# Relationship Between Preoperative Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios in the Probable Diagnosis of Malignant or Borderline Ovarian Tumors

**Tae Hui Yoon**
Daegu Catholic University Medical Center
**Eun Byeol Cho**
Daegu Catholic University Medical Center
**Ki Ho Seol**
Daegu Catholic University Medical Center https://orcid.org/0000-0001-6206-6425
**Jung Min Ryu**
Daegu Catholic University Medical Center https://orcid.org/0000-0003-0125-9754
**Youn Seok Choi** ( drcys@cu.ac.kr )
Daegu Catholic University Medical Center https://orcid.org/0000-0001-8901-9434

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# Abstract

**Background:** The purpose of this study was to investigate whether neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can be supplementary tools to differentiate benign, borderline, and malignant ovarian tumors.

**Methods:** This retrospective study reviewed the postoperative histopathology in patients with ovarian tumors (220 benign, 59 borderline, and 228 malignant). White blood cell, platelet, neutrophil and lymphocyte counts, percentage of neutrophils and lymphocytes, calculated NLR and PLR were analyzed between groups using complete blood count tests performed before surgery.

**Results:** The platelet count and PLR in borderline ovarian tumors tended to be statistically close to benign ovarian tumors, while the neutrophil and lymphocyte count, NLR tended to be statistically close to malignancy. The diagnostic cut-off value of NLR for differentiating between benign and borderline was 2.42, PLR for differentiating between borderline and malignancy was 140.96. When the NLR was 2.4 or higher, the odds ratio of borderline or malignant risk was 3.264. In the case of PLR, 140 or higher, the odds ratio of malignancy was 1.916. When both PLR and NLR were above each cut-off, the sensitivity of malignancy diagnosis was 51.5%, specificity was 77.0%.

**Conclusions:** In the case of borderline ovarian tumors, the NLR was higher than benign and similarly tend to malignancy, but the PLR was lower than malignancy and similarly tend to benign. We suggest that the NLR and PLR can be used as a supplementary tool for diagnosing benign, borderline, and malignant ovarian tumors in addition to imaging diagnosis and tumor markers such as CA125.


# Background

Ovarian tumors should not be biopsied before surgery because there is a risk of spreading and spillage of tumor cells into the abdominal cavity when a biopsy is attempted before surgery. Therefore, the probability of benign, borderline, and malignant tumors is estimated mostly based on radiologic findings before surgery. The radiologic findings that may suggest a malignant ovarian tumor include the presence of a solid portion, fixed in pelvic cavity, papillary growing pattern, irregular shape, rapid growth, an increase of Doppler signaling in the ovarian tumor, ascites, and cul-de-sac nodularity [1, 2]. However, even with these imaging findings, it is not easy to differentiate between benign and malignant ovarian tumors in some cases, and even more so in the case of borderline ovarian tumors.

Tumor markers such as CA125 and CA19-9 also play an adjunct role in the diagnosis of ovarian tumors, but are not diagnostic because of their low specificity [3]. Several studies have shown that hematologic findings such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are useful as a supplementary role in the differential diagnosis [4–12]. These studies reported that NLR and PLR levels tend to increase in malignant ovarian tumors. However, most of the studies to date have focused mainly on discriminating between benign and malignant ovarian tumors.

In the case of borderline tumors presumed using a frozen biopsy during ovarian tumor surgery, there are studies that evaluated the probability that the confirmatory diagnosis is malignancy [13, 14]. However, there are few studies on the discrimination of preoperative borderline from benign or malignant ovarian tumors. Therefore, the purpose of this study was to investigate whether NLR and PLR can be supplementary tools for the differential diagnosis of benign, borderline, and malignant ovarian tumors.

# Methods

From January 2002 to October 2020, patients diagnosed with benign, borderline, and malignant ovarian tumors through pathology after surgery at Daegu Catholic University Hospital were enrolled in this study. Based on the histopathological type of the ovarian tumor, an appropriate surgical method was selected and performed for each patient. In addition, appropriate staging surgery was performed for malignant ovarian tumors. Patients who did not undergo surgery in our hospital were excluded.

The patient's clinical characteristics including age, preoperative hematologic findings, and final biopsy results were reviewed retrospectively through medical records review. The hematologic findings analyzed in this study were white blood cell (WBC), platelet, neutrophil and lymphocyte counts, percentage of neutrophils and lymphocytes, NLR, and PLR. Patients with pre-existing infections, medical history of hematologic diseases, preoperative transfusion, other malignant diseases, and thrombolytic drugs were excluded as they could have a confounding effect on the results of this study.

The patients were divided into benign, borderline, and malignant ovarian tumor groups according to the final pathologic report.

Data were analyzed using IBM SPSS statistics version V25.0 (IBM, Armonk, NY, USA) and MedCalc Statistical Software version 19.4.0 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) for receiver operating characteristic (ROC) curve analysis.

One-way analysis of variance (ANOVA) was performed to compare the mean values for continuous variables, and post HOC analysis was performed using Fisher’s least significant difference. When the p-values were less than 0.05, statistically significant differences were established between the groups at a confidence interval of 95%.

ROC curve analysis was performed to establish the appropriate cut-off level. To set the best cut-off level, we obtained a cut-off level that maximizes Youden's J statistic (= sensitivity + specificity – 1). Sensitivity, specificity, and area under the curve (AUC) were calculated. To calculate the odds ratio, a binominal logistic regression was used. This study was approved by the ethics committees of the Daegu Catholic University hospital.

# Results

We included 507 patients in the study. According to the final histopathological results, 220 patients had benign ovarian tumors, 59 patients had borderline ovarian tumors, and 228 patients had malignant ovarian tumors.

Table 1 shows the comparison of clinical characteristics and complete blood count (CBC) between the study groups. The age range of each study group was significantly different because benign ovarian tumors occur at a relatively young age, while malignant ovarian tumors occur more often in older people. There was no significant difference in the WBC values among the three groups. However, there were significant differences in hemoglobin density, platelet count, neutrophil count, lymphocyte count, and percentage of neutrophils and lymphocytes. Platelet counts were significantly higher in the malignant ovarian tumor group than those in the benign and borderline groups. Neutrophil count was highest in the borderline group, and lymphocyte count was significantly lower in the benign group than that of the borderline and malignant groups.

Based on the CBC test performed in ovarian tumor patients, the calculated NLR and PLR were compared in Table 2. The calculated NLR was significantly higher in the borderline and malignant groups than in the benign group (Fig. 1). The NLR of the borderline group was the highest. The calculated PLR was significantly higher in the malignant group than in the benign and borderline groups (Fig. 2).

Patients with benign, borderline, and malignant ovarian tumors were evaluated using ROC curve analysis (Table 3 and Fig. 3,4). The diagnostic cut-off value, sensitivity, and specificity for NLR and PLR were calculated. When the diagnostic cut-off value that maximized Youden's J statistic of NLR and PLR were used for differentiating. The diagnostic cut-off value of NLR (AUC = 0.666, $p < 0.001$) for differentiating between benign and borderline ovarian tumors was 2.42, with a sensitivity of 60.2% and specificity of 69.1% (Fig. 3). The diagnostic cut-off value of PLR (AUC = 0.616, $p < 0.001$) for differentiating between benign and borderline ovarian tumors was 140.96 with a sensitivity of 60.0% and specificity of 56.9% (Fig. 4).

According to the results in Table 4, when the NLR was 2.4 or higher, the odds ratio of borderline or malignancy ovarian tumor risk was 3.264 (95% CI; 2.239–4.758, $p < 0.001$). In the case of PLR, 140 or higher, the odds ratio of malignancy ovarian tumor risk was 1.916 (95% CI; 1.334–2.752, $p < 0.001$).

# Discussion

Ovarian cancer has the highest mortality rate among gynecological cancers, and since most patients are asymptomatic, they are usually found in the advanced stage [15]. In particular, borderline ovarian tumors are difficult to predict and diagnose before the surgery and confirmation through final histopathology. In this study, we attempted to discriminate between benign, borderline, and malignant ovarian tumors through CBC tests performed before surgery in each patient. Inflammatory reactions contribute to the development and progression of tumor formation and oncogenesis [16, 17]. Due to the inflammatory reaction, blood components such as platelets, neutrophils, and lymphocytes are recruited to the tumor microenvironment [18]. Thrombocytosis can be observed in tumor formation and oncogenesis [19].

Compared to patients with benign ovarian tumors, the neutrophil count was higher, and the lymphocyte count was lower in patients with malignant ovarian tumors [20].

Therefore, until now, several reports reveal that NLR and PLR can be used as markers of systemic inflammatory responses. In various types of malignancies, NLR and PLR are being applied as markers that are useful in the diagnosis and prediction of prognosis. In several studies, there is a result that malignancy can be predicted diagnostically when NLR and PLR rise, and it is also associated with a worse prognosis. Seckin et *al.* suggested that the NLR cut-off value for the prediction of mucinous ovarian carcinoma was set at 2.18 ($p < 0.001$)[9]. Polat et *al.* reported that the optimal cut-off values to predict ovarian malignancy using NLR and PLR were 2.47 ($p = 0.02$) and 144.3 ($p = 0.05$) [10]. Backacak et *al.* reported that the cut-off value for PLR was 161.13 to distinguish malignant from benign ovarian tumors ($p < 0.001$) [12]. Ozaksit et *al.* reported that the cut-off value of PLR was 140 to discriminate malignant from benign ovarian tumors ($p < 0.001$) [11].

In this study, the diagnostic cut-off value of NLR for differentiating between benign and borderline ovarian tumors was 2.42, and the PLR for differentiating between benign and borderline ovarian tumors was 140.96. The exact diagnostic cut-off values for NLR and PLR for diagnosing malignant ovarian tumors have not been established yet. These results have similar values to other studies. In addition, as a result of the cross-sectional analysis, when both PLR and NLR were above each cut-off value, the sensitivity of malignancy was 51.5% and the specificity was 77.0%.

Based on this analysis, platelet count and PLR were significantly higher in malignant than in benign or borderline ovarian tumor groups, and borderline tumors tended to be statistically closer to benign tumors. The neutrophil count and NLR were significantly higher in the borderline or malignant than in the benign group, and borderline tumor parameters tended to be statistically closer to malignant tumors. Lymphocyte count was significantly lower in borderline or malignant tumors than in benign ovarian tumors, and borderline tumors tended to be statistically closer to malignant tumors. Therefore, the platelet count and PLR in borderline ovarian tumors tended to be statistically similar to benign ovarian tumors, and the counts of neutrophils, lymphocytes, and NLR tended to be statistically closer to malignant ovarian tumors. That is, if the NLR is higher than 2.4, there is a higher possibility of borderline or malignancy than benign tendencies. If the PLR is higher than 140.96, there is a higher possibility of malignancy than benign and borderline tendencies.

In addition to the fact that the platelet count, NLR, and PLR may be helpful in diagnosing ovarian tumors, several studies demonstrated these parameters may be used as a prognostic factor of the stage of the disease and may indicate a lower surgical outcome in cancer patients [21–24]. Kokcu et *al.* reported that NLR, PLR, and platelet count are independent prognostic factors for advanced stage malignant ovarian masses [25]. In another study, platelet count, NLR, and PLR were prognostic factors for progression-free survival (PFS) and overall survival (OS). Wang et *al.* reported that preoperative NLR was a significant predictor for poor PFS and OS in malignant ovarian masses [26]. It has also been reported to be related to chemotherapy resistance [27].

Some of the limitations of this study lie in its retrospective design and the lack of differentiation and comparison between histopathologic subtypes in each group. In addition, the number of patients with borderline ovarian tumors was relatively small. However, this is because the relative incidence of borderline ovarian tumors is lower than that of benign and malignant tumors.

# Conclusions

To this date, several studies have reported the diagnosis of benign and malignant ovarian tumors using NLR and PLR, but there have been few studies on borderline tumors. From our results, in the case of borderline ovarian tumors, NLR was higher than in benign ovarian tumors, but PLR was lower than in malignant tumors and tended to be similar to benign tumors. To discriminate ovarian tumors, we analyzed CBC tests performed before surgery in each ovarian tumor patient. The CBC test is performed as a preoperative routine, and it is it is widely available and inexpensive. Therefore, it can be used as a supplementary tool in diagnosing ovarian tumors in addition to radiologic diagnosis and tumor markers such as CA125. In conclusion, we suggest the usefulness of NLR and PLR as adjuncts to preoperative diagnosis of benign, borderline, and malignant ovarian tumors.

# Abbreviations

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; WBC: White blood cell; ROC: Receiver operating characteristic; ANOVA: One-way analysis of variance; AUC: Under the curve; CBC: Complete blood count; PFS: Progression-free survival; OS: Overall survival

# Declarations

### Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethics Committee of Daegu Catholic University hospital Ethical approval (approval number: CR-20-209-L). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was performed retrospective data collection, therefore informed consent was not possible in this study.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

There are no conflicts of interest to declare.


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### Author's contribution

THY : Data collection or management, Data analysis, Stastistics. EBC : Data collection or management. KHS : Data analysis, Stastistics. JMR : Data analysis, Manuscript writing/editing. YSC : Protocol/project development, Data analysis.


### Acknowledgements

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# Tables

Table 1 Comparison of clinical characteristics and complete blood count between study groups.

| | Pathology | Mean-standard deviation | ANOVA *P* value | Comparison group[a] | POSTHOC[b] *P* value |
|---|---|---|---|---|---|
| Age | Benign (N=220) | 43.0 ± 15.82 | $p < 0.001$ | 1 vs. 2 | NS |
| | Borderline (N=59) | 44.2 ± 13.0 | | 1 vs. 3 | $P < 0.001$ |
| | Malignant (N=228) | 52.1 ± 13.0 | | 2 vs. 3 | $P < 0.001$ |
| White blood cell (/□) | Benign | 6928.2 ± 2566.9 | $p = 0.104$ | 1 vs. 2 | NS |
| | Borderline | 7603.4 ± 3484.4 | | 1 vs. 3 | |
| | Malignant | 7353.1 ± 2397.8 | | 2 vs. 3 | |
| Hemoglobin (g/dl) | Benign | 12.6 ± 1.3 | $p < 0.001$ | 1 vs. 2 | NS |
| | Borderline | 12.7 ± 1.5 | | 1 vs. 3 | $P < 0.001$ |
| | Malignant | 12.1 ± 1.4 | | 2 vs. 3 | $P = 0.003$ |
| Platelet (/□) | Benign | 260895.5 ± 67806.1 | $p = 0.024$ | 1 vs. 2 | NS |
| | Borderline | 250525.4 ± 68577.5 | | 1 vs. 3 | $P = 0.032$ |
| | Malignant | 277008.8 ± 91142.3 | | 2 vs. 3 | $P = 0.023$ |
| Neutrophil count (/□) | Benign | 4243.8 ± 2371.9 | $p = 0.003$ | 1 vs. 2 | $P = 0.014$ |
| | Borderline | 5197.6 ± 3626.7 | | 1 vs. 3 | $P = 0.002$ |
| | Malignant | 4983.9 ±2332.5 | | 2 vs. 3 | NS |
| Lymphocyte count (/□) | Benign | 1965.2 ± 611.4 | $p < 0.001$ | 1 vs. 2 | NS |
| | Borderline | 1801.4 ± 632.5 | | 1 vs. 3 | $P < 0.001$ |
| | Malignant | 1714.1 ± 654.6 | | 2 vs. 3 | NS |
| Neutrophil (%) | Benign | 59.8 ± 10.0 | $p < 0.001$ | 1 vs. 2 | $P = 0.004$ |
| | Borderline | 64.7 ± 11.5 | | 1 vs. 3 | $P < 0.001$ |
| | Malignant | 65.9 ± 11.7 | | 2 vs. 3 | NS |
| Lymphocyte (%) | Benign | 30.4 ± 9.0 | $p < 0.001$ | 1 vs. 2 | $P = 0.007$ |
| | Borderline | 26.4 ± 9.7 | | 1 vs. 3 | $P < 0.001$ |
| | Malignant | 25.0 ± 10.1 | | 2 vs. 3 | NS |

Abbreviations; ANOVA: Analysis of variance, vs.: versus, NS: Nonspecific

[a] group 1: group of benign ovarian mass, group 2: group of borderline ovarian mass, group 3: group of malignant ovarian mass.

[b] POSTHOC analysis was done by Fisher's least significant difference.

Table 2 Comparison of calculated NLR and PLR between study groups.

| | Pathology | Mean-standard deviation | ANOVA *P* value | Comparison group[a] | POSTHOC[b] *P* value |
|---|---|---|---|---|---|
| NLR | Benign (N=220) | 2.5 ± 2.4 | $p = 0.001$ | 1 vs. 2 | $p = 0.008$ |
| | Borderline (N=59) | 3.8 ± 5.2 | | 1 vs. 3 | $p < 0.001$ |
| | Malignant (N=228) | 3.6 ± 3.1 | | 2 vs. 3 | NS |
| PLR | Benign | 145.0 ± 60.0 | $p < 0.001$ | 1 vs. 2 | NS |
| | Borderline | 153.7 ± 80.9 | | 1 vs. 3 | $p < 0.001$ |
| | Malignant | 186.0 ± 100.7 | | 2 vs. 3 | $p = 0.011$ |

Abbreviations; NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, ANOVA: Analysis of variance, vs.: versus, NS: Nonspecific.

[a] group 1: group of benign ovarian mass, group 2: group of borderline ovarian mass, group 3: group of malignant ovarian mass.

[b] POSTHOC analysis was done by Fisher's least significant difference.

Table 3 The diagnostic values of NLR and PLR.

| | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| NLR<br>Benign vs. borderline or malignancy | 2.42 | 60.2 | 69.1 |
| PLR<br>Benign or borderline vs. malignancy | 140.96 | 60.0 | 56.9 |

Abbreviations; NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, vs.: versus.

Table 4 Odds Ratios to each range of NLR and PLR for discriminate of ovarian tumor.

| | Odds ratio[a] | 95% CI | *P*-value |
|---|---|---|---|
| NLR ≥ 2.4 vs. < 2.4<br>Borderline or malignancy vs. Benign | 3.264 | 2.239 - 4.758 | *P* < 0.001 |
| PLR ≥ 140 vs. <140<br>Malignancy vs. benign or borderline | 1.916 | 1.334 - 2.752 | *P* < 0.001 |

Abbreviations; NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, vs.: versus, CI: Confidence interval

[a] Binominal logistic regression was done.

# Figures

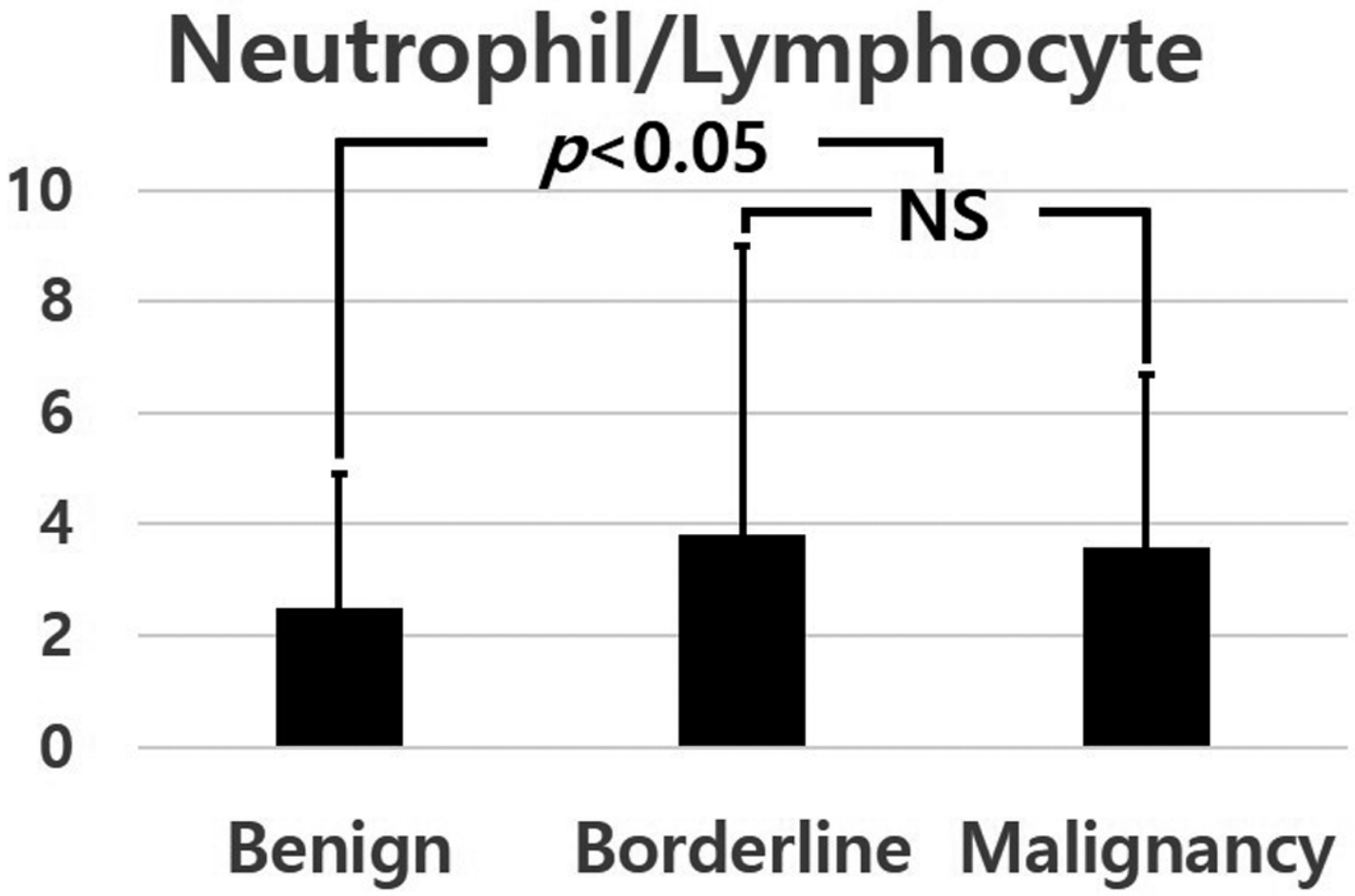


**Figure 1**

Comparison graph of calculated neutrophil-lymphocyte ratio between study group.

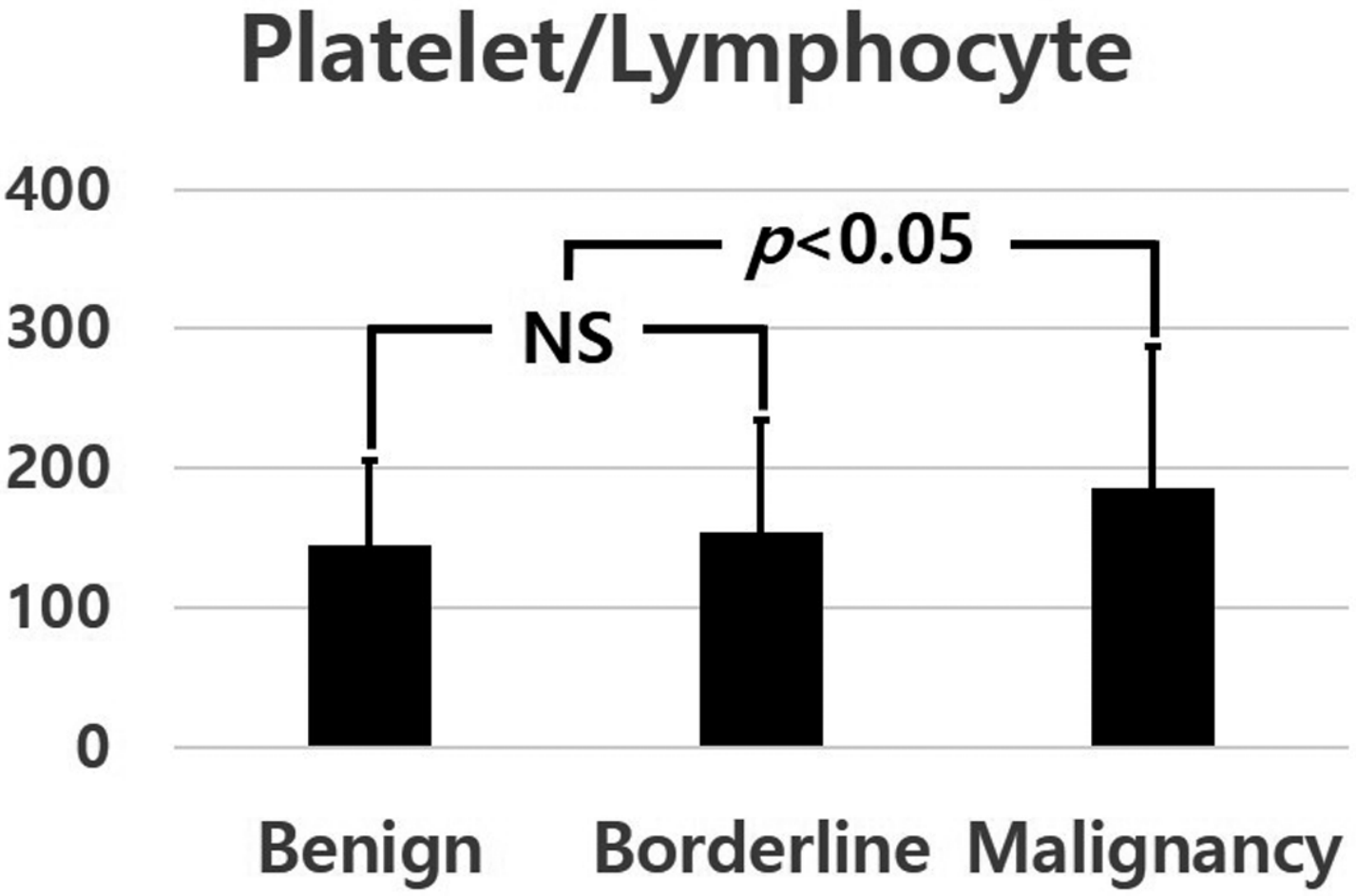


**Figure 2**

Comparison graph of calculated platelet-lymphocyte ratio between study group.

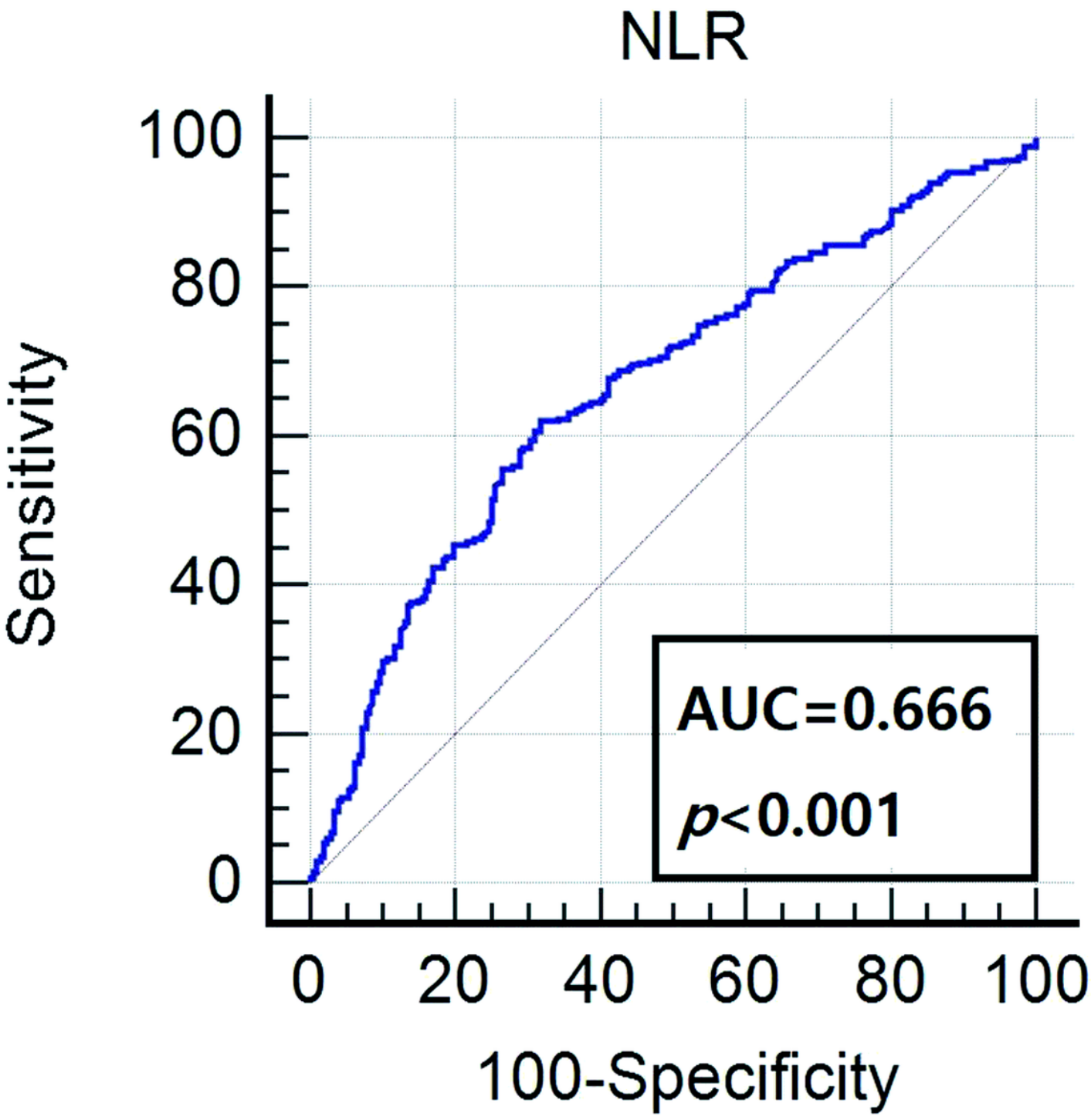


**Figure 3**

The diagnostic values of neutrophil-lymphocyte ratio determined by receiver operating characteristic curve. Abbreviations: NLR, neutrophil-lymphocyte ratio; AUC, area under curve.

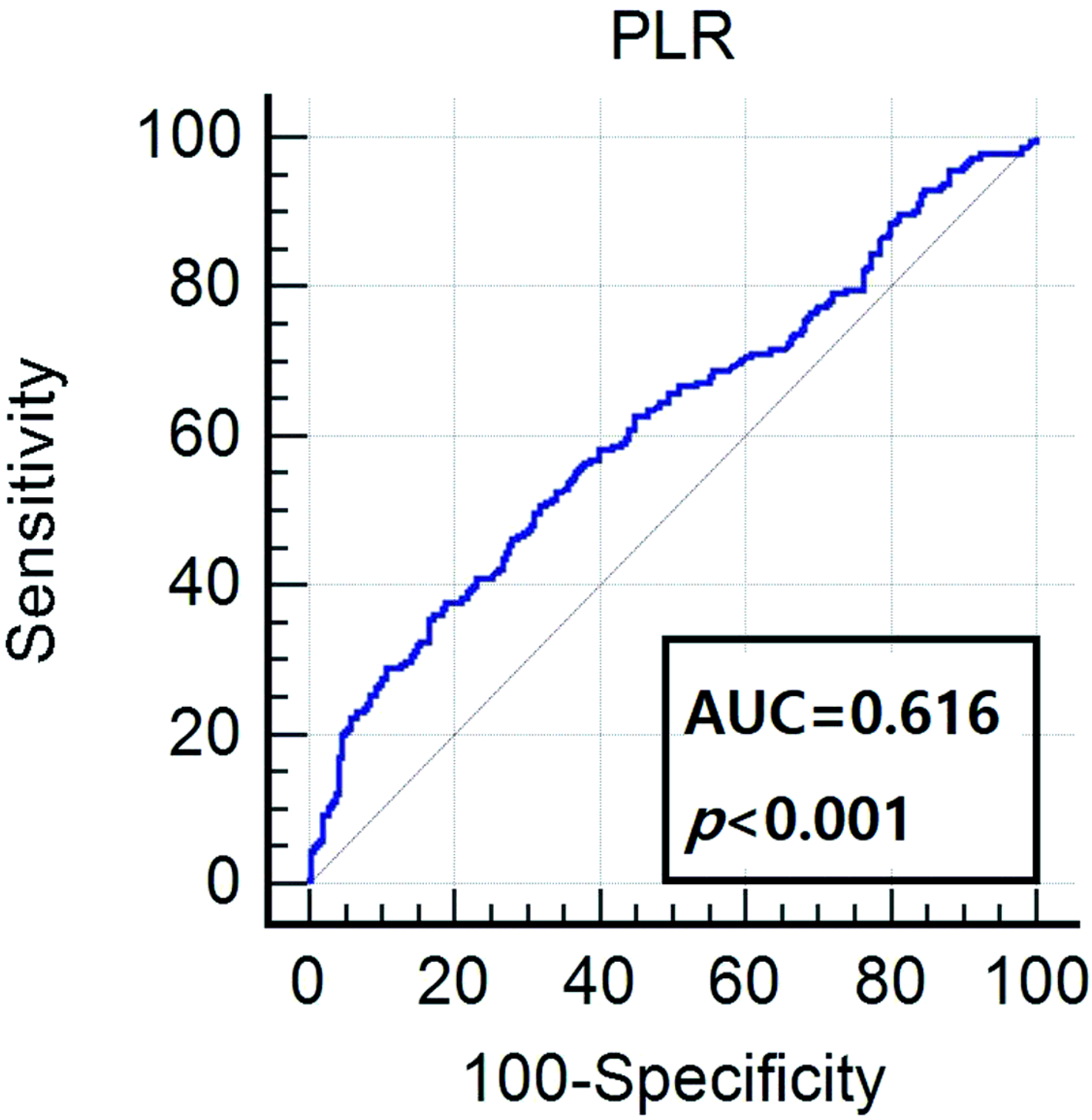


**Figure 4**

The diagnostic values of platelet-lymphocyte ratio determined by receiver operating characteristic curve. Abbreviations: PLR, platelet-lymphocyte ratio; AUC, area under curve.