

Development of Nomogram Models Based on Peripheral Blood Score and Clinicopathological Parameters to Predict Preoperative Advanced Stage and Prognosis for Epithelial Ovarian Cancer Patients

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Purpose: Nutritional and inflammatory states are crucial in cancer development. The purpose of this study is to construct a scoring system grounded on peripheral blood parameters associated with nutrition and inflammation and explore its value in stage, overall survival (OS), and progression-free survival (PFS) prediction for epithelial ovarian cancer (EOC) patients.

Patients and Methods: Four hundred and fifty-three EOC patients were retrospectively identified and their clinical data and relevant peripheral blood parameters were collected. The ratio of neutrophil to lymphocyte, lymphocyte to monocyte, fibrinogen to lymphocyte, total cholesterol to lymphocyte and albumin level were calculated and dichotomized. A scoring system named peripheral blood score (PBS) was constructed. Univariate and multivariate Logistic or Cox regression analyses were used to select independent factors; these factors were then used to develop nomogram models of advanced stage and OS, PFS, respectively. The internal validation and DCA analysis were performed to evaluate models.

Results: Lower PBS indicated a better prognosis and higher PBS indicated inferior. High PBS is associated with advanced stage, high CA125, serous histological type, poor differentiation, and accompanied ascites. The logistic regression showed age, CA125, and PBS were independent factors for the FIGO III–IV stage. The nomogram models for advanced FIGO stage based on these factors showed good efficiency. FIGO stage, residual disease, and PBS were independent factors affecting OS and PFS, the nomogram models composed of these factors had good performance. DCA curves revealed the models augmented net benefits.

Conclusion: PBS can be a noninvasive biomarker for EOC patients' prognosis. The related nomogram models could be powerful, cost-effective tools to provide information of advanced stage, OS, and PFS for EOC patients.

Keywords: inflammation, nutrition, ovarian cancer, predict model, peripheral blood

Introduction

The second most common cause of gynecologic cancer death is ovarian cancer with a survival rate 47% five years after diagnosis.¹ Each year, there are 239,000 new diagnosed ovarian cancer patients and 152,000 death cases reported.² About 90% of ovarian cancers are epithelial ovarian cancers (EOC).³ The early stage of the EOC has a relatively better prognosis of 5 years overall survival rate 61–87%, while for the advanced stage is 14–38%.⁴ Lack of early, specific signs and effective screening methods leads to a diagnostic delay and further worse prognosis. Unfortunately, over 75% of

EOC patients are diagnosed at advanced stage. Therefore, predictive methods of advanced stage and prognosis are needed to help making an appropriate treatment plan.

Chronic inflammation is a significant part of cancer development.⁵ The assessment of patients' systemic inflammatory response can be achieved by relevant indicators in peripheral blood. Nutritional status is also a factor associated with post-operative complications and cancer prognosis.^{6–8} The levels of albumin and total cholesterol can be used to evaluate the nutritional status of body, studies showed they are related to postoperative complications and prognosis.^{6,9} Some inflammation and nutrition related scoring systems such as Onodera's prognostic nutritional index (ONI), lymphocyte-to-monocyte ratio (LMR), systemic inflammation score (SIS), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and COUNT have been proved had clinical significance in gynecological cancer.^{9–16} Furthermore, a meta-analysis showed the level of fibrinogen is a prognostic predictor with better performance than the level of CA125, NLR and the ratio of platelet to lymphocyte, elevated levels of fibrinogen may be related to unfavorable prognosis.¹³ Although the inflammatory and nutritional markers are economical and available in clinical practice, the wide use of them is limited by inconsistent cutoff values, relatively low prediction accuracy, and small, weak studies. Few studies have built clinical nomogram models that use clinicopathological factors and peripheral blood parameters to predict EOC prognosis. The models based on clinicopathological factors are common and available for individuals. With the development of sequencing technology and precision medicine, predict models based on molecule or genomic sequence has been well established, but they are not convenient for every patient. Most people can only afford routine treatment and get general data. These all provide insights into constructing a new scoring system with peripheral blood parameters and further exploring its clinical significance.

Good staging methods, and predictive methods of prognosis can help doctors and patients have a better understanding of disease and choose appropriate therapeutic plans. Therefore, we first created a more practical scoring system consisting of peripheral blood parameters. Then, based on the system, we developed nomogram models to predict the patients' advanced stage before surgery, overall survival (OS) and progression-free survival (PFS) after primary surgery.

Materials and Methods

Patients Selection

It is a single-center retrospective study. We screened patients who were diagnosed with ovarian cancer and underwent primary surgery at Qilu Hospital from January 2014 to December 2018. Patients in these cases were excluded: non-epithelial, recurrent or metastatic ovarian cancer, neoadjuvant chemotherapy, infectious disease 15 days before surgery, malignant disease of other system, disease affecting immune or nutritional status such as hepatitis, systemic lupus erythematosus and so on. Patients in pregnancy or lactation, and underwent secondary surgery or only exploratory surgery were also excluded. Without loss of generality, those without complete clinical data or following-up data were excluded.

Data Collection

We got patients' clinical information such as age, menopausal state, pathological pattern, histological grade, Federation International of Gynecology and Obstetrics (FIGO) stage, chemotherapy, and comorbidities from electronic medical records. Laboratory examinations including routine blood tests, CA-125 (U/mL), serum albumin (g/L), and plasma total cholesterol (mmol/L) and fibrinogen (g/L) levels of patients were obtained within 15 days before surgery.

The following formulas were used to calculate Onodera's prognostic nutritional index (ONI), neutrophil-to-lymphocyte ratio (NLR), total cholesterol-to-lymphocyte ratio (TCLR), lymphocyte-to-monocyte ratio (LMR), and fibrinogen-to-lymphocyte ratio (FLR):

ONI = $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte number (/}\mu\text{L)}$;

NLR = $\text{neutrophil number (10}^9\text{/L)} / \text{lymphocyte number (10}^9\text{/L)}$;

TCLR = $\text{total cholesterol (mmol/L)} / \text{lymphocyte number (10}^9\text{/L)}$;

LMR = $\text{lymphocyte number (10}^9\text{/L)} / \text{monocyte number (10}^9\text{/L)}$;

FLR = $\text{fibrinogen (g/L)} / \text{lymphocyte number (10}^9\text{/L)}$;

The calculation of the systemic immune-inflammation index (SII), systemic inflammation score (SIS), and COUNT score were described in previous researches.^{12,17,18}

Follow-Up

These patients were followed up every year after surgery until death or May 31, 2021, whichever came first. The endpoints of this study were OS and PFS. OS and PFS were the time distance from surgery to death/the final follow-up and from surgery to disease progression/the final follow-up, respectively.

Statistical Analysis

The continuous variables of the normal distribution and non-normal distribution are presented as means \pm SD and medians plus interquartile, respectively. Categorical variables are presented as absolute counts and percentages. We use Fisher's exact test/Chi-square and Kruskal–Wallis test to handle categorical and continuous variables, respectively.

The optimal cutoff points of ALB, NLR, LMR, FLR, and TCLR were calculated based on OS with the R package “survminer”. Then the obtained cutoff values were used to dichotomize patients into two groups (high and low). We developed a scoring system named peripheral blood score (PBS) based on these five parameters: For each parameter, patient with a better prognosis gets 0 point, and patient with a worse prognosis gets 1 point. Then, add them up to get a total score. The survival outcomes were delineated by Kaplan–Meier curves, and Log rank test was used to compare the differences between the two groups, respectively. We created time-dependent receiver operating characteristic (ROC) curves and calculated the areas under the curve (AUC) to compare the discriminatory ability among the scoring systems.

We used univariate and multivariate binary logistic regression analyses to select associated factors of the FIGO III–IV stage. The independent factors were used to construct a nomogram model via “rms” package and internal validation was conducted. To demonstrate the consistency between observed probabilities and predicted probabilities, we delineated calibration plots performed with bootstrapping (1000 resamples). The P value of Hosmer–Lemeshow test >0.05 indicated good consistency. Then we plotted ROC curve with “pROC” package to assess the predictive accuracy. To evaluate the clinical practicality, we performed decision curve analysis (DCA) with the “ggDCA” package.

Univariate and multivariate Cox proportional hazards regression was used to select independent factors of OS and PFS. A LASSO regression was used to reduce data dimensionality and select variables, accompanied by 10 rounds of cross-validation. The selected variables were used to construct the nomograms via the “rms” R package. Then the models' performance was assessed by internal validation. The AUC of ROC curves and concordance index (C-index) curves were performed to assess the prognostic accuracy. Calibration plots for 1, 3, 5 years after surgery were performed with bootstrapping (1000 bootstrap resamples). C-index was used to assess the models' discrimination, and it was calculated with 1000 bootstrapping techniques. DCA was conducted to assess the clinical benefit of models. The R package “glmnet”, “survival”, “survivalROC” and “ggDCA” were used to analyze the related dataset.

Note. SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and R (version 4.2.0) were used to analyze the data.

Results

Patients Characteristics

Table 1 summarizes the clinical characteristics of 453 EOC patients. They were 54.66 ± 11.46 years old in average and 209 (46.1%) patients were postmenopausal. Most of them had serous ovarian cancer (75.5%) and poor differentiation (74.8%). The FIGO stage of patients was stage I–II in 137 (30.2%) cases, stage III–IV in 316 (69.8%) cases; 401 (88.5%) were known to have undergone chemotherapy. Two hundred and seventy-nine (61.6%) patients had residual disease <1 cm while 174 (38.4%) had residual disease ≥ 1 cm. Nearly half of the patients had CA125 levels ≥ 500 (U/mL), and 285 (62.9%) patients had ascites. Among the included 453 patients, 162 (35.8%) patients were classified into PBS group 0 (PBS 0 or 1), 216 (47.7%) into group 1 (PBS 2 or 3), and 75 (16.5%) into group 2 (PBS 4 or 5).

Survival Outcomes

The median follow-up was 36 months and 193 (42.6%) patients died during follow-up. The median OS and PFS were 63 and 40 months; the OS and PFS rates for 1 year were 76% and 69%, for 3 years were 59% and 45%, for 5 years were

Table I Baseline Characteristics of Patients

Characteristics	No. of Patients (%)
Age (years, mean \pm SD)	54.66 \pm 11.46
Menopause, n (%)	
Yes	209 (46.1%)
No	244 (53.9%)
Histological type, n (%)	
Serous	342 (75.5%)
Other	111 (24.5%)
Differentiation, n (%)	
G3	339 (74.8%)
G2	8 (1.8%)
G1	3 (0.7%)
Gx	103 (22.7%)
FIGO stage, n (%)	
I–II	137 (30.2%)
III–IV	316 (69.8%)
Residual disease, n (%)	
<1 cm	279 (61.6%)
\geq 1 cm	174 (38.4%)
CA125 (U/mL), n (%)	
\geq 500	231 (51.0%)
<500	222 (49.0%)
Chemotherapy, n (%)	
Yes	401 (88.5%)
No	10 (2.2%)
Unkown	42 (9.3%)
ASA Physical status, n (%)	
1	37 (8.2%)
2	379 (83.7%)
3	36 (8.0%)
4	1 (0.2%)
Ascites, n (%)	
Yes	285 (62.9%)
No	168 (37.1%)
PBS group, n (%)	
0	162 (35.8%)
1	216 (47.7%)
2	75 (16.5%)

Abbreviations: FIGO, Federation International of Gynecology and Obstetrics; ASA, American society of Anesthesiologists.

45% and 25%, respectively. The cutoff points of each peripheral blood marker variables are shown in [Table 2](#). Higher serum albumin, and LMR indicated favorable OS, whereas higher NLR, FLR, and TCLR indicated inferior OS (all $P < 0.001$, [Table 2](#) and [Figure 1A–E](#)).

Peripheral Blood Score (PBS) Construction

The following 5 parameters was used to construct PBS: serum albumin (better prognosis: ≥ 34.4 (g/L)), NLR (better prognosis: < 2.37), LMR (better prognosis: ≥ 2.51), FLR (better prognosis: < 2.02 (g/109)) and TCLR (better prognosis: < 3.81 (mmol/109)). Patients were divided into three groups: the patients had worse prognosis values for four or five parameters were classified as PBS 2, those with worse prognosis values for two or three parameters were assigned to PBS 1, and other patients

Table 2 Univariate Cox Analyses for OS of Peripheral Blood Factors

Characteristics	Cutoff	P-value	Categories	HR	95% CI
ALB	34.40	<0.001	Low vs High	2.14	1.46–3.14
NLR	2.37	<0.001	Low vs High	0.46	0.33–0.65
LMR	2.51	<0.001	Low vs High	1.78	1.30–2.44
FLR	2.02	<0.001	Low vs High	0.44	0.30–0.64
TCLR	3.81	<0.001	Low vs High	0.61	0.46–0.81

Abbreviations: ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; FLR, fibrinogen-to-lymphocyte ratio; TCLR, total cholesterol-to-lymphocyte ratio.

were assigned to PBS 0 (Figure 1G). The survival analysis of three PBS groups showed significantly different ($P < 0.001$, Figure 1F). The relationships between clinicopathological characteristics and PBS were analyzed (Table 3). Among the three groups, the distribution of histological type, differentiation, FIGO stage, residual disease after surgery, CA125 levels, and ascites before surgery was very different ($P = 0.021$, $P = 0.013$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$).

The time-dependent ROC curves with estimated AUC for each scoring system revealed that PBS consistently outperformed the other scoring systems (Figure 1H). Also, compared with the constituent part, the PBS was shown to be the system with higher AUC values (Figure 1I).

Independent Risk Factors for FIGO III-IV Stage in EOC Patients

Baseline clinical characteristics and clinicopathological features including peripheral blood parameters were analyzed by univariate and multivariate logistic regression. In the univariate logistic regression analysis, age, levels of CA125, NLR, FLR, ALB, TCLR, SII, COUNT, SIS, ONI, and PBS were associated with FIGO III–IV stage (all $P < 0.1$, Table 4). Then, these factors entered into the multivariate analysis. It showed age, level of CA125, and PBS were independent risk factors for the FIGO III–IV stage (OR = 1.03, 95CI%: 1.01–1.05; OR = 4.89, 95CI%: 2.98–8.03; OR = 1.68, 95CI%: 1.20–2.36, respectively, Table 4).

Nomogram Model for Predicting FIGO III-IV Stage

A nomogram for the FIGO III–IV stage was created based on the independent predictors selected in the logistic regression. It provided a method to quantify the probabilities (Figure 2A). Then, we use ROC curves and calibration plots to assess the nomogram's predictive accuracy. The ROC curve analysis showed the model's good efficiency in diagnosing FIGO III–IV stage of EOC patients (AUC = 0.782, Figure 2B). The calibration plots (Figure 2C) showed that the actual and the predicted probabilities had a good consistency ($P = 0.986$). DCA revealed that the model is beneficial to clinical practice (Figure 2D).

Univariate and Multivariate Cox Analyses for OS and PFS

We selected the independent risk factors for OS and PFS by univariate and multivariate Cox analyses (Table 5 and Table 6). Univariate analysis showed that CA125 levels and ascites before surgery, FIGO stage, age, PBS, histological type, differentiation, and residual disease after surgery were the factors associated with OS and PFS (all $P < 0.05$). In multivariate analysis, we found that FIGO stage, residual disease after surgery, and PBS were independent factors affecting OS (HR = 4.54, 95CI%: 2.54–8.09; HR = 0.69, 95CI%: 0.50–0.96; HR = 1.19, 95CI%: 1.07–1.33, respectively, Table 5) and PFS (HR = 3.47, 95CI%: 2.21–5.44; HR = 0.76, 95CI%: 0.58–1; HR = 1.16, 95CI%: 1.06–1.27, respectively, Table 6).

Nomogram Models for Predicting OS and PFS

To identify the most correlated factors of OS and PFS, we performed Lasso Cox analysis and 10 rounds of cross-validation (Figure 3). The values corresponding to the lambda 1se were chosen. Finally, FIGO stage, residual disease after surgery, and PBS were selected in both OS and PFS analysis, which were also independent factors of OS and PFS (Table 5 and Table 6).

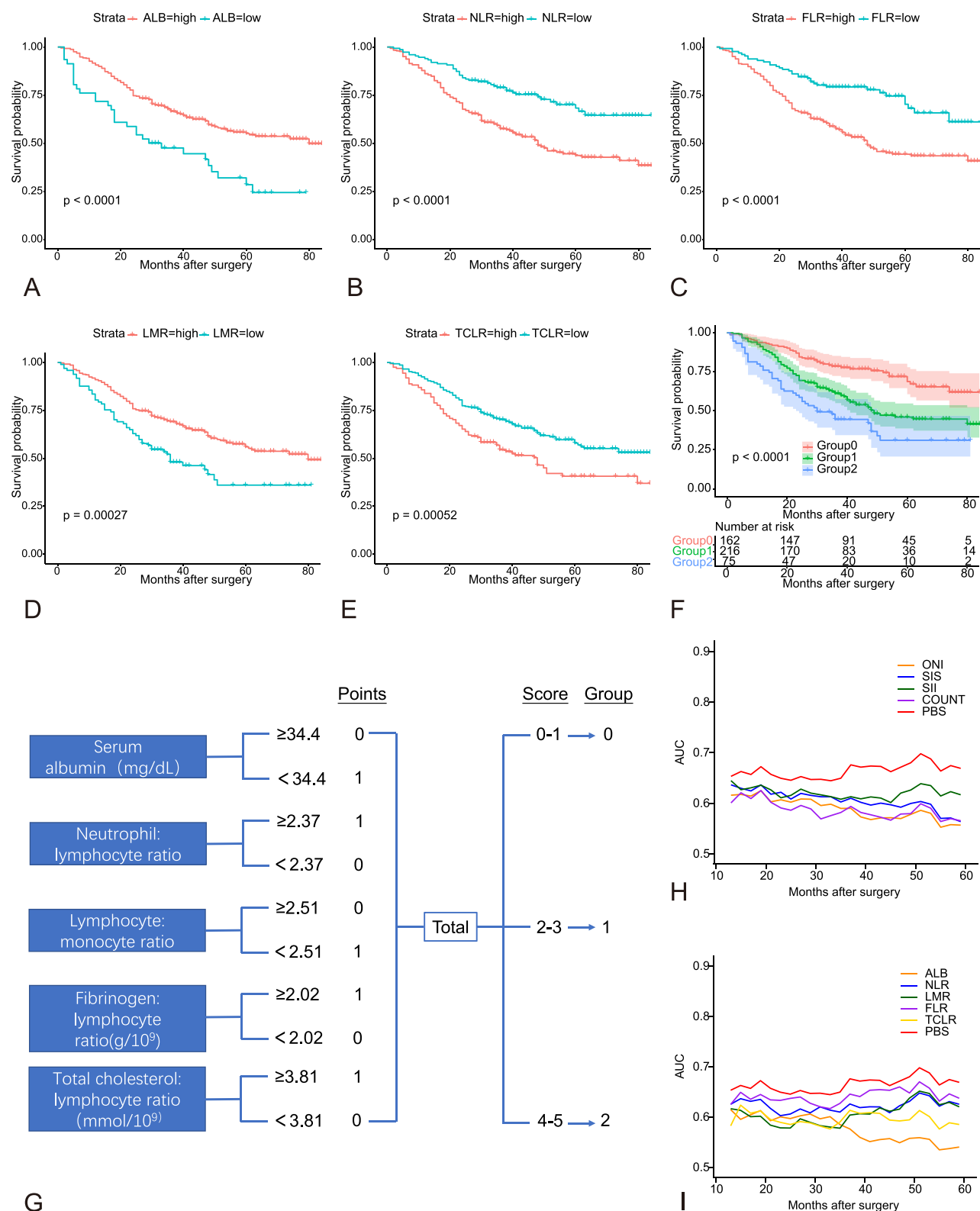


Figure 1 Construction of peripheral blood score (PBS). Survival analysis of albumin (A), NLR (B), FLR (C), LMR (D), TCLR (E), and PBS (F) based on overall survival. (G) Calculation of the peripheral blood score (PBS). (H and I) Analysis of the predictive accuracy of the different score systems through the months of follow-up, computed by the AUC of time-dependent ROC.

Table 3 Correlation Between the PBS and Clinicopathological Characteristics

Characteristics	PBS 0 Group (n=162)	PBS 1 Group (n=216)	PBS 2 Group (n=75)	P value
Age (years, mean \pm SD)	53.64 \pm 11.49	54.60 \pm 11.08	60 (20)	0.123 ^a
Menopause, n				0.401 ^b
Yes	68	106	35	
No	94	110	40	
Histological type, n				0.021 ^b
Serous	111	168	63	
Other	51	48	12	
Differentiation, n				0.013 ^c
G3	105	173	61	
G2	4	4	0	
G1	2	1	0	
Gx	51	38	14	
FIGO stage, n				<0.001 ^b
I–II	76	55	6	
III–IV	86	161	69	
Residual disease, n				<0.001 ^b
<1 cm	123	133	23	
\geq 1cm	39	83	52	
CA125 (U/mL), n				<0.001 ^b
\geq 500	64	115	52	
<500	98	101	23	
Chemotherapy, n				0.05 ^c
Yes	140	198	63	
No	7	1	2	
Unkown	15	17	10	
ASA, n				0.094 ^c
1	18	15	4	
2	136	182	61	
3	8	19	9	
4	0	0	1	
Ascites, n				<0.001 ^b
Yes	81	141	63	
No	81	75	12	

Note: ^aKruskal–Wallis test; ^bPearson chi-square test; ^cFisher's exact test.

Abbreviations: FIGO, Federation International of Gynecology and Obstetrics; ASA, American society of Anesthesiologists; PBS, peripheral blood score.

Then, prognostic nomogram models were developed based on the selected factors (Figure 4A and B). The AUC values and their corresponding 95% CIs of 1-, 3-, and 5-year OS were 74% (95% CI: 68–81%), 73% (95% CI: 68–79%), 73% (95% CI: 66–80%) for the OS nomogram model. For the PFS nomogram model, the AUC values for 1-, 3-, and 5-year PFS were 72% (95% CI: 65–79%), 73% (95% CI: 68–78%), and 70% (95% CI: 63–77%), respectively (Figure 4C and F). The calibration curves for different years (1-, 3-, 5-year) of OS and PFS rates were delineated with 1000 bootstrap samples and well overlapped with their reference lines (Figure 4D and G). Wider threshold probability ranges were demonstrated in the prediction of 5-year OS and PFS rates using DCA curves, which showed that the nomogram models increase net benefit (Figure 4E and H). The AUC of time-dependent ROC and time-dependent C-index curves were delineated in Figure 5. For the OS nomogram model, the C-index was 0.68 (95% CI: 0.64–0.72), and for the PFS nomogram model, it was 0.66 (95% CI: 0.63–0.70) after 1000 bootstrap samples to measure discrimination.

Table 4 Univariate and Multivariate Logistic Regression Analyses for FIGO III–IV

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Menopause (Yes VS No)	1.30	0.87–1.95	0.20	–	–	–
Age	1.03	1.01–1.05	<0.001	1.03	1.01–1.05	0.014
CA125 (≥500 VS <500)	5.9	3.72–9.35	<0.001	4.89	2.98–8.03	<0.001
NLR	1.46	1.25–1.7	<0.001	0.91	0.76–1.1	0.32
LMR	0.99	0.97–1.02	0.54	–	–	–
FLR	1.5	1.26–1.78	<0.001	1.04	0.77–1.4	0.81
ALB	0.96	0.92–1	0.07	0.90	0.76–1.07	0.23
TCLR	1.25	1.08–1.46	<0.001	0.93	0.73–1.18	0.55
SII	1	1–1	<0.001	1	1–1	0.18
COUNT	1.53	1.26–1.86	<0.001	1.09	0.74–1.6	0.67
SIS	1.87	1.42–2.47	<0.001	1.01	0.67–1.53	0.96
ONI	0.95	0.92–0.98	<0.001	1.12	0.94–1.34	0.20
PBS	1.73	1.46–2.04	<0.001	1.68	1.20–2.36	0.002

Abbreviations: ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; FLR, fibrinogen-to-lymphocyte ratio; TCLR, total cholesterol-to-lymphocyte ratio; SII, systemic immune-inflammation index; ONI, Onodera's prognostic nutritional index; SIS, systemic inflammation score; PBS, peripheral blood score.

The Application of Nomogram Models

For each element of the nomograms, patients can get point according to their actual values by comparing the visualized models (Figure 2A, Figure 4A and B). Total points were calculated by adding each elementary point. The relevant risks can be obtained by making a vertical line perpendicular to the total score point.

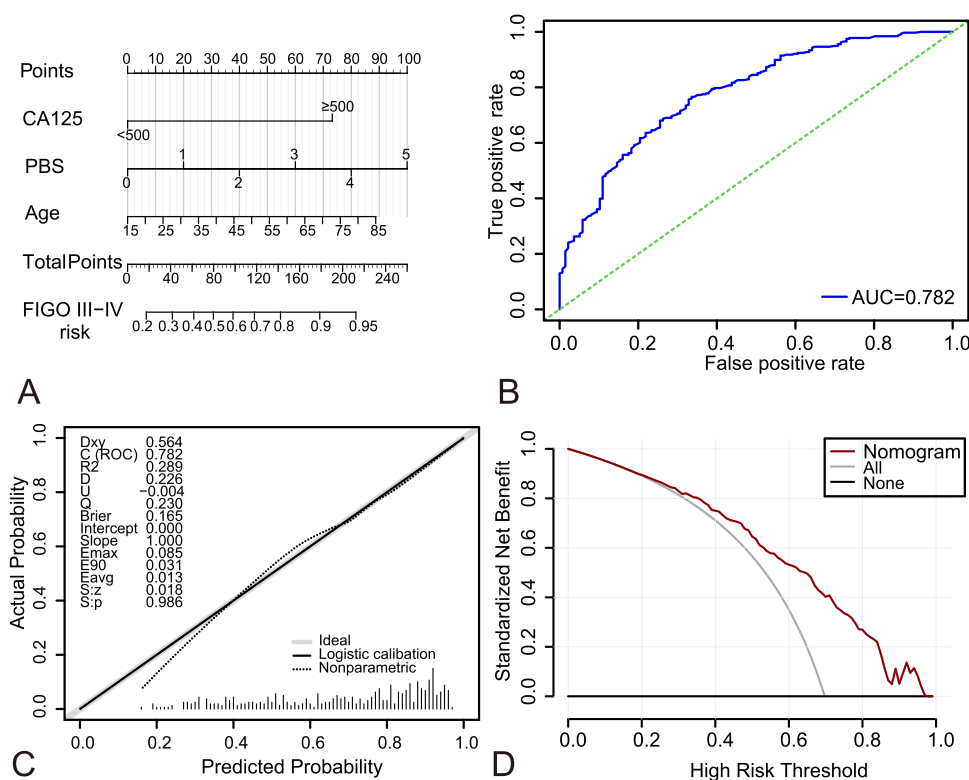


Figure 2 Nomogram model predicting advanced stage of EOC patients. (A) The nomogram for predicting advanced stage with CA125, PBS, and age. (B) The ROC curve for the nomogram. (C) The calibration plots for the nomogram. (D) Decision curve analyses of the nomogram.

Table 5 Univariate and Multivariate Cox Regression Analyses for OS

Characteristics	Univariate			Multivariate		
	HR	95% CI	P value	OR	95% CI	P value
Menopause (Yes VS No)	1.05	0.79–1.39	0.74	–	–	–
FIGO stage (III–IV VS I–II)	5.34	3.33–8.58	<0.001	4.54	2.54–8.09	<0.001
Histological type (Other VS Serous)	0.67	0.46–0.96	0.03	1.32	0.83–2.09	0.23
Differentiation (VS G3)						
G2	0.46	0.11–1.86	0.28	1.93	0.43–8.64	0.39
G1	0	0–Inf	0.99	0	0–Inf	0.99
Gx	0.56	0.38–0.83	0.004	1.39	0.84–2.33	0.20
Ascites (Yes VS No)	2.16	1.55–3.01	<0.001	1.18	0.81–1.71	0.39
Residual disease (<1 cm VS ≥1 cm)	0.37	0.28–0.50	<0.001	0.69	0.50–0.96	0.03
ASA (VS I)						
2	0.80	0.50–1.30	0.37	-	-	-
3	1.12	0.58–2.15	0.74	-	-	-
4	104.21	11.38–945.2	<0.001	-	-	-
Age	1.02	1.01–1.03	0.005	1.01	1.00–1.02	0.16
CA125 (≥500 VS <500)	1.67	1.25–2.23	0.001	1.01	0.73–1.39	0.95
PBS	1.37	1.23–1.51	<0.001	1.19	1.07–1.33	0.002
Chemotherapy (VS No)						
Yes	1.37	0.44–4.28	0.59	-	-	-
Unkown	1.51	0.45–5.14	0.51	-	-	-

Abbreviations: FIGO, Federation International of Gynecology and Obstetrics; ASA, American society of Anesthesiologists; PBS, peripheral blood score.

Table 6 Univariate and Multivariate Cox Regression Analyses for PFS

Characteristics	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Menopause (Yes VS No)	0.93	0.73–1.19	0.58	–	–	–
FIGO stage (III–IV VS I–II)	4.39	3.06–6.29	<0.001	3.47	2.21–5.44	<0.001
Histological type (Other VS Serous)	0.54	0.39–0.75	<0.001	0.97	0.65–1.46	0.90
Differentiation (VS G3)						
G2	0.49	0.16–1.54	0.23	1.91	0.55–6.6	0.31
G1	0	0–Inf	0.99	0	0–Inf	0.99
Gx	0.49	0.35–0.70	<0.001	1.24	0.79–1.94	0.34
Ascites (Yes VS No)	1.93	1.47–2.54	<0.001	1.06	0.78–1.44	0.72
Residual disease (<1 cm VS ≥1 cm)	0.41	0.33–0.53	<0.001	0.76	0.58–1	0.05
ASA (VS I)						
2	1	0.65–1.53	0.98	-	-	-
3	1.27	0.71–2.28	0.42	-	-	-
4	125.38	13.78–1140.73	<0.001	-	-	-
Age	1.01	1.00–1.02	0.017	1.00	0.99–1.01	0.69
CA125 (≥500 VS <500)	1.73	1.35–2.21	<0.001	1.09	0.82–1.43	0.55
PBS	1.31	1.20–1.43	<0.001	1.16	1.06–1.27	0.001
Chemotherapy (VS No)						
Yes	2.06	0.66–6.42	0.22	-	-	-
Unkown	1.93	0.58–6.45	0.29	-	-	-

Abbreviations: FIGO, Federation International of Gynecology and Obstetrics; ASA, American society of Anesthesiologists; PBS, peripheral blood score.

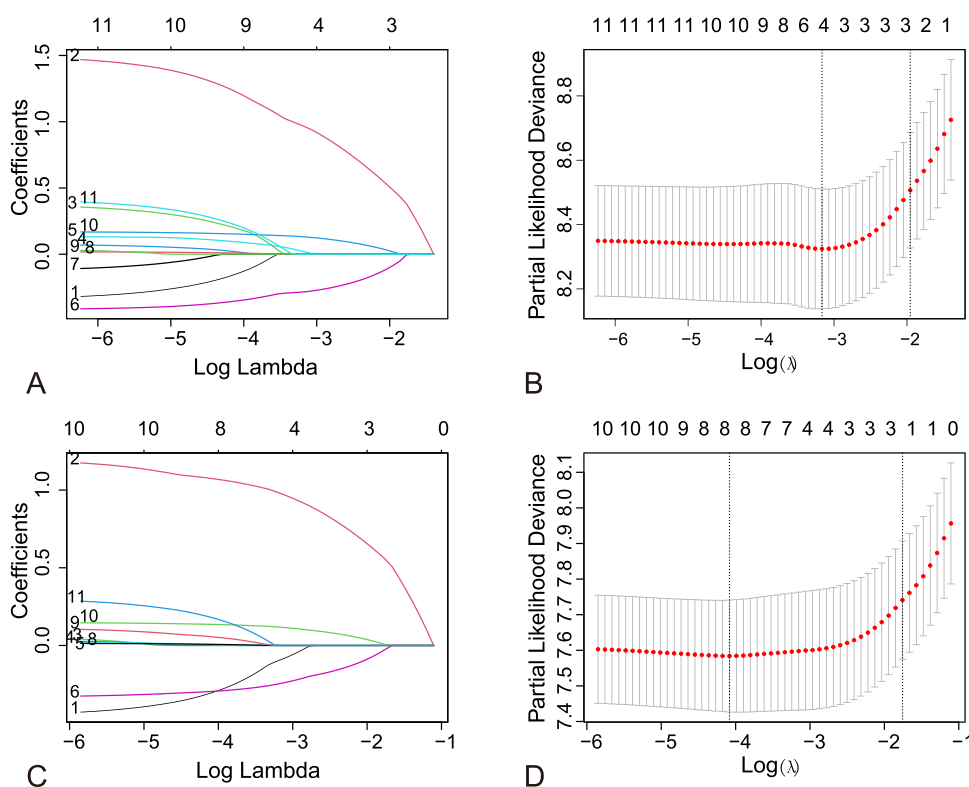


Figure 3 The LASSO regression was used to select elements of nomogram models. (A and C) LASSO coefficients of the whole factors were included in OS (A) and PFS (C) analysis. (B and D) Tenfold cross-validation for LASSO model parameter adjustment using 1-SE criteria for OS model (B) and PFS model (D).

Discussion

In the present study, we constructed a scoring system, PBS based on some peripheral blood parameters (the neutrophil counts, lymphocyte counts, monocyte counts, the levels of albumin, total cholesterol, and fibrinogen) and explored its relevance to the stage and prognosis of EOC patients. We proved PBS was an independent factor for FIGO III–IV stage, OS, and PFS. Then, we built the nomogram models based on the independent variables to predict the stage and the prognosis. Finally, the discrimination, calibration, and decision curve analyses indicated the models' good predictive ability and clinical practicability.

Studies have showed that inflammatory cells are crucial in cancer immunity, as they play both protumor and anti-tumor roles.⁵ It has been found inflammatory cells, such as neutrophils, macrophages, and lymphocytes, are usually present in tumor tissues.¹⁹ Neutrophils can help tumor cells invade, proliferate, metastasize and escape from immune surveillance. Various molecules are released from neutrophils' granules and cytoplasm, then they act on cancer and stroma cells in tumor microenvironment.²⁰ Lymphocytes can inhibit tumor cell's proliferation and metastasis, and induce their death, which plays a basic role in cancer defense.²¹ Monocytes can directly infiltrate tumors or differentiate into tumor-associated macrophages and further play a part in cancer development.²² Fibrinogen, also known as coagulation factor I, is essential for thrombosis. It also functions as an inflammatory regulator linked to the development of inflammatory microenvironment, tumor cell invasion, metastasis, and growth.²³ NLR has been proven to be associated with clinicopathological parameters, OS, PFS, and reaction to chemotherapy in EOC patients, a higher NLR predicts pessimistic results.^{11,16,24–28} Studies have shown LMR is associated with CA125 levels, ascites, histological grade, lymph node metastasis, and FIGO stage, a lower LMR means shorter OS and PFS.²⁹ Combining LMR and CA125 levels can improve the predictive accuracy of prognosis.³⁰ Wankyu Eo et al found preoperative LMR is an independent predictor of suboptimal cytoreduction.³¹ Elevated fibrinogen also can play roles of predicting EOC patients' survival outcome.¹³ We got similar results, but the cutoff values of NLR, LMR, and FLR were different from the studies. In our study, the cutoff values were 2.37, 2.51, and 2.02 for NLR, LMR, and FLR, respectively.

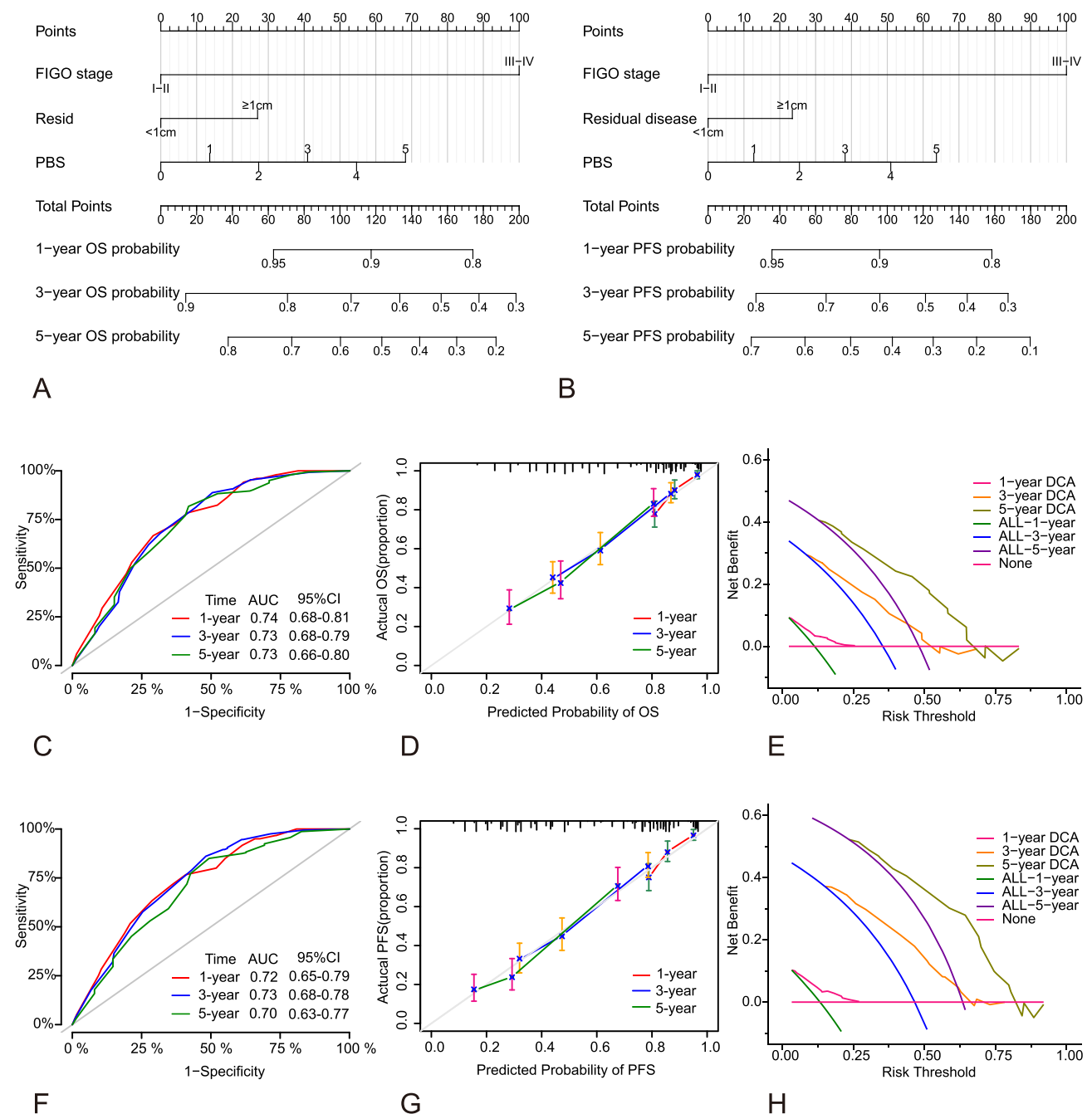


Figure 4 Nomogram models predicting prognosis of EOC patients. (A and B) The nomogram model predicting OS (A) and PFS (B) probability with FIGO stage, residual disease, and PBS. (C and F) The receiver operating characteristic (ROC) curve analyses showed the accuracy of 1-year, 3-year, and 5-year OS (C) and PFS (F). (D and G) Calibration curves showed the prediction ability of the nomogram models for OS and PFS. (E and H) The decision curve analysis of developed nomogram models for 1-year, 3-year, and 5-year OS (E) and PFS (H).

Levels of albumin usually represent malnutrition or cachexia in cancer patients with advanced stage. Recently, it has been found albumin has a guiding role in the prediction of complications and prognosis in EOC. Low albumin level means poor prognosis. D de Jong et al's research showed albumin can play a role in predicting suboptimal cytoreduction.³² It can also predict chemotherapy sensitivity when combined with D-dimer.³³ Cholesterol is important for cell membrane maintenance and energy metabolism, which is also closely linked to tumors' occurrence. Growing research links hypercholesterolemia to increased ovarian cancer risk.^{34,35} Composed of cholesterol level, albumin level, and lymphocyte count, CONUT score is related to ovarian cancer prognosis in retrospective studies.^{9,36}

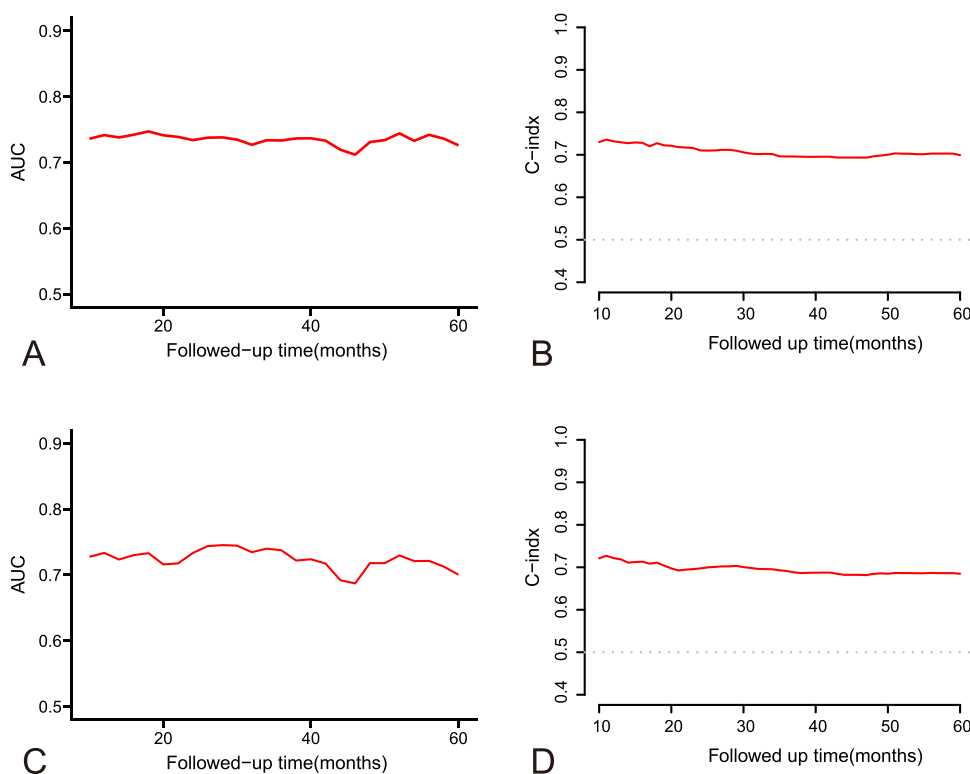


Figure 5 The performance of nomogram models predicting prognosis. (A and C) Time-dependent AUC of ROC for OS (A) and PFS (C). (B and D) Time-dependent C-index for the models predicting OS (B) and PFS (D).

We think the composite of the inflammatory and nutritional status may represent a condition, in which patients and cancer interact with each other. These all indicate inflammatory and nutritional parameters have essential value in the prediction of EOC patients' prognosis. The application is limited by their low sensitivity and specificity with AUC varies 0.63–0.709, although many scoring systems have been constructed to increase their availability.^{9–11,14,30,33,36} In our study, we constructed a scoring system named PBS, by dichotomizing the variables and value assignment. PBS had a better performance in predicting OS in EOC patients compared with existing scoring systems and single indicators. Patients with higher PBS often had more probability to have advanced FIGO stage, residual disease ≥ 1 cm, ascites, and higher CA125 levels. High PBS indicated a worse prognosis. This convenient score can be used in patient counseling. But PBS is composed of five parameters, which makes it seem a little complicated. We still need more prospective studies to explore its application. The final objective is to put PBS into clinical use like ROMA (Risk of Ovarian Malignancy Algorithm),³⁷ doctors and patients can get it easily from the output of instrument, whether it is complicated or not. Besides the prognostic value, the inflammatory nutritional parameters also have role in differential diagnosis. Relevant researches have proved the significant difference of NLR, LMR, fibrinogen between ovarian cancer group and control group. The AUC varies from 0.683 to 0.954, and the combination of CA125 can improve diagnostic efficacy.^{38–41} We will put devote part of our work on exploring the potential use of PBS in differential diagnosis in future.

There are many different types of models based on clinicopathological parameters, imaging characteristics, or genetic signature to predict the stage, pathologic types, surgical outcomes, and reaction to chemotherapy, OS, or PFS,^{42–48} but their practicability is limited partly owing to the expensive and redundant examination such as molecular diagnosis or genomic sequence. We urgently need models grounded on clinical variables with superior convenience. We performed univariable and multivariable analyses and confirmed FIGO stage, residual disease, and PBS were associated with OS and PFS, which is consistent with previous studies.^{49,50} However, CA125 and chemotherapy were not independent factors, which disagreed with some studies.^{51,52} This phenomenon can be attributed to the most included EOC patients having a high level of CA125 and experiencing chemotherapy, and we had limited information about chemotherapy

regime, cycles and response. Then, we constructed models which had good practicability and visualized them with the simple nomogram. The nomogram model for advanced stage of EOC patients had an AUC value of 0.782, the models for OS and PFS had AUC values of different years of OS and PFS rates >0.7, which means a good discrimination. We also proved the models' accuracy and clinical practicability. Those features all indicate that our models are accurate and feasible tools.

The study had some limitations. First, it was a single-center retrospective cohort. Second, we got this scoring system and these three models based on our data. Both PBS and nomogram models should be rigorously validated externally. Then, in the multivariable analyses, there were limited patients in some subgroups, which resulted in a wide range of confidence intervals (CIs). Last, we had limited data about chemotherapy, and the postoperative therapies of patients have some heterogeneity. These factors may cause bias of study. Further studies with larger sample size, good homogeneity and external validations are needed for the validation and generalization of our conclusions.

In summary, we constructed a scoring system and developed convenient and reliable tools. The tools included the peripheral blood parameters and clinicopathological parameters, it can be used to estimate the stage and prognosis of EOC patients and help doctors choose an optimal therapeutic schedule. It was proved that the models had a strong discriminatory ability, accuracy, and clinical practicability, which means they had a good predictive ability for advanced stage, OS, and PFS, respectively. The nomogram models could be convenient clinical tools for preoperative counseling, risk stratification, evaluating prognosis as well as recommending a sensible and individualized therapy approach.

Data Sharing Statement

Relevant data are available from the corresponding authors.

Ethics Statement

This study was approved by the ethics committee of Qilu Hospital, Shandong University (KYLL-202208-033). Patient informed consent was waived because the study collected patients' information retrospectively and did not provide information that can be used to identify individuals. The study was performed in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception and design, data acquisition, or data analysis and interpretation, participated in the drafting of the article or critically revising it for important intellectual content, agreed to submit to the current journal, gave final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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