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Systemic immune-inflammation index predicts prognosis in patients with epithelial ovarian cancer: A retrospective study

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HIGHLIGHTS

- SII is associated with stage, lymph node metastasis, and residual disease in EOC.
- SII was correlated with decreased survival in patients with EOC.
- The SII was an independent prognostic factor for patients with EOC.

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ABSTRACT

Objective. The study aimed to investigate the prognostic value of the systemic immune-inflammation index (SII) in patients with epithelial ovarian cancer (EOC).

Methods. A total of 553 EOC patients were retrospectively analyzed. 250 patients from West China Second University Hospital were assigned into the discovery cohort and 283 patients from The Affiliated Hospital of Southwest Medical University were assigned into the validation cohort. The correlation between SII and survival were analyzed using Cox regression analyses and Kaplan-Meier method. Prediction accuracy was evaluated with the receiver operating characteristics (ROC) curve.

Results. The high SII (≥612) was correlated with advanced FIGO stage, lymph node metastasis, and tumor recurrence. In univariate Cox regression, patients with high SII (≥612) had a significantly shorter progression-free survival (PFS) and overall survival (OS) compared to low SII patients (<612) in both cohorts. In multivariate Cox regression analysis, SII was an independent prognostic indicator for PFS (HR = 7.61, 95% CI 3.34–17.35, $P < 0.001$) and OS (HR = 6.36, 95% CI 2.64–15.33, $P < 0.001$) in the discovery cohort. These results were verified in the validation cohort.

Conclusion. High SII was correlated with poor survival in patients with EOC. The SII was an independent prognostic factor for patients with EOC.

1. Introduction

Epithelial ovarian cancer (EOC) accounts for 85–90% of all ovarian cancers [1]. More than 220,000 women are diagnosed with EOC annually worldwide [2], however, due to the lack of effective screening strategies, nearly 70% of the EOC patients are diagnosed at an advanced stage and 5-year overall survival rate of the advanced patients is still stagnant at roughly 40% [3]. In addition, advanced EOC patients are prone to relapse and resistant to chemotherapy [2]. Therefore, it's urgently necessary to identify some biomarkers to predict patients' prognosis and guide personalized treatment pre-operation.

Inflammation, a hallmark of cancer, has been demonstrated to play a critical role in tumorigenesis, angiogenesis, metastasis, and invasion [4–6]. Recently, several studies indicated inflammatory markers such as neutrophil count, lymphocyte count, platelet count, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) were also related to survival of patients and have prognostic value in various malignancies including colorectal cancer, renal cell cancer, cervical cancer, and endometrial cancer [7–10]. However, the predictive effect of inflammatory markers on survival in ovarian cancer patients is still controversial [11,12].

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In 2014, the systemic immune-inflammation index (SII), which integrated inflammatory markers including lymphocyte, neutrophil, and platelet counts, was constructed by Hu et al. and proved feasible in predicting poor outcome of patients with hepatocellular cancer [13]. It seemed that SII was more powerful in predicting prognosis of patients with cancer than NLR and PLR [13–15]. However, the prognostic value of SII for patients with EOC has not be elucidated. Thus, our study aimed to assess whether SII was a prognostic indicator for the survival in patients with EOC.

2. Materials and methods

This study was approved by the ethics committee of West China Second University Hospital, Sichuan University and The Affiliated Hospital of Southwest Medical University. Ovarian cancer patients who had undergone primary surgery from January 2009 to December 2012 in these two hospitals were retrospectively reviewed. The patients were divided into two cohorts, a training cohort (patients from West China Second University Hospital, Sichuan University) and a validation cohort (patients from The Affiliated Hospital of Southwest Medical University). Patients who underwent primary cytoreductive surgery and systematic lymphadenectomy and had a pathological diagnosis of EOC were enrolled in the study. Patients exclusion criteria are: (1) patients diagnosed with infections, other hematological disorders, or autoimmune disorders; (2) patients missed with preoperative complete blood count (CBC) test.

The clinical and pathological information including age, International Federation of Gynecologists and Obstetricians (FIGO) stage, peritoneal cytology, laterality, lymph node involvement, residual disease, grade, and histological subtype were obtained from the medical charts. The staging was performed according to the FIGO 2013 guidelines [16]. Meanwhile, platelets (P), lymphocytes (L), and neutrophils (N) counts were extracted from the preoperative CBC tests. In addition, the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII; $N \times P / L$) were calculated [13,17,18]. All patients were followed up as previously described [19]. Overall survival (OS) was calculated from the date of operation to the date of death or the last follow-up. Progression-free survival (PFS) was calculated from the date of operation to the date of the first cancer recurrence.

The X-tile 3.6.1 software (Yale University, New Haven, CT) was used for bioinformatic analysis of the training cohort data to determine the cutoff value of preoperative levels of SII, NLR, and PLR [20]. SII ≥ 612, NLR ≥ 5 and PLR ≥ 150 were considered as elevated levels.

Statistical analyses were performed using SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). After confirming the normality by Shapiro-Wilks test, the continuous data were compared by using the Student's *t*-test or Mann-Whitney test, while the categorical data were compared by using the chi-square test or Fisher's exact test. The Kaplan-Meier method and log-rank test were used to generate and compare survival curves. Univariate and multivariate analyses were calculated by the Cox proportional hazards regression model. Receiver operating characteristics (ROC) curves were used to define the differences in the area under the curves (AUC). A P value < 0.05 indicated a statistically significant difference; all P values were two-sided.

3. Result

3.1. Patient characteristics

The baseline characteristics of patients in both training and validation cohorts are described in Table 1. A total of 250 patients were enrolled in the training cohort, the median age of the patients was 53 years (range, 22–83). The median follow-up time was 46 months (range, 3–95). During the follow-up time, 111 (44.4%) patients have relapsed and 89 (35.6%) patients have died. In addition, a total of 283 patients enrolled in the validation cohort, the median age of the patients was 54 years (range, 33–79). The median follow-up time was 46 months (range, 2–95). During the follow-up time, 145 (51.2%) of these patients experienced a relapse and 121 (42.6%) have died.

Table 1
The baseline characteristics of patients in the training and validation cohorts.

Patient characteristics	Training cohort		Validation cohort	
	N = 250	%	N = 283	%
Median age, years (range)	53 (22–83)		54 (33–79)	
Histology				
Other	71	28.4	79	27.9
Serous	179	71.6	204	72.1
Grade				
1–2	66	26.4	79	27.9
3	184	73.6	204	72.1
FIGO stage				
I–II	70	28	58	20.5
III–IV	180	72	225	79.5
Laterality				
Unilateral	118	47.2	119	42
Bilateral	132	52.8	164	58
Residual disease				
<1 cm	213	85.2	235	83
≥1 cm	37	14.8	48	17
Peritoneal cytology				
Negative	154	61.6	161	56.9
Positive	96	38.4	122	43.1
Lymph nodes metastasis				
No	123	49.2	138	48.8
Yes	127	50.8	145	51.2
Chemotherapy				
Yes	197	78.8	216	76.3
No	34	13.6	38	13.4
Unknown	19	7.6	29	10.2
CA125 (U/mL)				
<35	22	8.8	6	2.1
≥35	228	91.2	277	97.9
Blood platelet count (10^9/L), Mean (range)	280 (91–635)		325 (43–580)	
Neutrophil count (10^9/L), Mean (range)	4.62 (0.96–20.3)		5.1 (0.82–13.62)	
Lymphocyte count (10^9/L), Mean (range)	1.83 (0.53–4.54)		1.56 (0.33–3.69)	

FIGO, International Federation of Gynecology and Obstetrics.

3.2. Association between the SII and patient clinicopathologic characteristics

The association between the SII and patient clinicopathologic characteristics in both cohorts were shown in Table 2. The high SII was significantly correlated with FIGO stage, lymph node metastasis, residual disease and recurrence in both cohorts (all P-value < 0.05). However, there were no significant differences between SII and age, histology, grade, and peritoneal cytology in both groups.

3.3. The prognostic role of the SII in the training cohort

In training cohort, survival analysis indicated that patients with high SII (SII ≥ 612) had a significantly shorter OS (HR = 2.25, 95% CI 1.48–3.41, P < 0.001) (Fig. 1A) and PFS (HR = 2.06, 95% CI 1.42–3.00, P < 0.001) (Fig. 1B). In univariate Cox analysis, our results indicated that tumor grade, stage, lymph node metastasis, residual disease, NLR, PLR, and SII were prognostic factors for OS and PFS (Table 3), whereas patients' age, tumor histology, and CA125 level had no prognostic significance for OS and PFS. A high SII was significantly associated with both shortened OS (P < 0.001) and PFS (P < 0.001) (Table 3). Moreover, the multivariable Cox regression analysis showed that SII was an independent prognostic factor for OS (HR = 6.36, 95% CI 2.64–15.33, P < 0.001) and PFS (HR = 7.61, 95% CI 3.34–17.35, P < 0.001) in patients with EOC (Table 4). In addition, we compared the predictive value of NLR, PLR and the SII for predicting survival and recurrence in patients with EOC. The AUC for the SII was 0.67 (95% CI, 0.60–0.74) and 0.68

Table 2
Correlation between the SII and clinicopathological characteristics (training cohort, n = 250 and validation cohort, n = 283).

Variable	SII					
	Training cohort			Validation cohort		
	<612 (n = 129)	≥612 (n = 121)	*P*-value	<612 (n = 135)	≥612 (n = 148)	*P*-value
Median age, years (range)	54 (22–83)	52 (34–76)	0.601	56 (33–75)	53 (34–79)	0.215
Histology						
Other	31	40	0.114	39	40	0.727
Serous	98	81		96	108	
Grade						
1–2	35	31	0.886	38	41	0.934
3	94	90		97	107	
FIGO stage						
I–II	46	24	0.007	37	21	0.006
III–IV	83	97		98	127	
Laterality						
Unilateral	58	60	0.526	57	62	0.955
Bilateral	71	61		78	86	
Residual disease						
<1 cm	116	97	0.03	119	116	0.029
≥1 cm	13	24		16	32	
Peritoneal cytology						
Negative	84	70	0.245	76	85	0.847
Positive	45	51		59	63	
Lymph nodes metastasis						
No	76	47	0.002	79	59	0.002
Yes	53	74		56	89	
Chemotherapy						
Yes	100	97	0.342	109	107	0.246
No	21	13		15	23	
Unknown	8	11		11	18	
Recurrence						
Yes	42	69	<0.001	57	88	0.004
No	87	52		78	60	
CA125 (U/mL)						
<35	19	3	0.001	3	3	1
≥35	110	118		132	145	
PLR, Mean (range)	116.16 (46.94–237.96)	205.38 (83.28–879.25)	<0.001	149.85 (46.99–330.77)	278.69 (122.73–970.45)	<0.001
NLR, Mean (range)	1.79 (0.38–4.06)	3.21 (1.72–38.3)	<0.001	2.23 (0.46–5.03)	3.24 (0.46–32.97)	<0.001

FIGO, International Federation of Gynecology and Obstetrics; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

(95% CI, 0.61–0.76) for OS and PFS, respectively, which was definitively superior to NLR and PLR (Fig. 2A and B).

3.4. Validate the prognostic role of SII in the validation cohort

In the validation cohort, we also found a significantly shorter OS (HR = 2.07, 95% CI 1.45–2.96, $P < 0.001$) (Fig. 1C) and PFS (HR = 1.62, 95% CI 1.17–2.24, $P = 0.004$) (Fig. 1D) for patients with high SII compared to patients with low SII. In univariate analysis, tumor grade, stage, lymph node metastasis, residual disease, NLR, and SII also found as prognostic factors for survival and relapse in patients with EOC (Table 3). However, PLR did not have prognostic value in the validation cohort (Table 3). Moreover, the multivariable Cox regression analysis also demonstrated that the high SII was significantly correlated with OS (HR = 1.96, 95%CI 1.09–3.63, $P = 0.024$) and PFS (HR = 2.71, 95%CI 1.48–4.93; $P = 0.001$) (Table 4). In addition, the predictive ability of the SII, assessed by AUC, was 0.69 (95% CI, 0.64–0.75) and 0.63 (95% CI, 0.56–0.69) for OS and PFS (Fig. 2C and D) respectively.

4. Discussion

The evidence is mounting that inflammation and related cells play a vital role in the establishment and progression of cancer via the secretion of cytokines and chemokines, stimulating angiogenesis and proliferation, and promoting metastatic spread [4]. In the tumor microenvironment (TME), neutrophils secret reactive oxygen species (ROS), proteinases and circulating vascular endothelial growth factors (VEGFs) to regulate tumor cell proliferation and metastasis and angiogenesis directly. Additionally, neutrophils also indirectly regulate TME by producing oncogenic cytokines and chemokines such as interleukin (IL)-1β, IL-6, IL-12, and TNF-α to promote additional inflammatory cell recruitment and activation [21]. Platelets induce epithelial-mesenchymal transition (EMT) and tumor metastasis by activating the synergistic interaction between TGFβ1/Smad and NF-κB pathways [22,23]. Meanwhile, platelets also reduce anoikis and promote metastasis through activating YAP1 signaling [24]. Lymphocytes have a crucial role in launching cytotoxic cell death to clear tumor cells [8]. Thus, cancer patients with T-lymphocytes infiltrating in tumor masses have a prolonged disease-specific survival [25].

In light of the close correlation between inflammation and cancers, several studies have investigated the prognostic value of inflammatory cells in different cancer types [7–10]. In ovarian cancer, NLR and PLR were considered as the most common prognostic markers in the previous studies. A study by Miao et al. suggested that EOC patients with lower values of NLR (NLR < 3.02) or PLR (PLR < 207) had longer PFS and OS [11]. However, in a recent study of Raungkaewmanee et al., PLR and NLR were not evaluated as the independent prognostic factors in patients with EOC [12]. In a study by Badora-Rybicka et al., they also proved PLR level was not an independent prognostic factor for PFS or OS [26]. Thus, further studies are needed to detect the prognostic significance of other inflammatory markers in EOC patients.

Recently, a novel inflammatory indicator called systemic immune-inflammation index (SII), which integrated inflammatory markers including lymphocyte, neutrophil, and platelet counts, was constructed by Hu et al. and proved feasible in predicting poor outcome of patients with hepatocellular cancer [13]. In the study, high SII was also pointed out to be relevant to the increased level of circulating tumor cells (CTCs) in the cancer patients, which were more likely to undergo

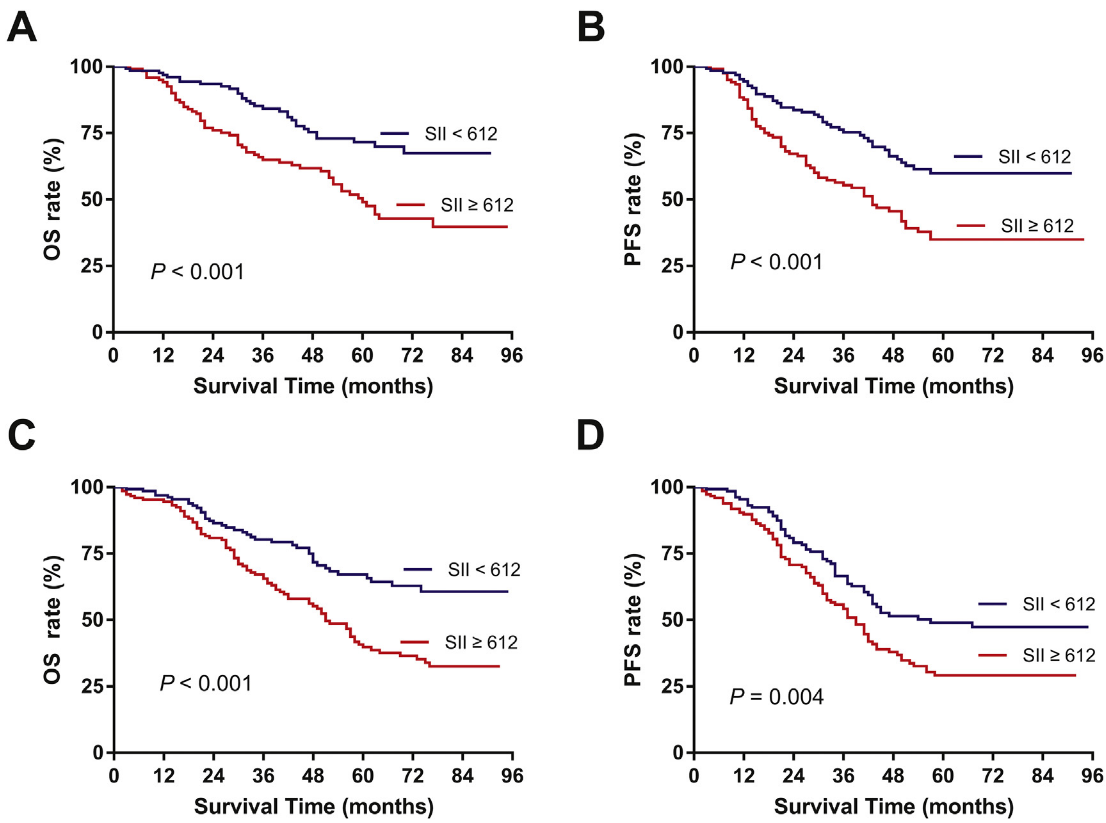

Fig. 1. The Kaplan–Meier analysis of OS and PFS for the SII in the training (A, B) and validation (C, D) cohorts.

tumor metastasis [13]. The prognostic value of SII has been proved in various cancers [15,17,18,27]. In study by Wang et al., they monitored the dynamic change of SII 6 times from pre-operation to post-operation and revealed that patients with persistently high SII or SII alternating from low level to high level had an elevated recurrence rate [14]. In addition, SII has been shown to be a predictor of the therapeutic efficacy of bevacizumab [17,18]. The EOC patients with high SII (≥730) level who received chemotherapy plus bevacizumab did not gain survival benefit compared to patients received chemotherapy alone [18]. In the present study, we mainly evaluated the prognostic significance of SII for EOC patients in two independent patients' cohorts. Additionally, the data of NLR and PLR were also analyzed to compare their prognostic value with SII. Our results demonstrated that the SII was correlated with FIGO stage, residual tumor size, LNs metastasis and tumor recurrence in patients with EOC. In univariable analysis, FIGO stage, LNs metastasis, SII, and NLR were significantly correlated with decreased PFS and OS, whereas in multivariable analysis, only SII and NLR remained as independent prognostic factors. In accordance with Raungkaewmanee et al. study, we did not find the PLR was a prognostic factor for survival by multivariable analysis [12]. Moreover, the predictive ability of SII was shown to be higher than that of the NLR by AUC curve.

Our study has a number of advantages and disadvantages. The advantage of our study is the data involved in the SII index are easily obtained from routine CBC tests and measuring of CBC is inexpensive, feasible and reproducible. Otherwise, compared to other inflammatory indexes, SII is able to comprehensively reflect the inflammatory and immune status of cancer patients, because it integrates more inflammatory and immune markers than common indexes like NLR and PLR [13]. The disadvantage of our study is that we did not compare the predictive performance of SII with another well-known inflammatory index - C reactive and protein (CRP), which was not included into our routine monitoring for cancer patients. To date, CA-125 and HE4 are still the most extensively used marker for EOC diagnosis, monitoring and

Table 3
Univariate Cox regression analyses of the SII with clinicopathologic characteristics.

Variable	Training cohort				Validation cohort			
	OS		PFS		OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.0 (0.97–1.02)	0.868	1.0 (0.98–1.02)	0.872	0.99 (0.97–1.01)	0.371	0.99 (0.97–1.01)	0.418
Histology (other vs. serous)	1.26 (0.99–1.85)	0.149	1.34 (0.92–1.72)	0.112	1.27 (0.99–1.62)	0.278	1.38 (0.94–1.54)	0.294
Grade (3 vs. 1–2)	2.21 (1.27–3.86)	0.005	1.67 (1.06–2.65)	0.029	1.13 (0.74–1.71)	0.581	1.16 (0.79–1.69)	0.453
FIGO stage (III–IV vs. I–II)	7.94 (3.66–17.19)	<0.001	9.53 (4.63–19.61)	<0.001	2.29 (1.37–3.83)	0.002	3.47 (2.03–5.95)	<0.001
LNM (yes vs. no)	3.44 (2.15–5.49)	<0.001	4.04 (2.62–6.21)	<0.001	1.49 (1.04–2.14)	0.031	1.96 (1.39–2.75)	<0.001
Residual disease (≥1 vs. <1)	1.42 (1.03–1.96)	0.033	1.42 (1.01–1.98)	0.048	2.24 (1.07–4.69)	0.033	2.36 (1.12–4.98)	0.024
CA125 (≥35 U/mL vs. <35 U/mL)	2.39 (0.7–4.01)	0.113	2.78 (0.83–4.12)	0.126	1.44 (0.45–4.54)	0.538	1.74 (0.72–6.75)	0.128
NLR (≥5 vs. <5)	2.79 (1.84–4.26)	<0.001	2.61 (1.78–3.81)	<0.001	2.45 (1.62–3.67)	<0.001	1.86 (1.31–2.63)	<0.001
PLR (≥150 vs. <150)	1.77 (1.16–2.71)	0.008	1.79 (1.23–2.61)	0.003	1.31 (0.84–2.04)	0.228	1.10 (0.75–1.61)	0.643
SII (≥612 vs. <612)	2.25 (1.45–3.48)	<0.001	2.07 (1.41–3.04)	<0.001	2.12 (1.45–3.10)	<0.001	1.62 (1.16–2.26)	0.005

LNM, lymph node metastasis; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic immune-inflammation index.

Table 4
Multivariate Cox regression analyses in the training and validation cohorts.

Variable	Training cohort				Validation cohort			
	OS		PFS		OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
FIGO stage (III–IV vs. I–II)	1.75 (0.92–3.31)	0.086	1.57 (0.89–2.74)	0.114	1.09 (0.72–1.65)	0.674	1.29 (0.89–1.89)	0.179
LNM (yes vs. no)	1.32 (0.78–2.26)	0.303	1.43 (0.88–2.34)	0.149	1.56 (0.82–2.97)	0.179	0.72 (0.43–1.2)	0.206
Residual disease (≥1 vs. <1)	1.21 (0.88–1.67)	0.238	1.51 (0.78–1.93)	0.134	1.57 (0.86–2.03)	0.322	1.54 (0.91–2.96)	0.138
NLR (≥5 vs. <5)	1.82 (1.05–3.16)	0.034	1.79 (1.09–2.96)	0.022	1.98 (1.09–3.63)	0.025	1.84 (1.06–3.19)	0.031
PLR (≥150 vs. <150)	0.96 (0.54–1.71)	0.888	1.13 (0.69–1.86)	0.635	0.64 (0.35–1.17)	0.147	1.11 (0.61–2.01)	0.738
SII (≥612 vs. <612)	6.36 (2.64–15.33)	<0.001	7.61 (3.34–17.35)	<0.001	1.96 (1.09–3.63)	0.024	2.71 (1.48–4.93)	0.001

LNM, lymph node metastasis; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, systemic immune-inflammation index.

evaluation of treatment efficacy [28]. Further investigation is still required to assess the predictive prognostic values of SII with these tumor markers. Last but not least, our study only concentrated on the baseline SII (SII value before surgery) and its relationship with patient's prognosis. In fact, the progression and recurrence of cancer is a multistage and dynamic process, only sustained high SII level was a powerful predictor of poor prognosis [14]. Therefore, the serial monitoring of the dynamic change of SII is likely to provide better measures to predict patient prognosis than the baseline SII, which seems to be a very promising direction for subsequent research.

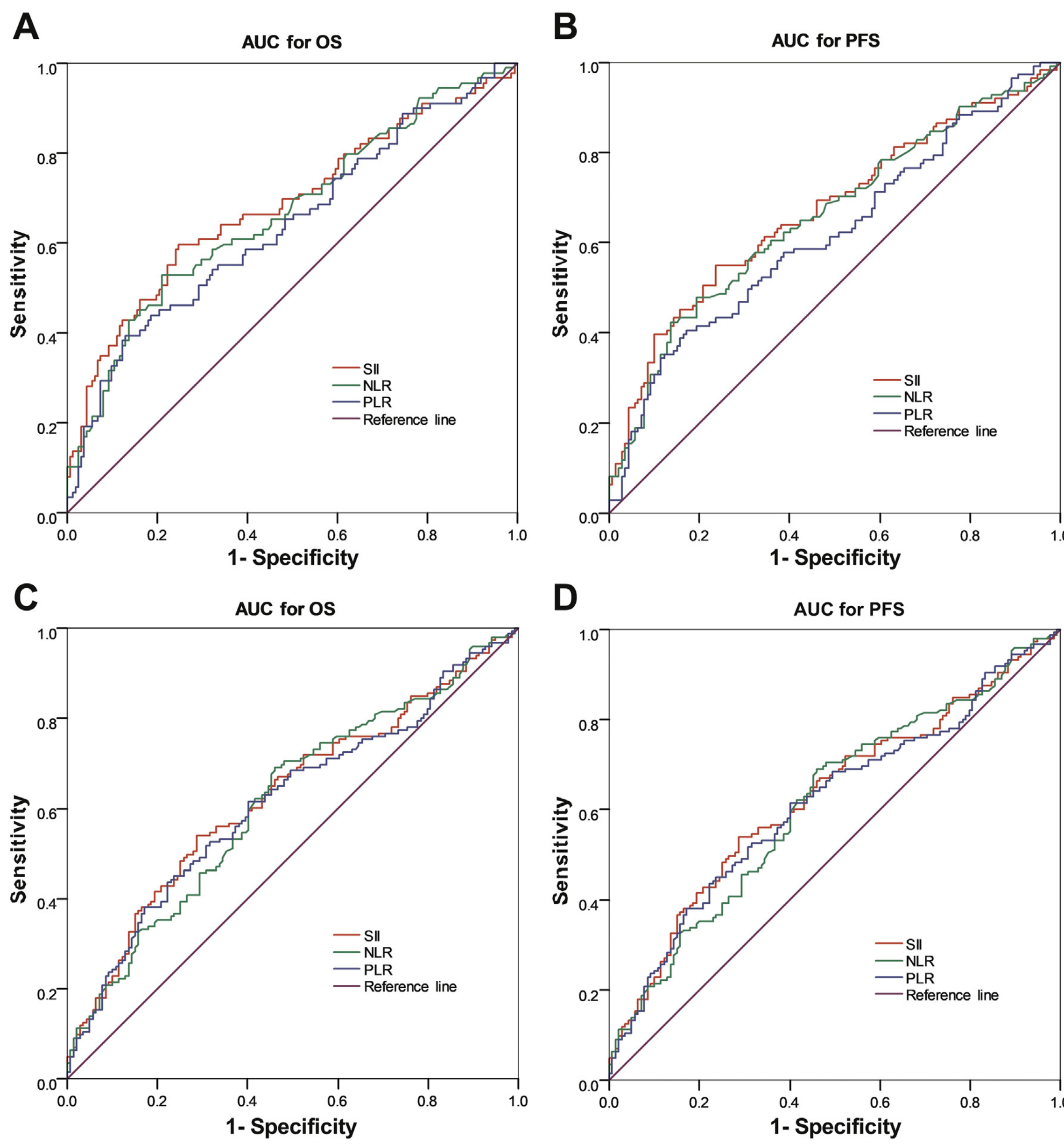

Fig. 2. Predictive ability of the SII was compared with NLR and PLR by ROC curves in the training (A, B) and validation (C, D) cohorts.

In conclusion, our retrospective study proved SII is a feasible and robust prognostic factor for oncological outcomes of EOC patients. However, further larger and prospective study is needed to validate our results.

Conflict of interest

The authors declare no conflict of interest.

Author contribution

Study conception and design: Dan Nie, Zhengyu Li; Data collection and analysis: Dan Nie, Han Gong Xiguang Mao; Writing and revising of the manuscript: Dan Nie, Zhengyu Li. All authors have reviewed the manuscript and approved of its submission.

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