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The role of changes in systemic inflammatory response markers during neoadjuvant chemotherapy in predicting suboptimal surgery in ovarian cancer

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ABSTRACT

Aim: The aim of this study was to investigate the possibility of using the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and platelet count and their dynamic changes during chemotherapy to predict suboptimal interval debulking surgery (IDS) in stage IIIC-IVA serous ovarian cancer (OC).
Method: Patients who underwent IDS after neoadjuvant chemotherapy (NAC) for stage IIIC-IVA serous OC at 3 centers between January 2008 and March 2018 were analyzed retrospectively. All women with complete blood counts both at diagnosis (T0) and after the completion of NAC but prior to IDS (T1) were included. An average of 3 weeks passed between IDS and the last cycle of NAC.
Results: A total of 214 patients were found suitable for the study. Suboptimal surgery was performed in 25.2% of the patients and optimal surgery was performed in 74.8%. The rate of change in NLR was calculated as [(NLR T0 – NLR T1)/NLR T0] × 100. A higher rate of change in NLR was found in the optimal surgery group. Recovery of thrombocytosis (When platelet count before NAC was >400,000/mm^3, recovery of thrombocytosis was defined as ≤400,000/mm^3 after NAC.) was found to have 85.7% sensitivity and 64.8% specificity in predicting suboptimal surgery ($P < 0.001$). According to both multivariate and univariate regression analysis, a large change in NLR (>17%) and recovery of thrombocytosis significantly predicted suboptimal surgery.

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Conclusion: To identify the likelihood of suboptimal surgery in advanced stage OC patients who undergo IDS after NAC, the dynamic change in NLR values can be examined.

ARTICLE INFO

Keywords: Systemic inflammatory response markers; Neoadjuvant chemotherapy; Suboptimal surgery; Ovarian cancer; Neutrophil-to-lymphocyte ratio; Interval debulking surgery; Thrombocytosis

Introduction

The most frequent and fatal female genital cancer is ovarian cancer (OC).[1] More than 75% of OC patients have advanced disease (International Federation of Gynecology and Obstetrics [FIGO] stage IIIC or IV) at initial diagnosis, and the 5-year survival rate of these patients is less than 30%.[1] The current standard treatment modality for advanced epithelial OC is initial debulking surgery followed by platinum-based chemotherapy.[2,3] Recently, interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) has become an alternative treatment strategy for advanced OC patients in whom nonoptimal cytoreduction during primary debulking surgery would be expected.[2,3]

An important predictor of prognosis in advanced OC is the extent of residual disease after cytoreductive surgery.[4,5] The current standard approach includes maximal surgical effort to leave a residual disease 0 cm in diameter.[6] Nevertheless, 25%-90% of women who cannot be cytoreduced optimally after exploratory laparotomy are afterward treated with NAC.[4,5] Various approaches based on evaluation of cancer antigen-125 (CA125) levels, radiological assessment of tumor spread, and recently, laparoscopically based scores have been investigated for their ability to define preoperatively each patient's likelihood to achieve optimal cytoreduction.[4,7] None of these methods has been completely accepted to predict optimal IDS surgery. The associations between inflammation and tumor development have attracted much interest recently. The neutrophil-to-lymphocyte ratio (NLR) is a marker for evaluating the systemic potential balance between neutrophil-dependent protumor inflammation and lymphocyte-associated antitumor immune response.[8] Increased NLR is associated with disease severity and poor prognosis in solid malignant tumors.[9] Thrombocytosis (platelet count >400,000) is associated with poor prognosis in OC.[10] To find the ideal method for predicting the possibility of an optimal surgical procedure prior to IDS, platelet count and NLR and platelet-to-lymphocyte ratio (PLR) values were investigated.

The aim of this study was to investigate the possibility that NLR, PLR, and platelet counts might predict suboptimal surgery at IDS in stage IIIC–IVA serous OC.

Materials and methods

Patients who underwent interval cytoreduction after NAC for FIGO stage IIIC–IVA serous OC at 3 centers (Tepecik Research and Treatment Hospital, Izmir; SadiKonuk Research and Treatment Hospital, Istanbul; SıtkıKoçman University Medicine Faculty, Muğla, Turkey) between January 2008 and March 2018 were analyzed retrospectively. Patients with borderline ovarian tumor and those who underwent primary cytoreduction, had a prior history of radiation therapy, had prior hysterectomy, or had synchronous malignancies, as well as those with incomplete medical records, nonserous histologic type, another systemic disease with the potential to affect NLR or PLR, or unavailable computed tomography (CT) images were excluded from the study.

Files of 237 patients with stage IIIC-IVA serous OC who underwent 3 cycles of NAC were reviewed. Three patients with rheumatoid arthritis and 7 patients with chronic obstructive pul-

monary disease (Another systemic disease with potential to affect NLR or PLR) were excluded from study. Thirteen patients were excluded because they had missing data. In total, 214 patients were included and analyzed in this study. Eleven patients treated with NAC were switched to second-line chemotherapy because of suboptimal response. Patients who received second-line chemotherapy were included to suboptimal surgery group. Ten patients who received hyper thermic intraperitoneal chemotherapy and underwent optimal IDS were included to the optimal surgery group. The study group's surgical and pathology reports were evaluated in terms of disease-related features, surgical and postoperative factors, and long-term results. The study was approved by the local ethics committee at our institution.

Patients' age, type of operation performed, histologic type, grade, stage, complete blood count, and CA125 level were analyzed from patient files. All women with stage IIIC or IVA serous ovarian carcinoma with complete blood counts both at diagnosis (T0) and after the completion of NAC but prior to IDS (T1) were included. If more than 1 complete blood count result was present, a result from between the 7th and 14th days before NAC was used as T0 for statistical analysis. A test result from between the 7th and 14th days after the last cycle of NAC was used as T1 for statistical analysis. There was an average of 3 weeks between IDS and the last NAC. Complete blood counts were performed with a Coulter LH 750 instrument (Beckman Coulter, Brea; CA). CA125 values were measured with a Roche E170 Modular System using the chemiluminescence method; concentrations are given in U/mL. The NLR value was found by dividing the absolute neutrophil count by the absolute lymphocyte count; the PLR value was found by dividing the absolute platelet count by the absolute lymphocyte count. The number of chemotherapy cycles and types received for NAC were reported.

Patients had CT scans within 1-2 weeks prior to NAC. A standard abdominopelvic CT scanning protocol was used. CT scans were performed with patients in the supine position. With oral and intravenous contrast (iohexol), images with a 5-mm collimation area through the abdomen and pelvis were obtained. Peritoneal implants, omental cake, diaphragm, superficial liver, stomach, intestinal, mesenteric involvement (tumor implants larger than 2 cm on small and/or large bowel mesentery), pelvic and paraaortic lymph node involvement (larger than 1 cm), large volume ascites (estimated amount $\geq$500 mL), pleural effusion, and tumor size were investigated according to CT reports.

Treatment was chosen by the attending physician or by the multidisciplinary tumor board at the institution. In particular, patients with poor performance status and/or those who had a low likelihood of achieving optimal ($\leq$1 cm) cytoreduction at our clinic underwent NAC-IDS. NAC regimens were platinum- and taxane-based and administered per standardized protocols during the study period. The intent of neoadjuvant treatment was 3 cycles of chemotherapy before IDS. Postoperatively, patients were treated with at least 3 cycles of additional chemotherapy. The general time interval from the completion of NAC to surgery was within 3 weeks.

After completion of 3 cycles of chemotherapy, patients underwent a CT scan to determine whether the residual disease volume appeared resectable. If it was deemed unresectable, patients received additional cycles of chemotherapy at that time.

All operations were carried out by surgeons experienced in gynecologic oncologic surgery. All tumors were staged according to the 2014 FIGO staging system.[11] In patients treated before 2014, stage was determined retrospectively based on surgical and pathologic assessment. Treatment policies were decided by the attending physician or by the multidisciplinary tumor board. All surgical specimens were examined and interpreted by gynecologic pathologists. Histologic classification was performed using the criteria defined by the World Health Organization.[12] Architectural grading was defined by standard FIGO criteria. Maximal cytoreduction was defined as no visible RD (microscopic RD) after surgery. Optimal cytoreduction was defined as $\leq$1-cm maximal diameter of the largest residual tumor nodule at the completion of the primary operation. Suboptimal cytoreduction was defined as $>$1 cm of RD. Lymphadenectomy was defined as the performance of pelvic and para-aortic lymph node dissection at the same time. We defined pelvic lymphadenectomy as the removal of lymphatic tissue in the external, internal, and common iliac and obturator regions. Para-aortic lymphadenectomy was defined as removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the level of

Table 1
Demographic and clinical characteristics on computed tomography of the study population.

	Suboptimal surgery (n = 54)	Optimal surgery (n = 160)	*P*
Age* (y)	58.8 (44-76)	57.0 (28-80)	0.298
Size of tumor* (mm)	84.8 (30-220)	86.1 (25-200)	0.837
CA125* (U/mL)	1504 (193-5000)	1276 (107-6532)	0.223
Peritoneal implants†	49 (90.7)	131 (81.9)	0.089
Omental deposits†	28 (51.9)	72 (45.0)	0.237
Diaphragmatic carcinomatosis†	17 (31.5)	31 (19.4)	0.052
Superficial liver deposits†	19 (35.2)	38 (23.8)	0.073
Stomach infiltration†	12 (22.2)	26 (16.3)	0.213
Bowel infiltration†	15 (27.8)	38 (23.5)	0.336
Mesenteric implants†	22 (40.7)	36 (22.5)	0.009
Pelvic LN involvement†	23 (42.6)	64 (40.0)	0.429
Paraaortic LN involvement†	25 (46.3)	39 (24.4)	0.002
Ascites†	41 (75.9)	107 (66.9)	0.141
Pleural effusion†	10 (18.5)	30 (18.8)	0.573
Stage†			0.317
-IIIC	42 (77.8)	131 (81.9)	
-IVA	12 (22.2)	29 (18.1)	
Grade†			0.403
-2	5 (9.3)	19 (11.9)	
-3	49 (90.7)	141 (88.1)	

LN, Lymph node; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
* mean (minimum-maximum).
† n (%).

the aortic bifurcation and up to the left renal vessels. In our daily practice, surgery is started by mini-laparotomy or diagnostic laparoscopy to evaluate the tumor burden and whether achieve optimal-maximal cytoreduction surgery is achieved after NAC. If we decide to achieve optimal or maximal cytoreduction than we convert midline incision and perfom the surgery. However, sometimes we can perform only tumor burden-reducing surgery. If we cannot decide to perform optimal-maximal cytoreduction surgery, we terminate the operation.

The normal distribution of variables was examined using Kolmogorov-Smirnov tests. $\chi 2$ and Fisher's tests were used to compare categoric variables. Student's t tests were used to compare normally distributed continuous variables, and Mann-Whitney U tests were used to compare variables that were not normally distributed. Receiver operating characteristic (ROC) analysis was used to determine cutoff, sensitivity, and specificity values. Logistic regression analysis was used to define predictive factors. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). All statistical analyses were performed using MedCalc software version 14.0 for Windows (MedCalc Software, Mariakerke, Belgium). In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

Patients in the study group had stage IIIC–IVA serous OC. All patients received 3 cycles of NAC. A total of 214 patients were found to be suitable for the study. Suboptimal surgery was performed in 54 (25.2%) patients, and optimal surgery in 160 (74.8%). Clinical imaging features by CT and demographic data of the patients are shown in Table 1. All patients received 3 cycles of carboplatin and paclitaxel as NAC treatment. Paclitaxel was administered at a dose of 175 mg/m^2 in association with carboplatin at an area under the curve (AUC) of 5 or 6. Neoadjuvant therapy cycles and types of surgery are shown in Table 2. Eleven of the women treated with NAC were switched to second-line chemotherapy because of suboptimal response. Patients who received second-line chemotherapy were included suboptimal surgery group.

Table 2
Primary therapies for the study groups.

	Suboptimal surgery (n = 54)	Optimal surgery (n = 160)	*P*
Type of neoadjuvant chemotherapy			
- Carboplatin paclitaxel	54 (100)	160 (100)	
Number of cycles			
-3	54 (100)	160 (100)	
Operation			<0.001
-Hysterectomyoopherectomy PPLND Om	16 (29.6)	160 (100)	
-Hysterectomy oopherectomy Om	4 (7.4)	–	
-Oopherectomy	5 (9.3)	–	
-None	29 (53.7)	–	
Intestinal surgery			<0.001
-Resection*	10 (18.5)	59 (36.9)	
-Tumor excision	1 (1.9)	28 (17.5)	
Distal pancreatectomy	–	11 (6.8)	
Appendectomy	1 (1.9)	55 (34.4)	<0.001
Splenectomy	–	26 (16.3)	
Diaphragm resection	–	8 (5.0)	
Peritonectomy			
-Pelvic peritonectomy	–	67 (41.9)	
-Total peritonectomy	–	37 (23.1)	
Liver resection	–	15 (9.3)	
Subtotal gastrectomy	–	4 (2.5)	
Hyperthermic intraperitoneal chemotherapy	–	10	

Om, Omentectomy; PPLND, Pelvic paraaortic lymph node dissection.
* Total colectomy + partial colectomy + ileum resection.

Complete blood counts and NLR and PLR at diagnosis (T0) and after the completion of NAC but prior to IDS (T1) are shown in Table 3. The NLR and PLR values at both T0 and T1 were significantly higher in the suboptimal surgery group. The rate of change in NLR was calculated as [(NLR T0 – NLR T1)/NLR T0] × 100. The rate of change in PLR was calculated as [(PLR T0 - PLR T1)/PLR T0] × 100. Higher rates of change in both NLR and PLR were found in the optimal surgery group.

The optimal rate of change in NLR and PLR was investigated using ROC analysis to distinguish suboptimal surgery. The ROC analysis is shown in Fig. 1. A rate of change in NLR of 17% (cutoff) and above was found to have 76.9% sensitivity and 90.7% specificity for predicting suboptimal surgery (AUC = 0.882; $P < 0.001$). The positive predictive value was 55.7%, and the negative predictive value was 96.0%. A rate of change in PLR of 16% (cutoff) and above was found to have 53.8% sensitivity and 68.5% specificity for suboptimal surgery (AUC = 0.656; $P = 0.005$). The positive predictive value was 36.8%, and the negative predictive value was 88.7%. Thrombocytosis was detected in 82 (38.3%) patients at T0, including 28 (51.8%) patients in the suboptimal group and 54 (33.7%) in the optimal group ($P = 0.018$). Recovery of thrombocytosis (When the platelet count before NAC was >400,000/mm^3, the definition of recovery from thrombocytosis was ≤400,000/mm^3 after NAC.) was found to have 85.7% sensitivity and 64.8% specificity for predicting suboptimal surgery ($P < 0.001$). The positive predictive value was 55.8%, and the negative predictive value was 89.7%.

Results of the regression analysis identifying parameters that can be used to predict suboptimal surgery are shown in Table 4. Cutoff values to predict suboptimal surgery for age (cutoff = 52 years; AUC = 0.540), tumor size (cutoff = 11 cm; AUC = 0.524), and CA125 (cutoff = 765; AUC = 0.556) were found by ROC curve analysis. AUC values were 636 for T0 NLR, 874 for T1 NLR, 882 for difference NLR. Statistical difference between groups was found to be higher in recovery of thrombocytosis ($P< 0.001$) than number of patients with thrombocytosis ($P= 0.018$). Therefore, in Table 4, the most significant parameters (difference NLR, PLR, and recovery of thrombocytosis) were used instead of using all significant parameters. According to both mul-

Table 3
Complete blood counts of the study population.

	Suboptimal surgery (n = 54)	Optimal surgery (n = 160)	*P*
Complete blood counts at T0*			
-Hemoglobin	11.6 ± 1.2	11.7 ± 1.2	0.572
-Neutrophil	7390 ± 2406	6006 ± 2276	0.001
-Lymphocyte	1996 ± 610	2125 ± 806	0.283
-Platelet ($\times 10^3$)	447± 147	338± 134	<0.001
-NLR	4.1 ± 1.9	3.4 ± 2.1	0.031
-PLR	241 ± 109	196 ± 141	0.037
Serum collection time (the day before NAC)	9.9 ± 1.8	9.5 ± 2.1	0.194
Complete blood counts at T1*			
-Hemoglobin	11.3 ± 1.1	11.6 ± 1.2	0.120
-Neutrophil	6285 ± 1936	3688 ± 1052	<0.001
-Lymphocyte	1911 ± 867	2218 ± 699	0.009
-Platelet ($\times 10^3$)	386 ± 162	264± 100	<0.001
-NLR	3.7 ± 1.8	1.8 ± 0.7	<0.001
-PLR	223 ± 112	131 ± 67	<0.001
Serum collection time (the day after last NAC)	10.3 ± 1.6	9.8 ± 2.1	0.114
Time between last NAC and IDS (d)*	21.8 ± 1.9	22.2 ± 2.1	0.185
Rate of change in NLR (%)†	5.9 (−17, 49)	36.5 (−3, 87)	<0.001
Rate of change in PLR (%)†	12.7 (−42, 52)	18.6 (−44, 85)	<0.001
Patients with thrombocytosis‡	28 (51.9)	54 (33.8)	0.018
Recovery of thrombocytosis‡	4 (14.2)	35 (64.8)	<0.001

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
* mean ± standard deviation.
† median (minimum, maximum).
‡ n (%).

Table 4
Logistic regression analysis for predictors of suboptimal surgery.

	Univariate			Multivariate		
	OR	95%CI	*P*	OR	95%CI	*P*
Age (>52 y)	1.8	0.8-3.9	0.094	2.6	0.7-10.2	0.146
Large tumor (>11 cm)	1.5	0.7-3.3	0.243	1.8	0.4-8.4	0.408
CA125 (>765 U/mL)	1.8	0.9-3.6	0.068	1.1	0.3-4.0	0.864
Peritoneal implants	2.1	0.7-5.9	0.131	2.2	0.5-9.5	0.255
Omental deposits	1.3	0.7-2.4	0.384	1.0	0.3-2.8	0.903
Diaphragmatic carcinomatosis	1.9	0.9-3.8	0.068	1.2	0.4-3.9	0.666
Superficial liver deposits	1.7	0.8-3.3	0.102	2.5	0.7-8.8	0.146
Stomach infiltration	1.4	0.6-3.1	0.323	0.9	0.1-4.5	0.896
Bowel infiltration	1.2	0.6-2.4	0.554	1.7	0.5-6.3	0.367
Mesenteric implants	2.3	1.2-4.5	0.010	2.4	0.6-8.7	0.172
Pelvic LN involvement	1.2	0.5-2.0	0.737	1.6	0.5-5.4	0.376
Paraaortic LN involvement	2.6	1.4-5.0	0.003	1.1	0.2-5.1	0.960
Ascites	1.5	0.7-3.1	0.215	0.7	0.2-2.5	0.651
Pleural effusion	0.9	0.4-2.1	0.970	2.4	0.6-9.7	0.213
Large change in NLR (≥17.0%)	0.1	0.1-0.2	<0.001	0.1	0.1-0.2	<0.001
Large change in PLR (≥16.0%)	0.2	0.1-0.4	0.002	0.4	0.1-1.4	0.177
Recovery of thrombocytosis	0.4	0.3-0.6	0.001	0.3	0.1-0.6	0.003

tivariate and univariate regression analysis, a large change in NLR (OR = 0.1, 95%CI = 0.1-0.2 for univariate analysis; OR = 0.1, 95%CI = 0.1-0.2 for multivariate analysis) and recovery of thrombocytosis (OR = 0.4, 95%CI = 0.3-0.6 for univariate analysis; OR = 0.3, 95%CI = 0.1-0.6 for multivariate analysis) significantly predicted optimal surgery.

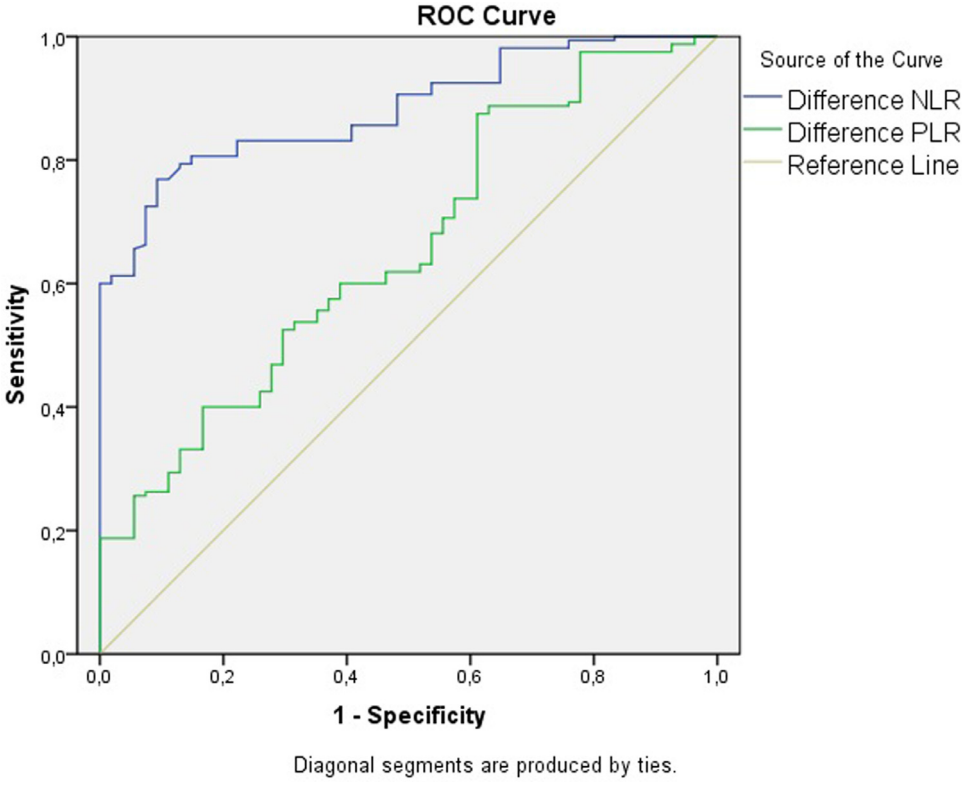

Fig. 1. Receiver operating characteristic (ROC) curve associated with the rate of change in NLR and PLR to identify patients likely to experience suboptimal surgery.

Discussion

The present retrospective review evaluated data for 214 stage IIIC–IVA serous OC patients who underwent IDS after platinum-based NAC, and examined the possibility that NLR, PLR, and platelet count might predict suboptimal surgery in such patients. Our results identified a large change in NLR as an independent predictor of optimal IDS. Moreover, recovery of thrombocytosis was detected more frequently at optimal surgery than with suboptimal surgery and was defined as an independent predictor of optimal IDS.

An important predictor of prognosis in advanced stage OC is optimal surgery.[4] Optimal IDS was achieved in 77.0%-85.8% of OC patients who underwent NAC.[2,3,13,14] In our study, the rate of optimal surgery was found to be 74.8% in stage IIIC–IVA serous OC patients after receiving 3 cycles of paclitaxel + carboplatin treatment. However, it is not possible to determine precisely who is a candidate for optimal surgery among patients who undergo interval cytoreduction surgery after NAC. NLR, PLR, and platelet count are among the recently studied systemic inflammatory response markers in several malignancies including advanced epithelial OC.[15-18]

Platelets, neutrophils, and lymphocytes have important roles in tumor immunology.[15] The inflammatory response involves systemic alterations triggered by circulating cytokines and chemokines, such as an increase in neutrophil count, a slight increase in platelet count, and a decline in lymphocyte count.[19-21] The production of bone marrow-stimulating cytokines, such as interleukin 6, tumor necrosis factor-alpha, and growth factors, which is triggered by malignant cells, contributes to thrombocytosis.[22] Neutrophils release cytotoxic mediators, including reactive

oxygen species and neutrophil elastase, that inflict damage to cellular DNA and promote cancer-associated angiogenesis.[15] Moreover, the release of inhibitory mediators suppresses the immune system and reduces lymphocyte count and function.[22] Platelets induce circulating tumor cell epithelial-mesenchymal transition and promote extravasation to metastatic sites.[17] These hematological changes have been suggested to be cornerstone events in the growth, progression, and spread of tumors.[19-21]

Suboptimal surgery in patients undergoing IDS after NAC may be increase morbidity in patients with poor prognosis. Therefore, it is very important for the patient and physician to know the likelihood that the surgery can be performed optimally before surgery. Studies on systemic inflammatory response markers in OC are still at a primitive stage. Patients with high NLR and PLR values have been shown to have shorter disease-free survival (DFS) and overall survival (OS) durations.[8,9,18] The rate of suboptimal surgery was higher in patients with high NLR values.[23] Moreover, high platelet value was associated with a poor prognosis in OC patients.[10,24] Eggemann et al found that a decrease in platelet count of less than 25% after chemotherapy was an unfavorable prognostic factor for overall survival.[25] Thrombocytosis was found to be significantly associated with residual tumor after the operation.[26] Kim et al showed that considering dynamic changes in NLR during NAC might help to estimate survival in advanced-stage OC.[15] In our cohort, we investigated changes during NAC in NLR, PLR, and platelet count as possible predictors of optimal surgery. Patients with a high likelihood of optimal surgery had significantly higher [(NLR T0 – NLR T1)/NLR T0] ratios (larger NLR change). A change in NLR of 17% (cutoff) and above was found to have 90.7% specificity and 96.0% negative predictive value for suboptimal surgery (AUC = 0.882). In other words, the likelihood of optimal surgery was found to be high in patients with a large change in NLR. Recovery of thrombocytosis was found to have 85.7% sensitivity and 89.7% negative predictive value for suboptimal surgery. Thus, a large change in NLR and recovery of thrombocytosis were independent predictors of optimal surgery.

This study has some limitations. First, the study was retrospective in design. As is true with any study on residual disease status, there is a possibility of interobserver variability in reporting the location and dimensions of residual tumors. However, we believe there were no biases such as selection bias because complete blood count results were obtained as close as possible to chemotherapy (for T0) or surgery (for T1). Second, the sample size was relatively small. Further studies with larger sample sizes and prospective research designs are recommended. Third, there is no consensus on the exact cutoff value for NLR, although previous studies have reported values of NLR for the prognosis of OC. In this study, the NLR cutoff value was selected using ROC analysis. Fourth, NLR is a nonspecific marker of inflammation. However, patients with other systemic diseases with the potential to affect NLR or PLR were excluded from the study, so no data on these patients were available. Despite these limitations, the similarities of the demographic characteristics in the study population and the analysis reports from expert pathologists increased the validity of our results and diminished these weaknesses.

In conclusion, to identify patients who are likely to have suboptimal surgery among advanced-stage OC patients who undergo IDS after NAC, the dynamic changes in NLR values can be examined. Patients with a small change in NLR can be given more cycles of NAC, or new treatment modalities may be considered rather than standard NAC treatment. Well-designed prospective studies with more patients are required to confirm our results.

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