

Research Article

Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Recurrent Ovarian Cancer

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Abstract

Objectives: The neutrophil-to-lymphocyte ratio (NLR) has been suggested as a prognostic biomarker in various malignancies, including ovarian cancer. However, its role in recurrent ovarian cancer remains unclear. This study aims to evaluate the prognostic significance of NLR in patients with recurrent ovarian cancer.

Methods: This retrospective study included 101 patients diagnosed with recurrent ovarian cancer between 2009 and 2021. Patients' demographic, clinical, and laboratory characteristics were collected from electronic medical records. Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were analyzed using Kaplan-Meier curves and Cox regression models.

Results: Among the 101 patients, 32 had an elevated NLR at diagnosis. Higher NLR levels were associated with significantly worse OS. Although the univariate analysis for PFS did not reach statistical significance, multivariate analysis confirmed that elevated NLR was an independent prognostic factor for both PFS and OS. Furthermore, the presence of bone and liver metastases negatively impacted survival outcomes.

Conclusion: NLR is a simple, cost-effective, and independent prognostic biomarker in recurrent ovarian cancer. Higher NLR levels correlate with worse survival outcomes, emphasizing its potential utility in clinical decision-making. Given the accessibility and cost-effectiveness of NLR measurement, our findings support its integration into clinical prognostic assessment in recurrent ovarian cancer.

Keywords: Ovarian cancer, neutrophil-lymphocyte ratio, recurrence, survival

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In the 2020 GLOBOCAN database, 313,959 new cases of ovarian cancer (OC) and more than 200,000 deaths were reported worldwide.^[1] Many patients are diagnosed at an advanced stage because they do not present early symptoms, which contributes significantly to the high mortality rate.^[2] Surgery, combined with neoadjuvant or adjuvant chemotherapy, remains the primary treatment for early-

stage OC, while chemotherapy is the standard approach for advanced disease.^[3] Although initial remission rates range from 60% to 80%, approximately 70% of patients with advanced-stage OC relapse within five years, and many develop drug resistance.^[4,5] The 5-year survival rate is as high as 95% for patients with early-stage OC, while this rate drops to less than 30% for those diagnosed at stage 3

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or 4.^[6] Given these challenges, predicting survival, ensuring early diagnosis, and assessing treatment response are of vital importance in the management of OC.

Inflammatory responses play an important role in OC prognosis. Uncontrolled inflammation not only drives tumor progression but also affects treatment outcomes. Blood-based markers of inflammation provide valuable information about systemic inflammation, but single parameters often fail to capture the full picture. Instead, composite indices of inflammation, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and prognostic nutritional index (PNI), offer greater predictive power due to their stability and sensitivity.^[3] Main systemic inflammation indicators include increased leukocyte and platelet counts, elevated C-reactive protein (CRP), and decreased albumin (ALB) levels.^[7-9] Several studies have investigated the prognostic value of systemic inflammatory response (SIR) markers, particularly PLR, CRP, and microRNAs, in cancer progression.^[10-12] Recent studies have highlighted NLR as a critical prognostic biomarker in multiple malignancies.^[13-16] As a minimally invasive, cost-effective, and easily accessible method, inflammatory marker assessment offers a practical approach in clinical settings.

Emerging evidence suggests that NLR, PLR, and MLR may help distinguish between benign and malignant ovarian tumors.^[17] NLR levels tend to be significantly higher in malignant ovarian cases and rank as the second most sensitive predictor of malignancy after cancer antigen 19-9.^[18]

This study aims to evaluate the prognostic significance of blood-based inflammatory markers, particularly NLR, at the time of diagnosis in patients with locally advanced and advanced ovarian cancer.

Methods

In this study, 101 patients with recurrent ovarian cancer who were diagnosed and treated in our center between 2009 and 2021 were included in the study. Demographic and clinical characteristics of the patients, laboratory parameters, histological diagnostic features and treatments they received were obtained retrospectively from electronic patient records.

Ethics committee approval for this study was obtained by the Hacettepe University Clinical Research Ethics Committee (Decision No: 2024/09-47, Date: 21.05.2024).

Descriptive statistics are presented as frequency (percentage), median, and interquartile range (IQR). Overall survival (OS) was taken as the time from the start of first-line treatment to the time of death from any cause. Progression-free

survival (PFS) was defined as the time from the start of second-line treatment to the time of disease progression or death; hence, progression was relevant from the start of subsequent treatment. Relative NLR was calculated using the formula (% neutrophil count, cells/ μ L)/(% lymphocyte count, cells/ μ L), and the median NLR value was taken as the reference cut-off value. Since there is no universally validated cut-off value for recurrent ovarian cancer, we used the median value (2.68) to stratify patients. Survival analyses were performed using the Kaplan–Meier method, and independent effects on OS and PFS were evaluated using the log-rank test. The significance of the differences between the groups was evaluated using the Mann-Whitney U test. Multivariate analyses were performed using the Cox regression analysis method. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

We included 101 patients in our study. At the time of diagnosis, 56 (55.4%) of our patients had stage 3 and the rest stage 4 disease. The majority of our patients were in the platinum-sensitive group (85.1%). There were 32 (31.7%) patients with NLR values equal to or higher than the median value (Table 1). The median age of the patients was 56 (IQR, 50-63). 80 (79.2%) of our patients had ECOG 0-1 performance status. Approximately 93% had serous histology. The NLR cut-off value was taken as 2.68, and patients with equal or higher values were divided into two groups as the NLR high group, and patients with values lower than this value were divided into the NLR low group. Accordingly, NLR levels were not significantly associated with age, ECOG performance status, disease stage, or platinum sensitivity (Table 2).

Furthermore, when comparing patients with low and high NLR values in univariate analyses, there was a significant decrease in PFS (Fig. 1) that did not reach statistical significance (10.6 vs 6.9, respectively, $p = 0.108$) but a statistically significant decrease in OS (Fig. 2) (29.8 vs 21.3, respectively, $p = 0.048$). Analysis of distant metastasis sites revealed that bone and lung metastases were significantly associated with reduced PFS, while liver and bone metastases were linked to shorter OS (Table 3). We found that ECOG and stage were factors affecting overall survival.

In multivariate analyses, we found that NLR marker was a statistically significant variable for both OS and PFS. In addition, we noticed that ECOG value caused a significant change in overall survival in both univariate and multivariate analyses (Table 4).

Table 1. Baseline characteristics of patients

Characteristic	n (%)
Total number of patients	101
Age (years), median	56 (IQR, 50-63)
Comorbidity	
Yes	50(49.5)
No	51 (50.5)
ECOG	
0	30 (29.7)
1	50 (49.5)
2	21(20.8)
Stage	
3	56 (55.4)
4	45 (44.6)
Histology	
Serous	94 (93.1)
Clear cell	4 (3.9)
Mucinous	3 (3.0)
Platinum sensitivity	
Sensitive	86 (85.1)
Resistant	15 (14.9)
NLR (median)	
<	69 (68.3)
≥	32 (31.7)
Second line treatment	
Liposomal doxorubicin	87 (86.1)
Gemcitabine	14 (13.9)
Site of metastasis	
Liver	26 (25.7)
Lung	21 (20.8)
Bone	7 (6.9)
Peritoneum	84 (83.2)

NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group Scale.

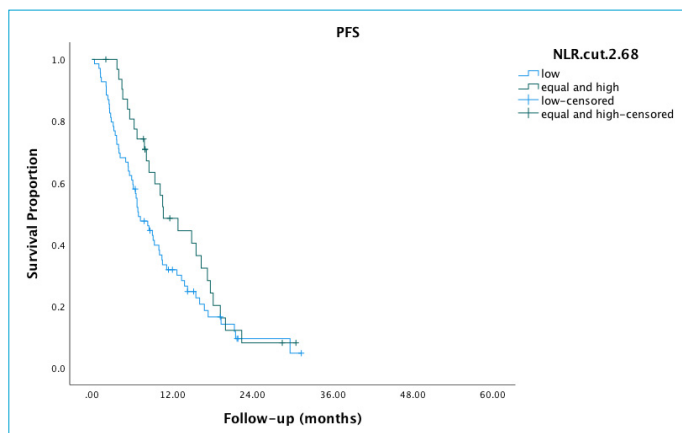
Table 2. Analysis of pathological and clinical characteristics according to NLR levels

	NLR		p
	Low	High	
Age			
<60	39	18	0.98
≥60	30	14	
ECOG			
0	21	9	0.96
1	34	16	
2	14	7	
Stage			
3	40	16	0.46
4	29	16	
Platinum sensitivity			
Sensitive	60	26	0.45
Resistant	9	6	

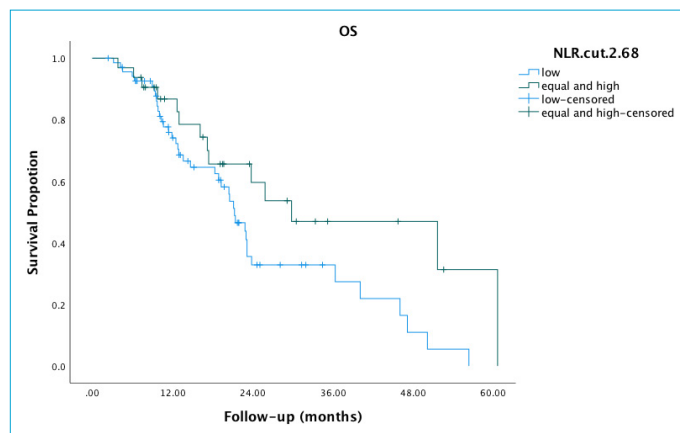
NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group Scale.

Discussion

Despite the progress in the diagnosis, surgery, chemotherapy, targeted therapies and immunotherapy of OC in the last decade,^[19-22] 5-year survival and disease recurrence rates remain at 39% and 70%, respectively.^[23, 24] The poor prognosis and high recurrence rate may be partly related to insufficiently effective markers for prognosis prediction. Consequently, the identification of new and reliable prognostic biomarkers for OC is necessary to inform and support clinical management. In this study, we examined the relationship between pretreatment NLR levels and survival in cases of recurrent ovarian cancer at diagnosis.

**Figure 1.** Kaplan–Meier curve illustrating the association between neutrophil-to-lymphocyte ratio (NLR) and progression-free survival (PFS).

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

**Figure 2.** Kaplan–Meier curve illustrating the association between neutrophil-to-lymphocyte ratio (NLR) and overall survival (OS).

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

Table 3. The factors affecting progression-free and overall survival

	PFS		OS	
	Median (95% CI)	p	Median (95% CI)	p
Age				
< 60	9.1 (4.8-13.4)	0.65	40.1 (12.8-67.3)	0.13
≥60	9.0 (7.5-10.6)		21.4 (17.6-25.2)	
ECOG				
0-1	9.3 (7.7-10.9)	0.09	23.1 (19.6-26.7)	0.01
2-3	6.6 (5.4-7.8)		17.4 (7.0-27.8)	
Stage				
3	10.4 (7.8-13.0)	0.10	25.8 (10.9-40.7)	0.01
4	6.7 (4.2-9.22)		17.4 (9.9-24.8)	
Platinum Sensitivity				
Sensitive	9.0 (6.8-11.2)	0.59	23.0 (20.4-25.6)	0.82
Resistant	8.5 (2.8-14.2)		21.3 (11.2-31.3)	
Comorbidity				
Yes	7.8 (6.2-9.5)	0.39	21.3 (16.4-26.1)	0.53
No	9.4 (7.0-11.7)		23.1 (19.7-26.5)	
Site of metastasis				
Liver (yes vs no)	5.9 (4.6-7.2) vs 9.3 (7.5-11.1)	0.35	18.3 (8.1-28.5) vs 23.8 (18.9-28.5)	0.02
Lung (yes vs no)	6.7 (3.4-10.0) vs 10.0 (7.9-12.1)	0.03	17.4 (9.6-25.2) vs 23.1 (20.4-25.8)	0.29
Bone (yes vs no)	4.6 (4.2-4.9) vs 9.3 (7.3-11.4)	0.004	10.0 (5.0-15.1) vs 23.1 (20.4-25.8)	0.04
Peritoneal (yes vs no)	6.7 (3.4-10.0) vs 10.2 (7.3-13.0)	0.17	21.4 (18.2-24.6) vs 23.1 (8.0-38.2)	0.62
Second-line treatment				
Liposomal doxorubicin	10.1 (8.6-11.6)	<0.001	23.1 (21.9-24.4)	<0.001
Gemcitabine	3.7 (2.7-4.7)		10.6 (9.4-11.9)	
NLR				
High	6.9 (4.7-9.1)	0.108	21.3 (18.5-24.0)	0.04
Low	10.6 (6.4-14.9)		29.8 (7.8-51.8)	

NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group Scale; PFS: progression-free survival; OS: overall survival.

Table 4. The factors affecting progression-free and overall survival in multivariate analysis

	PFS			OS		
	HR	95% CI	p	HR	95% CI	p
NLR						
Low vs high	0.59	0.36-0.98	0.04	0.46	0.23-0.92	0.03
Stage						
3 vs 4	1.51	0.84-2.69	0.16	2.09	0.94-4.67	0.07
ECOG						
0-1 vs 2-3	1.62	0.94-2.79	0.08	2.55	1.30-4.98	0.006
Platin sensitivity						
Sensitive vs resistant	1.09	0.59-1.99	0.77	0.91	0.42-2.16	0.90
Liver metastasis						
Absent vs present	0.65	0.45-1.64	0.65	0.86	0.47-2.49	0.86

NLR: neutrophil-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group Scale; PFS: progression-free survival; OS: overall survival.

In particular, higher NLR levels were associated with worse overall survival ($p=0.048$). Although the OS difference was 8.5 months, we consider this clinically meaningful in the context of recurrent disease, where survival outcomes are generally poor.

In patients with high NLR levels, multivariate analysis revealed a significant decrease in both PFS and OS ($p=0.043$ and 0.028 , respectively). Although PFS did not reach statistical significance in univariate analysis, the significant result in multivariate analysis may reflect the influence of confounding clinical variables that mask the true prognostic role of NLR. This finding is consistent with multiple studies in the literature, further supporting NLR as a prognostic marker.^[13, 25] A meta-analysis by Huang et al.^[16] demonstrated that elevated pre-treatment NLR levels were associated with worse OS and PFS in ovarian cancer patients.

Among our patients, 86 (85.1%) were platinum-sensitive, and 26 of these had high NLR levels. Although there was

a survival difference between platinum-sensitive and platinum-resistant patients, it did not reach statistical significance (PFS: $p=0.59$, OS: $p=0.82$) (Table 3).

Regarding the baseline characteristics of our patients, the majority had a diagnosis of serous OC. Approximately 32% of the patients had high NLR levels. A comparison between the low and high NLR groups revealed a statistically significant difference in OS (21.3 vs. 29.8 months, $p=0.048$). Although this difference did not reach statistical significance for PFS, our findings align with previous studies. For instance, Feng et al.,^[26] reported that elevated preoperative NLR levels were associated with poor cytoreduction outcomes, chemoresistance, and were an independent prognostic factor for PFS. Similarly, another study^[27] demonstrated that preoperative NLR serves as a prognostic biomarker for survival in epithelial ovarian cancer patients. This study also found that $\text{NLR} > 3.02$ was a significant predictor of platinum resistance, with high NLR levels negatively affecting both PFS and OS.^[27] In our study, the subgroup analysis included 15 platinum-resistant patients, six of whom belonged to the high NLR group.

When evaluating the relationship between distant organ metastases and survival, we found that bone metastases significantly affected both PFS and OS. Additionally, the presence of liver metastases led to a marked decrease in OS. Several studies^[28, 29] support these findings, and one study demonstrated that in metastatic ovarian cancer patients, not the number of distant metastases but rather the site of metastasis independently affected OS.^[30]

When dividing patients into two groups based on ECOG performance status (0-1 vs. 2-3), both PFS and OS were analyzed. A statistically significant difference in OS was observed in both univariate and multivariate analyses ($p=0.001$ and $p=0.006$, respectively), consistent with findings in multiple previous studies.^[31-33]

Our study has some limitations. First, there is a risk of selection bias as it is a single-center and retrospective study, which may limit the generalizability of our findings. Second, the small number of patients in our subgroup analyses may have reduced statistical power. Third, the predominance of serous histology in our cohort (93%) may limit generalizability. To make these findings more robust, larger, multicenter, and prospective studies are needed to help us better understand the relationship between systemic inflammation and ovarian cancer prognosis.

Conclusion

This study demonstrates that the neutrophil-to-lymphocyte ratio (NLR) is a significant prognostic marker in recurrent ovarian cancer. Higher NLR levels were associated

with poorer overall survival (OS), and multivariate analysis confirmed its role as an independent predictor of both progression-free survival (PFS) and OS. Given its ease of measurement and low cost, NLR appears to be a practical biomarker for clinical use. However, further studies with larger patient cohorts are needed to validate these findings.

Disclosures

Ethics Committee Approval: This study was approved by the Hacettepe University Clinical Research Ethics Committee (Decision No: 2024/09-47, Date: 21.05.2024).

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