

# Neutrophil/lymphocyte ratio in patients with atrial septal aneurysm

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**Background:** Systemic thromboembolism is a serious, major complication in patients with an atrial septal aneurysm (ASA). Paroxysmal atrial fibrillation (AF) is more common in patients with ASA than in the normal population. Neutrophil/lymphocyte ratio (NLR) has been associated with postoperative AF development in patients who have undergone cardiac surgery. This study investigated NLR in a group of ASA patients compared with a control group of healthy volunteers.

**Patients and methods:** The study group consisted of 40 patients with ASA; the control group consisted of 30 age-, sex-, and body mass index-matched healthy volunteers. All patients and control subjects underwent echocardiographic examination. No patient had a recent history of an acute infection or an inflammatory disease. Baseline NLR was measured by dividing neutrophil count by lymphocyte count.

**Results:** No statistically significant difference was found between the two groups in terms of basic characteristics. Mean NLR was significantly higher among persons with ASA compared with controls ( $3.4 \pm 1.5$  vs  $1.6 \pm 0.97$ ,  $P < 0.001$ ).

**Conclusion:** Our results suggest that a higher NLR, an emerging marker of inflammation, has a positive correlation with ASA. The measurement of NLR may be used to indicate an increased risk of arrhythmia, such as AF, in ASA patients.

**Keywords:** neutrophil-lymphocyte ratio, inflammation, arrhythmia

## Introduction

Atrial septal aneurysm (ASA) is a risk factor for arterial embolism because it frequently coexists with an atrial septal defect or patent foramen ovale and mitral valve prolapse. The incidence of ASA, depending on the imaging method, is reported to be 0.2%–4% with transthoracic echocardiography and 2%–8% with transesophageal echocardiography because of higher sensitivity.<sup>1–3</sup>

It was recently demonstrated that atrial dysfunction caused by paroxysmal atrial fibrillation (AF) is more common in patients with ASA than in the normal population, although the mechanisms of this dysfunction remain unclear.<sup>4</sup>

Elevated levels of systemic inflammatory markers have been found to be associated with incidences of cardiovascular diseases such as coronary artery disease, hypertension, and AF.<sup>5–7</sup> Total white blood cell (WBC) count and subtypes, such as neutrophil, lymphocyte, and neutrophil/lymphocyte ratio (NLR), can be used as indicators of systemic inflammation.<sup>8</sup>

In our study, we compared NLR between ASA patients and controls.

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## Methods

### Patient selection

Forty patients with ASA who had been identified during echocardiographic evaluation, performed for various reasons (15 males, 25 females; mean [ $\pm$  standard deviation] age  $54.4 \pm 16.3$  years), were entered into the present study. Thirty age-matched adults (12 males, 18 females; mean age  $49.8 \pm 11.2$  years) who had normal cardiac structures on echocardiography comprised the control group. Entry criteria included the presence of ASA determined by echocardiography and sinus rhythm on surface electrocardiogram. A physical examination, medical history, and blood biochemistry testing were conducted in both patient groups. The subjects were defined as hypertensive if their blood pressure was  $\geq 140/90$  mmHg or if they were receiving any antihypertensive medication. Diabetes mellitus was defined as a history of antidiabetic medication use or a fasting glucose level  $>126$  mg/dL. Smoking status was classified as smokers and those who had never smoked. Patients with coronary artery disease, heart failure, valve disease, cardiomyopathy, hypertension, diabetes mellitus, chronic lung disease, thyroid dysfunction, anemia, malignancy, renal and hepatic insufficiency, chronic inflammatory disease, pregnancy, septicemia, hematological disorders, known malignancy, WBC count  $>12,000$  cells per  $\mu\text{L}$  or  $<4000$  cells per  $\mu\text{L}$ , and high body temperature  $>38^\circ$  were excluded from the study. Also, patients who had a recent history of an acute infection or an inflammatory disease or had a history of stroke or cerebrovascular disorder were excluded from the study. All patients in the present study were in sinus rhythm, and none were taking cardioactive medications such as antiarrhythmics, antiplatelets, anticoagulants, antipsychotics, or antihistamines. Patients who had taken medication that can potentially interfere with the measurement of leukocyte counts, such as antigout or anti-inflammatory agents, were excluded from study.

### Echocardiographic measurements

Two-dimensional, M-mode, pulsed, and color-flow Doppler echocardiographic examinations of all subjects were performed by the same examiner using a commercially available device (Vivid 7 Pro [equipped with a 2–5 MHz phased-array transducer], GE Healthcare, Horten, Norway). During echocardiography, a single-lead electrocardiogram was recorded continuously.

ASA was detected by transthoracic echocardiography. Patients who had an ASA with a base  $>15$  mm and

protrusion  $>10$  mm were entered into the study. M-mode measurements were performed according to the criteria of the American Society of Echocardiography.<sup>9,10</sup>

Right atrial, left atrial, and left ventricular end-systolic and end-diastolic diameters were measured. Left ventricular ejection fraction was estimated using Simpson's rule.

### Laboratory analyses

Fasting blood glucose, serum creatinine, total cholesterol, electrolytes, and thyroid-stimulating hormone levels were recorded. Blood samples were drawn by venipuncture to perform routine blood chemistry.

Total and differential leukocyte counts were measured by an automated hematology analyzer. Absolute cell counts were used in the analyses.

### Statistical analyses

SPSS 16.0 statistical program (IBM Corporation, Armonk, NY, USA) was used for statistical study. All values are given as mean  $\pm$  standard deviation. Mean values of continuous variables were compared between groups using the Student's *t*-test or Mann–Whitney *U* test, according to whether they were normally distributed or not, as tested by the Kolmogorov–Smirnov test. A *P*-value of less than 0.05 was considered significant.

## Results

There were no statistically significant differences between the ASA group and controls in respect of age, sex, left atrial and left ventricular diameters, blood pressure, body mass index, and smoking status (Table 1).

When the inflammatory status of the study population was assessed according to leukocytes, neutrophils, and monocytes, neutrophils and NLR were higher ( $P < 0.001$ , respectively) and lymphocytes were lower ( $P < 0.001$ ) in patients with ASA than the controls. Other hematological parameters, including leukocyte, monocyte, hemoglobin, and platelet counts, were not statistically significantly different between the two groups (Table 2).

## Discussion

In the present study, we have found that NLR is significantly higher in patients with ASA.

ASA is a risk factor for arterial embolism. Potential mechanisms of stroke in patients with ASA include paradoxical embolism from a venous source, direct embolization from thrombi formed within the aneurysm, and the formation of thrombi as a result of atrial arrhythmias.<sup>11</sup>

**Table 1** Comparison of clinical and echocardiographic features of atrial septal aneurysm patients and controls

|                          | Patients<br>(N = 40) | Controls<br>(N = 30) | P-value |
|--------------------------|----------------------|----------------------|---------|
| Age (years)              | 54.4 ± 16.3          | 49.8 ± 11.2          | NS      |
| Male/female (n/n)        | 15/25                | 12/18                | NS      |
| LA diameter (mm)         | 33.5 ± 3.4           | 34.2 ± 3.6           | NS      |
| LVEDD (mm)               | 43.1 ± 4.1           | 44.2 ± 4.9           | NS      |
| LVESD (mm)               | 22.6 ± 2.7           | 24.4 ± 2.2           | NS      |
| RA diameter (mm)         | 33.5 ± 3.3           | 32.8 ± 3.1           | NS      |
| LVEF (%)                 | 64.2 ± 5.2           | 64.8 ± 5.3           | NS      |
| BSA (m <sup>2</sup> )    | 1.9 ± 0.5            | 1.8 ± 0.3            | NS      |
| SPAP (mmHg)              | 28.5 ± 3.8           | 25.4 ± 3.4           | NS      |
| SBP (mmHg)               | 121 ± 23             | 122.5 ± 25           | NS      |
| DBP (mmHg)               | 74.2 ± 11            | 80.3 ± 12            | NS      |
| BMI (kg/m <sup>2</sup> ) | 25 ± 3.5             | 23 ± 3.1             | NS      |
| Smoking (n)              | 10                   | 11                   | NS      |

**Abbreviations:** BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RA, right atrium; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure.

In previously published studies, the incidence of AF in ASA patients ranged from 0% to 23%.<sup>12</sup> Janion and Kurzawski<sup>13</sup> reported that P-wave dispersion and paroxysmal AF was more common in ASA patients. In another study,<sup>14</sup> it was reported that supraventricular arrhythmia and P-wave dispersion were more common in ASA patients than in control subjects.

The relationship between leukocytes and increased cardiovascular risk is well known. Horne et al<sup>15</sup> have aimed to determine the predictive ability of total WBC count and its subtypes for risk of death or myocardial infarction, and found that high neutrophil and monocyte counts and low

**Table 2** Comparison of biochemical parameters of atrial septal aneurysm patients and controls

|  | Patients<br>(N = 40) | Controls<br>(N = 30) | P-value |
|--|----------------------|----------------------|---------|
| Glucose (mg/dL)                              | 97.1 ± 13.9          | 93.3 ± 13.0          | NS      |
| Creatinine (mg/dL)                           | 0.7 ± 0.2            | 0.8 ± 0.3            | NS      |
| Total cholesterol (mg/dL)                    | 195.9 ± 52           | 199.2 ± 56           | NS      |
| Triglyceride (mg/dL)                         | 124 ± 26             | 125 ± 29             | NS      |
| Low-density lipoprotein cholesterol (mg/dL)  | 125.3 ± 9.5          | 133.7 ± 15           | NS      |
| High-density lipoprotein cholesterol (mg/dL) | 45.8 ± 9.5           | 44.9 ± 8.6           | NS      |
| Hemoglobin (g/dL)                            | 14.2 ± 2.5           | 14.3 ± 2.6           | NS      |
| Platelet count (×10 <sup>3</sup> )           | 248.5 ± 62.1         | 282.3 ± 79.2         | NS      |
| Leukocytes, mm <sup>3</sup>                  | 8832 ± 2238          | 8225 ± 2116          | NS      |
| Neutrophils, mm <sup>3</sup>                 | 6318 ± 2425          | 4686 ± 1311          | <0.001  |
| Lymphocytes, mm <sup>3</sup>                 | 1862 ± 625           | 2911 ± 837           | <0.001  |
| Monocytes, mm <sup>3</sup>                   | 586 ± 142            | 458 ± 124            | NS      |
| Neutrophil/lymphocyte ratio                  | 3.4 ± 1.5            | 1.6 ± 0.97           | <0.001  |

lymphocyte counts as well as high NLR are independently related to increased cardiovascular events. Işık et al<sup>16</sup> showed an independent relationship between NLR and coronary artery ectasia. Leukocyte subtype and NLR are also indicators of systemic inflammation.<sup>17,18</sup>

Recently, NLR has been proposed as a useful biomarker to predict cardiovascular risk.<sup>19,20</sup>

More recently, Gibson et al<sup>21</sup> speculated that high NLR has been associated with postoperative AF development in patients who have undergone cardiac surgery. Rienstra et al<sup>22</sup> examined the 936 participants in the Framingham Heart Study original cohort and found that an increased WBC count was associated with AF incident during 5 years of follow-up.

However, there are no studies on specific relationships between the inflammatory cells and paroxysmal AF in patients with ASA.

When two groups were compared in our study, neutrophil count and NLR of the patients with ASA were significantly higher than in the control group, and lymphocyte levels of ASA patients were significantly lower than lymphocyte levels of the controls.

In this comprehensive study, we have demonstrated that NLR is significantly higher in ASA patients than in control subjects, and it is thought that this may be related to paroxysmal AF and thromboembolism, which are more common in those patients.

## Conclusion

It was found in our study that there might be an association between ASA and NLR. The measurement of NLR may be used to indicate increased risk of arrhythmia such as AF. The most important restriction of our study was the limited number of patients. Another limitation in the current study was that we assessed leukocytes and subtypes by an automatic cell counter. More specific cell determinations could be performed by a flow cytometer with a cluster of differentiation antigens. The other limitations of our study were that it was not prospective, it did not include AF and stroke patients, and the patients were not followed up for arrhythmias and stroke.

We have shown for the first time that patients with ASA have higher NLR compared with controls. Further studies are required to determine the relationship between NLR and ASA.

## Disclosure

The authors report no conflicts of interest in this work.

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