

# Accurate use of neutrophil/lymphocyte ratio from the perspective of laboratory experts

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## Dear editor

I read with great interest the recent published article “Neutrophil/lymphocyte ratio in patients with atrial septal aneurysm” by Demir and Demir.<sup>1</sup> In this study, researchers compared the neutrophil/lymphocyte ratio (NLR) between patients with atrial septal aneurysm (ASA) and controls. It was reported that patients with ASA have higher NLR compared with controls.<sup>1</sup> There are some points that we would like to address from this study.

Firstly, a white blood cell (WBC) count of more than 12,000 cells per  $\mu\text{L}$ , or less than 4,000 cells per  $\mu\text{L}$ , was mentioned as one of the exclusion criteria.<sup>1</sup> However, the authors did not state why these values were used as the limits for inclusion. Whether a WBC count of more than 12,000 cells per  $\mu\text{L}$  is accepted as an indicator of inflammation or infection is unclear, and there is no mention of the literature that this value is based on, or which device (brand/model) was used for the WBC count. The WBC reference ranges may vary depending on many factors such as the population studied, the individual laboratory, and the instruments (eg, types of collection tubes) or measurement methods used (eg, waiting period prior to analysis).<sup>2,3</sup>

Secondly, despite comparing groups based on neutrophil and lymphocyte counts, there was no exclusion criteria specified for these parameters. According to Horne et al,<sup>4</sup> and as stated in the study,<sup>1</sup> high neutrophil, monocyte, and NLR counts, as well as low lymphocyte counts, are independently related to increased cardiovascular events. However, in this study, Table 2 shows an increased total lymphocyte count (TLC) in controls ( $2,911 \pm 837$  cells per  $\text{mm}^3$ ) draws attention rather than the low TLC of patients ( $1,862 \pm 625$  cells per  $\text{mm}^3$ ).<sup>1</sup> A TLC significantly higher than 2,900 lymphocytes in a  $\mu\text{L}$  of blood is generally considered to be an indicator of lymphocytosis in adults.<sup>3</sup> If you accept 2,900 cells per  $\text{mm}^3$  as the upper limit of the TLC, the differential diagnosis of lymphocytosis should be given to the controls included in the study. However, in several other sources 4,000 cells per  $\text{mm}^3$  is regarded as the upper limit of the TLC.<sup>5,6</sup> Additionally, although the TLC obtained from the patient group was relatively lower than in the control group, all results were within the reference values.<sup>3</sup> Therefore, it would not be correct to declare that the patient group had a low TLC. On the basis of this information, evaluation of the percentage of lymphocytes and neutrophils may also be important in patient groups with borderline TLC values. Automated blood counting instruments should provide percentage values for each type of WBC count.

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Thirdly, the measurement of NLR was suggested as an indicator of increased risk of arrhythmia, based on the association found between ASA and NLR in the study, however the physiopathological causes supporting this conclusion were not thoroughly discussed.<sup>1</sup> NLR has been used frequently to predict outcomes in patients with cancer and coronary artery disease.<sup>7,8</sup> Systemic inflammation is thought to be a risk factor for cardiovascular disease, and NLR, which integrates the detrimental effects of neutrophilia (an indicator of inflammation) and lymphopenia (an indicator of physiological stress), has emerged as a useful prognostic marker.<sup>8</sup> Possible causes affecting neutrophil/lymphocyte counts and the confounding factors which have a considerable effect on the clinical availability of NLR should be discussed in more detail in this study population.

Finally, NLR itself alone without other inflammatory markers may not accurately provide information about the prognosis of the patients. There are studies evaluating soluble P- and E-selectin, interleukin-6, and high-sensitivity C-reactive protein (hs-CRP) as indices of prothrombotic and proinflammatory activity in a similar group of patients.<sup>9,10</sup> While assessing the predictive values of parameters like NLR (derived from the ratios), and comparing them for validity and accuracy, proven markers will provide more reliable results every time.

In conclusion, the types of collection tubes, waiting period prior to analysis, instrumental parameters and reference ranges for each parameter must be specified as they are easily affected by analytical and preanalytical variables in studies based on laboratory results.<sup>11</sup>

## Disclosure

The authors report no conflicts of interest in this correspondence.

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