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ORIGINAL RESEARCH

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The importance of Delta prognostic nutrition index as an early success indicator of optimal cytoreductive surgery in epithelial ovarian cancer patients

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Abstract

Epithelial ovarian cancer (EOC) represents a significant cause of mortality among women with gynecological malignancies and is frequently diagnosed at an advanced stage. The role of inflammation and nutritional status in prognosis has prompted the evaluation of the Prognostic Nutritional Index (PNI) as a marker for surgical success and survival in EOC patients. This study aimed to investigate the relationship between preoperative, postoperative, and Delta-PNI values and the outcomes of optimal cytoreductive surgery (OCS) in EOC. A retrospective analysis was conducted on 255 patients with EOC, examining the early impact of PNI on surgical outcomes. PNI was calculated based on serum albumin levels and lymphocyte count. The study assessed the correlations between changes in PNI and the success of surgery, overall survival (OS), and progression-free survival (PFS). A higher preoperative PNI was associated with improved surgical success and better survival rates. Specifically, the OS in the OCS group was longer, averaging 104.89 $\pm$ 71.1 months, compared to 81.5 $\pm$ 72.04 months in the non-OCS group ($p = 0.016$). PFS was also longer in the OCS group, with a mean of 52.03 $\pm$ 52.13 months, versus 30.67 $\pm$ 44.5 months in the non-OCS group ($p = 0.002$). Delta-PNI proved to be a robust predictor of surgical success, with a Receiver Operating Characteristic (ROC) analysis yielding an Area Under the Curve (AUC) of 0.795 ($p < 0.001$), indicating high discriminative capability. Patients with a Delta-PNI above the optimal cut-off of 11.3 exhibited an extended PFS. The findings highlight the prognostic significance of PNI and Delta-PNI in EOC, suggesting that these metrics can significantly predict surgical success and survival outcomes. The Delta-PNI's association with longer PFS emphasizes its potential utility in preoperative risk assessment and patient management for EOC.

Keywords

Epithelial ovarian cancer; Prognostic nutritional index; Optimal cytoreductive surgery; Survival outcomes; Delta-PNI

1. Introduction

Epithelial ovarian cancer (EOC) remains a formidable challenge in gynecological oncology, ranking as one of the leading causes of cancer-related mortality among women worldwide [1]. Characterized by its aggressive nature and often presenting with non-specific symptoms, EOC is frequently diagnosed at advanced stages, thus posing significant clinical challenges [2]. The crucial role of primary cytoreductive surgery followed by platinum-based chemotherapy in the management of these patients is well-documented [3–5]. Nonetheless, the risk of recurrence is high, with a considerable proportion of patients experiencing relapse within months after treatment [6]. Complications associated with advanced-stage diagnosis, such as intra-abdominal metastases, cachexia, and ascites, are prevalent [7, 8].

In this context, the significance of inflammation in the oncogenesis and progression of cancer has been increasingly recognized [9]. In parallel, the Prognostic Nutritional Index (PNI), a composite indicator derived from albumin and peripheral blood lymphocyte, has emerged as a valuable prognostic tool. This index reflects the nutritional and immunological status of patients, serving as a predictor of surgical outcomes [10]. Individuals with lower PNI scores are often deemed to have impaired nutritional and immune function, correlating with poorer post-surgical or treatment prognoses [11, 12]. While various studies may employ different cut-off values to distinguish between high-risk and low-risk patients, the determination of an optimal PNI value for prognostic assessment tends to be contingent upon the specific patient cohort and

clinical setting [13, 14]. It is a multifaceted marker that reflects nutritional status and encompasses immune competence, primarily indicated by albumin levels and lymphocyte count. Although the predictive prowess of PNI has been illuminated in multiple cancer types, its narrative in the context of EOC, particularly its early period value following the surgery and the difference between its pre and postoperative values, remains uninvestigated [15, 16].

The study focuses on PNI's unexplored potential as an early success indicator for optimal cytoreductive surgery (OCS) in patients with EOC. While the correlation between cytoreduction quality and survival in ovarian cancer has been established and the preoperative PNI's prognostic merit acknowledged, we aimed to discern early postoperative PNI and Delta-PNI's role in forecasting cytoreduction efficacy and its impact on survival outcomes.

2. Materials and methods

2.1 Study design and setting

We conducted an exhaustive retrospective analysis, examining the medical archives of our institution to ascertain the potential role of preoperative, postoperative, and Delta-PNI as predictors of optimal cytoreductive surgery (OCS) in 255 patients with epithelial ovarian cancer (EOC). This study evaluated the influence of diverse factors, including the surgical approach, complexity of the procedure, stage of cancer, histological type, administration of neoadjuvant chemotherapy, delay in chemotherapy due to cytopenia, presence of pleural effusion, and disease extent. Our research aims to fill the existing knowledge gap regarding the predictive value of PNI on surgical outcomes and overall survival, proposing a novel parameter for clinical decision-making. At the core of this investigation is the hypothesis that PNI and Delta-PNI, reflecting the patient's nutritional and inflammatory status, could provide critical insights for clinicians, forecasting surgical success and survival trends.

2.2 Data acquisition

We conducted a thorough review of patient records to identify individuals diagnosed with Epithelial Ovarian Cancer (EOC) by our experienced pathologists and who underwent surgical staging at our institution. The study's integrity was maintained through strict inclusion criteria. Eligible participants were women aged 18 and older with a definitive histopathological diagnosis of EOC, ensuring diagnostic accuracy by having all surgical specimens reviewed by our in-house pathologists. We included patients who consistently attended postoperative follow-ups at our center and had complete data records to provide a detailed and longitudinal view of their clinical courses.

Exclusions were made for patients with different types of ovarian tumors, those lost to postoperative follow-up, and individuals who had surgery performed at other facilities. Cases with incomplete or inaccessible data were also excluded from the study.

2.3 Data parameters and analytical measures

Data extraction included the patient's age at the moment of diagnosis, anthropometric indices, and concurrent medical spectra to the intricate attributes of the tumor encompassing its histological categorization, stage, grade and salient lymphatic engagement. Laboratory determinants covered the preoperative and postoperative incarnations, including metrics like Ca-125, albumin, peripheral blood lymphocyte census, hemoglobin, and platelet tally. The PNI was calculated through $10 \times$ serum albumin (g/dL) + $0.005 \times$ total lymphocyte count [17]. Delta-PNI refers to the difference in PNI value over the surgical period (post–preop), indicating changes in a patient's nutritional and immune status, which can be critical for predicting surgical outcomes, survival rates, or the need for nutritional interventions.

2.4 Statistical analyze

We used SPSS v24 (IBM company, Chicago, IL, USA) for our statistical evaluations. Preliminary statistics set the stage for deeper analyses. Numerical variables underwent stringent distribution testing through visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk) tests. Depending on the distribution pattern, data were presented as either mean/standard deviation or median. For parametric data analysis, Students' *t*-tests facilitated group comparisons. Wilcoxon/Mann-Whitney U tests analyzed non-parametric datasets. The chi-square test was used to categorize data. The study employed Receiver Operating Characteristic (ROC) analysis to assess the PNI in preoperative and postoperative settings and its change (Delta-PNI), reflecting the efficacy of OCS. Patients with EOC were categorized based on Delta-PNI, with a PNI cut-off value of 11.3 identified as optimal for distinguishing surgical success (sensitivity, 74.1%; specificity, 78.7%). Kaplan-Meier Survival estimated the survival function from lifetime data, providing a way to visualize the probability of surviving past a specific time and generated for both overall Survival (OS) and Progression-free Survival (PFS) for the OCS and non-OCS groups with the Log-Rank Test (Mantel-Cox Test). All interpretations were based on a p-value threshold of < 0.05.

3. Results

3.1 Demographic characteristics

The mean age was similar between the two groups, at 61.4 ± 7.6 years for those not receiving OCS and 60.8 ± 8.52 years for the OCS ($p = 0.231$). Body Mass Index was also identical, with means of 28.03 ± 6.22 kg/m^2 for the non-OCS cohort and 28.35 ± 5.56 kg/m^2 for those undergoing surgery ($p = 0.677$). A notably longer duration of surgery was observed in the OCS, averaging 278.98 ± 235.9 min, as opposed to 182.4 ± 116.3 min in the non-OCS group ($p = 0.005$). Tumor diameters were comparable, with a mean of 11.76 ± 8.35 for the non-OCS and 11.1 ± 8.08 mm for the OCS group ($p = 0.586$) (Table 1).

TABLE 1. Demographic and pathological variables of the patients.

Variables	Optimal cytoreductive surgery		*p* value
	No	Yes	
Age, yr	61.44 ± 7.61	60.81 ± 8.52	0.231
Body mass index, kg/m^2	28.03 ± 6.22	28.35 ± 5.56	0.677
Duration of surgery, min	182.4 ± 116.3	278.9 ± 235.9	0.005
Tumor diameter, mm	11.76 ± 8.35	11.13 ± 8.08	0.586
Preoperative Ca-125 level, U/mL	1299.4 ± 141.0	1240.2 ± 1758.3	0.803
Postoperative Ca-125 level, U/mL	143.65 ± 254.40	177.46 ± 545.90	0.763
Overall survival, mon	81.5 ± 72.9	104.8 ± 71.1	0.016
Progression-Free Survival, mon	30.67 ± 44.51	52.03 ± 52.13	0.002
Preoperative-PNI	45.45 ± 6.21	49.81 ± 5.29	0.001
Postoperative-PNI	37.91 ± 6.02	36.03 ± 5.28	0.013
Delta-PNI	7.55 ± 6.91	13.77 ± 5.18	0.001

Abbreviations: Preoperative-PNI: Prognostic Nutritional Index calculated before the surgery; Postoperative-PNI: Prognostic Nutritional Index calculated after the surgery; Delta-PNI: The change in Prognostic Nutritional Index from preoperative to postoperative measurements.

3.2 Surgical characteristics and outcomes

The endometrioid type was observed in 11.4% (9/79) of the OCS and 14.4% (26/180) of the non-OCS, while the high-grade serous type was seen in 78.5% (62/79) of the non-OCS versus 65% (117/180) in the OCS. Clear cell type was 5.1% (4/79) of the non-OCS and 5% (9/180) of the OCS group, while the mucinous type was 1.3% (1/79) non-OCS and 2.8% (5/180) OCS. Stage 3 patients showed the highest rate of OCS at 56.7%, while Stage 4 had the lowest at 6.7%. The presence of pleural effusion was lower in the OCS (91.7%) compared to the non-OCS (68.4%). Pleural effusion was present in 31.6% (25/79) of the non-OCS and 8.3% (15/180) of the OCS group. All types are given in Table 2 with details. Our findings indicated a significant distinction in terms of prognosis. Patients with Stage IV cancer had poorer outcomes in terms of OS and disease-free survival compared to those with Stage III cancer, underlining the critical need for stage-specific therapeutic strategies and highlighting the aggressive nature of metastatic disease.

In the study, low-complexity surgical procedures were more common in the non-OCS (53.2%) compared to the OCS (23.3%). Conversely, high-complexity procedures were more prevalent in the OCS (34.4%) versus the non-OCS group (12.7%). Most patients in both groups underwent primary cytoreductive surgery plus adjuvant chemotherapy (PCS + ACT), with a slightly higher prevalence in the OCS (76.7% *vs*. 70.9%). Neoadjuvant chemotherapy (NAC) was less frequent in the non-OCS (24.4% did not receive NAC) compared to the OCS (72.6% did not receive NAC). Delays in chemotherapy due to cytopenia were more common in the OCS group (22.2% experienced delays) than in the non-OCS group (11.4%).

The OCS exhibited a more prolonged OS, with 104.89 ± 71.1 compared to 81.5 ± 72.04 ($p = 0.016$). PFS was similarly extended in the OCS, with a mean of 52.03 ± 52.13 versus 30.67 ± 44.5 months for non-OCS ($p = 0.002$). Preoperative-PNI was higher in the OCS (49.8 ± 5.29) compared to the non-OCS group (45.45 ± 6.21) ($p = 0.001$). The Postoperative-PNI was slightly lower in the OCS (36.03 ± 5.28) versus the non-OCS (37.9 ± 6.02) ($p = 0.013$). A more substantial change in the Delta-PNI was observed in the OCS, with a mean increase of 13.77 ± 5.18, compared to 7.55 ± 6.9 in the non-OCS ($p = 0.001$).

3.3 The ROC analysis of PNI

Preoperative PNI demonstrated a significant discriminative ability (area under the curve (AUC), 0.698; 95% CI, 0.628 to 0.768; $p < 0.001$). In contrast, Postoperative PNI showed reduced discriminative power (AUC, 0.410; 95% CI, 0.334 to 0.486; $p = 0.021$). Delta-PNI, representing the difference between preoperative and postoperative values, exhibited a high discriminative power (AUC, 0.795; 95% CI, 0.735 to 0.856; $p < 0.001$), suggesting that a reduction in PNI post-surgery correlates with successful cytoreductive surgery outcomes. Delta-PNI cut-off value of 11.3, identified as optimal for distinguishing surgical success, showed 74.1% sensitivity and 78.7% specificity (Fig. 1).

3.4 Survival analysis based on OCS status

We assessed the impact of OCS status on OS among the study subjects (Fig. 2). The estimated OS for participants without OCS was 124.3 (95% CI: 98.8–149.8), and the median OS was 82.1 (95% CI: 39.8–124). For participants with OCS, the estimated OS significantly increased to 216 (95% CI: 188.6–244.2), and the median OS time was markedly higher at 238.7 (95% CI: 186.5–291.3). When considering the overall cohort, the mean OS was 189.7 (95% CI: 168.7–210.4), and the median OS was 177 (95% CI: 153.8–200). OCS behaved as a significant factor in OS, with those exhibiting longer OS both in mean and median estimates ($p = 0.0001$).

Our analysis compared PFS between subjects with and without OCS, indicating the survival times differed ($p = 0.0001$).

TABLE 2. Surgical details of patients according to gaining optimal cytoreductive surgery.

Variables	Subgroup	Optimal cytoreductive surgery		*p* value
		No (n. %)	Yes (n. %)	
Surgical approach				
	PCS + ACT	56 (70.9)	138 (76.7)	0.323
	NAC + ICS + ACT	23 (29.1)	42 (23.3)	
Complexity				
	Low	42 (53.2)	42 (23.3)	0.001
	Medium	27 (34.2)	76 (42.2)	
	High	10 (12.7)	62 (34.4)	
Stages				
	Stage 1	9 (11.4)	43 (23.9)	0.001
	Stage 2	9 (11.4)	23 (12.8)	
	Stage 3	27 (34.2)	102 (56.7)	
	Stage 4	34 (43.1)	12 (6.7)	
Histological classification				
	Endometrioid	9 (11.4)	26 (14.4)	0.243
	High Grade Serous	62 (78.5)	117 (65.1)	
	Clear Cell	4 (5.1)	9 (5.1)	
	Mucinous	1 (1.3)	5 (2.8)	
	Mixed Type	2 (2.5)	14 (7.8)	
	Low Grade Serous	1 (1.3)	8 (4.4)	
	Transitional Cell Carcinoma	0 (0)	1 (0.6)	
NAC				
	None	19 (24.4)	130 (72.6)	0.001
	Yes	59 (75.6)	49 (27.4)	
Chemotherapy delay due to cytopenia				
	None	70 (88.6)	140 (77.8)	0.061
	Yes	9 (11.4)	40 (22.2)	
Pleural effusion				
	None	54 (68.4)	165 (91.7)	0.001
	Yes	25 (31.6)	15 (8.3)	
Disease involvement				
	Pelvis	14 (17.7)	53 (29.4)	0.001
	Lower Abdomen	13 (16.5)	63 (35.1)	
	Upper Abdomen	52 (65.8)	64 (35.6)	
Current status				
	Alive	34 (43)	135 (75)	0.001
	Deceased	45 (57)	45 (25)	
Delta-PNI groups				
	Low	60 (75.9)	46 (25.6)	0.001
	High	19 (24.1)	134 (74.4)	

Abbreviations: PCS + ACT: Primary Cytoreductive Surgery + Adjuvant Chemotherapy, NAC + ICS + ACT: Neoadjuvant Chemotherapy + Interval Cytoreductive Surgery + Adjuvant Chemotherapy; Delta-PNI: The change in Prognostic Nutritional Index from preoperative to postoperative measurements.

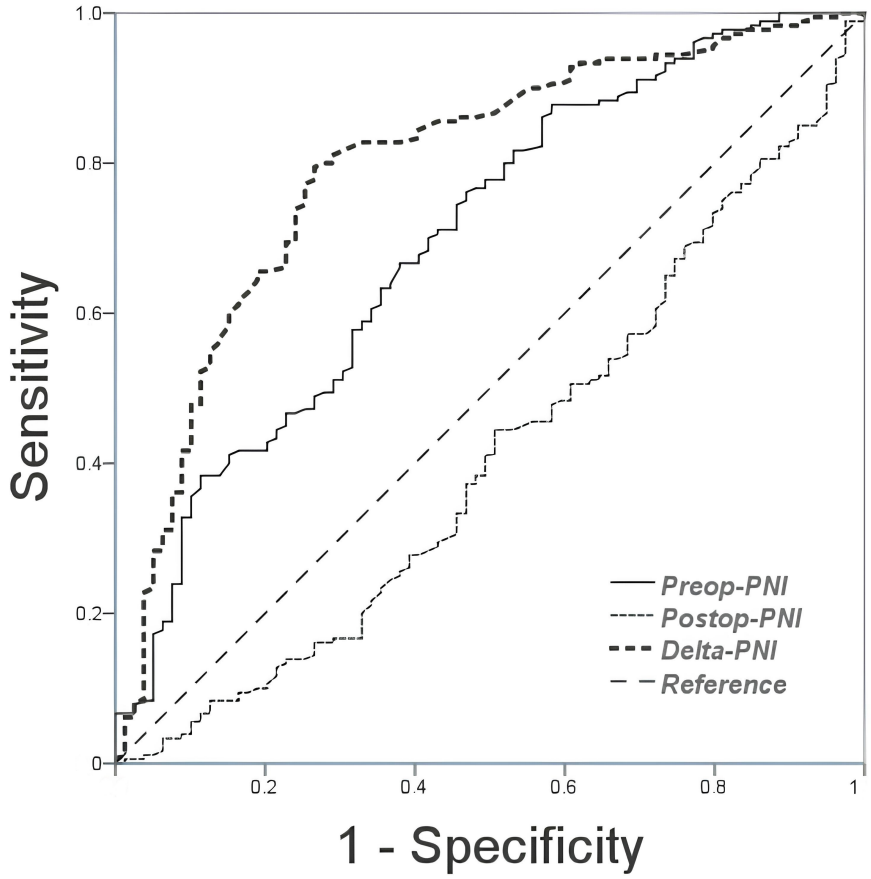

FIGURE 1. The ROC graph of preoperative, postoperative, and Delta-PNI showing the success of optimal cytoreductive surgery. Preop-PNI: Prognostic Nutritional Index calculated before the surgery; Postop-PNI: Prognostic Nutritional Index calculated after the surgery; Delta-PNI: The change in Prognostic Nutritional Index from preoperative to postoperative measurements.

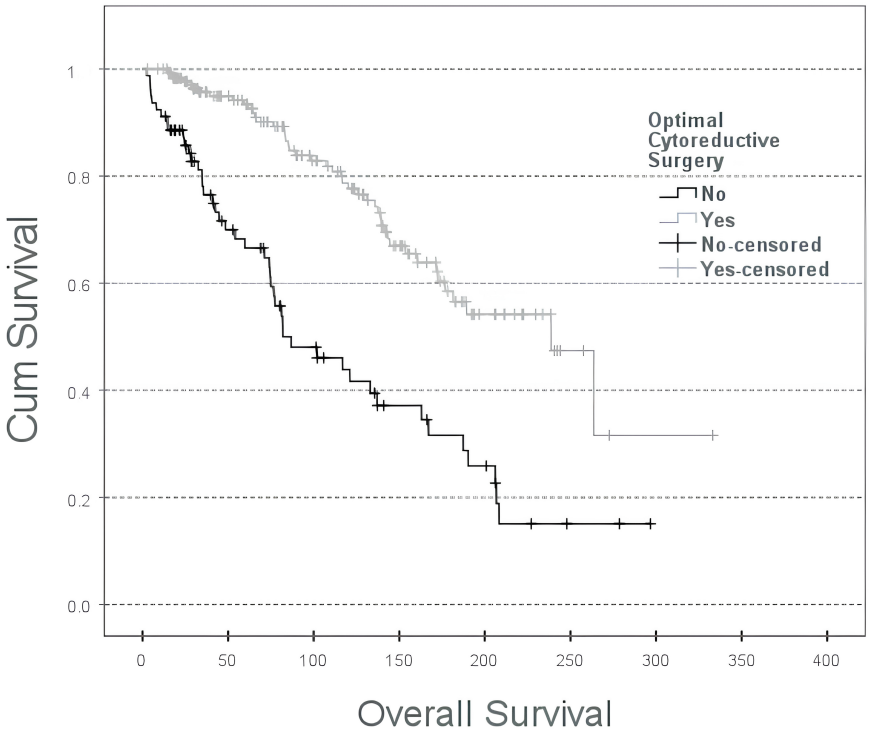

FIGURE 2. The impact of optimal cytoreductive surgery status on overall survival among the subjects with epithelial ovarian cancer.

Subjects without OCS demonstrated a mean PFS of 69.6 (95% CI: 42.4–96) and a median PFS of 27 (95% CI: 14–40.1). Those with OCS exhibited a higher mean PFS time of 152.8 (95% CI: 129.3–176), with the median PFS notably reaching 160. The overall PFS for the study was 129 (95% CI: 109.2–149.9), and the median was 132 (95% CI: 65.7–198) (Fig. 3).

3.5 Progression-free survival analysis by Delta-PNI groups

Participants in the Low Delta-PNI had a mean PFS time of 104.8 (95% CI: 78.3–131) and a median PFS of 44.8 (95% CI: 28.2–115). Those in the High Delta-PNI showed a higher PFS of 137.7 (95% CI: 113.5–162), with the median PFS substantially longer at 160 (95% CI: 27.5–292.1). The overall cohort had a mean PFS of 129.5 (95% CI: 109–149.8) and a median PFS time of 132 (95% CI: 65.5–198.2). These results suggest that Delta-PNI is associated with differences in PFS times, and a higher Delta-PNI is associated with longer PFS times, both in mean and median estimates ($p = 0.0001$) (Fig. 4).

4. Discussion

The present study analyzed significant insights into the effects of OCS on outcomes for EOC, employing a thorough analysis of demographic characteristics, surgical outcomes, and survival analysis. Our research, which incorporated preoperative, postoperative, and Delta-PNI values, has provided robust evidence highlighting the multifaceted role of early-period measured PNI values in assessing surgical success for patients undergoing OCS for EOC.

The prognostic nutritional index has been recognized as a pivotal, valuable biomarker for assessing patients' nutritional and inflammatory status, playing a role in predicting clinical outcomes across various cancer types [18]. In an insightful study conducted by Okadome *et al*. [19] involving esophageal cancer, a substantial correlation between low PNI values and adverse clinical outcomes was uncovered. Specifically, individuals within the low PNI cohort exhibited notably diminished overall survival rates, thereby highlighting the prognostic significance of PNI within this patient group [10]. Further corroborating these findings, research by Bozkaya *et al*. [20], which collectively examined 613 patients across two distinct cohorts—one with prostate cancer and another with metastatic non-small cell lung cancer—demonstrated that patients with lower PNI scores faced less favorable clinical outcomes. Particularly compelling evidence of PNI's predictive accuracy has been observed in gastric cancer. Xishan *et al*. [21] established a correlation between low PNI and poor prognosis. Moreover, the study by Hirahara *et al*. [22] showed a correlation between PNI and cancer-specific survival in the population, with lower PNI indicative of worse CSS outcomes. The PNI is a multifaceted marker that reflects nutritional status and encompasses immune competence, primarily indicated by albumin levels and lymphocyte count.

In the context of gynecological cancers, a meta-analysis examined the predictive value of PNI, focusing on ovarian cancer, cervical cancer, and a broader category encompassing all gynecological cancers [23]. It highlighted low PNI as

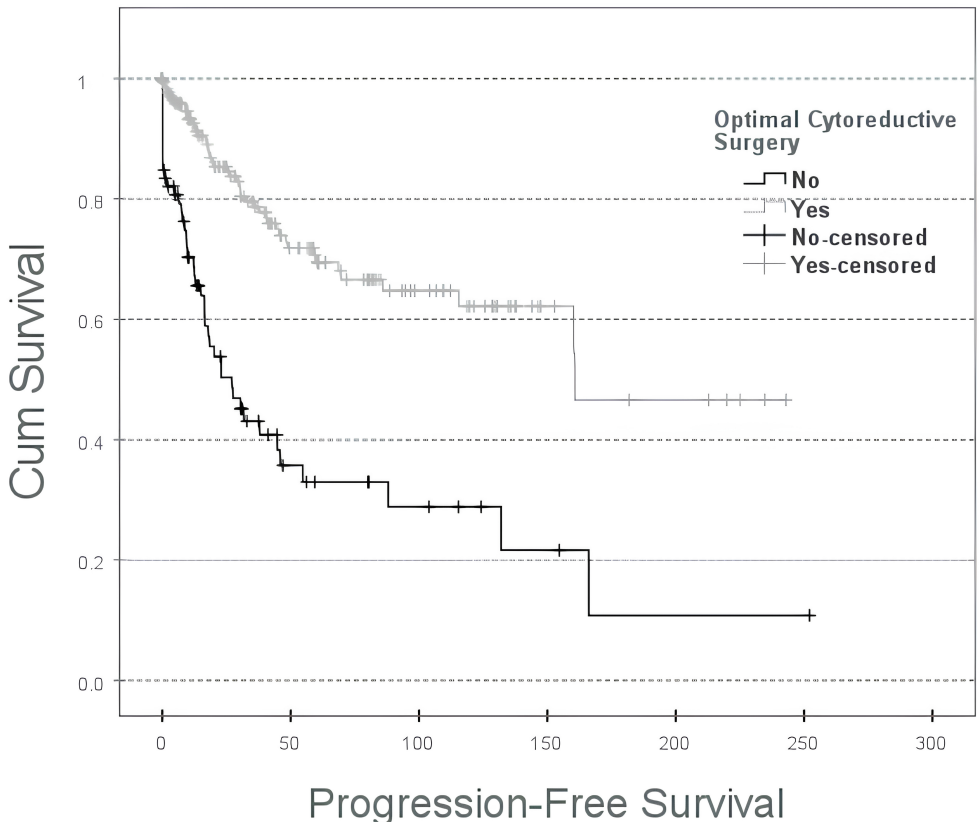

FIGURE 3. The impact of optimal cytoreductive surgery status on progression-free survival among the subjects with epithelial ovarian cancer.

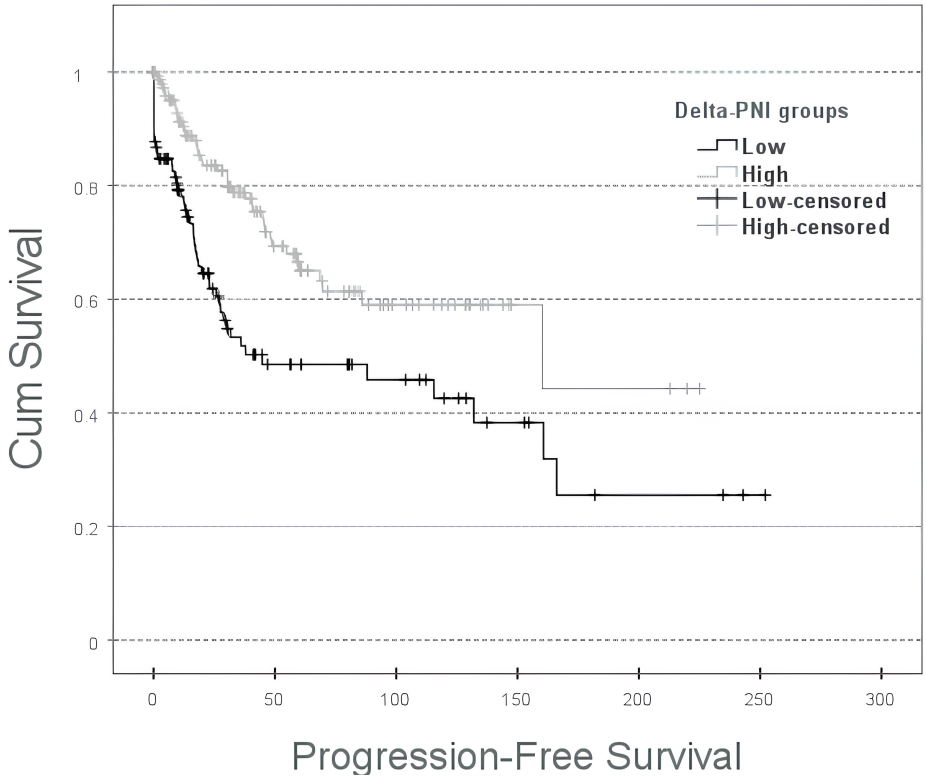

FIGURE 4. The importance of PNI value for Progression-free Survival among the subjects with epithelial ovarian cancer. Delta-PNI: The change in Prognostic Nutritional Index from preoperative to postoperative measurements.

a risk factor for reduced OS and PFS, with pooled hazard ratios for OS and PFS in ovarian cancer at 1.28 and 1.82 years, respectively. For cervical cancer, OS and PFS were significantly higher, at 2.96 and 2.54, respectively, indicating a pronounced risk associated with low PNI. In our research, the estimated OS for participants without OCS was 124.3 months. For participants with OCS, the estimated OS significantly increased to 216 months. OCS behaved as a significant factor in OS, with those exhibiting longer OS. Participants in the low Delta-PNI had a mean PFS of 104.8 months. Those in the high Delta-PNI showed a higher PFS of 137.7 months. Delta-PNI was associated with differences in PFS; a higher Delta-PNI is associated with longer PFS. Our research extends this narrative to the domain of EOC, providing robust evidence of the predictive value of PNI within this specific patient cohort. By analyzing preoperative, postoperative, and Delta-PNI values, our study reaffirms the established correlations and introduces the novel concept of Delta-PNI as an indicator of surgical success.

The notable difference in surgery duration between the groups underscores OCS's inherent complexity and aggressiveness. Despite the longer surgical times, our findings suggest that the meticulous effort to achieve optimal cytoreduction translates into improved survival outcomes, a conclusion that the prolonged OS and PFS in the OCS support. These results align with existing literature advocating for the prognostic importance of complete cytoreduction in ovarian cancer treatment, reinforcing the concept that the extent of tumor removal directly impacts patient prognosis. Regarding the difference between Stage III and Stage IV cancers, our findings indicated a distinction in prognosis. Stage IV cancer had poorer outcomes in terms of overall Survival and disease-free survival compared to those with Stage III cancer, underlining the critical need for stage-specific therapeutic strategies and highlighting the aggressive nature of the metastatic disease. Our study's exploration into the predictive value of preoperative and postoperative PNI and Delta-PNI presents a novel avenue for assessing OCS success. The association between a higher Delta-PNI and extended PFS further emphasizes the relevance of postoperative recovery and long-term outcomes of the patients.

As a strong point, our study provides strong evidence of the benefits of OCS and Delta-PNI through detailed analysis of patient demographics, surgical details, and outcomes backed by rigorous statistical methods like ROC and survival analysis. It highlights the predictive value of Delta-PNI levels for PFS, offering a new marker for assessing the early period of surgical success. It, however, was not without limitations. While our study did not initially focus on the neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios, these parameters merit consideration for their potential prognostic significance in ovarian cancer. The retrospective nature of the analysis could introduce selection bias, and the single-center design may limit the generalizability of the findings. Furthermore, the complexity of the EOC surgery and the heterogeneity of patient responses necessitate a cautious interpretation of the results. Prospective, multicenter studies with larger patient cohorts are needed to validate these findings and to explore the potential of integrating Delta-PNI into preoperative risk assessment models.

5. Conclusions

In conclusion, this study highlights the significant impact of OCS on survival outcomes in epithelial ovarian cancer patients, underscoring the value of aggressive surgical strategies and the importance of Delta-PNI for EOC's surgical success. The introduction of Delta-PNI as a potential indicator for assessing the early period surgical success opens new avenues for research and patient management. The findings beckon a paradigm shift towards a more integrated and personalized oncology care framework, where Delta-PNI serves as an indicator and a valuable guide for therapeutic surgical interventions. Future research should continue exploring the utility of PNI and Delta-PNI across different cancer types to refine patient assessment and surgical strategies, aiming for personalized and effective cancer surgery.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

BC—contributed to the conception, design, and data interpretation. ERG and HSS—jointly contributed to the manuscript's drafting, critical revisions for important intellectual content, and statistical analysis. KH and VK—collaborated on data collection. GG and TK—were instrumental in the literature review. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work, ensuring that questions related to accuracy or integrity are appropriately investigated.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted strictly following ethical principles and guidelines. Ethical approval was granted by the Institutional Review Board (IRB) before the commencement of the research. The approval was issued under the reference number 2021/02/15, dated 22 February 2021. All participants were informed about the study's aims and procedures and provided written informed consent before their inclusion. The research team ensured that all data were collected, processed, and stored in compliance with the relevant data protection regulations and ethical standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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