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RESEARCH

Prognostic significance of prognostic nutritional index in high-grade serous ovarian cancer: a comparative analysis with other prognostic factors

Yüksek dereceli seröz over kanserinde prognostik nutrisyonel indeksin prognostik önemi: diğer prognostik faktörlerle karşılaştırmalı analizi

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Abstract

Purpose: High-grade serous ovarian cancer (HGSOC) has high recurrence and mortality rates despite treatment advances. The prognostic nutritional index (PNI) shows promise in other cancers, but its role in HGSOC is unclear. This study aimed to evaluate PNI's prognostic value in HGSOC and establish an optimal cutoff for mortality prediction.

Materials and Methods: This retrospective cohort evaluated 332 patients with HGSOC from 2010-2020. The age range, body mass index (BMI), menopausal status, parity status, presence of comorbidities, American Society of Anesthesiologists (ASA) scores, the presence of ascites, cancer antigen 125 (CA-125), neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, disease stage, recurrence status, platinum resistance, attainment of optimal cytoreduction, and PNI were evaluated. PNI relationship with other factors affecting prognosis was evaluated.

Results: The Mean PNI was 41.8±8.7, with a cutoff of ≤44.6 (96.84% sensitivity, 81.69% specificity) for mortality prediction. PNI was a stronger predictor (AUC=0.932) than CA-125 (AUC=0.588). Low PNI (≤44.6) was significantly linked with advanced disease, platinum resistance, preoperative ascites ≥ 1 L, more recurrences, lower 5-year survival, and higher mortality. Multivariate analysis showed low PNI as an independent mortality predictor (OR: 136.82, 95% CI: 54.6-342.4), along with preoperative ascites > 1 L and disease recurrence.

Conclusion: A low preoperative PNI strongly predicts higher mortality in HGSOC patients than in CA-125 patients. This accessible and cost-effective biomarker may aid in assessing risks, guiding increased monitoring, and

Öz

Amaç: Yüksek grade seröz over kanseri (HGSOC), tedavisindeki gelişmelere rağmen yüksek rekürrens ve ölüm oranlarına sahiptir. Prognostik nütrisyonel indeks (PNI)'in prognostik önemi diğer kanserlerde umut verici görünse de, HGSOC'daki rolü belirsizdir. Çalışmamız, HGSOC' de PNI' in prognostik anlamını ve mortalite için optimal cutoff değerini belirlemeyi hedeflemiştir.

Gereç ve Yöntem: Bu retrospektif kohort çalışmada; 2010-2020 yılları arasında HGSOC tanılı, 332 hasta değerlendirdi. Hastaların yaş aralığı, vücut kitle indeksi (VKİ), menopoz durumu, parite durumu, komorbidite varlığı, Amerikan Anestezistler Derneği (ASA) skorları, asit varlığı, kanser antijeni 125 (CA-125), nötrofil-lenfosit oranı, trombosit-lenfosit oranı, hastalık evresi, nüks durumu, platin direnci, optimal sitoredüksiyon elde edilmesi ve PNI değerlendirildi. PNI' in prognozu etkileyen diğer faktörlerle ilişkisi değerlendirildi.

Bulgular: Ortalama PNI 41.8±8.7 idi. Mortalite tahmini için eşik değer ≤44.6 alındığında %96.84 sensitivite, %81.69 spesifite belirlendi. PNI, CA-125'e (AUC=0.588) göre daha güçlü tahmin edici olarak bulundu (AUC=0.932). Düşük PNI (≤44.6) değeri; ileri evre hastalık, platin direnci, ≥1L pre-operatif asit varlığı, daha fazla nüks, daha düşük 5 yıllık sağkalım ve daha yüksek mortalite ile anlamlı olarak ilişkili bulundu. Çok değişkenli analizde mortalite öngörüsünde >1L preoperatif asit varlığı, hastalık nüksü, düşük PNI'nın (OR: 136.82, %95 CI: 54.6-342.4) bağımsız prediktif faktörler olarak saptandı.

Sonuç: HGSOC hastalarında düşük preoperatif PNI değeri mortaliteyi güçlü bir şekilde tahmin etmektedir ve CA-125'ten daha iyi sonuçlar vermektedir. Bu sonuçların

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customizing treatments. Further studies are necessary to confirm these results in various populations.
Keywords:. CA-125; high-grade serous ovarian cancer; mortality; platinum resistance; prognostic nutritional index.

çeşitli popülasyonlarda doğrulanması için daha fazla çalışmalara ihtiyaç vardır.
Anahtar kelimeler: CA-125; yüksek grade seröz over kanseri; mortalite; platin direnci; prognostik nütrisyon indeksi

INTRODUCTION

High-grade serous ovarian cancer (HGSOC) remains one of the most lethal gynecological malignancies, characterized by insidious onset and late-stage diagnosis in the majority of patients[1]. The overall survival of HGSOC patients remains unsatisfactory despite a combination of cytoreductive surgery and platinum-based chemotherapy because of the high recurrence and mortality rates[1]. Simple, reliable, and inexpensive prognostic markers are urgently needed for risk stratification, prediction of response to therapy, and guidance of personalized treatment. This need is critical because of the complexities in managing advanced-stage HGSOC, requiring crucial decisions on primary vs. interval cytoreduction, use of HIPEC, and maintenance therapies such as PARPis and bevacizumab[2].

Despite using complex treatments, including targeted therapies such as PARPis, with notable benefits for some patients, five-year survival rates remain low, especially in advanced stages, and recurrence rates are high[3,4]. A significant challenge in this endeavor is the profound intratumoral heterogeneity characteristic of HGSOC, spanning gene expression, copy number variations (CNVs), and single-cell profiles, which contribute to therapeutic resistance and varied treatment responses[5]. Recent multi-omics studies using scRNA-seq and spatial transcriptomics have enhanced our understanding of heterogeneity. These studies identified distinct tumor clones, evolutionary paths, and key cell communication networks, such as MDK-NCL, revealing novel therapeutic targets and insights into the tumor microenvironment[5]. This pursuit of improved markers is driven by the shortcomings of current screening tools, as shown by the UKCTOCS trial indicating no survival benefit from ovarian cancer screening and the ongoing search for strong prognostic indicators[6]. Current research explores factors such as stemness-related gene signatures and new composite indices such as the Ovarian Neoadjuvant Chemotherapy Prognostic Index (ONCPI), which combines chemotherapy response scores with inflammation indicators, including the neutrophil-to-lymphocyte ratio (NLR)[4, 5].

The prognostic nutritional index (PNI), which is derived from serum albumin and lymphocyte counts, is a straightforward, objective, and affordable indicator of a patient's nutritional and immune status. In other cancers, the PNI is a key predictor of patient outcomes, indicating its potential use in HGSOC[5-9]. PNI's prognostic utility is based on the importance of nutritional status and immune competence in cancer progression and therapy response. Malnutrition can weaken immune function and tissue repair, whereas systemic inflammation, as shown by lymphocyte counts, affects the tumor environment. The prognostic value of PNI in HGSOC is limited and somewhat contradictory, despite the recognized roles of the tumor microenvironment and systemic inflammation in ovarian cancer progression[5]. Some studies on general ovarian cancer populations or mixed histological subtypes have recognized the importance of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as significant prognostic indicators[5,6], as well as the systemic immune inflammation index showing promise[7,8]. However, evidence for PNI is less consistent, with studies reporting conflicting results due to limited sample sizes, diverse patient populations, and varying PNI cutoff values[9-13]. Current studies indicate that high PNI correlates with better survival outcomes (overall, progression-free, and cancer-specific survival)[14,15]. Recent research shows that a decreasing PNI is linked to poorer overall survival in HGSOC, with variable predictive value depending on the cancer stage[5,16]. Another study found that PNI (>51.2 for best outcomes) and the Naples Prognostic Score were significantly associated with postoperative ovarian cancer survival[7]. However, the value of PNI in HGSOC compared to established prognostic factors is still uncertain and requires further study.

We aimed to investigate PNI's prognostic value in HGSOC, comparing it against established prognostic indicators including age, FIGO stage, and platinum resistance. We hypothesized that PNI is an independent predictor of survival in HGSOC patients. Furthermore, we sought to establish an optimal threshold value for PNI in predicting mortality in patients with HGSOC. This study

contributes to the literature by focusing specifically on the HGSOC subtype and potentially offering clearer insights into the role of PNI. We hypothesized that a lower PNI would be independently associated with poorer survival outcomes and adverse clinicopathological features in patients with HGSOC.

MATERIALS AND METHODS

Sample

Patients with histopathologically confirmed HGSOC, primary surgical treatment (after receiving neoadjuvant chemotherapy, either primary or interval debulking surgery) at our institution, and available preoperative blood parameters (albumin level and lymphocyte count) for PNI calculation were eligible. Patients with other histological subtypes of ovarian cancer, synchronous malignancies, primary treatment at another institution, or incomplete medical records regarding key prognostic variables or follow-up data were excluded. Previous studies suggested a 2.0 mortality hazard ratio between low and high PNI groups in ovarian cancer, with 60-65% prevalence of low PNI[16,17]. A sample size of 236 patients, accounting for 10% loss to follow-up, was required to achieve 95% power. We used G*power 3.1 software in this analysis. In this study, 332 patients were included, which is considerably more than the minimum requirement. The reasons for this include adopting a conservative approach, the need for a larger sample size for secondary analyses, accounting for missing data and exclusions in the retrospective design, and multiple comparisons such as ROC curve comparisons and multivariable modeling. This large sample size enabled robust statistical results by providing over 99% power to detect the primary outcome.

Of the initial 497 patients, 165 were excluded as they did not follow the study protocol. Consequently, the final analysis comprised 332 patients with complete data for all examined parameters.

Procedure

We studied a retrospective cohort at the Department of Gynecologic Oncology, Faculty of Medicine, Çukurova University, a tertiary referral center. Data collection and abstraction were performed by trained medical personnel familiar with gynecologic oncology records. The study, approved by the Local Research Ethics Committee of Çukurova University (IRB number: 118, Date: January 7, 2022), involved a retrospective review of the medical records of 497 HGSOC patients from January 2010 to December 2020.

We noted age, body mass index (BMI, kg/m^2), menopausal status (premenopausal or postmenopausal), parity, comorbidities, ASA physical status classification according to the American Society of Anesthesiologists, pre-operative ascites volume (<1 L or ≥1 L), preoperative serum CA-125 level(U/mL), preoperative platelet-to-lymphocyte ratio (PLR), preoperative neutrophil-to-lymphocyte ratio (NLR), and residual tumor size after cytoreductive surgery (optimal cytoreduction was considered as the presence of a residual tumor <1 cm and suboptimal cytoreduction if ≥1 cm). Disease stage was reported based on the revised FIGO Staging System 2014. Patients were categorized into two groups: early stage, FIGO stages I-II and advanced stage, FIGO stages III-IV.

The formula for calculating PNI is provided as: PNI = [10 x serum albumin level (g/dL)] + [0.005 x total lymphocyte count (count/mm^3)][15]. Blood samples for PNI, NLR, and PLR calculations were taken within one week before surgery or for patients receiving neoadjuvant chemotherapy (NACT) before the initiation of NACT.

Recurrence status was noted based on the corresponding dates of recurrence, death, or the last follow-up. Patients were termed platinum-sensitive if their disease recurred more than 6 months following conclusion of platinum-based chemotherapy; otherwise, they were deemed platinum-resistant. Overall survival (OS) refers to the duration from the time of diagnosis until death or the most recent follow-up. Progression-free survival (PFS) is defined as the period from diagnosis to disease recurrence or progression, or to the last follow-up if no such event has occurred.

Statistical analysis

The data set was performed using IBM SPSS software version 23.0. Categorical data are given in terms of percentages and counts. The mean ± standard deviation (SD) or median and interquartile range (IQR) was indicated for continuous variables. To evaluate the distribution of the continuous variables, the Shapiro-Wilk test was performed. Comparisons of categorical variables (menopausal status, stage, platinum resistance, etc.) between PNI

groups (low vs. high) were done using either the chi-square test or Fisher's exact test, if suitable. Comparisons of continuous variables (age, CA-125, etc.) between two independent groups (e.g., PNI low vs. high) were done using the independent samples t-test (for normally distributed data) or Mann-Whitney U test for data not following a normal distribution. Receiver Operating Characteristic (ROC) curve was used to find out the best cutoff values for PNI, CA-125, NLR, and PLR in predicting 5-year mortality as well as their discrimination power by looking at the Area Under the Curve (AUC). The Kaplan-Meier method was used to do survival analyses for OS and PFS; then, the log-rank test was applied to see differences between groups. Independent factors related to death were identified using multivariate logistic regression. Factors that were significant on the univariate analysis or deemed important clinically were entered into the multivariate model. Variable inclusion for the final model followed a backward stepwise approach. ORs and 95% CIs were computed. A two-sided p-value <0.05 was taken as significant in all tests.

RESULTS

A total of 332 patients diagnosed with HGSOC were included in this study. The mean follow-up period was 61.3 ± 38.8 months. Demographic and clinical characteristics, including age, BMI, menopausal status, parity, comorbidities, distribution of ASA scores, and FIGO stage, are shown in Table 1. Optimal cytoreduction (residual disease <1 cm) was achieved in 229 (72.7%) patients, whereas 86 (27.3%) patients had suboptimal cytoreduction (Table 1). Regarding disease stage, 113 (34.0%) patients were classified as early stage (FIGO I-II) and 219 (66.0%) were advanced-stage (FIGO III-IV). Disease recurrence was detected in 201 patients (60.5%) during the follow-up period. At the time of the last follow-up, 188 (56.6%) patients died. A 5-year survival was observed in 146 patients (44.0%).

Table 1. Demographic and clinical data

Parameter	Number (n)/ Mean±SD	Percentage (%)/ Median (Min-Max)
Age	54.6±12.1	55 (22-86)
Age range		
<50	123	37.0
50-65	154	46.4
>65	55	16.6
Menopause		
Premenopausal	115	34.6
Postmenopausal	217	65.4
Parity		
Nulliparous	46	13.9
Parous	276	86.1
BMI	29.9±6.1	29.7 (15.6-50.6)
Comorbidity	129	38.9
ASA		
1	206	62.0
2	112	33.7
3	14	4.3
Presence of ascites during surgery		
None	171	51.5
< 1 lt	42	12.7
> 1 lt	107	32.2
Unknown	12	3.6
Tumor load after cytoreduction		
<1 cm	229	72.7
≥1 cm	86	27.3
Stage		
Early 1+2	113	34,0
Late 3+4	219	66,0

BMI: Body Mass Index, ASA: American Society of Anesthesiologists Physical Status Classification System.

The mean preoperative CA-125 level for all cases was 764.7 U/mL. For patients who received neoadjuvant chemotherapy, the mean CA-125 level before the first cycle was 2762.7 U/mL. The mean PNI for the entire cohort was 41.8 ± 8.7. Laboratory results, including NLR and PLR, are presented in Table 2. ROC curve analysis determined the optimal cutoff values for predicting mortality: PNI (≤44.6), CA-125 (>380 U/mL), NLR, and PLR (Supplementary Figure 1). A CA-125 cutoff of >380 U/mL predicted mortality with 49.07% sensitivity and 67.59% specificity (AUC=0.588, p=0.012). A PNI cutoff of ≤44.6 predicted mortality with 96.84% sensitivity and 81.69% specificity (AUC=0.932, p<0.001). The NLR and PLR cut-off values were not statistically significant predictors of mortality (p>0.05). The AUC value for PNI (0.932) was substantially higher than that for CA-125 (0.588), indicating the superior discriminatory ability of PNI in predicting mortality (Table 3). PNI showed a weak negative correlation with NLR (r=-0.250, p<0.05) and a moderate negative correlation with PLR (r=-0.335, p<0.05) (Supplementary Figure 2).

Table 2. Laboratory values

Parameter	**Mean±SD**	**Median (Min-Max)**
CEA (ng/ml)	21.4±183.9	1.34 (0.06-2581)
CA19.9 (U/ml)	102.9±422.0	10 (0-4603)
CA15.3 (U/ml)	94.7±314.9	27.2 (2.3-3741)
Pre NACT CA125 (U/ml)	2762.7±5273.1	1399 (0-39228)
Preoperative CA125 (U/ml)	764.7±1162.2	251 (11-5089)
Albumin (g/L)	3.04±0.7	3.1 (0.9-4.8)
Lymphocyte (10^3/μL)	1936.1±682.6	1800 (600-5240)
Neutrophil (10^3/μL)	5914.8±3031.7	5600 (800-19400)
Platelet (10^3/μL)	337.2±129.7	315 (78-912)
NLR	3.42±2.2	2.95 (0.3-14)
PLR	197.5±110.3	172.3 (32.23-691.3)
PNI	41,8±8,7	40,4 (18,55-59,8)
	Number (n)	**Percentage (%)**
PNI*		
<48.8	283	85.2
>48.8	49	14.8
PNI (Cut-Off)**		
<44.6	210	63.3
>44.6	122	36.7

CEA: carcinoembryonic antigen, CA 19.9: cancer antigen 19-9, CA 15.3: cancer antigen 15.3, Pre NACT CA125: Pre Neoadjuvant chemotherapy cancer antigen 125, CA 125: cancer antigen 125, NLR: Neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNI: Prognostic Nutritional Index, PNI*: Cut-off of PNI value according to literature, PNI**: Cut-off of PNI value according to Roc Curve test

Table 3. Diagnostic test performance of Ca 125, PNI, NLR, and PLR values according to mortality

	Ca125 (U/ml)	**NLR**	**PLR**	**PNI**
AUC 95%-Cl (%)	0.588 (0.527-0.648)	0.515 (0.459-0.569)	0.523 (0.468-0.578)	0,932 (0.900-0.957)
Cut-off	>380	≤1.69	≤105.8	≤44.6
Sensitive (%) 95%-Cl (%)	49.07 (41.1-57.1)	21.05 (15.5-27.5)	24.21 (18.3-30.9)	96.84 (93.3-98.8)
Spesitive 95%-Cl (%)	67.59 (57.9-76.3)	88.03 (81.5-92.9)	85.92 (79.1-91.2)	81.69 (74.3-87.7)
PPV 95%-Cl (%)	69.3 (62.2-75.6)	69.1 (56.8-79.1)	69.7 (58.8-78.8)	87.6 (83.3-90.9)
NPV 95%-Cl (%)	47.1 (42.2-52.1)	45.1 (42.8-47.4)	45.9 (43.3-48.5)	95.1 (89.8-97.7)
P	**0.012**	0.647	0.462	**<0.001**

* p<0,05, **p<0,001, Roc curve test

CA 125: cancer antigen 125, NLR: Neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNI: Prognostic Nutritional Index

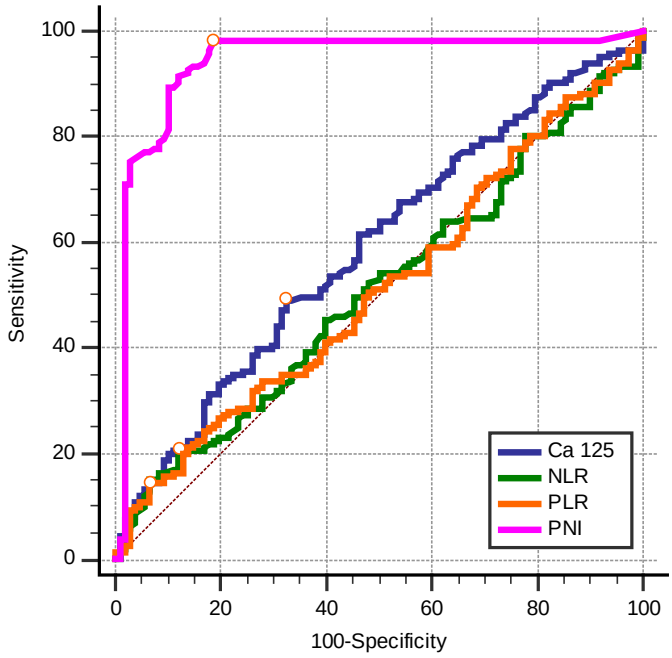

Figure 1. Diagnostic test performance of PNI, CA 125, NLR, and PLR values for predicting mortality.

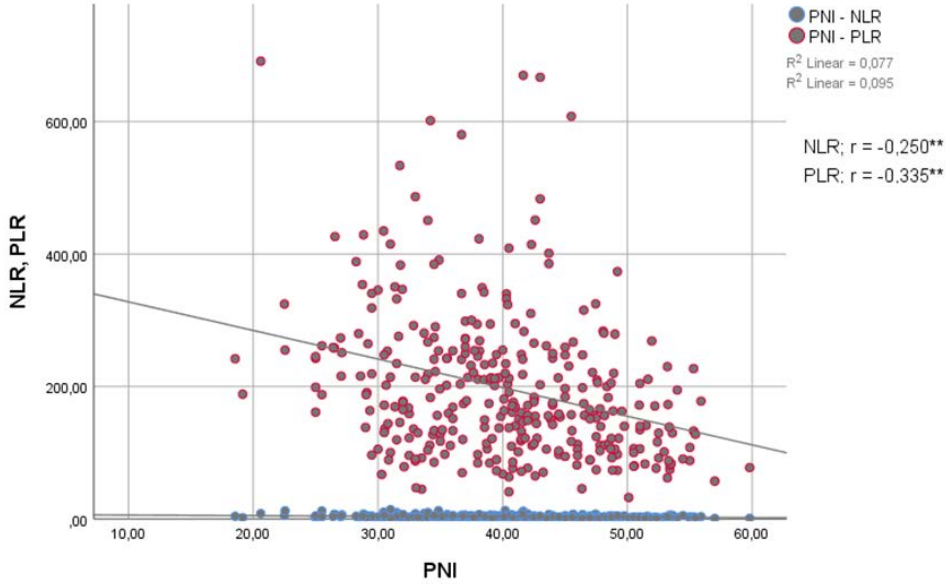

Figure 2. Relationship between PNI, NLR, and PLR values.

Patients were divided into two categories according to the PNI cutoff; low PNI (≤44.6) and high PNI (>44.6). Table 4 shows how the prognostic parameters relate to the PNI categories. A low PNI was significantly associated with stage of the disease at more advanced (p<0.001), platinum resistance (p=0.001), preoperative ascites ≥1 L (p=0.002), a higher rate of recurrence (p<0.001), lower 5-year survival rates (p<0.001), overall mortality rate (p<0.001) (Supplementary Figure 3), older age (p=0.015), and preoperative CA-125 levels (p=0.041). There were no significant associations between the PNI and other parameters listed in Table 4 (p>0.05). Logistic regression analysis showed that low PNI patients had significantly higher odds of platinum resistance (OR: 3.543, p=0.025). In a multiple logistic regression analysis, a PNI ≤44.46, presence of preoperative ascites >1 L, and an increased recurrence rate were identified as independent predictors of mortality. Specifically, a PNI ≤44.46 was associated with significantly increased mortality (OR: 136.82, 95% CI: 54.6-342.4, p<0.001), as was the presence of preoperative ascites >1 L (OR: 52.9, 95% CI: 2.9-985.7, p=0.008), and recurrence (OR: 306.1, 95% CI: 35.1-2669.0, p<0.001) (Table 5).

Table 4. Relationship between low-high PNI values and other parameters

	PNI <44.6 (Low) n(%)	**PNI >44.6 (High) n(%)**	**p**
Age range			
<50	72 (34.3)	51 (41.8)	
50-65	97 (46.2)	57 (46.7)	0.123
>65	41 (19.5)	14 (11.5)	
Menopause			
Pre-menopause	64 (30.5)	51 (41.8)	
Post-menopause	146 (69.5)	71 (58.2)	0.037
Parity			0.763
Nulliparity	28 (13.3)	18 (14.8)	
Parous	12 (5.7)	9 (7.4)	
> 2 births	170 (81)	95 (77.9)	
Comorbidity	79 (37.6)	50 (41)	0.544
ASA			
1	132 (62.9)	74 (60.7)	0.906
2	69 (32.9)	43 (35.2)	
3	9 (4.3)	5 (4.1)	
Tumor burden after cytoreduction			
< 1 cm	130 (65)	99 (86.1)	<0.001
≥ 1cm	70 (35)	16 (13.9)	
Stage			
Early	44 (21)	69 (56.6)	<0.001
Advanced	166 (79)	53 (43.4)	
Platinum therapy			
Platinum sensitive	157 (74.8)	109 (89.3)	0.001
Platinum resistant	53 (25.2)	13 (10.7)	
Ascites during surgery			
Unknown	7 (3.3)	5 (4.1)	0.002
Absent	93 (44.3)	78 (63.9)	
<1 liter	28 (13.3)	14 (11.5)	
> 1 liter	82 (39)	25 (20.5)	
Recurrence	175 (83.3)	26 (21.3)	<0.001
> 5 years	44 (21)	102 (83.6)	<0.001
Mortality			
Alive	26 (12.4)	116 (95.1)	<0.001
Exitus	184 (87.6)	6 (4.9)	

ASA: American Society of Anaesthesiologists Physical Status Classification System.

Table 5. Evaluation of factors determining mortality with multivariate analysis.

	p	Odd Ratio	95% Confidence Interval	
			Lowest	Highest
<50 years old	0.518			
50-65 years old	0.259	0.195	0.011	3.38
>65 years old	0.299	0.192	0.009	4.321
Menopausal	0.851	1.301	0.084	20.222
PNI Group (<44.6)	**<0.001**	136.821	54.657	342.499
Advanced Stage	0.056	7.061	0.948	52.588
No Ascites during Surgery	0.065			
Ascites during Surgery (<1 L)	0.608	2.039	0.134	31.088
Ascites during Surgery (>1 L)	**0.008**	52.967	2.846	985.689
Ascites during Surgery (unknown)	0.999	-	-	
Recurrence (Yes)	**<0.001**	306.073	35.100	2668.951
Platinum Resistant	0.288	3.169	0.378	26.593
Constant	0.999	0.001		

PNI: Prognostic Nutritional Index.

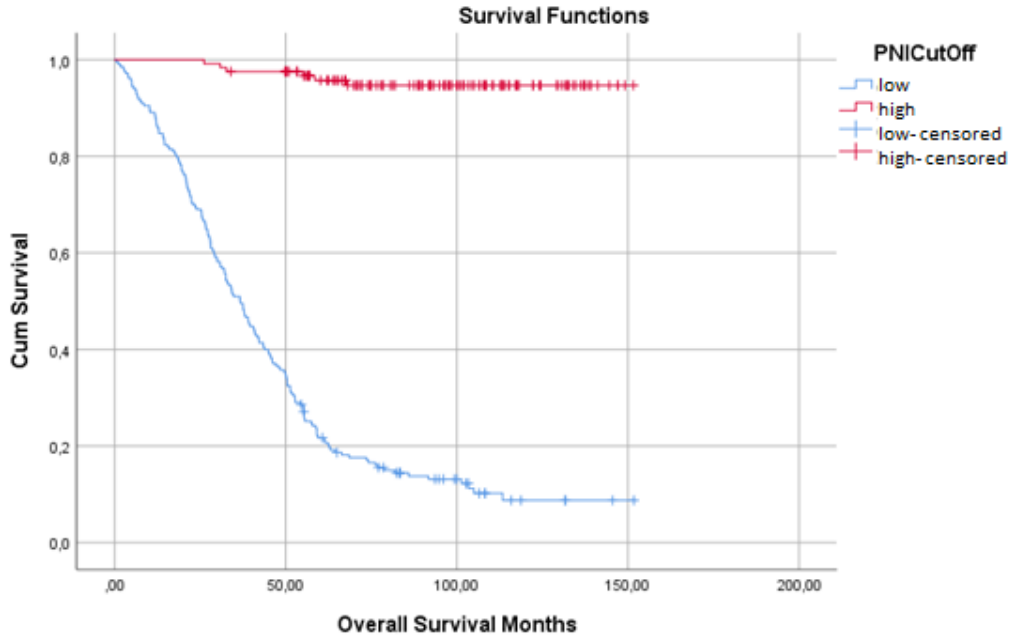

Figure 3. Kaplan-Meier overall survival curves comparing patients with low PNI (≤44.6) and high PNI (>44.6).

As for progression-free survival, it was noted that PFS is significantly shorter in nulliparous patients (p=0.005), and also in those with ≥1 L ascites (p=0.001) and advanced-stage disease (p<0.001). No statistically significant correlation existed between PNI and PFS in this cohort (p=0.072).

DISCUSSION

The clinical outcome in patients with HGSOC is influenced by a complex interplay of tumor-related factors, such as the extent of disease and biological aggressiveness, and patient-related factors, including

nutritional status, systemic inflammation, and overall physiological function[4]. Given the persistent challenges in early detection and the high frequency of recurrence in HGSOC, recent research has increasingly focused on identifying and validating novel biomarkers and prognostic factors. Our study analyzed a range of clinical, pathological, and inflammation-based parameters, including PNI, in a cohort of patients with HGSOC. A key finding of our study is that PNI was a stronger predictor of mortality (AUC=0.932) than the commonly used tumor marker CA-125 (AUC=0.588) in this population. Consistent with expectations, older age, advanced FIGO stage, and postmenopausal status were associated with poorer prognosis. Importantly, a PNI value of ≤44.6 was identified as a significant predictor for high-risk mortality and was associated with shorter overall survival times.

The prognostic utility of PNI has been investigated in various cancers, but its specific role in ovarian cancer, particularly HGSOC, has yielded somewhat inconsistent results in previous literature, often attributed to small sample sizes, heterogeneous study populations (mixing various histological subtypes), and differing PNI cutoff values[5-9]. For instance, a study involving 344 patients with epithelial ovarian cancer (histology not exclusively HGSOC) identified an association between reduced PNI levels and decreased survival durations[4]. However, Komura et al.[17], in a study of 164 patients with early stage epithelial ovarian cancer, found no association between preoperative PNI and OS, possibly because of the predominantly early stage population. Another study reported that a low PNI was linked to higher mortality rates, increased CA-125 levels, and the presence of ascites[5]; however, this study also concluded no correlation between preoperative PNI and OS in their multivariate analysis, which contrasts with our findings regarding OS.

A study by Zhang et al.[18] involving 237 patients diagnosed with stage III ovarian cancer (half with serous histology) identified a preoperative PNI threshold of 47.2 as predictive for platinum resistance, survival duration, CA-125 levels, residual tumor, histological subtype, and malignant ascites. In line with this research, our study also demonstrated a notable association between a low PNI value (≤44.6) and factors indicative of poor prognosis, including platinum resistance, advanced cancer stage, significant ascites (≥1 L), high preoperative CA-125 levels, and suboptimal cytoreduction. The meta-analysis by Dai et al.[10], which included 2,050 ovarian cancer patients (mixed histology), reported positive correlations between PNI and longer survival times and highlighted PNI as a crucial prognostic factor with varying cutoffs (42.9 to 48.8). Our findings, with a similar cutoff, showed that a high PNI score was associated with significantly longer OS (146.0±2.2 months vs. 47.6±2.9 months for low PNI).

Ascites is a common finding in ovarian cancer, present in approximately 20% of early-stage and 80-90% of advanced-stage cases, and it is well established that patients without significant ascites tend to have better 5-year survival rates[19]. Our analysis revealed that the presence of ascites ≥1 L at surgery was associated with a low PNI value and emerged as an independent prognostic factor for HGSOC mortality. It is plausible that large-volume ascites contributes to a lower PNI through mechanisms such as protein loss into the peritoneal cavity (reducing serum albumin) and systemic inflammation. Regular paracentesis, if performed, could also affect albumin levels. Malnutrition, often exacerbated by tumor-related metabolic effects, bowel obstruction, and malignant ascites, is prevalent in gynecological cancer patients, particularly those with advanced HGSOC, as noted by Laky et al.[12] (20% malnutrition rate). PNI reflects not only nutritional status via albumin but also systemic inflammation via lymphocyte count, both of which can influence cancer growth and metastasis[8]. Yilmaz et al.[20], in a study of 273 epithelial ovarian cancer patients, identified PNI as having the highest AUC among several inflammatory markers, with a predictive cutoff of 42.1, and found PNI to be an independent prognostic factor for survival.

Regarding other inflammatory markers, Keskin et al.[21] found elevated NLR to be an important inflammatory biomarker for malignant ovarian masses. While we examined the relationship between NLR/PLR and mortality, our study did not find their threshold values to be statistically predictive of mortality in our HGSOC cohort, although PNI showed weak to moderate negative correlations with NLR and PLR. This suggests that PNI might capture a more comprehensive aspect of the host's systemic inflammatory and nutritional status relevant to HGSOC prognosis than NLR or PLR alone in this specific cancer subtype.

Our study strongly indicates that a PNI value below the identified cutoff is a significant independent predictor of a higher mortality rate in HGSOC

patients. This aligns with broader research on PNI in oncology, including findings by Komura et al.[22] in epithelial ovarian cancer, where pretreatment PNI was more effective than platelet count in forecasting disease-specific survival. As PNI is partly based on albumin, which reflects nutritional status and systemic inflammation, our results support the role of PNI as an important prognostic indicator.

While the primary management of ovarian cancer involves surgery and chemotherapy, recurrence is common in advanced stages. Platinum resistance significantly worsens patient survival. Our analysis revealed that low PNI was associated with a higher likelihood of recurrence and platinum resistance. Many factors influence PFS in ovarian cancer, including disease stage, CA-125 levels, age, genetic mutations, extent of cytoreduction, and treatment modality. In our cohort, while PNI was a strong predictor of OS, its association with PFS did not reach statistical significance (p=0.072), although a trend might be suggested. Factors such as nulliparity, ascites, and advanced stage significantly predicted shorter PFS.

Our study had several strengths. First, we included patients managed at a single tertiary center over a 10-year period, potentially ensuring consistency in treatment approaches and data recording. Second, by focusing exclusively on patients diagnosed with HGSOC, the most common and aggressive histopathological subtype, we achieved a more homogeneous study population, which can provide clearer insights specific to this subtype. The direct comparison of PNI with CA-125, NLR, and PLR in predicting mortality is another strength of this study.

However, this study also had limitations. The most significant limitation is its retrospective design, which carries the inherent risks of selection bias and reliance on previously recorded data, potentially leading to missing or inconsistent documented variables for some initially screened patients. Since this study was conducted in one center, the results cannot be generalized to other populations or healthcare settings unless they have different patient management protocols and demographics. The PNI was calculated only once (either preoperatively or pre-NACT). Serial measurements of PNI during treatment and follow-up would provide more dynamic prognostic information. Although the important prognostic factors were controlled, unmeasured confounders that could influence the observed associations might still exist. Information on specific molecular subtypes or genetic mutations (e.g., BRCA status), which are known to influence prognosis in HGSOC, was not uniformly available for all patients in this retrospective cohort and thus could not be included in the multivariate analysis.

In conclusion, our study showed that low preoperative PNI was a better predictor of increased mortality in HGSOC patients than CA-125, and it was independent. A low PNI was associated with several adverse clinicopathological features. These include advanced-stage disease suboptimal cytoreduction, significant ascites, platinum resistance, and higher recurrence rates. Since PNI is easily accessible and cheap, the above findings place it as a useful tool in prognostic assessment for HGSOC patients to highlight high-risk individuals who may need more intensive monitoring or an individualized therapeutic approach. Further research is required to validate these findings. Prospective multicenter studies are needed to confirm the prognostic utility of PNI in diverse HGSOC populations and to explore its role in guiding clinical decision-making. Investigating the impact of nutritional interventions or immunomodulatory therapies aimed at improving PNI in high-risk patients could be a promising avenue for future clinical trials. Additionally, exploring the biological mechanisms underlying the association between low PNI and poor outcomes in HGSOC could unveil new therapeutic targets. Integrating PNI with other molecular and imaging biomarkers may also lead to more refined prognostic models for HGSOC.

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