included in the present study. We analyzed the relation between the LMR and the angiographic severity of CAD. The SYNTAX score (SxS) was used for assessing the severity of coronary atherosclerosis.**

**RESULTS: The neutrophil-to-lymphocyte ratio (N/L ratio), platelet size distribution width (PDW), neutrophil and uric acid levels were significantly higher in the stable angina pectoris group than in the control group. The LMR was significantly lower in the stable angina pectoris group than in the control group (4.5±3.2 *vs.* 6±2.9, $p < 0.001$). The MPV/L ratios were similar in both groups. Patients with elevated SYNTAX scores (>32) had lower LMR values (3.2±1.5 *vs.* 4.6±3, $p = 0.002$). The monocyte count/HDL-C ratio (MHR) was significantly higher in patients with stable CAD than in the control group (0.015±0.008 *vs* 0.009±0.004, $p < 0.001$); however, it was similar in the higher SYNTAX score (>32) and lower SYNTAX score groups (0.018±0.007 *vs.* 0.014±0.008, $p = 0.056$). Using multivariate logistic regression analysis, we found that only the LMR was an independent predictor of the high SYNTAX scores in patients with stable angina pectoris.**

**CONCLUSIONS: The LMR, an inexpensive and easily measurable laboratory variable, is significantly associated with the presence of CAD and high SYNTAX scores in patients with stable angina pectoris.**

*Key Words:*
Stable coronary artery disease, Lymphocyte-to-monocyte ratio, SYNTAX score.

## Introduction

Inflammation influences the development and progression of coronary atherosclerosis[1]. Peripheral haematological markers, especially leukocytes subtypes, such as the neutrophil-to-lymphocyte ratio (N/L ratio) and the lymphocyte-to-monocyte ratio (LMR), can be used as an indicator of systemic inflammation. A growing body of evidence from clinical and epidemiological studies[2-6] suggests a possible association between haematological markers and coronary artery disease (CAD). Lymphocytes, neutrophils, and monocytes play a central role in the inflammatory response. The N/L ratio is widely used as a prominent marker for inflammation and coronary atherosclerosis[5,7]. However, few studies[8-10] have evaluated the association between the LMR, MHR, and CAD. The severity of CAD is a predictor of cardiovascular mortality. Therefore, in this investigation, we aimed to determine the association between the LMR and the severity of CAD in patients with stable CAD.

## Patients and Methods

### Patients

A total of 239 consecutive patients routinely referred for coronary angiography for stable angina pectoris were included in the study after the following exclusions: acute coronary syndrome, left ventricular dysfunction (left ventricular ejection fraction < 50%), any predominant non-cardiac chronic disease (infection, acute or chronic inflammatory disease, severe valvular heart disease, renal or hepatic insufficiency) and known malignant disease. The patients were divided into two groups.



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Group 1 was comprised of patients with CAD, and group 2 consisted of those without CAD. Patients with CAD were divided into two groups: low SYNTAX score (SxS) (< 32) and high SxS (> 32) groups. Patients experiencing recurrent episodes of chest pain despite optimal medical treatment, those with a positive treadmill test, or those with findings compatible with new ischemia discovered by electrocardiogram (ECG) or myocardial perfusion scintigraphy underwent coronary angiography (CAG). Diabetes mellitus (DM) was defined as a fasting blood glucose level of ≥ 126 mg/dl on two occasions (or if the patient was receiving treatment for the disease). Hypertension was defined as blood pressure of 140/90 mm Hg or greater, or a history of antihypertensive drug use. Dyslipidaemia was defined as a low-density lipoprotein cholesterol level of 130 mg/dL or greater (or if the patient was taking a hypolipidemic drug). The Local Ethical Committee approved the study protocol (Ethical No.: 2018-136).

### Coronary Angiography

Coronary angiography was performed using the standard Judkins technique. The angiographic characteristics, which included lesion location and stenosis percentage, of all coronary lesions in the index coronary angiogram were obtained by reviewing the angiograms. Two experienced cardiologists blinded to the study protocol carried out the angiographic analysis. The SxS, which is an angiographic tool used for grading the complexity of CAD, was used to evaluate the severity of atherosclerosis. Each coronary lesion with at least 50% stenosis in vessels at least 1.5 mm in diameter must be scored. The SxS was calculated with an SS calculator 2.1 (www.syntaxscore.com)[11].

### Laboratory Measurements

In all cases, blood samples were drawn at admission before starting the patients on any medication. All laboratory tests were performed immediately after sampling. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes. Hemoglobin, monocyte and white blood cell (WBC) counts were measured using a Cell-Dyne counter (Cell-dyne 3700, Abbott Laboratories, Abbott Park, IL, USA). The N/L ratio was obtained by dividing the total neutrophil count by the lymphocyte count. The mean platelet volume/lymphocyte (MPV/L) ratio was obtained by dividing the total MPV count by the lymphocyte count. The LMR was obtained by dividing the total monocyte count by the lymphocyte count. The estimated glomerular filtration rate (e-GFR) was determined using the Cockcroft-Gault equation. All measurements were performed in the hospital's central laboratory.

### Statistical Analysis

All analyses were performed using the **S**tatistical **P**ackage for the **S**ocial **S**ciences (SPSS) version 20.0 (released 2011, IBM statistics for Windows version 20, IBM Corp., Armonk, NY, USA). All data are presented as mean ± standard deviation unless otherwise stated. Comparisons of parametric values between the two groups were performed using an independent samples *t*-test. Meanwhile, comparisons of the non-parametric values between the two groups were performed using the Mann-Whitney U-test. Categorical variables were compared with the Chi-square test. A logistic regression analysis was performed to assess the predictors of high SxS. Variables with a significance level of $p < 0.1$ based on univariate analysis were included in the multivariate logistic regression analysis model, and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. The ability of the platelet distribution width (PDW) value to predict high SxS was analyzed using a receiver operating characteristics (ROC) curve analyses. When a significant cut-off value was observed, the sensitivity and specificity values were presented. All statistical tests were two-sided, and statistical significance was determined as a $p$-value < 0.05. An analysis of variance (ANOVA) is a widely used tool for analyzing differences among three or more groups. In our study, there were two groups, so we did not use an ANOVA.

## Results

The patients' demographic and clinical properties, divided by group, are shown in Table I. Of the 293 participants, 221 had angiographically proven CAD, and 72 had almost normal coronary arteries (G50% luminal diameter stenosis). The N/L ratio, PDW, neutrophil and uric acid levels were significantly higher in the stable angina pectoris group than in the control group. The LMR was significantly lower in the stable angina pectoris group than in the control group (4.5±3.2 *vs.* 6±2.9, $p < 0.001$). The MPV/L ratio was similar in both groups, while the MHR was significantly higher in patients in the stable CAD group than

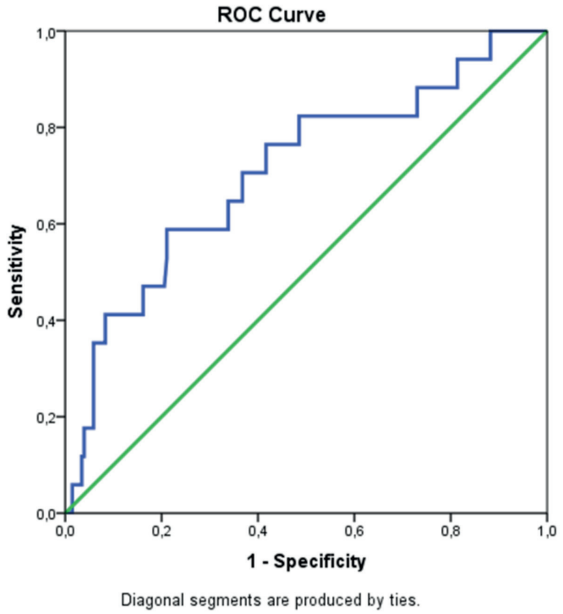


**Figure 1.** Receiver operating characteristic (ROC) curve for lymphocyte/monocyte ratio as a predictor of high Syntax score.

in those in the control group (0.015±0.008 *vs.* 0.009±0.004, $p < 0.001$).

We divided the study population into two subgroups according to SxS. Patients with elevated SxS (>32) had lower LMR values (3.2±1.5 *vs.* 4.6±3, $p = 0.002$). The MHR was non-significantly higher in the higher SxS group (>32) than in the lower SxS group (0.018 ±0.007 *vs.* 0.014±0.008, $p = 0.056$). The neutrophil count was significantly lower in the higher SxS group. There were no differences between groups regarding age, sex and the other laboratory parameters (Table II).

To further explore the independent predictor(s) of slow coronary flow, various multiple regression models were analyzed based on traditional and non-traditional risk factors affecting higher SxS. In the multiple logistic regression analysis, we adjusted for age, hypertension, diabetes mellitus, GFR, LMR and N/L ratio, and only the LMR (OR = 0.625, 95% CI = 0.398-0.982, $p = 0.041$) was found to be an independent correlate of the high SxS in patients with stable angina pectoris. Using ROC, we explored the relationship between preprocedural LMR and higher SxS. The AUC was 0.708 (95% CI: 0.575-0.844; $p < 0.001$). Using a cut point of 0.263, preprocedural LMR predicted higher SxS with a sensitivity of 76% and a specificity of 60% (Figure 1).

**Table I.** Baseline clinical and laboratory characteristics of coronary artery disease and control groups.

| | No CAD (n=72) | CAD (n=221) | *p*-value |
|---|---|---|---|
| Age, years | 57.7±12 | 65.6±10 | <0.001 |
| Male gender | 29 (40.3%) | 163 (73.8%) | <0.001 |
| Hypertension | 35 (48%) | 96 (43%) | 0.676 |
| Diabetes mellitus | 18 (25%) | 99 (44.8%) | 0.001 |
| Smoking | 4 (5.6) | 21 (9.5) | 0.616 |
| Hyperlipidemia | 30 (41.7%) | 105 (47.5%) | 0.262 |
| Previous history of MI | 101 (18.3%) | 18 (22.8%) | 0.357 |
| Previous history of CABG | 17 (3.1%) | 5(6.3%) | 0.179 |
| Hemoglobin (g/dl) | 13.3±1.5 | 13.3±1.9 | 0.854 |
| Uric acid | 4.8±1.5 | 6.1±1.8 | <0.001 |
| Mean platelet volume (fl) | 9±1.4 | 8.9±1.4 | 0.578 |
| PDW, % | 18±2.3 | 19.3±1.8 | <0.001 |
| Neutrophil count ($10^9$/L) | 4.2 ±1.3 | 4.9±2 | 0.006 |
| N/L ratio | 1.9±0.9 | 2.4±1.4 | 0.009 |
| P/L ratio | 112.8±39 | 116.8±49 | 0.554 |
| Plateletcrit | 0.210±04 | 0.213 ±0.5 | 0.720 |
| L/M ratio | 6±2.9 | 4.5±3.2 | <0.001 |
| M/HDL ratio | 0.009±0.004 | 0.015±0.008 | <0.001 |
| MPV/L ratio | 4.2 ±1.7 | 4.4 ±1.8 | 0.571 |
| LDL cholesterol (mg/dl) | 126.3±39 | 116.9±45 | 0.141 |
| HDL cholesterol (mg/dl) | 51.8±12 | 42.2±11 | <0.001 |
| Triglyceride (mg/dl) | 146±66 | 159±81 | 0.222 |
| eGFR (mL/min/1.73 $m^2$) | 94.6±19.8 | 83±23.5 | <0.001 |

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; L/M ratio, lymphocyte/monocyte ratio; MPV/L ratio, MPV/lymphocyte ratio; N/L ratio, neutrophil/lymphocyte ratio; P/L ratio, platelet/lymphocyte ratio; PDW, platelet distribution width.

**Table II.** Demographic and biochemical data of the patients categorized according to Syntax score.

| | Syntax 1-32 (n=204) | Syntax >32 (n=17) | *p*-value |
|---|---|---|---|
| Age, years | 65±10 | 66±11 | 0.708 |
| Male gender | 148 (81.3%) | 15 (78.5%) | 0.250 |
| Hypertension | 87 (33.9%) | 9 (57%) | 9 (57%) |
| Diabetes mellitus | 92 (24,5%) | 7 (34,2%) | 0.205 |
| Smoking | 18 (36.3) | 3 (37.5) | 0.210 |
| Hyperlipidemia | 95 (7.4%) | 10 (40.5%) | 0.449 |
| Previous history of MI | 101 (18.3%) | 18 (22.8%) | 0.357 |
| Previous history of CABG | 17 (3.1%) | 5 (6.3%) | 0.179 |
| Hemoglobin (g/dl) | 13.3±1.5 | 13.6±1.8 | 0.612 |
| Uric acid | 6±1.6 | 6.6±1.8 | 0.193 |
| Mean platelet volume (fl) | 8.9±1.4 | 8.7±1.3 | 0.501 |
| PDW, % | 19.4±2.3 | 18.8±1.7 | 0.245 |
| Neutrophil count ($10^9$/L) | 4.2 ±1.3 | 4.9±2 | 0.006 |
| N/L ratio | 2.4±1 | 3±1.5 | 0.085 |
| P/L ratio | 116±50 | 127±42 | 0.381 |
| Plateletcrit | 0.210±05 | 0.203 ±0.5 | 0.350 |
| L/M ratio | 4.6±3 | 3.2±1.5 | 0.002 |
| M/HDL ratio | 0.014±0.008 | 0.018 ±0.007 | 0.056 |
| MPV/L ratio | 4.3 ±1.6 | 4.9 ±1.7 | 0.189 |
| LDL cholesterol (mg/dl) | 115±38 | 126±46 | 0.376 |
| HDL cholesterol (mg/dl) | 42±11 | 39±11 | 0.257 |
| Triglyceride (mg/dl) | 157±68 | 190±85 | 0.110 |
| eGFR (mL/min/1.73 $m^2$) | 83±22 | 72±23 | 0.070 |

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; L/M ratio, lymphocyte/monocyte ratio; MPV/L ratio, MPV/lymphocyte ratio; N/L ratio, neutrophil/lymphocyte ratio; P/L ratio, platelet/lymphocyte ratio; PDW, platelet distribution width.

## Discussion

In the present work, we found that the LMR was an independent predictor of the severity of CAD in patients with stable CAD. Our study is one of the few in literature evaluating the association between the LMR and CAD. Recently, Ji et al[12] reported that the LMR was significantly associated with the severity of CAD as assessed by SxS. Consistently, we showed this association in patients with stable angina pectoris.

Inflammation plays a central role in the pathogenesis of CAD. Scholars[2,13,14] suggested that the NLR, and more recently the LMR, may be used as a marker of inflammation. Although several haematological cells, including white blood cells, neutrophils, eosinophils, lymphocytes, and monocytes have been linked with CAD, the LMR ratio combines two independent markers of inflammation, which are calculated by dividing the lymphocyte to monocyte. Both a high monocyte count and a low lymphocyte count were linked with coronary atherosclerosis[7,14]. Therefore, the LMR could be used as a marker of coronary atherosclerosis. Low lymphocyte counts have been linked with increased cardiovascular risk. In contrast, a high monocyte count was recently found to be an independent predictor of cardiovascular mortality in older Korean people[15]. Blood monocytes are recruited into the intima and subintima, differentiate into macrophages in response to several locally produced cytokines and initiate the atherosclerotic process[16]. Monocytes may also modulate the progression and development of coronary atherosclerosis through the activation of pro-inflammatory cytokine secretion[17]. Fan et al[9] sought to find the association between the LMR and plaque vulnerability as assessed by virtual histology intravascular ultrasound in patients with stable angina. Their study suggested that the LMR could be used to identify the vulnerable plaques in stable angina. Murat et al[18] showed an inverse association between the LMR and bare-metal stent restenosis in patients with stable CAD. It was also reported that an increased LMR could predict well-developed coronary collateral circulation in stable CAD patients[19]. In addition, the LMR has been found to be associated with in-hospital and long-term major adverse cardiac and cerebrovascular events in patients with ST-elevation myocardial infarction (STEMI)[8]. In our study, the LMR but not the NLR was associated with the severity of CAD. Recently, the MHR has been linked with CAD. Acıkgoz et al[20] reported that the LMR

**Table III.** Independent predictors of a high syntax score in multivariate logistic regression analysis.

| | Variables P | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|
| Age | 0.994 | 0.947-1.049 | 0.831 |
| Hypertension | 1.734 | 0.591-5.092 | 0.316 |
| DM | 0.803 | 0.278-2.607 | 0.866 |
| Smoking | 2.167 | 0.470-9.963 | 0.301 |
| eGFR | 0.986 | 0.965-1.007 | 0.191 |
| L/M ratio | 0.625 | 0.398-0.982 | 0.041 |
| N/L ratio | 0.973 | 0.669-1.434 | 0.885 |

Abbreviations: eGFR, estimated glomerular filtration rate; L/M ratio, lymphocyte/monocyte ratio; N/L ratio, neutrophil/lymphocyte ratio

was associated with short- and long-term mortality in patients with STEMI who were treated with primary percutaneous coronary intervention (PCI), suggesting that this simple marker may be useful for predicting long-term outcomes in these patients. Two papers[21,22] examined the association between the severity of coronary atherosclerosis and the SxS in patients with CAD undergoing coronary angiography. In these researches, the MHR was found to be significantly associated with SxS. In contrast, in the present study, the MHR was significantly higher in patients with stable CAD, but there was no significant association between the MHR and the severity of CAD in patients with stable CAD who were undergoing coronary angiography.

## Conclusions

We found that the LMR is an independent predictor of the severity of CAD in patients with stable CAD undergoing coronary angiography. The MHR was significantly higher in patients with stable CAD, but it was not significantly associated with the severity of CAD. The LMR is an inexpensive and easily measurable laboratory variable that could be used as a novel risk marker of cardiovascular disease.

### Conflict of Interest

The Authors declare that they have no conflict of interest.

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