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Predictive value of preoperative systemic immune-inflammation index and prognostic nutrition index in patients with epithelial ovarian cancer

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Abstract

Background This study aimed to evaluate the predictive value of Prognostic Nutritional Index (PNI), Systemic Immunoinflammatory Index (SII), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) in patients with epithelial ovarian cancer (EOC). Also, to explore the predictive value of a new scoring system combining PNI and SII (coPNI-SII) in patients with EOC.

Methods In this study, 154 patients with EOC were analyzed and classified according to the best cut-off values for SII, PNI, PLR, and NLR. Spearman's rank correlation was used to analyze the correlation of variables. The Kaplan–Meier survival curve and log-rank test were used to investigate the relationship between inflammatory indicators and overall survival (OS), which was then followed by a multivariate Cox proportional hazards model. All patients were categorized into three groups based on PNI-SII scores. The coPNI-SII score ranged from 1 to 3 as follows: score of 1, high PNI (≥ 48.98) and low SII(< 998.87); score of 2, high PNI and high SII or low PNI and low SII; score of 3, low PNI and high SII. To assess the prognostic value of coPNI-SII in patients with EOC.

Results The areas under the ROC curves for SII, PNI, PLR, NLR, and coPNI-SII were 0.814, 0.814, 0.780, 0.769, and 0.860, respectively. The optimal cut-off values for SII, PNI, PLR, and NLR were 998.87, 48.98, 217.63, and 2.61, respectively. The Kaplan–Meier analysis showed that the OS of the patients in the high PNI group, low SII group, low NLR group, and low PLR group was significantly higher than that of the patients in the low PNI group, high SII group,high NLR group, and high PLR group ($p < 0.01$). SII ($P = 0.034$), PNI ($P = 0.013$), FIGO staging ($P = 0.009$), ascites ($P = 0.003$), CA199 ($P = 0.003$), HE4 ($P = 0.028$), residual lesions ($P = 0.022$), and margins of incision ($P < 0.001$) were found to be significant prognostic indicators of OS by multifactorial Cox regression analysis. There was a significant inverse relationship between the PNI and SII (r = -0.484; $P < 0.01$). EOC patients with a coPNI-SII score of 1 had a higher 5-year OS rate ($P < 0.05$) than EOC patients with a coPNI-SII score of 2 or 3. When taking into account both the SII and PNI, the predictive value rose.

Conclusion Interestingly, we found that low preoperative PNI and high SII were strong indicators of poor prognosis in patients with EOC. The combination of SII and PNI can enhance the accuracy of prognosis.

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Keywords Epithelial ovarian cancer, Prognostic nutrition index, Systemic immune-inflammation index, Overall survival, Prognosis

Introduction

Ovarian cancer (OC) is a heterogeneous malignancy, which is estimated to reach 310,000 new cases and up to 200,000 deaths per year worldwide [1]. Epithelial Ovarian carcinoma (EOC) is the most common subtype of ovarian cancer and ranks fifth in female cancer deaths [2]. Due to the lack of distinctive signs and symptoms and effective early diagnostic strategies, more than 60% of patients with EOC are in advanced stages at the time of diagnosis, and their 5-year survival rate is less than 50% with poor prognosis [3, 4].Although systemic treatment of OC is becoming increasingly advanced, there has been no significant improvement in the prognosis of OC patients, most patients eventually relapse and develop drug resistance, and the side effects caused by chemotherapeutic agents seriously affect the quality of life of patients [5]. Therefore, it is important to find specific indicators that can predict the survival outcome after EOC to improve the clinical early warning of the disease to guide the treatment strategy, which is important to promote good disease regression.

A growing number of studies have shown an association between ovarian cancer development and prognosis and the systemic inflammatory response [6, 7]. Systemic inflammation can be assessed by hematological and biochemical markers, and some of the common inflammatory biomarkers comprising these, such as SII, NLR, PLR, and lymphocyte to monocyte ratio (LMR), as well as the C-reactive protein (CRP) to albumin ratio (CAR), have been reported to be of predictive value in different fields. Some of these inflammatory biomarkers have been shown to be associated with OC and are important predictors of OC [8–11]. PNI is calculated from lymphocyte counts and serum albumin and is used to assess the immune and nutritional status of cancer patients [11, 12]. Miao et al. [13] found PNI to be an independent prognostic factor in patients with OC. Further studies found that decreased PNI was a strong predictor of poor prognosis in OC, especially for stage III cases. In addition, when PNI was combined with other known prognostic factors to predict the prognosis of OC, the value of its application was significantly enhanced [14]. Despite consistent reports on the prognostic value of these inflammatory factors, publications detailing the correlation between OS and SII, PNI, NLR, and PLR in EOC patients are still scarce.

Therefore, the main objective of this study was to evaluate EOC patients who had undergone radical resection or ovarian tumor cytoreduction by incorporating SII, PNI, NLR, and PLR. In addition, we evaluated the correlation between these markers and OS. In addition, we evaluated the correlation between PNI and these biomarkers. Previous studies have demonstrated the value of coSII-PNI in predicting efficacy and assessing prognosis in the translational treatment of esophageal squamous cell carcinoma [15], lung neuroendocrine tumors [16], and advanced gastric cancer [17]. However, previous studies often used a single inflammatory index for prognostic assessment and efficacy prediction in ovarian cancer patients [18]. Therefore, in this research, we established the coPNI-SII novel scoring system to investigate its prognostic significance for EOC patients.

Materials and methods

Patient selection

Patients with initial diagnoses of ovarian cancer who visited Shandong University-affiliated Linyi People's Hospital between January 2016 and December 2020 were gathered for this study. The inclusion criteria were as follows:(1) tumors diagnosed as epithelial ovarian cancer by pathological histology; (2) underwent fully staged surgery, including total hysterectomy, adnexectomy, total pelvic/para-aortic lymph node dissection, and peritoneal cytology; (3) initially diagnosed without preoperative antitumor treatment, including targeted therapy, immunotherapy, radiation, chemotherapy, and traditional Chinese medicines; (4) patients with detailed clinicopathological data and preoperative serum laboratory data of patients with complete follow-up data. Patients exclusion criteria are (1) patients with non-epithelial ovarian cancer; (2) patients with other cancers in combination; (3) patients who underwent neoadjuvant therapy before surgery; (4) patients with preoperative infectious diseases, such as lung infection, urinary tract infection, etc.; (5) patients with autoimmune diseases and hematologic disorders; (6) patients with nutritional deficiency diseases caused by cancer malignancy in addition to cancer malignancy; and (7) patients with missing clinical data or lost visits. The study was approved by the Medical Ethics Committee of Linyi People's Hospital.

Follow-up and definitions

Finally, A total of 154 EOC patients were retrospectively analyzed. Clinical data were obtained from the electronic case database, including clinical characteristic

information and laboratory data. Laboratory data were collected by fasting one week before surgery, including routine blood tests, biochemical tests, and tumor marker tests. Clinical characteristic data of EOC patients included age, FIGO stage, choroidal infiltration, ascites, metastatic lesions in the abdominal cavity, Laterality, margins residual lesions, etc. The formulas for calculating SII, PNI, NLR, and PLR were as follows: SII = platelet count (10^9/L) × neutrophil count (109/L)/lymphocyte count (10^9/L), PNI = serum albumin (g/L) + lymphocyte count (10^9/L) × 5, PLR = platelet count (10^9/L)/lymphocyte count (10^9/L), NLR was calculated as neutrophil count (10^9/L)/lymphocyte count (10^9/L).

Follow-up methods mainly included outpatient follow-up, hospitalization follow-up, and telephone follow-up. In this study, the endpoint we observed was OS, defined as the time from the diagnosis of EOC to the patient's death or the follow-up cut-off date, which was December 2020 in this study. The ovarian cancer stage was classified based on the International Federation of Gynecology and Obstetrics (FIGO).

Statistical analysis

Statistical analysis of our study data was done through SPSS version 25.0. Normally distributed measures were described using $x \pm s$ and non-normal measured variables were described using median (interquartile range). Measured variables were also converted to categorical variables through the median for further analysis. Also, the cut-off values of PLR, NLR, SII, and PNI were further determined based on reciever operating characteristic (ROC) curve used to identify those with the highest Youden index. Categorical variables were presented as frequencies and percentages and were compared using the χ^2. The relationship between PNI and SII, NLR, and PLR was analyzed by Spearman correlation analysis. Kaplan–Meier method was used for survival analysis by univariate analysis of variance and assessment of variance was done using log-rank test. The Cox regression model was used for multivariate analysis which in turn identified OS-related prognostic factors. Hazard ratios (HR) and 95% confidence intervals (CI) were used as indicators commonly used to assess relative risk. A *P* value less than 0.05 was considered statistically significant.

Results

Clinicopathological features and inflammatory biomarkers

A total of 154 patients with EOC were included in this study, the median age of the patients was 55 years (range, 17-78 years), 85 cases were aged ≥ 55 years old and 69 cases were aged < 55 years old; 86 cases were in FIGO stages I and II, and 68 cases were in stages III and IV; 92 cases were in the range of unilateral adnexa involvement and 62 cases were in the range of bilateral adnexa involvement; lymph nodes transfer positive 56 cases, lymph nodes transfer negative 98 cases; 24 cases of positive vascular infiltration and 130 cases of negative vascular infiltration; 19 cases of residual lesions in the naked eye and 135 cases of no residual lesions in the naked eye; 24 cases of positive margins and 130 cases of negative margins; 78 cases of positive peritoneal metastatic lesions and 76 cases of negative peritoneal metastatic lesions; 92 cases of ascites and 62 cases of no ascites; Ascites exfoliative cytology was positive in 53 cases and negative in 101 cases; 56 patients died until the cutoff of follow-up. fibrinogen (FIB), Leukocyte, glycan antigen 125 (CA125), glycan antigen 199 (CA199), human epitope protein 4 (HE4), and carcinoembryonic antigen (CEA), with a median of 4.23 (3.34–4.89), 6.63 (5.49–8.50) for SII, PLR and NLR, respectively, 325.85 (79.19–1000), 13.13 (7.81–29.01), 244.5 (94.58–565.50), 1.84 (1.09–2.67), 966.87 (604.82–1374.27), 206.53 (142.11–260.53) and 2.9 (2.04-4.01). The mean ALB and PNI were 40.87 ± 4.73 and 49.40 ± 6.01, respectively. Detailed clinicopathologic features and inflammatory biomarkers are shown in Table 1.

Optimal thresholds for inflammatory biomarkers

The ROC curves were utilized to choose the optimal cut-off values of SII, PNI, PLR, and NLR for predicting OS. The results showed that the optimal cut-off values of SII, PNI, PLR, and NLR for predicting OS were 998.87, 48.98, 217.63, and 2.61, respectively. the AUC of SII was 0.814 (95%Cl:0.746–0.881, Youden index = 0.533, sensitivity = 0.839, specificity = 0.694, $P < 0.01$). The AUC for PNI was 0.814 (95% CI: 0.744–0.883, Youden index = 0.576, sensitivity = 0.821, specificity = 0.755, $P < 0.01$). The AUC for PLR was 0.780 (95% Cl: 0.707–0.853, Youden index = 0.485, sensitivity = 0.732, specificity = 0.735, $P < 0.01$). the AUC for NLR was 0.769 (95%Cl: 0.694–0.843), Youden index = 0.558, sensitivity = 0.946, specificity = 0.612, $P < 0.01$) (Fig. 1). Patients were divided into two groups for further analysis based on the best cut-off value: low SII group (< 998.87, $n = 77$) or high SII group (≥ 998.87, n = 77); low PNI group (< 48.98, $n = 70$) or high PNI group (≥ 48.985, $n = 84$); low PLR group (< 217.63, $n = 86$) or high PLR group (≥ 217.63, $n = 68$); low NLR group (< 2.61, $n = 63$) or high NLR group (≥ 2.61, $n = 91$).

Correlations between NLR, PLR, PNI, and SII and clinicopathologic features

The correlation between NLR, PLR, PNI, and SII with clinicopathological parameters in EOC patients is shown in Table 2. Our findings suggested that NLR was significantly correlated with FIB, Leukocyte, CA125, HE4, ALB, FIGO stage, Laterality, lymph node metastasis, residual lesion, incisal margin, abdominal

Table 1 Baseline Characteristics of the Epithelial ovarian cancer patients enrolled in the study

Characteristics	Total(*N* = 154)
Age	55(49–64)
< 55	69
≥ 55	85
FIB	4.23(3.34–4.89)
< 4.23(N = 77)	77
≥ 4.23(N = 77)	77
Leukocyte	6.63(5.49–8.50)
< 6.63(N = 77)	77
≥ 6.63(N = 77)	77
CA125(U/mL)	325.85(79.19–1000)
< 305.9(N = 77)	77
≥ 305.9(N = 77)	77
CA199(U/mL)	13.13(7.81–29.01)
< 13.39(N = 77)	77
≥ 13.39(N = 77)	77
HE4(pmol/L)	244.5(94.58–565.50)
< 220.31(N = 69)	69
≥ 220.31(N = 85)	85
CEA(ng/L)	1.84(1.09–2.67)
< 1.84(N = 77)	77
≥ 1.84(N = 77)	77
ALB	40.87 ± 4.73
< 41.55	70
≥ 41.55	70
FIGO Stage	
Ⅰ、Ⅱ	86
Ⅲ、Ⅳ	68
Laterality	
Unilateral	92
Bilateral	62
Lymph nodes metastasis	
Postive	56
Negative	98
Vascular infiltration	
Positive	24
Negative	130
Residual disease	
Postive	19
Negative	135
Specimen incisal margin	
Postive	24
Negative	130
Abdominal metastases	
Postive	78
Negative	76
Ascites	
Yes	92
No	62
Ascites exfoliation cytology	
Postive	53
Negative	101
Death	
Yes	56
No	98
SII	996.87(604.82–1374.27)
< 998.87	77
≥ 998.87	77
PNI	49.40 ± 6.01
< 48.98	70
≥ 48.98	84
PLR	206.53(142.11–260.53)
< 217.63	86
≥ 217.63	68
NLR	2.9(2.04–4.01)
< 2.61	63
≥ 2.61	91

Data are expressed as median (interquartile range) for non-normally distributed continuous variables

Data are expressed as mean + SD for normally distributed continuous variables

Abbreviations: *FIB* Fibrinogen, *ALB* Serum albumin, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio

metastatic lesion, and ascites ($P < 0.05$). PLR was correlated with age, FIB, CA125, CA199, HE4, ALB, FIGO stage, Laterality, lymph node metastasis, Specimen incisal margin, abdominal metastatic lesion, ascites, and ascites exfoliative cytology were significantly correlated ($P < 0.05$).

Furthermore, low PNI was more common in patients with age ≥ 55 years, CA125 ≥ 305.9, HE4 ≥ 220.31, ALB < 41.55, FIGO stage III-IV, lesion involvement bilaterally, lymph node metastasis, residual lesion, positive incisal margin, positive abdominal metastatic lesion, ascites, positive ascites exfoliative cytology, as opposed to high PNI ($P < 0.05$). The two groups were similar in terms of FIB, Leukocyte, CA199, CEA, and vascular infiltration ($P > 0.05$).

In contrast, patients with high SII were more likely to be associated with age ≥ 55 years, FIB ≥ 4.23, Leukocyte ≥ 6.63, CA125 ≥ 305.9, CA199 ≥ 13.39, HE4 ≥ 220.31, ALB < 41.55, late FIGO stage, lymph node nodal metastasis, lesion involvement bilaterally, positive margins, abdominal metastatic lesions, ascites and vascular infiltration were significantly correlated ($P < 0.05$). There was no significant correlation with CEA, residual lesions, and positive ascites exfoliative cytology ($P > 0.05$).

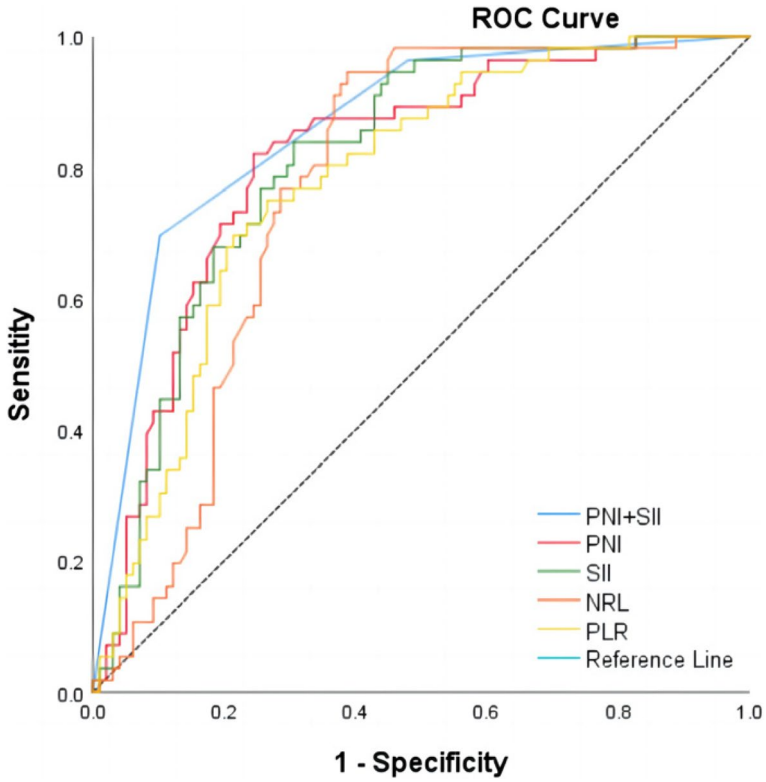

Fig. 1 ROC curves for PNI, SII, NLR, and PLR in EOC patients. The AUC for PNI was 0.814 (95% CI:0.744–0.883, $P < 0.01$). The AUC for SII was 0.814 (95% CI:0.746–0.881, $P < 0.01$). NLR had an AUC of 0.769 (95% CI: 0.694–0.843, $P < 0.01$). PLR had an AUC of 0.780 (95% CI: 0.707–0.853, $P < 0.01$). coPNI-SII had an AUC was 0.860 (95% CI: 0.800–0.921, $P < 0.001$). Abbreviations: *EOC* epithelial ovarian cancer,*AUC* Area under the curve,*OS* overall survival,*SII* systemic immune-inflammation index,*PNI* prognostic nutritional index,*NLR* neutrophil-to-lymphocyte ratio,*PLR* platelet-to-lymphocyte ratio,*coPNI-SII* combination of SII and PNI

Kaplan–meier survival analysis

Kaplan–Meier survival analysis showed an OS of 43 months for patients with SII ≥ 998.87. median OS was 40 months for patients with PNI < 48.98. median OS was 42 months for patients with PLR ≥ 217.63. median OS was 47 months for patients with NLR ≥ 2.61. The overall rate of death was low in patients in the SII < 998.87, PNI ≥ 48.98, PLR < 217.63, and NLR < 2.61 groups, with > 50% of patients surviving during the observation period. Among them, the survival time was compared between SII, PNI, NLR, and PLR groups, and the difference was statistically significant ($P < 0.01$) (Fig. 2).

Prognostic value of inflammation-based biomarkers

The prognostic value of inflammatory biomarkers was investigated using a univariate approach. As shown in Table 3, our findings indicated that SII, PNI, PLR, and NLR were significantly correlated with the prognosis of OS ($P < 0.001$). In addition, age, CA125, CA199, HE4, ALB, FIGO staging, side of lesion involvement, lymph node metastasis, vascular infiltration, residual lesion, margins, ascites, and ascites exfoliative cytology were significant prognostic factors associated with OS ($P < 0.05$). Subsequently, Multivariate Cox regression analysis revealed that CA199 ($P = 0.003$,HR = 0.35,95%CI = 0.17–0.70), HE4 ($P = 0.028$, HR = 2.89, 95%CI = 1.12–7.46), FIGO ($P = 0.009$, HR = 4.22, 95%CI = 1.43–12.46), residual lesions ($P = 0.022$, HR = 3.18, 95%CI = 1.18–8.58), Specimen incisal margin ($P < 0.001$, HR = 5.63,95%CI = 2.22–14.29), ascites ($P = 0.003$, HR = 5.95, 95%CI = 1.86–18.98), SII ($P = 0.034$, HR = 3.09, 95%CI = 1.09–8.81) and PNI ($P = 0.013$, HR = 0.20, 95%CI = 0.06–0.71) were all independent prognostic indicators of poor OS (Table 3).

Further studies found that PNI was negatively correlated with SII, NLR, and PLR (r = -0.484; $P < 0.01$, r = -0.476; $P < 0.01$, r = -0.592; $P < 0.01$) (Fig. 3).

Prognostic value of coPNI-SII in postoperative EOC

Finally, we assessed the prognostic value of coPNI-SII in patients with EOC. We scored high PNI and low SII as 1, high PNI and high SII or low PNI and low SII as 2, and low PNI and high SII as 3. The difference between

Table 2 Correlations between the NLR, PLR, PNI, SII and clinicopathological variables in patients with EOC

Variablese	NLR		*P* value	PLR		*P* value	PNI		P value	SII		*P* value
	< 2.61	**≥ 2.61**		**< 217.63**	**≥ 217.63**		**< 48.98**	**≥ 48.98**		**< 998.87**	**≥ 998.87**	
Age			0.057			0.035*			0.006*			0.015*
< 55	34	35		45	24		23	46		42	27	
≧55	29	56		41	44		47	38		35	50	
FIB			0.001*			0.009*			0.052			0.002*
< 4.23	42	35		51	26		29	48		48	29	
≧4.23	21	56		35	42		41	36		29	48	
Leukocyte			< 0.001*			0.330			0.517			< 0.001*
< 6.63	45	32		46	31		33	44		54	23	
≧6.63	18	59		40	37		37	40		23	54	
CA125			< 0.001*			< 0.001*			< 0.001*			< 0.001*
< 305.9	44	33		60	17		19	58		52	25	
≧305.9	19	58		26	51		51	26		25	52	
CA199			0.251			0.023*			0.195			0.036*
< 13.39	28	49		36	41		39	38		32	45	
≧13.39	35	42		50	27		31	46		45	32	
HE4			< 0.001*			< 0.001*			< 0.001*			< 0.001*
< 220.31	40	29		53	16		16	53		46	23	
≧220.31	23	62		33	52		54	31		31	54	
CEA			0.140			1.000			1.000			0.259
< 1.84	36	41		43	34		35	42		42	35	
≧1.84	27	50		43	34		35	42		35	42	
ALB			0.005*			0.003*			< 0.001*			0.036*
< 41.55	23	54		34	43		63	14		32	45	
≧41.55	40	37		52	25		7	70		45	32	
FIGO			< 0.001*			< 0.001*			< 0.001*			< 0.001*
I、II	50	36		66	20		22	64		58	28	
III、IV	13	55		20	48		48	20		19	49	
Laterality			0.002*			0.004*			0.010*			< 0.001*
Unilateral	47	45		60	32		34	58		57	35	
Bilateral	16	46		26	36		36	26		20	42	
Lymph nodes metastasis			0.007*			< 0.001*			< 0.001*			< 0.001*
Postive	15	41		17	39		38	18		17	39	
Negative	48	50		69	29		32	66		60	38	
Residual disease			0.033*			0.075			0.002*			0.086

Table 2 (continued)

Variablese	NLR		*P* value	PLR		*P* value	PNI		P value	SII		*P* value
	< 2.61	≥ 2.61		< 217.63	≥ 217.63		< 48.98	≥ 48.98		< 998.87	≥ 998.87	
Postive	3	16		7	12		15	4		6	13	
Negative	60	75		79	56		55	80		71	64	
Specimen incisal margin			0.016*			< 0.001*			0.023*			0.001*
Postive	4	20		4	20		16	8		4	20	
Negative	59	71		82	48		54	76		73	57	
Abdominal metastasis			< 0.001*			< 0.001*			< 0.001*			< 0.001*
Postive	20	58		28	50		49	29		27	51	
Negative	43	33		58	18		21	55		50	26	
Ascites			0.004*			0.001*			< 0.001*			0.009*
Yes	29	63		41	51		58	34		38	54	
No	34	28		45	17		12	50		39	23	
Vascular infiltration			0.084			0.128			0.068			0.026*
Postive	6	18		10	14		15	9		7	17	
Negative	57	73		76	54		55	75		70	60	
Ascites exfoliation cytology			0.106			0.009*			0.007*			0.127
Postive	17	36		22	31		32	21		22	31	
Negative	46	55		64	37		38	63		55	46	

Abbreviations: *FIB* Fibrinogen, *ALB* Serum albumin, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio

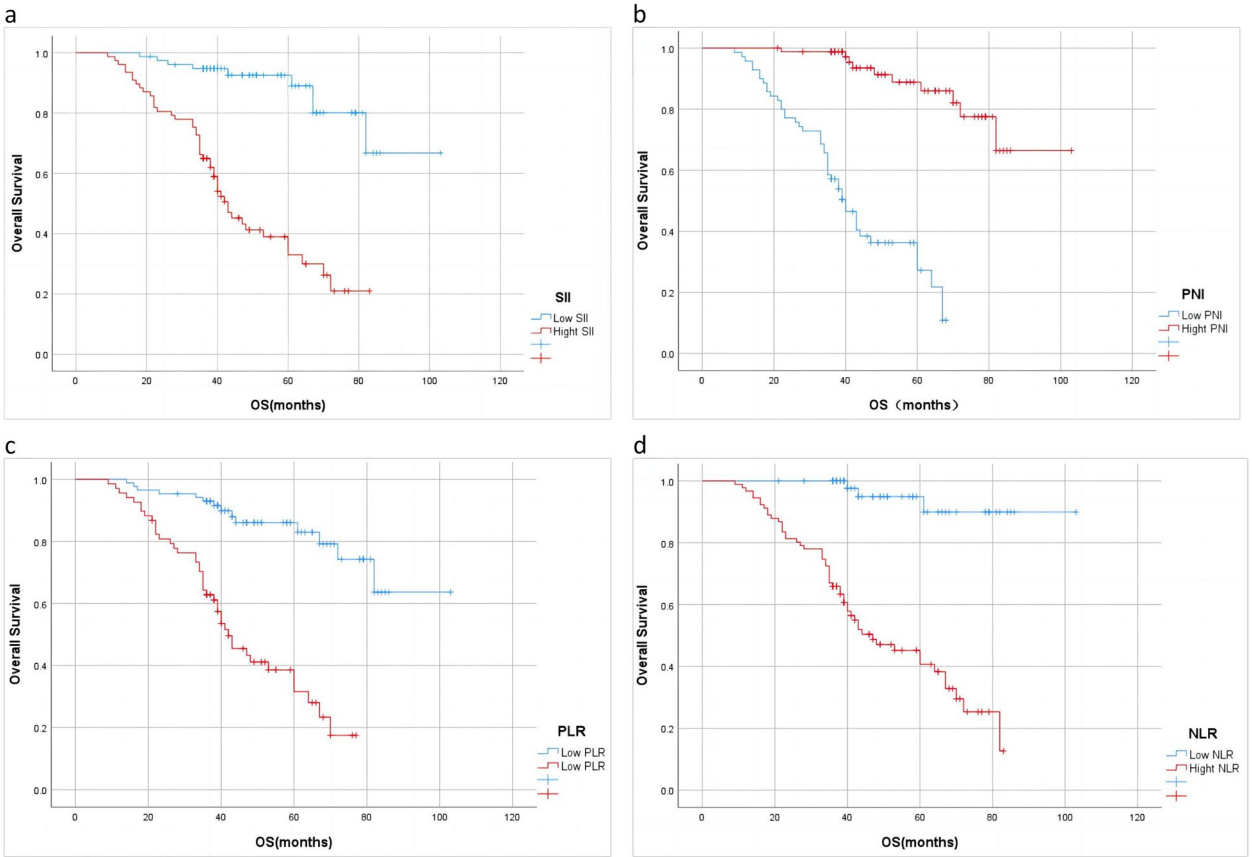

Fig. 2 Kaplan–Meier survival curves for OS of EOC patients were calculated based on SII, PNI, PLR, and NLR. **a**:OS of patients in the low SII group was significantly better than that in the high SII group ($P < 0.01$); **b**:OS of patients in the low PNI group was significantly worse than that in the high PNI group ($P < 0.01$); **c**:OS of patients in the low PLR group was significantly better than that of patients in the high PLR group ($P < 0.01$); **d**:OS of patients in the low NLR group was significantly better than that in the high NLR group ($P < 0.01$)

the three groups was statistically significant ($P < 0.001$) (Fig. 4a).

A subgroup analysis was then performed to assess the prognostic value of coPNI-SII when EOC patients were stratified by FIGO staging. The results showed that the 5-year OS rate of EOC patients with a coPNI-SII score of 1 had a better prognosis than that of EOC patients with a coPNI-SII score of 2 or 3, regardless of whether they were in FIGO stage I or II (Fig. 4b) or III or IV (Fig. 4c) ($P < 0.05$).

We further compared the predictive ability of PNI, SII, NLR, PLR, and coPNI-SII for a 5-year OS rate in EOC patients by ROC curve analysis (Fig. 1).The AUCs of PNI, SII, NLR, PLR and coPNI-SII were 0.814 (95% CI:0.744–0.883), 0.814 (95%CI:0.746–0.881), 0.769 (95%Cl: 0.694–0.843), 0.780 (95%Cl:0.707–0.853), and 0.860 (95%Cl:0.800–0.921). Compared with SII or PNI alone, we found that coPNI-SII had the largest AUC, suggesting that coPNI-SII is the most accurate predictor of these metrics and could be used as an alternative prognostic staging tool for EOC patients.

Discussion

Inflammation plays an important role in human tumourigenesis, progression, malignant transformation, and anti-immunotherapy [19]. There was research that inflammatory biomarkers are strongly associated with clinical characteristics and survival of ovarian cancer patients [7]. Our study evaluated the prognostic role of PNI, SII, NLR, and PLR in patients with EOC. A multivariate survival analysis identified both SII and PNI were independent predictors after surgery in patients with EOC, but not NLR and PLR. Similarly in other studies, SII and PNI were found to have better predictive value in assessing the prognosis of malignant tumors as compared to PLR and NLR [20, 21]. In addition, the predictive power of SII and PNI was shown to be higher than that of NLR and PLR by AUC curves [21]. This is consistent with our findings. To our knowledge, this is the first time that the prognostic value of four preoperative inflammatory markers in EOC patients was compared in a single study.

The mechanisms by which increased systemic inflammatory response and low nutritional status promote

Table 3 Univariate and multivariate Cox proportional hazards regression models for overall survival in patients with EOC

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	P	HR	95%CI
Age						
< 55	Ref					
≥ 55	0.006*	2.20	5.06—23.75	0.365	1.39	0.68—2.84
FIB						
< 4.23	Ref					
≥ 4.23	0.275	1.34	0.79—2.28			
Leukocyte						
< 6.63	Ref					
≥ 6.63	0.138	1.50	0.88—2.55			
CA125						
< 325.95	Ref					
≥ 325.95	< 0.001*	10.96	5.06—23.73	0.071	2.42	0.93—6.32
CA199						
< 13.13	Ref					
≥ 13.13	0.009*	0.48	0.28—0.83	0.003*	0.35	0.17—0.70
HE4						
< 244.5	Ref					
≥ 244.5	< 0.001*	7.91	3.58—17.48	0.028*	2.89	1.12—7.46
CEA						
< 1.84	Ref					
≥ 1.84	0.563	0.85	0.50—1.45			
ALB						
< 41.55	Ref					
≥ 41.55	< 0.001*	0.24	0.13—0.44	1.000	1.00	0.35—2.82
FIGO Stage						
I/II	Ref					
III/IV	< 0.001*	12.95	6.15–27.30	0.009*	4.22	1.43–12.46
Laterality						
Unilateral	Ref					
Bilateral	< 0.001*	2.53	1.48—4.34	0.067	0.54	0.28—1.04
Lymph nodes metastasi						
Negative	Ref					
Postive	< 0.001*	0.23	0.13—0.39	0.258	1.54	0.73—3.27
Vascular infiltration						
Negative	Ref					
Postive	< 0.001*	0.30	0.16—0.56	0.665	1.19	0.54—2.62
Residual disease						
Negative	Ref					
Postive	< 0.001*	0.26	0.14—0.49	0.022*	3.18	1.18—8.58
Specimen incisal margin						
Negative	Ref					
Postive	< 0.001*	0.20	0.11—0.35	< .001*	5.63	2.22—14.29
Ascites						
Negative	Ref					
Postive	< 0.001*	0.13	0.06—0.28	0.003*	5.95	1.86—18.98
Ascites exfoliation cytology						
Negative	Ref					
Postive	< 0.05*	0.50	0.29—0.84	0.071	1.92	0.95—3.90

Table 3 (continued)

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	P	HR	95%CI
SII						
< 998.87	Ref					
≥ 998.87	< 0.001*	7.54	3.67–15.49	0.034*	3.09	1.09—8.81
PNI						
< 49.75	Ref					
≥ 49.75	< 0.001*	0.07	0.03—0.17	0.013*	0.20	0.06—0.71
PLR						
< 217.63	Ref					
≥ 217.63	< 0.001*	6.01	3.2—11.3	0.451	0.72	0.30—1.70
NLR						
< 2.61	Ref					
≥ 2.61	< 0.001*	16.39	5.11—52.56	0.258	2.32	0.54—9.94

Abbreviations:*CI* confidence interval, *HR* hazard ratio, *FIB* Fibrinogen, *ALB* Serum albumin, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio

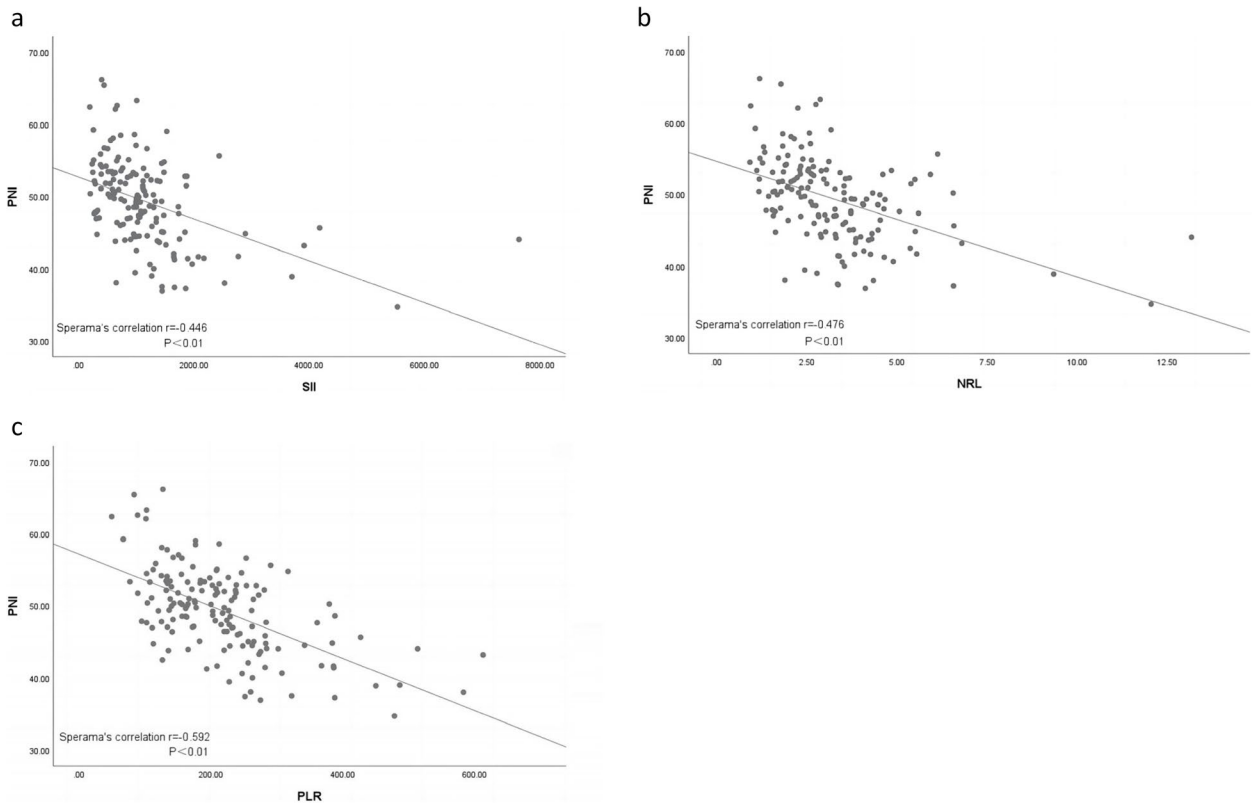

Fig. 3 **a**: correlation between PNI and SII; **b**: correlation between PNI and NLR; **c:** correlation between PNI and PLR

tumor cell angiogenesis, invasion, metastasis, and evasion of immune surveillance are unknown, but hypotheses have been proposed in previous research. The following are possible explanations for the poor prognosis of low PNI and high SII in patients with EOC. Usually, patients with high SII tumors develop thrombocytosis, neutrophilia, and lymphocytopenia, and these cells accumulate in blood vessels and release factors such as platelet-derived growth factor, vascular endothelial growth factor, and TGF-β, which are

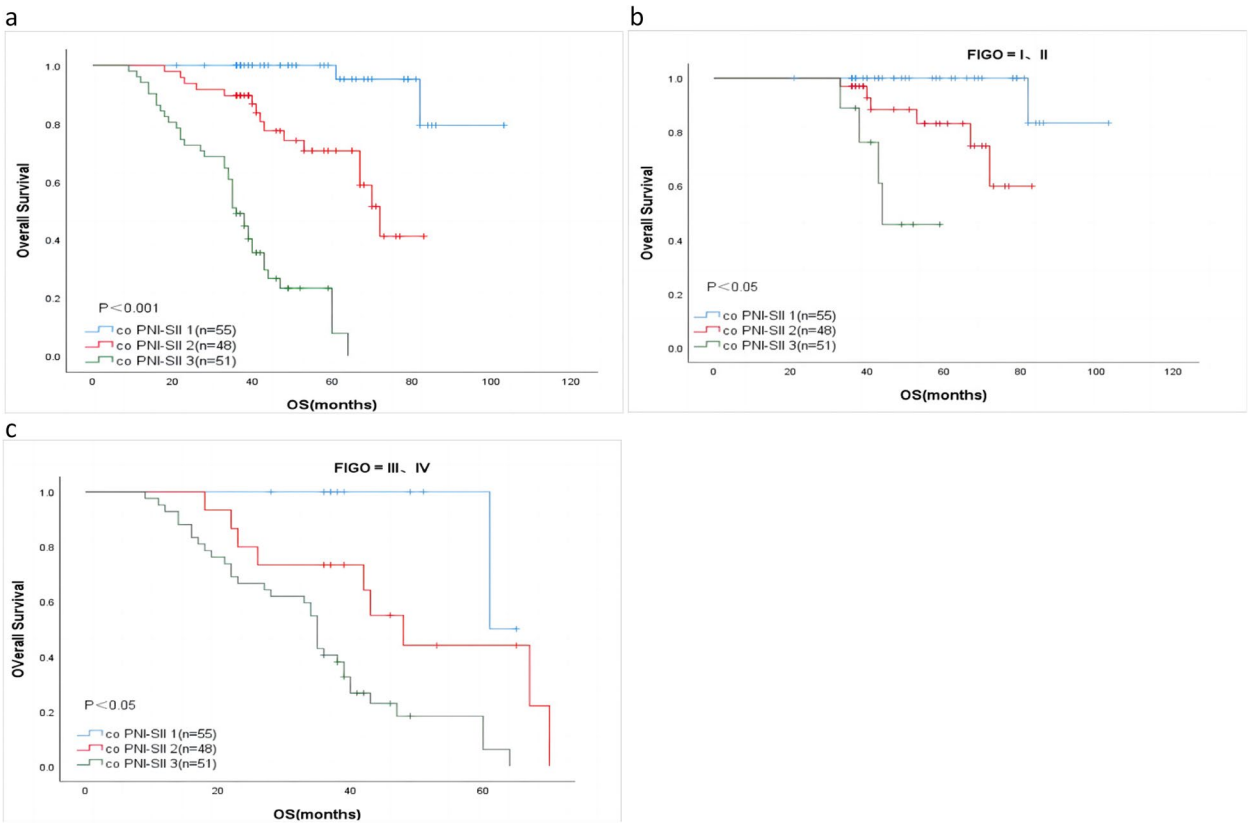

Fig. 4 **a**: Kaplan–Meier survival curves for OS according to the combination of SII and PNI in EOC patients. ($P < 0.001$) **b**: 5-year survival curves for EOC patients in stages I and II; **c**: 5-year survival curves for EOC patients in subgroups III and IV. coPNI-SII: combination of SII and PNI

involved in the biological behavior of the cancer cells [22, 23]. In addition, thrombopoietin and inflammatory mediators secreted by tumor cells stimulate platelet growth, which further accelerates cancer cell angiogenesis, facilitates cancer cell proliferation, and hinders cancer cell lysis, thereby promoting tumourigenesis and progression [24]. In ovarian cancer, it has been found that thrombocytosis promotes ovarian secretion of the inflammatory cytokine interleukin 6 (IL-6) and induces hepatic production of thrombopoietin to stimulate platelet production [25]. In addition, platelets induce epithelial-mesenchymal stromal (EMT) transformation and tumor metastasis through activation of the TGF-β1/Smad and NF-kB signaling pathways [7, 26]. In a mouse model, Hu et al. found that platelets promoted ovarian cancer tumor cell growth through high expression of platelet-derived TGF-β1, whereas lack of TGF-β1 was associated with slow growth, reduced neoangiogenesis, and attenuated platelet extravasation in ovarian cancer tumor cells [27]. Thus, two aspects of inflammation in tumor therapy are the activation of anti-tumor immune cells, which in turn enhances the capacity of the immune system and the suppression of pre-cancerous immune cells or impediment of immunosuppressive effects by inhibiting key targeting signaling pathways [28].

In the tumor microenvironment, neutrophils secrete chemokines, cytokines, proteases, and reactive oxygen species to stimulate tumor vascular growth, and tissue remodeling and down-regulate the immune responsiveness of anti-tumor cells, which are involved in tumor progression, metastasis, and recurrence [6, 29, 30]. In contrast, lymphocytes, as the primary immune cells, are involved in the body's immune response to tumor cells and play a crucial role in their elimination. In addition, lymphocytopenia enhances the malignant biological behavior of tumor cells [31, 32]. In conclusion, this could explain why high SII is associated with poorer prognosis in patients with EOC. Therefore, EOC patients with high preoperative SII could benefit from early postoperative anti-inflammatory therapy or immunotherapy.

PNI can reflect nutritional status and immune condition, which are closely associated with malignancy prognosis [16]. A meta-analysis of 2050 OC patients who underwent surgical treatment, showed that the OS of patients with low PNI was significantly worse than

that of patients with high PNI, and was also associated with ascites, late FIGO staging, larger residual tumor lesions, and higher CA125 [33]. Those reports were consistent with our results. In addition, some studies have found muscle loss in ovarian cancer patients with low PNI and serum albumin, which is independently associated with poorer survival outcomes [34]. In our study, we found that low preoperative PNI was significantly associated with clinical features such as age ≥ 55 years, CA125 ≥ 305.9, HE4 ≥ 220.31, AIB < 41.55, late FIGO stage, lesion involvement of bilateral adnexa, lymphatic metastases, residual lesions, positive specimen margins, metastatic lesions in the abdominal cavity, ascites, and positive ascites exfoliative cytology. There is an association between these clinical features and the degree of EOC development, thus affecting the prognosis of patients. In addition, few studies have examined the relationship between nutritional status and systemic inflammation in patients with EOC. We discovered a significant negative correlation between preoperative PNI and SII, PLR, and NLR in patients with EOC, Which suggests that there is a link between body immunity, nutritional status, and inflammation, which together affect tumor progression and prognosis. Malnutrition is reported to attenuate anti-immunity against tumors and increase inflammatory responses. At the same time, tumor-induced inflammation and cytokines released from inflammation can exacerbate protein catabolism and depletion of fat reserves in skeletal muscle, leading to cachexia and poor prognosis in patients with malignant tumors [28, 35].

Interestingly, our found that both PNI and SII were independent prognostic factors in EOC patients by multifactorial COX analysis. Meanwhile, we established a combined PNI and SII scoring system and explored its prognostic value in EOC patients. Our data showed that EOC patients with a coPNI-SII score of 1 had the best prognosis, while those with a score of 3 had the worst prognosis. In addition, coPNI-SII was significantly associated with OS in the FIGO staging subgroup.

We further compared the predictive ability of PNI, SII, NLR, PLR, and coPNI-SII for OS in EOC patients by ROC curve analysis. We found that coPNI-SII had a larger AUC, which indicated that coPNI-SII had a stronger predictive ability than both of them alone, and could better assess the preoperative nutritional status and inflammatory response of EOC patients, which could help clinicians to make a better treatment plan.

However, this study still has some limitations. first, there is still a controversy about the optimal critical value of these inflammatory biomarkers to predict survival. The cut-off values obtained in different studies with different sample sizes vary [25]. Large-scale, prospective, and multicentre studies are also needed to determine uniform optimal cut-off values and to confirm our results in the future. Then, other already reported inflammatory and nutritional indicators were not included in the analysis of this study, including C-reactive protein to albumin ratio, Glasgow prognostic score, lymphocyte to monocyte ratio, monocyte to lymphocyte ratio, and platelet to centrocyte ratio. Thirdly, this study did not analyze the disease-free progression period of EOC patients, nor did it perform subgroup analyses based on postoperative adjuvant therapies such as chemotherapy and targeted therapies because of the lack of relevant data.

Conclusion

Taken together, these studies suggest that preoperative SII and PNI, as easily accessible biomarkers, are viable indicators of prognosis in patients with EOC. Meanwhile, coPNI-SII improves the accuracy of predicting EOC patients than either indicator alone. This can help clinicians identify poor prognostic factors and guide multimodal interventions early for individualized treatment and monitoring to optimize survival outcomes.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

Not applicable.

Authors' contributions

J. C and L. J made substantial contributions to analysis and manuscript drafting. R. L, and X. Z, Y.C., and Z. H. contributed to the conception, design, and acquisition of data. T. L contributed to the revision and final approval of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The collection of patient's clinical data was approved by the Ethics Committee of Linyi People's Hospital in accordance with the Declaration of Helsinki (202405-H-039). Informed patient consent was not required as the study was retrospective in nature and analyzed patient data anonymously. A statement from the Ethics Committee of Linyi people's Hospital waived the need for informed consent.

Consent for publication

The authors afrm that all participants provided informed consent for publication of the data collected for the study.

Competing interests
The authors declare no competing interests.

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