Relationship Between Myocardial Perfusion Scintigraphy Findings and Neutrophil Lymphocyte Ratio

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Introduction

Coronary artery disease (CAD) is an important cause of mortality and morbidity that is increasing in prevalence worldwide[1]. Atherosclerosis, responsible for the etiology and development of CAD, is defined as a progressive inflammatory disease[2-4]. Many studies have found that basic inflammatory cells, including leucocytes and their sub-types, are responsible for adverse events in cardiovascular disease[5-9]. High neutrophil and low lymphocyte counts are strongly associated with cardiac events and the risk of mortality in CAD[10,11].

The neutrophil lymphocyte ratio (NLR), a new index is, reportedly an inflammatory biomarker for cardiovascular results in CAD patients[12]. Myocardial perfusion scintigraphy (MPS), which shows the physiological significance of CAD, is a frequently chosen imaging method, as it is non-invasive and based on functional parameters[13]. Neutrophils are known to be the first cells to reach ischemic myocardial tissue[14]. The aim of this study was to research the relationship between simple and applicable methods of MPS and NLR, based on the potential relationship of the neutrophil response to myocardial ischemia.

ABSTRACT

Introduction: The neutrophil lymphocyte ratio (NLR) is a new predictor for cardiovascular risk and mortality. We investigated the association between the NLR and myocardial perfusion scintigraphy (MPS), a powerful prognostic tool for predicting adverse cardiovascular outcomes.

Materials and methods: A total of 558 patients were included in our study. Patients were divided into groups according to the MPS findings and coronary angiography (CAG) results. Their hematologic and biochemical data were obtained. The neutrophil lymphocyte ratio was calculated, and the relationship between the groups and the NLR was statistically analysed.

Results: The NLR was statistically higher in the patients with ischemia detected with MPS, than in patients who had normal MPS values (2.52 ± 1.62 and 2.13 ± 1.07, respectively). Therefore, the NLR was similar between patients who were both CAG positive and had ischemic MPS. In addition, the NLR was similar for patients who had both normal MPS and CAG negative. NLR was detected as an independent predictor for coronary artery disease on logistic regression analysis (p = 0.005, OR = 1.29, 95% CI: 1.082 - 1.539).

Conclusion: The NLR is an independent predictor for coronary artery disease. This novel index is a beneficial identifier to interpret the results of MPS in terms of increasing diagnostic accuracy.

Key words: Myocardial perfusion scintigraphy, neutrophil lymphocyte ratio, coronary artery disease.

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Materials and methods

Study population
A total of 558 patients for whom demographic, clinical and laboratory data were available, and who were referred to our department for MPS with suspected or known CAD between January 2012 and December 2013, were included in the study. The MPS findings from the patients were retrospectively re-evaluated in light of anamnesis (risk factors) and laboratory data. While evaluating risk factors, ‘positive’ was accepted as diabetes mellitus with a fasting blood sugar $\geq 126$ mg/dl or use of anti-diabetic medication, hypertension with a systolic blood pressure $\geq 140$ mm Hg, a diastolic blood pressure $\geq 90$ mm Hg or use of anti-hypertensive medication, hyperlipidaemia with total cholesterol $\geq 200$ mg/dl, LDL $\geq 130$ mg/dl, or use of cholesterol-lowering medication. Family history of sudden cardiovascular death before the age of 65 years, myocardial infarction (MI) or coronary revascularization, active smoking or a past cigarette habit of 10 packets/year were also accepted as positive risks. The patients were divided into two groups based on MPS findings: normal and ischemic. One hundred and twenty-seven patients with ischemia, who were identified in MPS results, had coronary angiography (CAG) performed; those with lesions determined on CAG were grouped as ‘CAD’, while those without lesions were grouped as ‘normal’ (Figure 1).

A history of hematological diseases, cancer and systemic inflammatory diseases, use of anti-inflammatory or antibiotic medication, and renal or liver failure were determined as exclusion criteria. In addition, patients with fixed defects in MPS were excluded.

Biochemical and hematological parameters
Blood samples collected after 12 hours starvation had hematological parameters (neutrophil, leucocyte, eosinophil and monocyte) determined using the electrical impedance method on an automatic blood count device (Beckman Coulter LH 750). Neutrophil count (N) was divided by lymphocyte count (L) to calculate the N/L ratio. Biochemical parameters (glucose, urea, creatinine, total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)) were measured using the colorimetric method (Abbott Laboratories; Illinois, USA).

Myocardial perfusion scintigraphy protocol and analysis
For the gated MPS study, technetium-99 sestamibi (Tc-99m MIBI) was used in a single-day protocol. Depending on what was appropriate for the patient, a pharmacological stress test was carried out using effort/adenosine; after injections, stress and at-rest images were obtained by synchronizing a double-headed gamma camera (Siemens e.cam) with ECG. Semiquantitative visual analysis of the images was performed using a 17-segment model and a 5-point scoring system (0: normal, 1: mildly reduced, 2: moderately reduced, 3: severely reduced, and 4: absent uptake). The sum of segment scores at stress (SSS), scores at rest (SRS), and differences between stress and rest score (summed difference score [SDS]) were calculated. Patients were divided into groups based on their SDS combined with their SSS. Patients with an SDS $\geq 2$ and an SSS $\geq 4$ were considered to have myocardial ischemia; patients with an SDS < 2 and an SSS < 4 were considered normal. Additionally quantitative gated SPECT (QGS) program was used on the Siemens e.soft workstation. According to the gated MPS findings, the patients were divided into two groups: normal (n = 431) and ischemia (n = 127). The patients diagnosed with ischemia and who underwent CAG (n = 127) were examined in two groups, normal and CAD. The NLR of each of these groups was compared.

Statistical analysis
The patients’ data are given as mean and standard deviations for continuous variables and as percentages for categorical variables. For a simple two-way comparison of categorical variables, the chi-square test was used. The t-test and the one-way ANOVA were used to compare continuous variables in groups. The sensitivity and specificity of NLR values for CAD were evaluated using receiver operating curve (ROC) analysis. Independent factors for CAD were examined using logistic regression analysis. A p value $< 0.05$ was accepted as statistically significant. The Statistical Package for Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis.

Results
The MPS findings for the 312 (56%) female and 246 (44%) male patients were evaluated as 431 normal and 127 ischemic. Classic risk factors were
significantly higher in those with ischemic MPS than those with normal MPS (Table 1).

According to the MPS findings, when the hematological data of the patients in the two groups are compared, patients who tested positive for CAD had significant differences in leucocyte, neutrophil and NLR compared to patients with normal MPS (Table 2).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MPS Normal (n = 431)</th>
<th>MPS Ischemia (n = 127)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>174 (40%)</td>
<td>72 (57%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>207 (48%)</td>
<td>77 (61%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>96 (22%)</td>
<td>41 (32%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>123 (29%)</td>
<td>56 (44%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>196 (46%)</td>
<td>63 (50%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Smoking</td>
<td>83 (19%)</td>
<td>15 (12%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Age, years</td>
<td>54 ± 12</td>
<td>59 ± 11</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Table 1: Comparison of demographic characteristics of the MPS groups.
*Chi-Square tests, **Independent sample t test. MPS - myocardial perfusion scintigraphy

According to the MPS findings, when the hematological data of the patients in the two groups are compared, patients who tested positive for CAD had significant differences in leucocyte, neutrophil and NLR compared to patients with normal MPS (Table 2).

<table>
<thead>
<tr>
<th>Hematological data</th>
<th>MPS Normal (n = 431)</th>
<th>MPS Ischemia (n = 127)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocyte, x10³/mm³</td>
<td>7.3 ± 1.9</td>
<td>7.7 ± 2.1</td>
<td>0.035</td>
</tr>
<tr>
<td>Neutrophil, x10³/mm³</td>
<td>4.4 ± 1.6</td>
<td>4.8 ± 1.9</td>
<td>0.022</td>
</tr>
<tr>
<td>Lymphocyte, x10³/mm³</td>
<td>2.2 ± 0.6</td>
<td>2.2 ± 0.7</td>
<td>0.29</td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>13.9 ± 1.5</td>
<td>13.9 ± 1.6</td>
<td>0.959</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>41.7 ± 3.9</td>
<td>41.8 ± 4.2</td>
<td>0.697</td>
</tr>
<tr>
<td>Platelets, x10³</td>
<td>259 ± 66</td>
<td>252 ± 65</td>
<td>0.276</td>
</tr>
<tr>
<td>NLR</td>
<td>2.13 ± 1.07</td>
<td>2.52 ± 1.62</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2: Comparison of hematological data from patients with normal and ischemic MPS findings.
*Independent sample t tests. MPS - myocardial perfusion scintigraphy; NLR - neutrophil/lymphocyte ratio

Comparing the biochemical data of those considered to have CAD according to MPS findings (ischemia groups) with those having normal MPS, glucose, creatinine and lipid levels were found to be significantly higher in the patients with MPS appropriate for CAD (Table 3). The 127 patients with ischemia diagnosed by MPS findings underwent coronary angiography. Of these patients, 81 were positive on CAG (64%) while 46 (36%) had normal CAG. When these patients are evaluated, the CAG negative patients were similar in terms of gender, diabetes mellitus, hypertension and hyperlipidemia those with MPS normal.

<table>
<thead>
<tr>
<th>Biochemical test results</th>
<th>MPS Normal (n=431)</th>
<th>MPS Ischemia (n=127)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>99±22</td>
<td>111±26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.73±0.14</td>
<td>0.84±0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>169±40</td>
<td>202±100</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>125±68</td>
<td>163±63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42±9</td>
<td>39±8</td>
<td>0.034</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>105±29</td>
<td>120±28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Comparison of glucose, creatinine and lipid parameters of groups (MPS normal and MPS ischemia).
*Independent sample t test. HDL - High density lipoprotein; LDL - Low density lipoprotein; MPS - Myocardial perfusion scintigraphy

Hematological parameters in the CAG positive groups were observed to be significantly high (Table 4). Comparing patients positive for CAD (CAG positive; n = 81) and those negative for CAD (MPS normal and CAG normal; n = 477), leucocyte, neutrophil levels and NLR were again significantly higher in the CAD patients (independent sample t-test, p < 0.007; 0.001; 0.003, respectively). At a value of 1.90, NLR has a sensitivity of 67% and a specificity of 52% for a diagnosis of CAD (p=0.001, AUROC: 0.611, 95%CI 0.542-0.680) (Figure 2).
When independent markers for CAD are evaluated by logistic regression analysis, classic risk factors (apart from smoking) and NLR are found to be independent markers for CAD (Table 5).

**Discussion**

In this study, a strong and significant relationship was found between ischemic findings on MPS and NLR, an inflammatory biomarker reported in many publications as a prognostic indicator of CAD. It is interesting to note that the NLR is similar in patients with ischaemia, as identified on MPS but without lesions on CAG, and those patients with normal MPS findings.

Many factors are responsible for the formation and development of atherosclerosis, within the etiology of CAD. Among these factors, inflammation plays a major role\(^2\)-\(^4\). Many studies have focused on the role of inflammation in CAD and its relationship with certain inflammatory biomarkers\(^1\)-\(^4\). Danesh et al.\(^1\), in a wide-ranging meta-analysis of the relationship between coronary heart disease and a variety of inflammatory markers, such as fibrinogen, C-reactive protein, albumin, and leucocytes, reported that the leucocyte count may be an independent predictor of coronary heart disease. In our study, there was a significant difference in terms of leucocytes, neutrophils, and NLR between the MPS normal group and the CAD positive group.

Neutrophils are one of the first types of inflammatory cells to reach damaged myocardial tissue after acute myocardial ischemia\(^1\)-\(^4\). Based on this, many studies have examined the relationship between the size of the infarction, as observed with non-invasive myocardial perfusion scintigraphy and neutrophil counts\(^2\)-\(^3\). Dogan et al.\(^2\) found a strong link between infarction size and neutrophil count on a study using scintigraphy \((r = 0.602, p < 0.001)\). Again, in a study examining the relationship between cardiac positron emission tomography (PET) and NLR in 683 patients with known or suspected CAD, a strong relationship was shown between chronic disrupted myocardial perfusion and NLR\(^2\).

Similarly, in our study, a significant relationship was found between ischemia patients, as identified on MPS, and CAD positive patients on CAG and between MPS and CAG normal patients. In addition, NLR levels were similar in patients with normal CAG findings and normal MPS results. These findings indicate that, when interpreting MPS findings, especially for cases with suspected ischemia, NLR may be an additional criterion to examine.

A study by Amaro et al.\(^2\) showed that a high leucocyte count may contribute to the onset and development of CAD. In the same study, it was determined that age, gender, cholesterol and triglyceride levels, smoking and leucocyte count were independent markers for coronary heart disease. In this study, NLR, age, diabetes, hypertension and male gender were independent predictors for CAD.

Madjid et al.\(^2\) reported that a high leucocyte count increased CAD mortality and morbidity. In addition, the authors reported that leucocytosis was an independent predictor for acute MI. Similarly, in
our study, leucocyte counts were significantly higher in the patients with ischemia identified on MPS and in the CAD positive patient group on CAG.

Kaya et al.,(26) in a study examining the relationship between severity of CAD and NLR, found that an NLR > 2.5 showed a 62% sensitivity and a 69% specificity for severe atherosclerosis, and reported that it was a predictor for severe atherosclerosis. Horne et al.,(9) in a study researching the leucocyte subtype that best reflected increased cardiovascular risk, showed that the total leucocyte count was an independent predictor for death or MI in CAD patients. However, the most important risk predictor was NLR, which increased risk by 2.2 times (>4.71 compared with <1.96). Kalay et al.,(27) showed that a high NLR was a predictor of the progression of coronary atherosclerosis; in this study, the progression rate was significantly increased in patients with a high NLR (NLR cut-off value of 3.5: RR: 2.267, 95% CI: 1.068–4.815, p = 0.03).

Sonmez et al.,(28) conducted an observational study of the presence and complexity of CAD and its relationship with NLR, and reported that NLR was a strong clinical parameter. In CAD positive patients on angiography with a cut-off of 1.95 for NLR, both the sensitivity and specificity were 69%. In our study of CAD diagnosis, a cut-off NLR of > 1.90 had a sensitivity of 67% and a specificity of 52% (p = 0.001, AUROC: 0.611, 95% CI: 0.542–0.680). A study by Sonmez et al. That showed the relationship between the presence of coronary artery disease and NLR found similar values for cut-off, sensitivity and specificity for NLR as in our study. A study by Kaya and Kalay found a cut-off value higher than that used in our study, and this was linked to the group of CAD patients with a higher NLR than was expected. These two studies researched the relationship between NLR and disease progression and severity, rather than diagnosis of CAD.

Again, in many studies of acute coronary syndrome(29, 30) and stable CAD(31) patients, a high NLR was a predictive value for unwanted cardiac events. In this study, high NLR values were predictive for ischemic findings on MPS, similar to age, diabetes, male gender and hypertension, all of which were also observed to be predictors for CAD.

This study had several limitations. The primary limitation of our study was the small sample size. A small sample size has low statistical power and, thus, may yield false-negative results. Second, this was a study with a cross-sectional design.

Thus, our results cannot be extended to the general population. However, we believe that our findings provide a valuable contribution to the relationship between the NLR ratio and suspicion of ischemia on MPS. Future prospective larger multicentre studies are required to confirm our results.

Conclusion

This study once again shows that inflammation affects atherosclerosis. Reported as an inflammatory biomarker, we believe the NLR may reduce the rate of false positivity and help to correctly interpret perfusion defects, especially in cases of suspected of ischemia on MPS. The use of these simple and inexpensive methods may aid correct diagnosis in the CAG patient group. Prospective studies with broader patient groups will be beneficial in revealing the full value of this index for MPS.

References


Contribution of Authors
A - Research concept and design; ANK, BC, FE
B - Collection and/or assembly of data; ANK, FE, SO
C - Data analysis and interpretation; ANK, BK, GO
D - Writing the article; ANK, GO
E - Critical revision of the article; BC, SO
F - Final approval of article; FE, ANK

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