Original Article

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# Pretreatment neutrophil-to-lymphocyte ratio and its dynamic change during neoadjuvant chemotherapy as poor prognostic factors in advanced ovarian cancer

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**Objective**
The purpose of this study was to determine the prognostic implications of the pretreatment neutrophil-to-lymphocyte ratio (NLR) and its dynamic change during chemotherapy in patients with advanced epithelial ovarian cancer undergoing neoadjuvant chemotherapy.

**Methods**
We performed a retrospective analysis of 203 patients who underwent neoadjuvant chemotherapy prior to interval debulking surgery for advanced-stage ovarian cancer at Yonsei Cancer Hospital between 2007 and 2015. Pretreatment NLR was evaluated before starting neoadjuvant chemotherapy. Change in NLR was defined as the post-neoadjuvant NLR value divided by the initial value. The correlation of NLR and its dynamic change with chemotherapy response score, response rate, and recurrence was analyzed.

**Results**
The NLR ranged from 0.64 to 22.8. In univariate analyses, a higher pretreatment NLR (>3.81) was associated with poor overall survival (OS), but not progression-free survival (PFS). Through multivariate analysis, high pretreatment NLR was shown to be an independent parameter affecting OS, but not necessarily PFS. Changes in NLR during chemotherapy were better predictors of PFS than baseline NLR. Patients with increased NLR during chemotherapy showed significantly poor PFS, and this change was an independent predictor of PFS.

**Conclusion**
Pretreatment NLR and its dynamic change during chemotherapy may be important prognostic factors in patients who undergo neoadjuvant chemotherapy.

**Keywords:** Biomarkers; Neutrophils; Ovarian neoplasms; Prognosis; Treatment outcomes

## Introduction

Epithelial ovarian cancer is a leading cause of mortality related to cancer among women worldwide [1], and its incidence and mortality rates are increasing in the Republic of Korea [2,3]. Although the standard treatment for epithelial ovarian cancer had been primary debulking surgery followed by platinum-based cytotoxic chemotherapy, a new promising option of interval debulking surgery (IDS) after neoadjuvant chemotherapy has been suggested [4]. Data of several randomized controlled trials have shown reduction in perioperative morbidity and mortality and increase in the possi-

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bility of a complete resection of tumors during cytoreductive surgery [5,6]. Although the initial response to chemotherapy is almost 70%, most women with advanced-stage ovarian cancer who develop platinum resistance are known to have poor prognosis [7,8]. Therefore, it is necessary to develop biomarkers for individual evaluation of treatment outcome and prognosis.

Since the process of inflammation underlies cancer growth and metastasis, several systemic inflammatory response (SIR) markers have been studied for their use in prediction of clinical outcomes and prognosis of several cancer types [9-13]. Neutrophil-to-lymphocyte ratio (NLR) is one of the recently studied SIR markers in gynecologic malignancies including advanced epithelial ovarian cancer [14-16]. However, in the context of neoadjuvant chemotherapy, evidence for the use of NLR markers as an outcome predictor is still insufficient.

Therefore, this study aimed to evaluate the role of pretreatment NLR in predicting response to neoadjuvant chemotherapy and assess the prognostic role of NLR and dynamic change of NLR during neoadjuvant chemotherapy in advanced epithelial ovarian cancer.

## Materials and methods

Patients (n=203) who were diagnosed with advanced epithelial ovarian cancer and received neoadjuvant chemotherapy between 2007 and 2015 at Yonsei Cancer Hospital were retrospectively identified. The retrospective study protocol of this study was approved by our Institutional Review Board (registration number: 4-2015-1158).

Retrospective chart review was performed to identify all patients who underwent neoadjuvant chemotherapy after diagnosis of advanced-stage ovarian cancer. The inclusion criteria were as follows: 1) pathologically proven epithelial ovarian cancer, 2) the International Federation of Gynecology and Obstetrics (FIGO) stage III, IV, and 3) received at least 1 cycle of neoadjuvant chemotherapy after diagnosis and underwent IDS. A total of 197 women met the inclusion criteria. Gynecologic oncology team comprising of 5 surgeons conducted all procedures and 2 dedicated in-house pathologists reviewed all microscopic slides based on the World Health Organization criteria.

From medical records and pathologic reports, we collected clinical and pathologic data including age, tumor histology, American Society of Anesthesiologists (ASA) score, serum carbohydrate antigen-125 (CA-125) concentration, FIGO stage (revised 2014 version), residual tumor size after IDS, total chemotherapy cycles, neutrophil count, lymphocyte count, patient's disease status at last contact, date of last visit, and date of disease progression or recurrence. Chemotherapy response rate was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) [17]. Furthermore, data of the cause and date of death were extracted from death certificates obtained from the Korea National Statistical Office.

Taxane plus platinum combination chemotherapy regimens were used in neoadjuvant settings. Neoadjuvant chemotherapy, IDS, and postoperative adjuvant chemotherapy were performed according to the National Comprehensive Cancer Network (NCCN) guidelines [4].

All patients were radiologically evaluated after every 3 cycles of neoadjuvant chemotherapy. Moreover, if patients had an increased CA-125 during follow-up, radiological evaluation was performed.

Routine blood tests on peripheral vein blood samples were performed before the start of every chemotherapy cycle in all patients. Pretreatment NLR was determined prior to the initiation of neoadjuvant chemotherapy by calculating the absolute neutrophil count divided by the lymphocyte count, which was obtained as part of the complete blood cell count. Post-neoadjuvant chemotherapy NLR was determined considering the results of the preoperative blood test, which was performed approximately 2 weeks after the last cycle of neoadjuvant chemotherapy. Change in NLR was obtained by dividing the post-neoadjuvant NLR value by the initial value. When this ratio was >1, it was classified as the "increased group," whereas all other cases were classified as the "maintained group" [18]. In cases where the patients were given granulocyte colony stimulating factor (G-CSF) due to neutropenia, the lowest absolute neutrophil count value prior to G-CSF administration was chosen.

Progression-free survival (PFS) was set as the time interval from the beginning of the treatment (neoadjuvant chemotherapy) to the progression or recurrence of the disease. Overall survival (OS) was set as the time interval from the beginning of the treatment (neoadjuvant chemotherapy) to the date of patient death or last visit.

## Results

Of 203 patients who were diagnosed and received neoadjuvant chemotherapy for ovarian cancer, 197 were suitable for analysis. The patient's baseline characteristics are summarized in Table 1.

NLR ranged from 0.64 to 22.8, with a median level of 3.81. Receiver operating characteristic (ROC) analysis was used to determine the cut-off values of NLR. ROC analysis showed that for the NLR value of 3.81, the specificity was 52.9% and the sensitivity was 51.2%. A high pretreatment NLR was associated with residual disease (RD) (not R0) after IDS (*P*=0.043). Moreover, it was associated with poor response rate after neoadjuvant chemotherapy (*P*=0.069) and platinum-resistant recurrence (*P*=0.074) (Table 2). Kaplan-Meier curves showed that, compared with higher NLR, lower baseline NLR was associated with longer PFS, but this difference was not statistically significant (Fig. 1A). Moreover, in the univariate analysis, a lower baseline NLR was associated with a better OS than a higher baseline NLR (*P*=0.008) (Fig 1B). In the multivariate analysis, when adjusted for age, histology, ASA score, serum CA-125 levels, FIGO stage, residual disease, and total cycles of chemotherapy, a lower baseline NLR was an independent prognostic factor for OS (hazard ratio [HR], 1.89; 95% confidence interval [CI], 1.11–3.24) (Table 3).

**Table 1.** Baseline characteristics

| Characteristics | Value |
|---|---|
| Age (yr) | 57 (27–80) |
| Histology | |
| HGSC | 180 (91.4) |
| Non-HGSC | 17 (8.6) |
| ASA score | |
| 1 | 51 (26.3) |
| 2 | 92 (47.4) |
| 3 | 50 (25.8) |
| 4 | 1 (0.5) |
| CA-125 (U/mL) | 1,825.7 (44.3–30,000) |
| FIGO stage | |
| IIIB | 7 (3.6) |
| IIIC | 45 (22.8) |
| IVA | 89 (45.2) |
| IVB | 56 (28.4) |
| RD after IDS (cm) | |
| NGR | 72 (36.6) |
| ≤0.5 | 63 (32.0) |
| ≤1 | 27 (13.7) |
| ≤2 | 5 (2.5) |
| >2 | 8 (4.1) |
| Unknown | 22 (11.2) |
| Total cycles of chemotherapy | |
| <6 | 8 (4.1) |
| ≥6 | 189 (95.9) |
| Regimen of neoadjuvant chemotherapy | |
| Taxane+carboplatin | 197 (100.0) |

Data are shown as median (range) or number (%).
HGSC, high-grade serous carcinoma; ASA, American Society of Anesthesiologists; CA-125, carbohydrate antigen-125; FIGO, International Federation of Gynecology and Obstetrics; RD, residual disease; IDS, interval debulking surgery; NGR, no gross residual disease.

Dynamic change in NLR during neoadjuvant chemotherapy showed prognostic value for PFS in our cohort. NLR changes ranged from 0.02 to 7.14. The area under ROC curve for NLR changes (0.632; 95% CI, 0.548–0.715) was higher than the area under ROC curve for pretreatment NLR (0.544; 95% CI, 0.456–0.632) for predicting recurrence. Kaplan-Meier curves showed significantly poor PFS in patients with increased NLR during neoadjuvant chemotherapy (*P*=0.006; Fig. 2A). In the multivariate analysis, change in NLR was an independent prognostic factor for PFS (HR, 2.07; 95% CI, 1.32–3.25; Table 3). For OS, trends were observed, but there was no significant difference between the 2 groups (Fig. 2B).

Analysis of NLR in patients who showed NLR changes during chemotherapy (low pretreatment NLR with maintained NLR, low pretreatment NLR with increased NLR, high pretreatment NLR with maintained NLR, and high pretreatment NLR with increased NLR) showed that patients with high pretreatment NLR with increased NLR during neoadjuvant chemotherapy had the shortest PFS and OS (HR, 2.12; 95% CI, 1.08–4.15 and HR, 2.43; 95% CI, 1.00–5.88, respectively; Fig. 3).

## Discussion

In this study, we investigated the predictive and prognostic value of NLR for ovarian cancer patients undergoing neoadjuvant chemotherapy. Results showed that high pretreatment NLR was not only associated with RD after IDS, poor response to neoadjuvant chemotherapy, and platinum resistant recurrence, but also served as a statistically significant independent

**Table 2.** Comparison between the high neutrophil-to-lymphocyte ratio and low NLR groups

| Characteristics | Low NLR group | High NLR group | *P*-value |
|---|---|---|---|
| Age (yr) | | | 0.643 |
| ≤65 | 67 (72.0) | 72 (76.6) | |
| >65 | 26 (28.0) | 22 (23.4) | |
| ASA score | | | 0.476 |
| ≤2 | 71 (76.3) | 69 (73.4) | |
| ≥3 | 22 (23.7) | 25 (26.6) | |
| CA-125 (U/mL) | | | 0.994 |
| ≤2,000 | 48 (51.6) | 49 (52.1) | |
| >2,000 | 43 (45.7) | 44 (46.8) | |
| Missing | 2 (0.7) | 1 (1.1) | |
| RD after IDS | | | 0.043 |
| R0 | 41 (44.1) | 28 (29.8) | |
| Not R0 | 52 (55.9) | 66 (70.2) | |
| No. of CRS | | | 0.213 |
| 1 | 2 (2.1) | 6 (6.3) | |
| 2 | 36 (38.7) | 37 (39.4) | |
| 3 | 32 (34.4) | 24 (25.5) | |
| Missing | 23 (24.7) | 27 (28.8) | |
| Platinum resistant recur | | | 0.074 |
| No | 74 (79.6) | 64 (68.1) | |
| Platinum resistant recur | 19 (20.4) | 30 (31.9) | |
| RR (by imaging study) | | | 0.069 |
| CR+PR | 80 (86.0) | 75 (79.8) | |
| SD+PD | 8 (8.6) | 17 (18.1) | |
| Missing | 5 (5.4) | 2 (2.1) | |

Data are shown as number (%).
NLR, neutrophil-to-lymphocyte ratio; ASA, American Society of Anesthesiologists; CA-125, carbohydrate antigen-125; RD, residual disease; IDS, interval debulking surgery; CRS, cytoreductive surgery; RR, response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

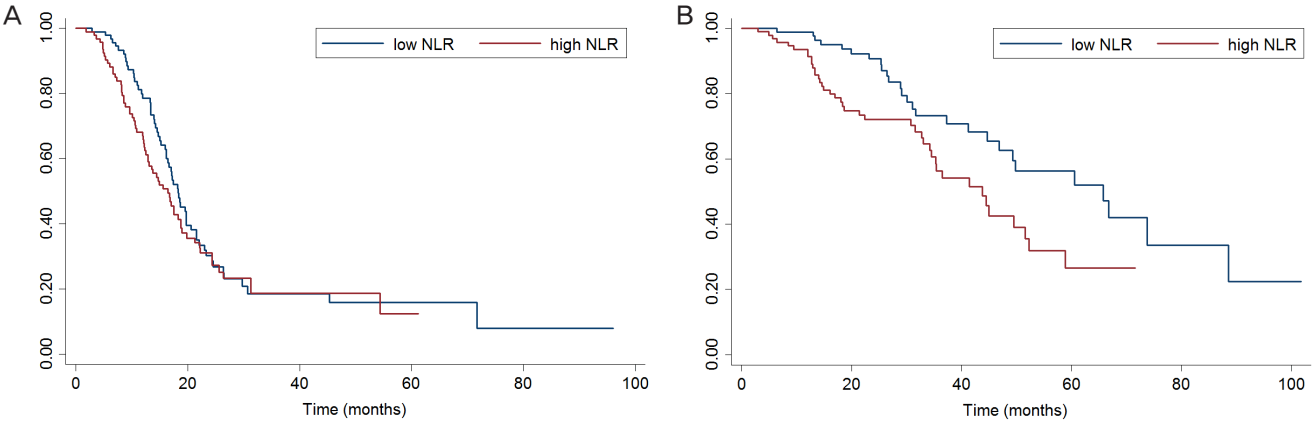


**Fig. 1.** Kaplan-Meier curve of (A) (*P*=0.725) progression-free survival and (B) (*P*=0.008) overall survival stratified by neutrophil-to-lymphocyte ratio (NLR) level.

**Table 3.** Multivariate analysis for progression-free survival and overall survival

| Variables | PFS (95% CI) | OS (95% CI) |
|---|---|---|
| Pretreatment NLR | | |
| <3.81 | 1.00 | 1.00 |
| >3.81 | 1.25 (0.86–1.83) | 1.89 (1.11–3.24) |
| NLR change | | |
| Maintained | 1.00 | 1.00 |
| Increased | 2.07 (1.32–3.25) | 1.56 (0.84–2.91) |

Adjustment for age, histology, American Society of Anesthesiologists, carbohydrate antigen-125, International Federation of Gynecology and Obstetrics stage, residual disease, and total cycles of chemotherapy.
PFS, progression-free survival; CI, confidence interval; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio.

predictor of OS. Furthermore, the dynamic change in NLR, defined as the ratio of preoperative NLR to pretreatment NLR, was a valuable prognostic marker of recurrence and PFS.

Neutrophils and lymphocytes are key players in tumor immunology [19]. Neutrophils release cytotoxic mediators including reactive oxygen species and neutrophil elastase that inflict damage to cellular DNA and promote cancerassociated angiogenesis [20,21]. Leukocytopenia inhibits neoplastic cell apoptosis [22]. In recent years, neutrophil count, lymphocyte count, and their combinations (NLR) have been repeatedly reported to have prognostic value in various cancers such as bladder, pancreatic, breast, and colorectal cancers [10-13]. Reports on the prognostic value of NLR dynamic changes have also been published for other cancers [18,23].

However, the studies on NLR in ovarian cancer setting are

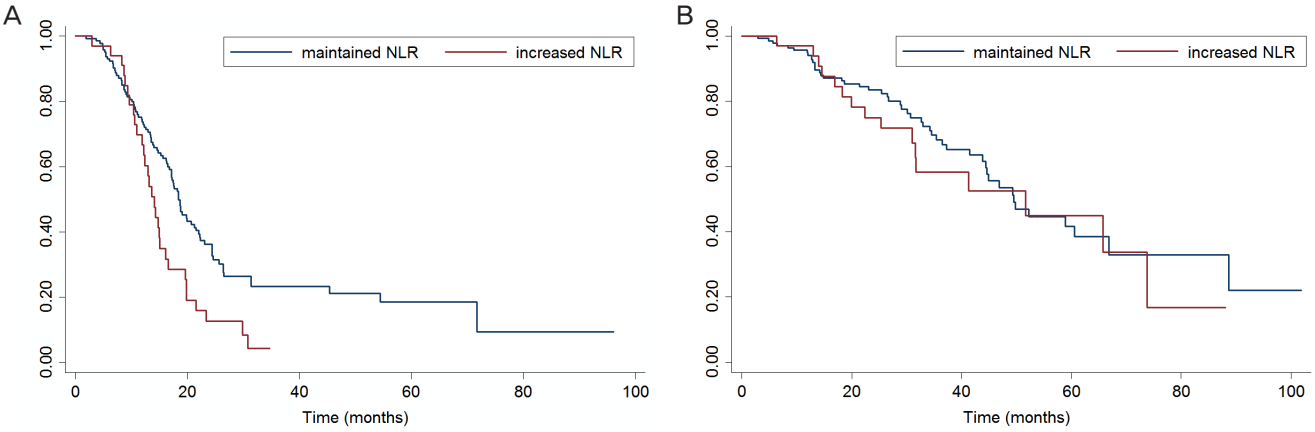


**Fig. 2.** Kaplan-Meier curve of (A) ($P$=0.006) progression-free survival and (B) ($P$=0.320) overall survival stratified by change of neutrophil-to-lymphocyte ratio (NLR).

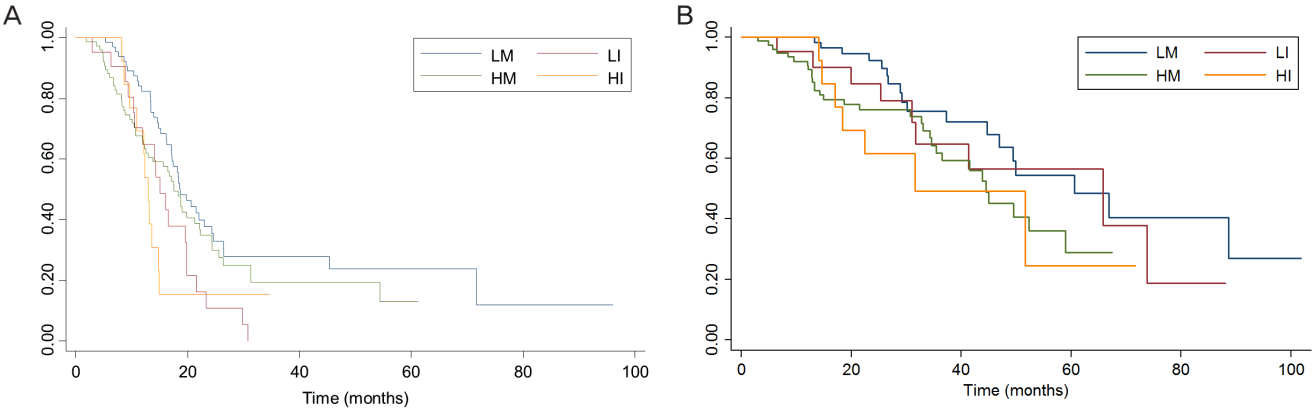


**Fig. 3.** Kaplan-Meier curve of (A) progression-free survival and (B) overall survival according to pretreatment neutrophil-to-lymphocyte ratio (NLR) and dynamic change in NLR. LM, low pretreatment/maintained during chemotherapy; LI, low pretreatment/increased during chemotherapy; HM, high pretreatment/maintained during chemotherapy; HI, high pretreatment/increased during chemotherapy.

still at primitive stage. NLR levels of epithelial ovarian cancer patients were compared with healthy controls including benign ovarian tumors in a previous study [24]. They suggested that the increased NLR level might serve as a cost-effective method of differentiating ovarian cancers from benign ovarian cysts. Furthermore, Williams et al. [25] suggested that high NLR levels were associated with an advanced FIGO stage, greater tumor grade, and more extensive ascites in ovarian cancer patients. Several studies on patients who underwent primary debulking surgery for epithelial ovarian cancer have reported the prognostic significance of preoperative NLR. For example, Feng et al. [15] suggested that preoperative NLR has high predictive and prognostic significance in high-grade serous ovarian cancer patients. Miao et al. [14] suggested that preoperative NLR is an independent prognostic marker for platinum-based chemotherapy after primary debulking surgery.

To our knowledge, this is the first report that describes the prognostic significance of pretreatment NLR level and its dynamic changes in advanced-stage ovarian cancer patients undergoing neoadjuvant therapy.

There are limitations to this analysis. First, this is a retrospective study of previously obtained medical records. Although we utilized data obtained from the electronic medical records, biases such as selection bias may exist. Further studies with larger sample size and prospective research design are recommended. Second, there is no consensus on the exact cut-off value for NLR, although previous studies have reported the value of NLR for the prognosis of ovarian cancer [14,15,25-30]. In this study, NLR cut-off value of 3.81 was selected using ROC analysis using the procedure reported in other studies [14,24,29]. Some other previous studies used a median level of NLR to determine the cut-off value [15,25-28,30]. This lack of consensus on the cut-off makes NLR difficult to be used in daily clinical practice. Thus, developing a nomogram of NLR will be beneficial. Third, NLR is a nonspecific marker of inflammation. Therefore, another systemic disease could have affected the NLR value.

In conclusion, our preliminary analysis showed the possibility of utilizing NLR levels as prognostic markers in advanced-stage ovarian cancer patients who will undergo neoadjuvant chemotherapy. In addition, considering dynamic changes in NLR during chemotherapy might help to estimate a more accurate prognosis in advanced-stage ovarian cancer. NLR can be easily obtained from routine blood tests, thus providing opportunities for future research as a convenient and cost-effective biomarker.

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## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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