Comparison of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio levels in ovarian cyst among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia

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**Objective:** Ovarian cancer is the most common malignancy of women and generally diagnosed at advanced stage therefore tends to have poor prognosis. The inflammatory process is proven involved in malignancy mechanism which Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have potential as independent prognostic markers. This research was to evaluate NLR and PLR levels in ovarian cysts among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan

**Materials and Methods:** This research is a comparative case-control study conducted at Department of Obstetrics and Gynecology at RSUP H. Adam Malik Medan on December 2019 – February 2020. The research sample were 40 patients diagnosed with ovarian cysts and epithelial ovarian cancer, respectively. Bivariate analysis was done with independent T test if data was normally distributed or Mann Whitney if not normally distributed. All results will use a significance value <0.05.

**Results:** Median NLR level in ovarian cancer group was 2.45 (1.06 – 38.44) and in ovarian cysts group was 2.34 (1.44 – 3.78). Median PLR levels in ovarian cancer group was 12813.94 (3178.08 – 19040.0) and in ovarian cysts group was 11138.15 (5026.18 – 22839.51). Based on analysis test, it was found that there was no statistically significant difference of NLR and PLR levels in ovarian cancer compared to ovarian cysts (p>0.05).

**Conclusion:** NLR and PLR levels between ovarian cancer and ovarian cyst patient in RSUP H. Adam Malik Medan shows no difference in value. NLR and PLR can still be used as a marker for malignant process in patient suspected with malignancy.

1. Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have potential as independent prognostic markers for ovarian cancer.
2. This research was to evaluated NLR and PLR levels in ovarian cysts with epithelial ovarian cancer patients at RSUP H. Adam Malik Medan.
INTRODUCTION

Based on GLOBOCAN data in 2018, ovarian cancer is most common malignancy with 6th and 10th order for all cancers. There were around 13,310 (7.1%) new cases in 2018. Approximately 70% of women with ovarian cancer are diagnosed at stadium 3 and 4 with 5-year survival only 40%. When disease is detected at early stage, prognosis is much better and 5-year survival rate approaches 90%. Cancer development and metastasis are influenced by inflammation and immunology. The Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) are indicators of systemic and immunological inflammation. NLR and PLR are markers of systemic inflammatory response, which function as an independent prognostic markers in ovarian cancer for poor clinical outcome. Williams et al. in his study at 2014 stated that elevated NLR levels was connected with advance stage disease, moderate to poor histological and pathological differentiation, and unfavorable prognosis. Previous studies have shown diagnostic value of NLR in benign ovarian cysts is 2.25 and PLR for benign ovarian cysts is 128.08, while NLR value for ovarian cancer is 3.54 and PLR for ovarian cancer is 198.87. In addition, Miao et al. explained that elevated NLR levels is linked with more severe PFS. In Chen et al. study, The ovarian cancer group had considerably greater platelet counts and PLR than the endometriosis group. Platelet count and PLR are available parameters that are useful in detecting ovarian cancer.

From several studies that have been carried out, there is some controversy over NLR and PLR value in patients with ovarian cancer and ovarian cysts, which are correlated with prognosis and course of patient’s disease. Based on this phenomena, researchers want to compare NLR and PLR cut off values in patients with ovarian cancer and ovarian cysts to see if they may be used as an independent predictive diagnostic for malignant cases.

MATERIALS AND METHODS

This research is a comparative case-control study conducted at Department of Obstetrics and Gynecology at RSUP H. Adam Malik Medan on December 2019 – February 2020. This study consisted of 40 patients diagnosed with ovarian cysts and epithelial ovarian cancer at Department of Gynecology-Oncology RSUP H. Adam Malik Medan, respectively. The inclusion criteria in this research were ovarian cyst patients who had been confirmed histopathologically and who had medical records at RSUP H. Adam Malik Medan and epithelial ovarian cancer patients who had been confirmed histopathologically and who had medical records at RSUP H. Adam Malik Medan. While exclusion criteria were patients with epithelial ovarian cancer and ovarian cysts who had other concurrent oncological diseases, patients with epithelial ovarian cancer and ovarian cysts who had other diseases such as heart valve disorders, viral infections, autoimmune diseases, blood disorders that could affect neutrophil values, lymphocytes and platelets significantly, patients with epithelial ovarian cancer and ovarian cysts who did not have routine preoperative blood laboratory data and complete operating reports, patients with epithelial ovarian cancer and ovarian cysts with other gynecological diseases.

Researchers conducted a search of histopathological data that had been examined by Anatomical Pathology from ovarian cysts and epithelial ovarian cancer patients. Then, anthropometric records, such as height and weight, were recorded from medical record data. In medical record, researchers took data on complete blood counts, patient age, and history of parity, NLR and PLR. This study had received ethical approval through the Health Research Ethics Committee of the Faculty of Medicine Universitas Sumatera Utara.

Statistical analysis

To assess frequency distribution of study sample characteristics based on age, parity, neutrophils, platelets, and lymphocytes, univariate and multivariate statistical analysis were performed. To assess normality of data distribution, Kolomogorov-Smirnov normality test was used. Bivariate analysis was done with independent T test was if the data was normally distributed or Mann Whitney test if the data was not normally distributed. All results will use a significance value <0.05. Data will be presented in tabulated form.

RESULTS AND DISCUSSION

Based age, research patients with ovarian cancer were 31 patients (77.5%) aged 18-49 years and as many as 9 patients (22.5%) aged 50 years, while research patients with ovarian cysts were 29 patients (72.5%) aged 18-49 years, as many as 10 patients (25.0%) aged 50 years, and as many as 1 person (2.5%) aged <18 years. Based on menopausal status, majority of research patients who were not menopausal experienced ovarian cancer as many as 33 patients (82.5%) and 34 patients (84.6%) for each group.
Table 1. Research patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ovarian cancer</th>
<th>Ovarian cyst</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>18-49</td>
<td>31</td>
<td>29</td>
<td>72.5%</td>
</tr>
<tr>
<td>≥50</td>
<td>9</td>
<td>10</td>
<td>25.0%</td>
</tr>
<tr>
<td>Menopause Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>6</td>
<td>15.4%</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>34</td>
<td>84.6%</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>5</td>
<td>8</td>
<td>20.5%</td>
</tr>
<tr>
<td>Secundi-Multiparous</td>
<td>14</td>
<td>8</td>
<td>20.5%</td>
</tr>
<tr>
<td>Grandemultiparous</td>
<td>21</td>
<td>24</td>
<td>59.0%</td>
</tr>
</tbody>
</table>

Table 2. Differences in mean levels of NLR and PLR in ovarian cancer and ovarian cysts patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR Ovarian Cancer</td>
<td>5.27</td>
<td>8.39</td>
<td>2.45</td>
<td>1.06</td>
<td>38.44</td>
<td>0.351</td>
</tr>
<tr>
<td>Ovarian Cyst</td>
<td>2.38</td>
<td>0.48</td>
<td>2.34</td>
<td>1.44</td>
<td>3.78</td>
<td></td>
</tr>
<tr>
<td>PLR Ovarian Cancer</td>
<td>20881.74</td>
<td>31973.82</td>
<td>12813.94</td>
<td>3178.08</td>
<td>190400.0</td>
<td>0.285</td>
</tr>
<tr>
<td>Ovarian Cyst</td>
<td>11894.29</td>
<td>4814.34</td>
<td>11138.15</td>
<td>5026.18</td>
<td>22839.51</td>
<td></td>
</tr>
</tbody>
</table>

* Mann Whitney Test

Based on parity, research patients of ovarian cancer with grandemultipara were 21 patients (52.5%) and 24 patients (59.0%) respectively. There was no difference between age, menopause status or parity between patients with ovarian cancer and those with ovarian cysts (p>0.05).

Median NLR level in ovarian cancer group was 2.45 (1.06 – 38.44) and in ovarian cysts group was 2.34 (1.44 – 3.78). The median PLR level in ovarian cancer group was 12813.94 (3178.08 – 1904.00) and in ovarian cysts group was 11138.15 (5026.18 – 22839.51). The analysis test revealed that there was no statistically significant difference in NLR and PLR levels between patients with ovarian cancer and those with ovarian cysts (p>0.05).

In this research, it was found that patients with ovarian cancer were dominated by patients aged 18-49 years (77.5%), followed by patients aged 50 years (22.5%). Meanwhile, ovarian cysts group are also dominated by patients aged 18-49 years (72.5%), followed patients aged <18 years (2.5%) and patients aged 50 years (25%). Based on analysis results, there was no difference patients aged between ovarian cancer and ovarian cysts group. This is different from previous studies. Nurlailiyan’s research found that of 82 ovarian cancer patients, only 1.2% of patients aged <20 years old, followed by 12.2% aged 20-34 years old, 37.8% aged 35-50 years old, and largest age group was those aged over 50 years which is 48.8%. In women with ovarian cancer, the mean age at diagnosis was 63 years old, and age was a major risk and prognosis factor; therefore the prognosis of elderly patients is worse, with progression-free survival (PFS) and overall survival results proportional to age.12

In this research, it was also found that 33 (82.5%) patients with ovarian cancer had not experienced menopause, and ovarian cyst patients who have not experienced menopause as many as 34 people (84.6%). Each year, over 23,000 cases of epithelial ovarian cancer are reported in the United States, with a median age at diagnosis being 63 years old.13 Although postmenopausal women account for more than two-thirds of ovarian cancer incidences, the majority of established risk factors arise predominantly when women are in their twenties or thirties. According to one study, menopausal age is negatively connected to the development of ovarian cancer. These studies suggest that menopause at a later age is associated with an increased risk of ovarian cancer.14

The majority of postmenopausal ovarian cancer patients are between the ages of 60 and 64 worldwide; with the median age upon diagnosis in developed countries is 63 years old. According to the research by Shen et al, 38% of women diagnosed with epithelial ovarian cancer and 76% of women diagnosed with borderline epithelial ovarian cancer were diagnosed before menopause, implying that the age at diagnosis of ovarian cancer in Chinese (Asian) women is younger than in Caucasians. Therefore, it is crucial to study if Asian women’s younger age at diagnosis could explain their poor clinical prognosis.15,16
Tumor-associated inflammation is thought to have a key role in carcinogenesis and tumor progression. In clinical practice, assessing tumor inflammatory response is simpler and less expensive. The immune system's function in disease remission or progression has been studied, and hematological markers such as leukocytes have been postulated as diagnostic and prognostic criteria in a variety of malignancies. The NLR has been suggested as simple index of systemic inflammatory response in patients with cancer. NLR and PLR are considered as predictive factors in survival of ovarian cancer patients. In addition, preoperative NLR and PLR can help differentiate malignant ovarian masses from benign ovarian masses.

In this research, Mean NLR value for ovarian cancer group was 5.27, median was 2.45 and SD was 8.39 and Mean NLR value for ovarian cysts group was 2.38, median was 2.34 and SD was 0.48. The statistical test result showed the p value of this comparison was 0.351. Based on this result, NLR levels did not differ statistically between ovarian cancer and ovarian cyst patients (p>0.05).

In this research, Mean PLR value for ovarian cancer group was 20881.74, median was 12813.94 and SD was 31973.82 compared to Mean PLR value for ovarian cysts group was 11894.29, median was 11138.15 and SD was 4814.34. The statistical test results result showed the p value of this comparison was 0.285. Based on this result, there was no statistically significant difference in PLR levels between ovarian cancer patients and ovarian cysts patients (p>0.05).

In this research, we analyzed calculation of NLR and PLR as markers of inflammation in epithelial ovarian cancer and ovarian cysts patients. Statistical studies on each level of NLR and PLR revealed no statistically significant connection between NLR and PLR levels and the prevalence of epithelial ovarian cancer and ovarian cysts (p>0.05). However, mean and median NLR values of subjects with ovarian cancer had higher values (5.27 and 2.45) than subjects with ovarian cysts which could have clinical significance (2.38 and 2.34).

This is not in accordance with study by Yildirim. It is found that individuals with ovarian cancer had significantly elevated NLR and PLR levels (p <0.05 and p <0.001). According to a multivariate analysis, greater NLR and PLR levels predicted ovarian cancer at a cut-off value of 3.35, with 55% sensitivity and 81% specificity for NLR. (95% CI: 0.544-0.752, p <0.05) and cut-off value of 572.9, with 100% sensitivity and 83% specificity for PLR (95% CI: 0.192-0.381, p=0.001). According to the findings of the study, preoperative NLR and PLR readings could detect ovarian cancer in patients with adnexal masses.

Another study with differing results included 316 patients with benign adnexal masses and 253 patients with malignant adnexal masses were treated surgically. From that study, values of NLR, PLR, neutrophil, CA-125, and platelets were higher in malignant compared with benign cases (p <0.01), and can be used to detect ovarian malignancy at an early stage, it will improve treatment options, and increased survival rates.

Although there was no significant difference between PLR values between ovarian cancer and ovarian cysts patients, the results showed that overall PLR values for ovarian cancer were higher than for ovarian cysts patients.

This study contains various limitations. The use of a case control design in a retrospective study made determining external variables difficult owing to technical constraints and many risk factors that were not clearly informed. Furthermore, this study was only taken from RSUP H. Adam Malik Medan as national referral hospital which has different characteristics of patients with ovarian cancer and ovarian cysts, such as number of comorbidities that have not been detected since admission. The data collected failed to prove statistically association between mean NLR and PLR levels in patients with ovarian cancer and ovarian cysts due to the small number of samples, research factors, and short research period, sample data in this study. The strength of this study is this is the first study to assess difference of mean NLR and PLR levels in patients with epithelial ovarian cancer and ovarian cysts therefore it can be used as a basis for future research.

**CONCLUSION**

NLR and PLR levels between ovarian cancer and ovarian cyst patient in RSUP H. Adam Malik Medan shows no difference statistically. However, NLR and PLR levels are still an inflammatory process that is linked to malignancy mechanism and this result does not hinder the use of obtaining NLR and PLR levels in patients with suspected malignancy. Further studies need to obtain larger sample with less random characteristics to maximize the outcome of this study.

**DISCLOSURES**

**Acknowledgment**

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**Conflict of interest**

There are no conflicts of interest among the authors.

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**Author Contribution**

All authors participated to all aspects of this study, including preparation, data collection and analysis, drafting, and approval for publishing.

**REFERENCES**


