The relationship of neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) parameters with mortality in intensive care unit (ICU) patients

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INTRODUCTION

Nowadays, the actual focus is the improving clinical outcomes of patients with critical illness in intensive care unit (ICU). Their C-reactive protein (CRP) reactions are higher than the normal patients because of the severe inflammation reactions within their bodies. Thus, their mortality rate is high and critical which is approaching 35% among patients with expected stays of more than three days in ICU [1]. Therefore, there are many parameters to evaluate the immune system response properly. Antibodies play a critical role in the immune system and protection against viral and bacterial infections within the body.

Leukocytes are classified into two main groups: granulocytes and nongranulocytes (agranulocytes). The granulocytes, mainly which include neutrophils, eosinophils, and basophils, have granules in their cell cytoplasm and also have a multilobed nucleus. Leukocytes and granulocytes involved in certain autoimmune diseases and in immediate-type hypersensitivity [2].

The term granulocyte includes neutrophil, eosinophil, basophil, mast cells, dendritic cells, monocyte-macrophages, and phagocytes while lymphocytes consist of natural killer cells and some cells specialized under the “T” and “B” lymphocyte groups [2]. Especially, neutrophilic granulocytes are very effective in inflammatory reactions and the immune system. While the granulocytes are called innate immunity, leukocytes are termed in the acquired immune system [3].

Throughout a person life, innate immune system is observed predominantly. If an antigen across the body barriers, it first encounters with innate defense system (granulocytes). This innate response is often triggered by recognizing general characteristics found in large groups of microorganisms. In other words, this response is not specific to a single microorganism. In the presence of a microorganism that crosses body barriers, eicosanoids and some cytokines are secreted from damaged or infected cells, and these stimuli mediate the formation of the first response by the immune system against infection, called inflammation [4]. The four main symptoms of inflammation are described as fever, redness, pain and swelling. The cause of the redness in the
damaged area is the enlargement of the blood vessels. Neutrophils migrate to the heavily damaged area with the effect of both the enlargement of the blood vessels and the molecules called leukotrienes found in the secreted cytokines. Neutrophils constitute approximately 50-60% of leukocytes in the blood [5]. Neutrophils are named as “neutrophils” because their granules do not tend to bind to the dyes used in histological examination. Neutrophils are produced in the bone marrow and then pass into the bloodstream [6].

Lymphocytes, like neutrophils, are produced in the bone marrow, but unlike granulocytes, they can fulfill their functions after going through a maturation process [7]. The lifespan of lymphocytes can range from a few weeks to several years. This period is considerably longer compared to neutrophils.

The neutrophil/lymphocyte ratio (NLR) is an indicator that is calculated using the neutrophil and lymphocyte values in the whole blood test, and its popularity is increasing day by day. NLR is generally accepted as an indicator of sub-clinical inflammation [8-10]. This study will focus mainly on short-term mortality predicting with the important parameters as CRP, NLR, age, and gender on ICU patients. So rapid and predictive results could be obtained, a significant criterion for the clinician in the assessment of severity of illness of ICU patients and likelihood of survival of the critically ill.

**MATERIAL AND METHOD**

The results obtained from the samples taken from the ICU between January 1, 2015, and August 31, 2019 (retrospective file scan) by examining the HSYS (public health system of Turkish Ministry of Health) records of the patients. In this study, hemogram and biochemical analysis parameters are analyzed for research purposes, as follows:

1. CRP,
2. neutrophil,
3. lymphocyte, and
4. immatur granulocyte count are “IG”.

The files were examined within the scope of the research by dividing these parameter values in the hemogram into groups such as age and genders. The process of leaving the hospital was evaluated as exit and outpatient exit. The data obtained as a result of the evaluation were prepared in accordance with the statistical methodology.

### Table 1. Some baseline characteristics of patient groups and difference analysis results

<table>
<thead>
<tr>
<th></th>
<th>Non-exit (n=286)</th>
<th>Exit (n=298)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean±SD</td>
<td>57.13±21.44</td>
<td>68.70±16.69</td>
<td>0.000*</td>
</tr>
<tr>
<td>Gender: n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>125 (43.7)</td>
<td>147 (49.3)</td>
<td>0.100a</td>
</tr>
<tr>
<td>Male</td>
<td>161 (56.3)</td>
<td>151 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>11.65±7.43</td>
<td>12.50±6.68</td>
<td>0.800*</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1.26±1.04</td>
<td>1.15±1.17</td>
<td>0.006*</td>
</tr>
<tr>
<td>NLR</td>
<td>13.36±13.08</td>
<td>17.48±25.80</td>
<td>0.029*</td>
</tr>
<tr>
<td>CRP</td>
<td>122.36±103.90</td>
<td>167.27±141.10</td>
<td>0.000*</td>
</tr>
<tr>
<td>IgG</td>
<td>0.30±0.72</td>
<td>0.38±0.60</td>
<td>0.005*</td>
</tr>
<tr>
<td>IgG percent</td>
<td>1.84±1.17</td>
<td>2.56±1.55</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Note. *Mann Whitney U test; aFishing’s exact test; & SD: Standard deviation

### Table 2. Spearman’s rho correlation analysis results for mortality related factors

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.266*</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.056</td>
<td>0.174</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0.010</td>
<td>0.800</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>-0.114*</td>
<td>0.006</td>
</tr>
<tr>
<td>NLR</td>
<td>0.090*</td>
<td>0.029</td>
</tr>
<tr>
<td>CRP</td>
<td>0.214*</td>
<td>0.000</td>
</tr>
<tr>
<td>IgG</td>
<td>0.144*</td>
<td>0.005</td>
</tr>
<tr>
<td>IgG percent</td>
<td>0.175*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note. *p<0.05 & **p<0.01

**Statistical Methods**

Age and mortality parameters described with frequency analysis, whereas scale parameters were described with means and standard deviations. Fischer’s exact test was used for gender differences between patient groups. Kolmogorov Smirnov test was used for normality of scale parameters. Since all parameter distributions were non-normal, nonparametric tests were used.

Mann Whitney U test was used for differences of scale parameters. Spearman’s rho test was used for correlation between parameters, and binary logistic regression analysis was used for multivariate analysis. SPSS 17.0 for analysis at 95% confidence interval with 0.05 significance level.

**RESULTS**

272 were female and 216 were male of the patients. The results in Table 1 were obtained when they were divided into two groups as exitus and non-exitus. There was no difference between the two groups in terms of gender. Age factor was found to be significantly higher in the group with exitus compared to the nonexitus group (p<0.000). Age, NLR, CRP, IgG, and IgG percent levels of exitus group patients were significantly higher than non-exitus group (p<0.05). Lymphocyte level of non-exitus group was significantly higher (p<0.05) than exitus group (Table 1).

Spearman’s rho correlation analysis results showed that age, CRP, NLR, IgG, and IgG percent parameters had positive and significant correlation with mortality, whereas lymphocyte has significant and negative correlation with mortality (p<0.05) (Table 2).

At multivariate level, effects of age and CRP on mortality at ICU were significant (p<0.05). However, effects of lymphocyte, NLR and IgG were insignificant (p>0.05). Since IgG and IgG percent parameters were cointegrated, and same parameters, IgG percent parameter was excluded from multivariate analysis (Table 3).

Both age and CRP means of exitus group were significantly higher (Figure 1 and Figure 2).

**DISCUSSION**

Today, laboratory tests play a very important role in the diagnosis of diseases, determination of prognosis and selection of medical treatments to be applied. The most important medical decision tool that can guide clinicians during the evaluation of laboratory tests is the reference
interval. The reference interval refers to the range of numbers obtained from a population of reference individuals using a number of statistical methods, in which the measurement results for that test can be considered normal. 

There are many studies in the literature investigating the relationship of NLR value with different clinical conditions. However, due to the fact that the reference intervals in blood parameters vary depending on both age and gender, the differences between the measurement methods also affect the measurement results, and the differences between the populations have an effect on the reference values, studies in which reference intervals are determined for male and female genders in different age groups are quite difficult and limited.

The mortality rate among patients admitted to the ICU depends on many factors such as the underlying cause, age, duration of mechanical ventilation, and the severity of the disease. Mortality rates have been reported to range from 14% to 41.1% worldwide [11]. There are many factors affecting mortality in the ICU. When these factors are examined, NLR is accepted as an indicator of sub-clinical inflammation. Inflammation is a body’s process for fighting against things that harm it, like infections, injuries, and toxins, in an attempt to heal itself. When something damages your cells, your body releases chemicals that trigger a response from your immune system.

In the present study, not only NLR values of intensive care patients, but also hemogram tests and age, NLR, CRP, and IgG value analyzes were performed. In particular, considering the importance of NLR in mortality, there are many studies in the literature investigating the relationship between NLR values and some diseases. It has been reported that NLR values in community-acquired pneumonia are higher than 13 in hospitalized patients, NLR values are higher than 18 in patients followed in the ICU, and mortality rate is quite high in patients with NLR values of 23 or higher [12]. In addition, it has been reported that the prognosis is worse in patients with metastatic prostate cancer with an NLR value above five, and NLR values may be useful in making the decision for immunotherapy [5]. There are many studies in the literature investigating the relationship of NLR value with different clinical conditions. However, studies in which reference intervals in blood parameters vary depending on both age and gender and other biochemical analyzes are very limited.

The aim of this study is to make sense of the mortality relationship between NLR and CRP values. While the non-exitus group showed significantly higher ratio of lymphocyte, as expected, exitus patients demonstrated high level of NLR, CRP, and IgG. Additionally, most of the exitus patients are observed in older ages [13]. The most mortality is observed in patients with high CRP value. CRP level is very effective on immune system of the body which is adversely effective on it. CRP is usually measured in milligrams of CRP per liter of blood (mg/L). Normal CRP levels are typically below 3.0 mg/L [4]. However, not only in ICU patients this level is significantly higher but also lymphocyte is observed in lower rates. In a study conducted on a population of 1,070 people without any health problems or complaints, it was reported that there is a strong correlation between diabetes and hypertension, which includes chronic inflammatory processes, and NLR values above 2.57 [14].

In a study conducted in Turkey, it was reported that a NLR value above 3.5 was significantly correlated with the diagnosis of acute appendicitis in childhood acute appendicitis with a suitable clinical picture [15]. Inflammation is a body’s process for fighting against things that harm it, like infections, injuries, and toxins, in an attempt to heal itself. When something damages your cells, your body releases chemicals that trigger a response from your immune system. NLR is accepted as an indicator of sub-clinical inflammation [10]. Thus, this study is important because the comparison of mean laboratory values between hospital exitus and non-exitus patients will be useful.

**Table 3.** Binary logistic regression analysis results for mortality related factors

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI for OR Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.034</td>
<td>0.006</td>
<td>31.74</td>
<td>0.000</td>
<td>1.035</td>
<td>1.023</td>
<td>1.047</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>0.019</td>
<td>0.096</td>
<td>0.037</td>
<td>0.847</td>
<td>1.019</td>
<td>0.843</td>
<td>1.231</td>
</tr>
<tr>
<td>NLO</td>
<td>0.007</td>
<td>0.006</td>
<td>1.380</td>
<td>0.240</td>
<td>1.007</td>
<td>0.995</td>
<td>1.020</td>
</tr>
<tr>
<td>CRP</td>
<td>0.002</td>
<td>0.001</td>
<td>5.027</td>
<td>0.025</td>
<td>1.002</td>
<td>1.000</td>
<td>1.004</td>
</tr>
<tr>
<td>IgG</td>
<td>0.204</td>
<td>0.173</td>
<td>1.389</td>
<td>0.239</td>
<td>1.227</td>
<td>0.873</td>
<td>1.723</td>
</tr>
<tr>
<td>Constant</td>
<td>-2.625</td>
<td>0.460</td>
<td>32.514</td>
<td>0.000</td>
<td>0.000</td>
<td>0.072</td>
<td></td>
</tr>
</tbody>
</table>

Note. SE: Standard error & CI: Confidence interval

**Figure 1.** Age distribution of patient groups and differences (Source: Authors)

**Figure 2.** CRP distribution of patient groups and differences (Source: Authors)
to reveal statistically importance in differences of little clinical relevance and predictive power.

**Author contributions:** SZMK: provided support on academic consultancy and administrative process management throughout the entire research process and in the analysis of results; YA: provided support on academic consultancy and administrative process management throughout the entire research process and in the analysis of results, designed the figures; & NPC, YU, YTS, EAA, & EK: provided support on throughout the entire research process and in the analysis of results. All authors have agreed with the results and conclusions.

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**Declaration of interest:** No conflict of interest is declared by authors.

**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

**REFERENCES**


