Leukocyte Count and Neutrophil/Lymphocyte Ratio as Predictor of Mortality in Sepsis Patients

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ABSTRACT

Mortality in septic patients remains high despite much progress in understanding the definition, pathophysiology, and management of sepsis through sepsis bundles. The definition of sepsis changed from initially an inflammatory process caused by infection to organ dysfunction due to the host’s response to infection.1 Until now, many attempts have been made to reduce mortality through diagnosis and management based on pathophysiological knowledge including prognostic factors, which continue to be studied. Quick and precise treatment is needed, resulting in urgency for parameters that can be used to estimate the severity and predict the survival of sepsis subjects at an early stage.2

Both leukocyte count and Neutrophil/Lymphocyte Ratio (NLR) are relatively inexpensive routine tests for infectious patients. Several studies of leukocytes, total neutrophils, total lymphocytes, and NLR were carried out as alternative parameters for monitoring the severity and as prognostic factors.2,6

The research objectives are to determine the difference in the leukocyte count and NLR based on the outcome of sepsis patients and to evaluate their role in predicting mortality.

METHODS

This study was an observational cohort. The subjects of this study were patients diagnosed with sepsis by the clinicians in charge based on a SOFA score > 2.9. The subjects were treated in the Raden Mattaher Hospital Jambi ICU during the study period. The study variables were the leukocyte count and NLR at the time of diagnosis at 0 and 24, 72, and 144 hours. The outcomes were divided into survivor and non-survivor groups. Inclusion criteria: patients diagnosed with sepsis. Exclusion criteria: patients with hematological malignancies. Research ethics were obtained from the Health Research Ethics Commission FKIK Jambi University number B/788/UN21.8/PT.01.04/2019. Research consent was
obtained from the patient or family. Venous blood samples were taken. NLR value consisting of absolute neutrophil and lymphocyte counts was analyzed with an Abbott CD-Ruby SN 71350BG hematology analyzer.

RESULTS AND DISCUSSIONS

There were a total of 34 sepsis patients in the ICU of Raden Mattaher Hospital, which consisted of 20 (58.82%) males and 14 (41.18%) females (Table 1).

The mean age of the subjects was 51.94±15.19 years, the mean age of the non-survivors group was 50.07±15.22 years and the mean age of the survivor group was 50.93±17.60 years. There was no significant difference in age in both groups with p=0.750. A total of 22 (64.71%) subjects had ages of 19-60 years and 12 (35.29%) subjects had ages>60 years (Figure 1).

Table 1. Leukocyte count and NLR of sepsis patients in ICU

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>n</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
<td>0 hour</td>
<td>34</td>
<td>13.91 (3.28-34.18) **</td>
</tr>
<tr>
<td>$(10^9/\mu L)$</td>
<td>24 hour</td>
<td>26</td>
<td>15.47±7.30*</td>
</tr>
<tr>
<td></td>
<td>72 hour</td>
<td>18</td>
<td>14.58±5.84*</td>
</tr>
<tr>
<td></td>
<td>144 hour</td>
<td>11</td>
<td>14.77±5.90*</td>
</tr>
<tr>
<td>NLR</td>
<td>0 hour</td>
<td>34</td>
<td>12.78 (2.95-54.12) **</td>
</tr>
<tr>
<td></td>
<td>24 hour</td>
<td>26</td>
<td>17.14±10.39*</td>
</tr>
<tr>
<td></td>
<td>72 hour</td>
<td>18</td>
<td>9.27 (0.05-35.22) **</td>
</tr>
<tr>
<td></td>
<td>144 hour</td>
<td>11</td>
<td>8.48 (3.77-42.96) **</td>
</tr>
</tbody>
</table>

* parametric data: mean+SD, ** non-parametric data: median (range)

Table 2. The difference in median of leukocyte count and NLR between survivor and non-survivor group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Survivor Median (range)</th>
<th>Non-Survivor Median (range)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count</td>
<td>0 hour</td>
<td>14.44 (3.28-21.29)</td>
<td>15.26 (11.85-25.57)</td>
<td>0.006 a</td>
</tr>
<tr>
<td>$(10^9/\mu L)$</td>
<td>24 hour</td>
<td>14.28 (11.39-19.91)</td>
<td>19.59 (8.69-33.48)</td>
<td>0.302 b</td>
</tr>
<tr>
<td></td>
<td>72 hour</td>
<td>13.61 (8.08-16.49)</td>
<td>17.58 (8.06-20.47)</td>
<td>0.157 b</td>
</tr>
<tr>
<td></td>
<td>144 hour</td>
<td>11.87 (8.96-28.73)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>0 hour</td>
<td>9.06 (4.36-12.78)</td>
<td>12.60 (8.08-42.82)</td>
<td>0.042 a</td>
</tr>
<tr>
<td></td>
<td>24 hour</td>
<td>10.69 (8.41-17.31)</td>
<td>23.79 (20.40-29.73)</td>
<td>0.643 b</td>
</tr>
<tr>
<td></td>
<td>72 hour</td>
<td>9.35 (7.7-11.85)</td>
<td>16.74 (0.05-29.73)</td>
<td>0.402 a</td>
</tr>
<tr>
<td></td>
<td>144 hour</td>
<td>8.32 (3.77-42.96)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

a non-parametric Mann-Whitney U test, b parametric independent samples test

There were a total of 34 research subjects, which consisted of 14 (41.18%) survivors and 20 (58.82%) non-survivors (Table 2).

The turning point of the ROC curve for leukocyte count on mortality in sepsis patients was 15.49 X 103/µL (Figure 2). The diagnostic value of leukocyte count to predict the outcome of a 144-hour evaluation of sepsis patients was as follows: sensitivity of 71.1%; specificity of 70.6%; AUC=0.713; p < 0.001.
The turning point of the ROC curve for NLR at 0 hour on the mortality of sepsis patients was 13.2 (Figure 3). The diagnostic value of the NLR to predict the outcome of 144-hour valuation of sepsis patients was as follows: sensitivity of 65.8%; specificity of 66.7%; AUC=0.665; p=0.005.

The leukocyte count > 15.49X10^3/µL at initial diagnosis was able to predict the death of sepsis patients with a Hazard Ratio (HR) of 4.001 compared to a leukocyte count < 15.49X10^3/µL. The survival rate of patients with leukocyte count < 15.49X10^3/µL and > 15.49X10^3/µL was 89.4% and 64.3%, respectively, with significant differences (p=0.0002).

NLR > 13.2 at initial diagnosis was able to predict death in sepsis patients with HR 3.370 compared to NLR < 13.2. The survival rate of patients with NLR < 13.2 and NLR > 13.2 was 87.2% and 66.7%, respectively, with significant differences (p=0.001) (Figure 4).

The leukocyte immune response to physiological stress such as tissue damage, severe trauma, sepsis, and major surgery is characterized by increased neutrophil and decreased lymphocyte count. Stress inflammation can be indicated by the ratio of the percentage of neutrophils to the percentage of lymphocytes or known as NLR. The NLR in normal conditions is less than 5. In pathological conditions due to severe infection or systemic inflammation, the NLR will increase thereby enabling the evaluation of systemic inflammation.

This study involved 34 sepsis patients who were treated in the ICU and monitored for up to 144 hours, which were divided into the survivor group (14 patients) and the non-survivor group (20 patients).

The leukocyte count was significantly different between both groups at 0 hour; however, there was no significant difference after 24, 72, and 144 hours. This might be due to the treatment and course of the disease, which affected the leukocyte count. The turning point of the ROC curve for the leukocyte count on mortality in sepsis patients was 15.49X10^3/µL with a sensitivity of 71.1% and a specificity of 70.6%. Values above 15.49X10^3/µL were able to predict the death of sepsis patients with an HR of 4.001 compared to those whose values were below the turning point. The survival rate of patients with a leukocyte count below the turning point value was 89.4% compared to that above the turning point value of 64.3% (p=0.0002).

Contrastingly, a study by Hendianingtyas, which analyzed a relationship between the leukocyte count

![Figure 3. ROC curve of NLR on mortality of sepsis patients](image1)

![Figure 4. Survival rate based on (a). leukocyte count with a turning point value of 15.49 X10^3/µL and (b). NLR with a turning point value of 13.2](image2)
and high levels of procalcitonin (PCT) as a marker of bacterial infection to sepsis in the ICU of Dr. Kariadi General Hospital Semarang found that the PCT level in 3 groups was <0.5 ng/mL; 0.5-2 ng/mL and >2 ng/mL with leukocyte counts of 7.27, 13.8 and 8.2, which were not statistically significant. This indicated that the leukocyte count could not be used as a parameter of the severity of the infection. A similar finding was also reported in a study by Dharma et al. that there was no significant correlation between the leukocyte count and procalcitonin levels. Higher procalcitonin indicates the severity of the disease, which has an impact on the outcome. A study by Singer et al. also suggested a low leukocyte count as a marker for severe infection/sepsis.

There was a significant difference of NLR at 0 hour between both groups, which were monitored up to 144 hours, with a turning point value of 13.2. NLR with this turning point was able to predict the risk of death in sepsis patients with HR 3.370. The survival rate of patients with a score below the turning point of 13.2 was 87.2% compared to that above a value of 13.2, which was 66.7% (p=0.001).

This study was in line with other studies, which suggested that the absolute neutrophil count alone can be used as a determinant factor for sepsis with a turning point value of 10710/mm³ in early-onset neonatal sepsis. Russel et al. in a systematic review and meta-analysis also suggested that NLR was useful as a biomarker of infection, especially bacterial and viral influenza, and in critically ill sepsis patients. In addition, there was a significant relationship between NLR and the outcome of sepsis patients.

A study by Yang et al. on COVID-19 patients in China showed that NLR with a turning point of >3.3 indicated a prognostic value of a change in disease severity from mild to severe. COVID-19 patients with age > 49.5 years and NLR > 3.3, 46% gained weight on an average of 6.3 days, whereas COVID-19 patients with age < 49.5 and NLR < 3.3 were able to be cured and go home within 13.5 days. The similar finding was also reported in a study by Wang et al. on ARDS patients in Shanghai China, which showed that the survivor group of ARDS had a lower NLR value than the non-survivor group with a turning point value of 14 with HR 1.532.

A similar finding was also reported by Shimoyama on patients with gastrointestinal perforation showing that NLR with a turning point of 13.28 and HR 1.257, a sensitivity of 62.5%, and a specificity of 66.7% was able to predict mortality. In addition, the report by Altas et al. showed that a turning point value of 11.3 was able to predict mortality of pneumonia patients in the ICU; every increase of 1 point in NLR value led to a 5% increased mortality and the combination of NLR value with SOFA value and APACHE II value could help predict mortality more accurately.

The results of this study were different from a study by Rehman et al. on 168 patients at the AgaKhan Teaching Hospital, which showed that NLR was a good marker for predicting sepsis but was unable to predict mortality. A study by Dafitri et al. in Padang showed no correlation between NLR and PCT and no correlation between NLR and disease outcome. The similar finding was found by Colakoglu et al. in patients with acute abdominal surgery in Turkey, which reported significant mean platelet volume. A report by Yildiz on 398 patients with sepsis and septic shock in the Turkish ICU showed that higher NLR was reported in sepsis patients and higher 28-day mortality was reported in the septic shock group. There was no relationship between NLR at admission and 28-day mortality.

The different results of NLR as a predictor of mortality among several studies and the results of this study might be due to differences in the etiology of the disease, different turning point values with wide variations, and different lengths of observation to assess mortality.

CONCLUSIONS AND SUGGESTIONS

Leukocyte count > 15.49X10³/μL and NLR > 13.2 at the initial diagnosis of sepsis were able to predict death at 144-hour evaluation. Leukocyte count > 15.49X10³/μL and NLR > 13.2 was able to be a predictor of mortality and an indicator of a need for aggressive management in sepsis patients.

A further study with a larger number of samples was needed.

REFERENCES

10. Shimoyama Y, Umegaki O, Agui T, Kadono N, Minami T. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are superior to other inflammation-based prognostic scores in predicting mortality of patients with gastrointestinal perforation. JA Clinical Reports, 2017; 3: 49.