Association of neutrophil count and neutrophil to lymphocyte ratio with coronary artery ectasia: A cross-sectional study

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Abstract

Introduction: Coronary artery ectasia (CAE), characterized as diffuse dilatation of epicardial coronary arteries, has been shown to be associated with risks of death and myocardial infarction. Neutrophil count and neutrophil to lymphocyte ratio (NLR) are cost effective, available and rapidly measurable inflammatory markers. In this study we decided to investigate the association between these factors as inflammatory markers and CAE severity.

Methods: In this cross-sectional study, 577 patients who underwent coronary angiography from September 2016 to September 2017 were evaluated. Based on the angiography findings, patients were divided into four groups: (1) normal coronary artery, (2) coronary artery disease (CAD), (3) low risk CAE and (4) high risk CAE.

Results: In CAE group, 61 patients (52.1%) had one vessel involvement and were defined as low risk and 56 patients (47.9%) had two or more vessel involvement and were grouped as high risk CAE. NLR was non-significantly higher in CAD group and high-risk CAE group (2.61±0.51 and 2.33±0.11 respectively). Absolute neutrophil count was significantly higher in CAD and high risk CAE groups.

Conclusion: Our study showed that patients with a high risk of CAE have higher neutrophil count. Therefore, inflammation might be a risk factor for CAE.
between elevation of MPV and CAE. On the other hand, the increase in MPV is related to the severity of the disease.

Since in previous studies simultaneous measurement of NLR and MPV and their relationship with severity of CAE have not been performed, in this study we decided to investigate the association between these inflammatory markers and CAE severity; and compare these findings with the results in healthy people and patients with CAD.

**Methods**

This study is a cross-sectional descriptive analytical study. A total number of 577 patients, who underwent coronary angiography at Seyed-al-Shohada hospital, Urmia, Iran, from September 2016 to September 2017 were evaluated.

Blood samples (a volume of 5 mL) were taken from antecubital vein prior to coronary angiography. Vacuum tubes containing 15% K3 ethylenediaminetetraacetic acid (EDTA) were used to hold the samples until analysis was done within 30 minutes of being obtained. Coulter* LH 780 automated hematology analyser with an electrical impedance method (Beckman Coulter Inc., Brea, CA, USA) based on the manufacturer’s instructions was used to assess platelet, neutrophil and lymphocyte counts. NLR was calculated through manually dividing the digital neutrophil and lymphocyte counts in $10^9$/mm$^3$ unit volume.

After obtaining blood samples, the patients underwent angiography via Judkins technique with a Siemens Axiom Artis FC diagnostic device (Siemens Healthcare GmbH, Forchheim, Germany). An amount of 350 mg/ml Iohexol (Amersham Health, Co. Cork, Ireland) was administered (as the contrast agent) to each patient after catheterization. Left anterior oblique, right anterior oblique, and cranial, caudal and horizontal positions were the target points in angiography in this study. All angiographic procedures were conducted by two angiography specialists.

Based on angiographic findings, the patients were divided into four groups. The first group, patients with high risk and low risk CAE, the second group, patients with CAD and the third group patients with normal coronary artery angiography. Afterward, the patients in the first group were divided to two groups; low risk patients with one vessel involvement and high risk patients with more than one vessel involvement.

Exclusion criteria were defined as simultaneous CAE and stenosis, malignancy and its related treatments, immunosuppressive use, chronic inflammatory diseases, valvular heart disease, history of myocardial infarction and percutaneous coronary intervention (PCI).

Data collection was performed from patients’ recordings. Blood cell count, neutrophil and lymphocyte count, NLR and MPV were measured before angiography in all groups.

**Statistical analysis**

The categorical results were presented as mean ± standard deviation (SD), and frequency (percentage). ANOVA and LSD tests were used for comparing the mean of variables of different groups. Statistical analysis was done by SPSS 23. A $P$ value <0.05 was considered as statistically significant.

**Results**

In this cross-sectional study, 577 patients were included. 230 patients had coronary artery disease (CAD), 230 patients had normal coronary artery in their coronary angiography and 117 patients had CAE. 324 patients (56.2%) were male and 253 patients (43.8%) were female. Patients with CAD were older than CAE group (60.1±10.41 vs 57.6±12.4 years old respectively, $P>0.05$). In CAE group 61 patients (52.1%) had one vessel involvement and defined as low risk and 56 patients (47.9%) had two or more vessel involvement and grouped as high risk CAE. Gender did not have significant association with the severity of CAE ($P>0.05$). Diffused ectasia involving entire coronary artery was seen in 13% of men and 5% of women with isolated ectasia. Patients’ characteristics and laboratory data are shown in Table 1.

Figure 1 shows correlation of neutrophil count and CAD and CAE. CAD and high risk CAE had significant association with neutrophil count.

MPV and CAD and CAE did not have any association (Figure 2). Number of lymphocytes was lower in CAD and low risk CAE; although it was not significant in comparison to the control group (Figure 3).

Figure 4 shows non-significant higher NLR in CAD and CAE groups in comparison to the control group.

**Table 1. Patients’ data according to four groups of coronary artery angiography**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAD n=230</th>
<th>High risk CAE n=56</th>
<th>Low risk CAE n=61</th>
<th>Control group n=230</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender/male, n (%)</td>
<td>149 (64.8)</td>
<td>42 (75)</td>
<td>37 (60.6)</td>
<td>160 (69.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>60.1±10.4</td>
<td>58.7±11.5</td>
<td>57.6±12.4</td>
<td>59.21±9.47</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>61 (26.5)</td>
<td>13 (23.2)</td>
<td>15 (24.6)</td>
<td>51 (22.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>35 (15.2)</td>
<td>9 (16)</td>
<td>10 (16.3)</td>
<td>42 (18.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>4927.5±158.07</td>
<td>4464.1±264.45</td>
<td>4268.6±115.62</td>
<td>3993.16±190.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>2239.37±54.67</td>
<td>2325.14±68.35</td>
<td>2239.14±100.82</td>
<td>2325.14±68.35</td>
<td>0.74</td>
</tr>
<tr>
<td>Neutrophil to lymphocyte ratio</td>
<td>2.24±0.51</td>
<td>2.33±0.11</td>
<td>2.28±0.16</td>
<td>1.98±0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean platelet volume</td>
<td>9.5±0.05</td>
<td>9.52±0.12</td>
<td>9.22±0.87</td>
<td>9.36±0.05</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Neutrophil count and NLR in coronary artery ectasia

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Figure 1. Correlation between neutrophil count, coronary artery disease and coronary artery ectasia. * \( P > 0.05 \), ** \( P < 0.05 \).

Figure 2. Correlation between mean platelet volume, coronary artery disease and coronary artery ectasia. * \( P > 0.05 \), ** \( P < 0.05 \).

Figure 3. Correlation between lymphocyte count, coronary artery disease and coronary artery ectasia. * \( P > 0.05 \), ** \( P < 0.05 \).

Figure 4. Correlation between neutrophil to lymphocyte ratio, coronary artery disease and coronary artery ectasia. * \( P > 0.05 \), ** \( P < 0.05 \).

Discussion
Our study showed that NLR and neutrophil count were higher in CAE and CAD patients in comparison to the control group; but only neutrophil count had significant association. Previous studies showed that neutrophils, monocytes and eosinophils had direct and lymphocytes had inverse association with CAD,\(^6\) Similarly our study showed a higher neutrophil count and lower lymphocyte count in CAD group compared with control group, but the association of lymphocyte count was not significant. Since CAE has been shown to have associated with risks of death and myocardial infarction, it has been investigated in many recent articles.\(^7\) CAE is probably a multifactorial disease with unknown definite etiology. Genetic factors, hypertension, smoking, and diabetes mellitus are suggested as its etiologies. Previous studies showed its prevalence ranging from 3% to 8% of coronary angiographies and 0.22%-1.4% of autopsies which are lower than the prevalence of CAE in our study.\(^8\) Our study showed that high risk CAE was seen in 9.75 and low risk CAE in 10.6% of patients. Diffused CAE was more prevalent in men, maybe because of having more risk factors of atherosclerosis. NLR, as an indicator of systemic inflammation has been shown to have significant correlation with cardiovascular diseases. NLR can be calculated from complete blood count with differential is an inexpensive marker of inflammation. Nowadays many researchers use NLR for risk stratification of cardiovascular diseases. Previous studies have shown a significant associated between arterial stiffness and high coronary calcium score and NLR. In patients undergoing PCI, higher NLR is associated with higher long-term mortality.\(^9\)

Our study showed that NLR was higher in CAD group, followed by high risk CAE group; but this association was not statistically significant. Balta et al showed a significant association between NLR and CAD and CAE compared to control group. In this study, NLR was not different significantly among CAE and CAD patients.\(^10\) Contrary to this study, our study did not show any significant association between MPV and CAE or CAD, although these groups had higher MPV value in comparison to the control group. Işık et al also showed that on admission, NLR with a cut-off point of 2.37 could predict isolated CAE (OR=6.03, 95% CI 2.61-13.94, \( P < 0.001 \)). Hypercholesterolemia and obesity were other independent risk factors for isolated CAE.\(^11\) Shereef et al also showed a significant association between NLR and CAE. They showed that NLR with a sensitivity of 52.5% and specificity of 100% (\( P < 0.001 \)) and a cut-off point of 2.65 could predict CAE.\(^12\) Other studies showed that the...
role of inflammation might be more prominent in pure ectasia in comparison to CAD. Turhan et al by studying 32 patients with isolated ectasia and 32 patients with CAD showed that patients with isolated CAE had higher levels of plasma soluble ICAM-1, VCAM-1 and E-selectin, in favor of more severe chronic inflammation in this group of patients. Yildirim et al found higher intensities of surface inflammatory markers such as CD-86 on the surface of monocyte derived dendritic cells in those with concomitant CAE and CAD in comparison to CAD patients without CAE and normal controls ($P < 0.001$). Turhan et al showed that patients with pure ectasia had higher levels of CRP as an inflammatory biomarker, in comparison to pure CAD group. They suggested severe inflammation as a possible predisposing factor for CAE. In another study patients with CAE in their coronary angiography showed a significantly higher concentrations of IL-1b, TNF-α, and IL-10. Our study also showed that neutrophil count was significantly higher in CAD and high-risk CAE patients.

Different studies with different biomarkers have shown strong association between CAE and inflammation. The duration and intensity of inflammation and the underlying factors for this inflammatory process is not established yet. It seems that finding the pathophysiology of CAE needs controlled clinical trials; and observational studies are not enough strong to explain these underlying factors and their interactions, resulting in inflammation and CAE.

Limitations of study
A cohort study could help to get better results; and retrospective method of our study may have limited generalization of our results in general population.

Conclusion
Our study showed that patients with a high risk of CAE had higher neutrophil count; and inflammation might be a risk factor for CAE.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval
The study protocol was approved by the Ethics Committee of Urmia University of Medical Sciences (Code number: 94-01-32-2788).

Author's contributions
Study design, BR; study conduction, NJO; data gathering, SGH & HK; literature review and critic, AS; writing, RH.

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