RESEARCH ARTICLE

Araştırma Makalesi

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Geliş Tarihi / *Received* : April 08, 2025
Kabul Tarihi / *Accepted* : August 28, 2025

Bu makalede yapılacak atıf
Cite this article as
Güner FC, Iltar E, Güney MC,Cantürk RS, Doğan S, Doğan NU, Tuncer HA, Şimşek T.
Predictive Value of Immune-Inflammatory Indices in Epithelial Ovarian Cancer
Akd Med J 2026;12: 1-7

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Presentation: Preliminary data from this study were presented as an oral presentation at the National Congress jointly organized by the Turkish Society of Gynecologic Oncology and the Society of Cervical Pathologies and Colposcopy, held in Ankara, Turkey, on December 5–7, 2024.

Predictive Value of Immune-Inflammatory Indices in Epithelial Ovarian Cancer

Epitelyal Over Kanserinde İmmün-İnflamatuar İndekslerin Prediktif Önemi

ABSTRACT

Objective

This study aimed to evaluate the prognostic significance of systemic immune-inflammatory indices, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), in patients with epithelial ovarian cancer (EOC).

Material and Methods

A retrospective analysis was conducted in patients with EOC diagnosed at Akdeniz University Hospital between 2005 and 2019. Patients with hematologic malignancies, autoimmune disorders, chronic inflammatory diseases, or a history of other cancers were excluded. Preoperative and postoperative hematologic parameters were recorded. The prognostic value of immune-inflammatory indices was assessed using nn-Meier survival analysis, Cox regression, and receiver operating characteristic (ROC) analysis.

Results

A total of 264 EOC patients were included. Postoperative SII and NLR values were significantly higher than the preoperative levels ($p<0.001$). Higher postoperative SII and NLR were associated with serous histology, malignant cytology, and advanced-stage disease. ROC analysis showed that postoperative SII predicted omental metastasis (AUC=0.654, $p<0.001$), advanced-stage disease (AUC=0.641, $p<0.001$), and 3-year survival (AUC=0.663, $p<0.001$). Kaplan-Meier analysis revealed shorter overall survival in patients with high postoperative SII and NLR ($p<0.001$). Multivariate Cox regression confirmed that high postoperative SII (HR=2.45, $p<0.001$) and NLR (HR=1.89, $p=0.001$) as independent prognostic factors.

Conclusion

Postoperative immune-inflammatory indices, particularly SII and NLR, are significant prognostic markers in EOC. Their association with advanced disease and poor survival highlights their potential clinical utility. Further studies are needed to confirm these findings.

Key Words

Epithelial ovarian cancer, Systemic immune-inflammation index, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Prognosis, Survival

DOI: 10.53394/akd.1666986

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ÖZ

Amaç

Bu çalışmada epitelyal over kanseri (EOC) hastalarında sistemik immün-inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) gibi sistemik immün-inflamatuar indekslerin prognostik öneminin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler

Akdeniz Üniversitesi Hastanesi'nde 2005-2019 yılları arasında tanı konulan EOC hastaları üzerinde retrospektif bir analiz yapıldı. Hematolojik maligniteleri, otoimmün hastalıkları, kronik inflamatuar hastalıkları olan veya başka kanser öyküsü bulunan hastalar çalışmadan dışlandı. Ameliyat öncesi ve sonrası hematolojik parametreler toplandı. İmmün-inflamatuar indekslerin prognostik değeri Kaplan-Meier sağkalım analizi, Cox regresyonu ve alıcı işletim karakteristiği (ROC) analizi kullanılarak değerlendirildi.

Bulgular

Toplam 264 EOC hastası çalışmaya dahil edildi. Ameliyat sonrası SII ve NLR değerleri ameliyat öncesine göre anlamlı derecede yüksekti ($p<0.001$). Ameliyat sonrası yüksek SII ve NLR değerleri seröz histoloji, malign sitoloji ve ileri evre hastalık ile ilişkiliydi. ROC analizi postoperatif SII'nin omental metastazı (AUC=0.654, $p<0.001$), ileri evre hastalığı (AUC=0.641, $p<0.001$) ve 3 yıllık sağ kalımı (AUC=0.663, $p<0.001$) öngördüğünü göstermiştir. Kaplan-Meier analizi, ameliyat sonrası SII ve NLR değeri yüksek olan hastalarda genel sağ kalımın daha az olduğunu göstermiştir ($p<0.001$). Çok değişkenli Cox regresyonu, yüksek postoperatif SII (HR=2.45, $p<0.001$) ve NLR'nin (HR=1.89, $p=0.001$) bağımsız prognostik faktörler olduğunu doğruladı.

Sonuç

Ameliyat sonrası immün-inflamatuar indeksler, özellikle SII ve NLR, EOC'de önemli prognostik belirteçlerdir. İlerlemiş hastalık ve kötü sağ kalım ile olan ilişkileri, potansiyel klinik faydalarını vurgulamaktadır. Bu bulguları doğrulamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Epitelyal over kanseri, Sistemik immün-inflamasyon indeksi, Nötrofil-lenfosit oranı, Trombosit-lenfosit oranı, Prognoz, Sağkalım

INTRODUCTION

Epithelial ovarian cancer (EOC) constitutes the predominant form of ovarian malignancy, accounting for approximately 85–90% of cases (1). Due to its insidious onset and lack of specific early symptoms, nearly 70% of patients are diagnosed at advanced stages, with a reported five-year survival rate of only 40% (2). In light of these challenges, the identification of reliable prognostic markers that can inform treatment planning and anticipate disease progression has gained considerable importance.

Various molecular markers, such as survivin, Ki-67, and topoisomerase IIα, have been studied for their potential prognostic value in EOC, yet they have shown limited applicability in routine clinical practice (3).

In recent years, systemic inflammation has been increasingly acknowledged as a key contributor to oncogenesis and tumor progression, influencing immune surveillance, angiogenesis, and cellular proliferation (4).

Among inflammation-based indices, the Systemic Immune-Inflammation Index (SII), which incorporates neutrophil, lymphocyte, and platelet counts, was first introduced by Hu et al. in 2014 as a prognostic tool in hepatocellular carcinoma (5). Other indices, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have also been shown to reflect the host immune response and tumor burden, with demonstrated utility across various malignancies, including gastrointestinal, endometrial, and cervical cancers (6-8).

There is growing evidence suggesting that elevated levels of systemic inflammatory markers are associated with unfavorable outcomes in gynecological cancers, including EOC (9). Despite this, further research is required to elucidate the prognostic value of these markers across different disease stages and histological subtypes.

The objective of this study was to assess the prognostic significance of the SII in patients diagnosed with epithelial ovarian cancer, with particular emphasis on its association with disease stage, tumor histopathology, and overall survival.

MATERIALS and METHODS

This retrospective study was conducted at Akdeniz University and received approval from the Clinical Research Ethics Committee prior to initiation. We reviewed the medical records of patients who had been diagnosed with epithelial ovarian cancer between 2005 and 2019. Patients with coexisting hematologic malignancies, autoimmune disorders, chronic inflammatory diseases, or a history of other cancers were excluded to ensure a more homogeneous study population.

The dataset included demographic and clinical information such as age at diagnosis, menopausal status, gravidity, FIGO stage, and progression details. Hematological data-specifically hemoglobin levels and neutrophil and lymphocyte counts-were also collected. Patients were categorized into early-stage (FIGO stages I–II) and advanced-stage (FIGO stages III–IV) groups. Blood samples were obtained within two weeks before surgery and again on the third postoperative day for comparison of pre- and post-surgical inflammatory markers. Histopathological data were retrieved from the hospital's pathology department records. However, information regarding perioperative blood transfusions was not available in the patient records; thus, their potential impact on hematologic parameters could not be assessed.

Inflammatory indices were calculated using standard formulas: NLR was derived from the ratio of neutrophils to lymphocytes, PLR from platelets to lymphocytes, and SII was calculated as the platelet count multiplied by neutrophil count and divided by the lymphocyte count.

Statistical analyses were performed using IBM-SPSS 23.0. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), while categorical variables were presented as numbers and percentages. The Shapiro-Wilk test was used to assess normality. Differences in categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when expected frequencies were <5 in >20% of cells. Due to the non-normal distribution, the Mann-Whitney U test was used for comparing two independent groups.

Survival analysis was performed using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values for inflammatory indices, and the area under the curve (AUC) was calculated to assess diagnostic performance. A two-tailed p-value of <0.05 was considered statistically significant, at a 95% confidence interval.

RESULTS

The demographic and hematologic characteristics of the 264 included patients were summarized in Table I.

Table I. Demographic and Clinical Characteristics of the Patients.

Variable	Min	Max	Mean	SD
Age (years)	21	85	56,64	12,44
Preoperative Hb (g/dL)	6,20	15,60	11,83	1,54
Preoperative HCT (%)	4,30	47,00	35,39	4,93
Preoperative MCV (fL)	9,00	103,70	83,11	8,68
Preoperative NEU (×10⁹/L)	,36	14,90	4,55	2,77
Preoperative LYM (×10⁹/L)	,12	6,80	2,03	1,10
Preoperative PLT (×10³)	73	1123	347,75	145,60
Preoperative PLR	33,80	3116,67	255,66	294,15
Preoperative NLR	0,17	21,56	2,87	2,82
Preoperative SII	40,35	6447,17	955,35	911,49
Postoperative Hb (g/dL)	6,80	14,60	10,19	1,50
Postoperative HCT (%)	2,00	309,00	32,49	24,55
Postoperative PLT (×10³)	60	942	297,47	134,70
Postoperative NLR	0,09	63,33	8,26	7,94
Postoperative SII	23,02	21186,14	2428,19	2625,29

Hb, Hemoglobin concentration; HCT, Hematocrit; MCV, Mean corpuscular volume; NEU, Neutrophil count; LYM, Lymphocyte count ; PLT, Platelet count ; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index

The age range was 21–85 years, with a mean age at diagnosis of 56.6±12.4 years. Preoperative hemoglobin and hematocrit levels were 11.8±1.5 g/dL and 35.4±4.9%, respectively. Preoperative neutrophil and lymphocyte counts were 4.55±2.77×10/L and 2.03±1.10×10/L, respectively. Among the patients included in the study, 56.8% (n = 150) had serous tumors, while the remaining 43.2% (n = 114) were diagnosed with non-serous subtypes. According to the FIGO staging system, just over a quarter (26.1%) were classified as early-stage cases, whereas the majority (73.9%) presented with advanced-stage disease. A systematic lymphadenectomy was performed in 180 patients, of whom 72 were foundto have lymph node metastases, corresponding to a metastasis rate of 40% within this subgroup. Omental metastases were also relatively common, observed in 167 individuals (63.3%) within the cohort. Further details on tumor histopathology and staging are presented in Table II.

Table II. Histopathological Profiles of Patients And Staging Results.

Parameter		N	%
Tumor Histology	Serous	150	56,8
	Non-serous	114	43,2
Stage	Early stage	69	26.1
	Advanced stage	195	73.9
Cytology	Benign	115	43,6
	Malignant	149	56,4
Systemic lymphadenectomy	Not performed	84	31.8
	Performed	180	68.2
Lymph node status	No metastasis	108	60.0
	Metastasis present	72	40.0
Omental metastasis	Absent	97	36.7
	Present	167	63.3
3-year survival	Not alive	86	32,6
	Alive	178	67,4

Analysis of inflammatory markers revealed that postoperative day 3 SII (2428.2±2625.3) and NLR (8.3±7.9) were significantly higher than the preoperative values ($p<0.001$). Postoperative SII was significantly higher in serous histology compared to non-serous cases (1800.6 vs. 1368.0, $p=0.039$). Patients with malignant cytology had significantly higher postoperative NLR (7.5 vs. 5.2, $p=0.003$) and SII (1981.2 vs. 1318.8, $p=0.001$) than those with negative cytology. These comparisons are illustrated in Table III.

To determine the predictive value of postoperative inflammatory indices, ROC curve analyses were performed. The SII demonstrated moderate discriminative ability for predicting omental metastasis (AUC=0.654, $p<0.001$), advanced-stage disease (AUC=0.641, $p<0.001$), and 3-year survival (AUC=0.663, $p<0.001$). Similarly, postoperative NLR showed predictive capacity with AUC values of 0.643, 0.634, and 0.688 for the respective outcomes ($p<0.01$ for all). These results are visualized in Figure 1.

Kaplan–Meier survival analysis further highlighted the prognostic relevance of these indices. Patients with postoperative SII values below the determined cutoff of 3265.3 experienced a significantly longer mean overall survival of 112.6 months, in contrast to 50.7 months for those with higher SII values (log-rank $p<0.001$). Likewise, individuals with postoperative NLR values under 5.3 had a mean survival of 131.0 months, whereas those with elevated NLR levels had a notably shorter survival duration of 73.9 months (log-rank $p<0.001$). These survival trends are illustrated in Figure 2.

Table III. Diagnostic Value of Preoperative and Postoperative Inflammatory Markers.

		NLR	P	PLR	P	SII	P	PO NLR	P	PO SII	P
Tumor Histology	Serous	2.0 (0.2 – 21.6)	0.288	196.2 (33.8 – 3116.7)	0.158	709.6 (40.4 – 6447.2)	0.140	7.6 (0.09 – 63.3)	0.114	1800.6 (23.0 – 20456.7)	**0.039**
	Non-serous	1.8 (0.4 – 13.1)		158.8 (43.7 – 2033.3)		618.9 (115.0 – 3100.3)		5.4 (0.15 – 46.5)		1368.0 (46.0 – 21186.1)	
Stage	Early stage	2.8 (0.6 -10.5)	**0.004**	194.6 (56.7- 766.0)	0.702	846.5 (115.0 – 3217.2)	0.249	6.5 (0.2 – 46.5)	**0.030**	1819.5 (46.0 – 11629.0)	**0.025**
	Advanced stage	2.9 (0.2 – 21.6)		277.3 (33.8 – 3116.7)		993.9 (40.3 – 6447.2)		8.9 (0.1 – 63.3)		2643.6 (23.0 – 21186.1)	
Cytology	Benign	2.1 (0.6 – 21.6)	0.061	163.5 (54.6 – 766.0)	0.679	652.9 (115.0 – 5025.3)	0.458	5.2 (0.1 – 46.5)	**0.003**	1318.8 (23.0 – 21186.1)	**0.001**
	Malignant	1.9 (0.2 – 19.3)		163.7 (33.8 – 3116.7)		642.3 (40.3 – 6447.2)		7.5 (0.2 – 63.3)		1981.2 (67.8 – 20456.7)	
Systemic lymphadenectomy	Not performed	2.8 (0.6 – 13.1)	0.895	243.5 (33.8 – 3116.7)	0.648	966.0 (66.2 – 5025.3)	0.897	9.0 (0.1 – 63.3)	0.285	2712.2 (23.0 – 20456.7)	0.230
	Performed	2.9 (0.2 – 21.6)		261.3 (43.7 – 2158.3)		950.4 (40.4 – 6447.2)		7.9 (0.2 – 46.5)		2295.6 (23.5 – 21186.1)	
Lymph node status	No metastasis	2.7 (0.5 – 10.5)	0.446	256.7 (46.6 – 2158.3)	0.773	898.4 (115.0 – 4062.2)	0.351	7.4 (0.2 – 46.5)	0.191	2158.2 (46.0 – 21186.1)	0.342
	Metastasis present	3.1 (0.2 – 21.6)		268.3 (43.7 – 720.3)		1028.4 (40.4 – 6447.2)		8.7 (0.3 – 30.0)		2501.8 (23.5 – 8392.2)	
Omental metastasis	Absent	2.6 (0.5 – 10.5)	0.256	196.3 (54.7 – 766.0)	**0.002**	807.7 (115.0 – 3867.9)	**0.026**	6.3 (0.2 – 46.5)	**0.001**	1752.8 (23.5 – 11629.0)	**0.001**
	Present	3.0 (0.2 – 21.6)		290.2 (33.8 – 3116.7)		1041.1 (40.4 – 6447.2)		9.3 (0.1 – 63.3)		2820.5 (23.0 – 21186.1)	
3-year survival	Not alive	2.0 (0.3 – 19.3)	0.894	149.1 (33.8 – 3116.7)	**0.035**	613.3 (66.2 – 6447.2)	0.450	9.0 (0.1 – 52.2)	**0.001**	2586.5 (23.0 – 21186.1)	**0.001**
	Alive	2.0 (0.2 – 21.6)		183.2 (50.4 – 2158.3)		670.2 (40.4 – 5025.3)		5.2 (0.2 – 63.3)		1436.9 (23.5 – 20456.7)	

NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PO, Postoperative. Note. *P* values in bold are statistically significant.

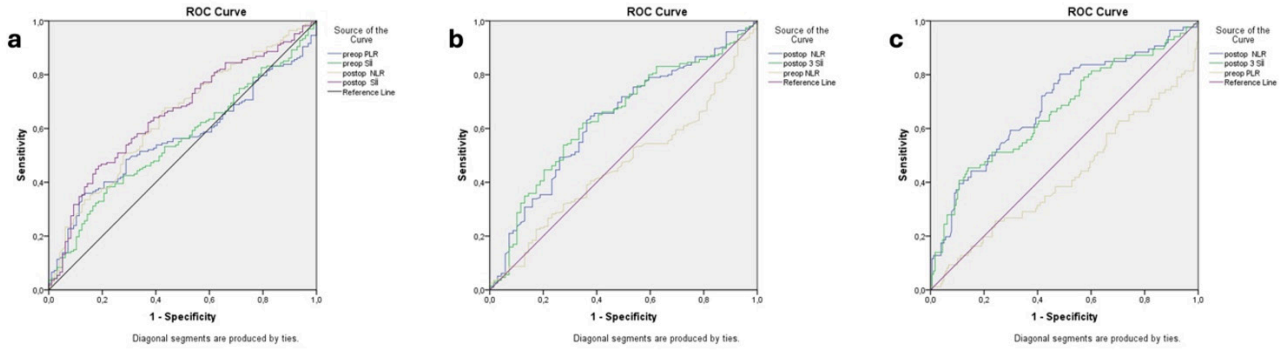


Figure 1. Prognostic Performance of Postoperative Immune-Inflammatory Indices Based on ROC Analysis
(a) In the ROC curve analysis for omental metastasis, the area under the curve (AUC) and p-values for the preoperative PLR, preoperative SII, postoperative day 3 NLR, and postoperative day 3 SII were calculated as 0.562 ($p = 0.094$), 0.553 ($p = 0.148$), 0.643 ($p < 0.001$), and 0.654 ($p < 0.001$), respectively. (b) In the ROC curve analysis for advanced-stage disease, the AUC and p-values for preoperative NLR, postoperative day 3 NLR, and postoperative day 3 SII were 0.465 ($p = 0.390$), 0.634 ($p = 0.001$), and 0.641 ($p < 0.001$), respectively. (c) In the ROC analysis for patients with survival less than three years, the AUC and p-values for preoperative PLR, postoperative day 3 NLR, and postoperative day 3 SII were found to be 0.420 ($p = 0.035$), 0.688 ($p < 0.001$), and 0.663 ($p < 0.001$), respectively.

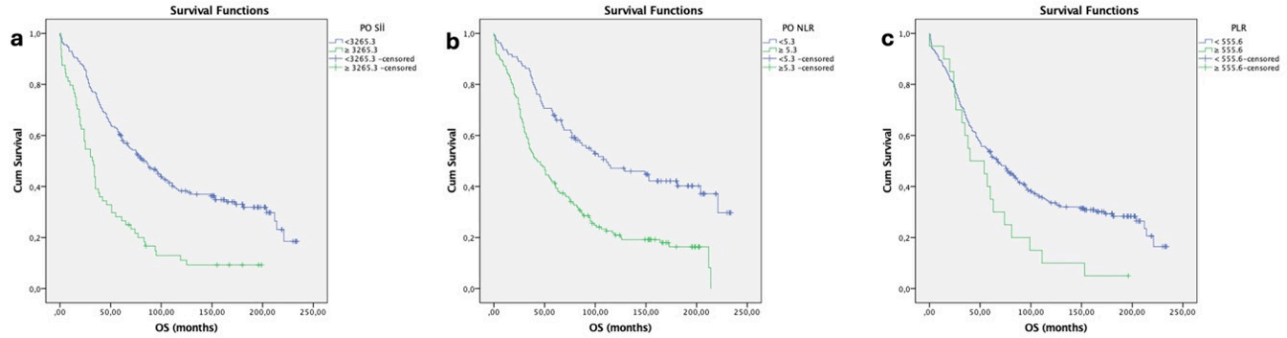


Figure 2. Prognostic Significance of Postoperative Immune-Inflammatory Markers Based on Kaplan–Meier Survival Analysis
(a) The optimal cutoff value for the postoperative day 3 systemic immune-inflammation index (SII) was determined to be 3265.3. Patients with SII values below this threshold exhibited significantly longer survival durations (Log-rank $p < 0.001$). (b) For the postoperative day 3 neutrophil-to-lymphocyte ratio (NLR), the identified cutoff value was 5.3. Patients with NLR values below this threshold demonstrated significantly improved survival outcomes (Log-rank $p < 0.001$). (c) Using a cutoff value of 555.6 for the preoperative platelet-to-lymphocyte ratio (PLR), Kaplan–Meier analysis showed that patients in the low PLR group had longer survival; however, the difference reached only borderline statistical significance (Log-rank $p = 0.022$).

Taken together, these findings suggest that elevated levels of postoperative SII and NLR are associated with markedly reduced overall survival. Even after accounting for relevant clinical variables, the association between increased inflammatory markers and poorer outcomes remained statistically significant. This underscores the potential utility of SII and NLR as prognostic tools in routine clinical evaluation.

DISCUSSION

Inflammatory processes have long been implicated in cancer biology, influencing tumor initiation, progression, and immune evasion (4, 10). The present study reinforces the prognostic significance of systemic inflammatory markers, particularly the Systemic Immune-Inflammation Index and Neutrophil-to-Lymphocyte Ratio, in patients with epithelial ovarian cancer. Our analysis demonstrated that postoperative SII and NLR levels were significantly elevated compared to preoperative values, suggesting that the surgical intervention and tumor burden may trigger heightened inflammatory responses. Elevated postoperative SII and NLR were also associated with adverse clinicopathological features, including serous histology and malignant cytology. These findings align with the hypothesis that tumor-induced systemic inflammation plays a critical role in disease aggressiveness (4, 11, 12). Furthermore, the predictive value of both SII and NLR was supported by ROC analysis, which showed moderate accuracy for forecasting omental metastasis, advanced-stage disease, and three-year survival. These results underscore the potential of these indices as accessible, cost-effective biomarkers for clinical risk assessment (9, 13).

Survival analysis revealed that patients with elevated postoperative SII and NLR had markedly reduced overall survival. This observation is consistent with previous studies that highlight the role of inflammation in promoting a tumor-permissive microenvironment (4, 14, 15). Unlike single-parameter markers, SII incorporates multiple components of the immune system and may thus provide a more comprehensive assessment of systemic inflammatory status (5).

Although earlier studies have explored the prognostic utility of NLR and PLR in ovarian and other malignancies, fewer have emphasized the role of postoperative measurements (7, 8, 16, 17). Our findings contribute to a growing body of evidence that suggests postoperative inflammatory markers may offer superior prognostic insight com-

pared to their preoperative counterparts (18). In addition, our study observed that patients with malignant cytology tended to have relatively lower preoperative NLR values and higher postoperative NLR values. While the biological or clinical significance of this pattern remains uncertain, previous literature has suggested that preoperative NLR may reflect tumor-associated immune suppression and systemic inflammatory imbalance (19).

Although the findings of this study are promising, certain limitations should be acknowledged. As a retrospective, single-center study, the generalizability of the results may be constrained. Furthermore, this research did not include comparisons with other well-established inflammatory or prognostic markers, such as C-reactive protein, which might have provided additional context or strengthened the predictive value of the indices assessed. Additionally, data on perioperative blood transfusions were not consistently recorded in patient files; therefore, the potential influence of transfusions on postoperative hematologic indices could not be entirely excluded. This represents another limitation of the study.

Nonetheless, the results support the potential clinical relevance of postoperative SII and NLR as prognostic indicators in epithelial ovarian cancer. Their strong association with both disease severity and overall survival suggests that these markers could be integrated into routine postoperative evaluation. To strengthen the evidence base and enhance clinical applicability, larger-scale, prospective studies conducted across multiple centers are necessary.

CONCLUSION

This study emphasizes the prognostic potential of postoperative immune-inflammatory markers-especially the SII and NLR—in patients with epithelial ovarian cancer. The correlation between these indices and indicators of aggressive tumor behavior and reduced survival suggests they might play a valuable role in clinical decision-making. To confirm their utility and determine appropriate clinical thresholds, further validation through robust, prospective multicenter studies is recommended.

Ethics Committee Approval

This research complies with all relevant national regulations, institutional policies, and is in accordance with the tenets of the Helsinki Declaration. It has been approved by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (Approval Number: KAEK-170, Approval Date: 22/02/2023).

Informed Consent

This study was retrospective in nature and based exclusively on data derived from patient laboratory findings and medical records, with no direct contact with patients. Therefore, obtaining informed consent was not required. Nevertheless, all patient rights were respected, and data were anonymized in accordance with the principles of the Declaration of Helsinki.

Author Contributions

Concept – F.C.G., S.D., U.D.; Design – F.C.G., E.I., M.C.G., R.S.C., S.D., H.A.T., T.Ş.; Supervision – S.D., U.D., H.A.T., T.Ş.; Resources – S.D.; Data Collection and/or Processing – F.C.G., E.I., M.C.G., R.S.C.; Analysis and/ or Interpretation - F.C.G., E.I., M.C.G., R.S.C., S.D., U.D., H.A.T., T.Ş.; Literature Search – F.C.G., E.I., M.C.G., R.S.C.; Writing Manuscript – F.C.G., E.I., S.D.; Critical Review – S.D., U.D., H.A.T., T.Ş.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Declaration of AI and AI-Assisted Technologies in the Writing Process: The authors declare that no artificial intelligence (AI) or AI-assisted technologies were used in the writing, preparation, editing, analysis, or revision of this manuscript. All content was created, reviewed, and approved solely by the authors.

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