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Nomogram Models for Predicting Survival of Esophageal Cancer based on Aggregate Index of Systemic Inflammation, Neutrophil-to-Lymphocyte * Platelet Ratio and Controlled Nutritional Status Score

Huike Wang[1#], Xi Luo[1#], Qian Wei[1], Jianxiang Xing[1], Taiying Lu[1] and Feng Wang[1*]

Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Henan Province, China

Correspondence should be addressed to Feng Wang, Department of Oncology, The First Affiliated Hospital of Zhengzhou University, No.1 Eastern Jianshe Road, Zhengzhou, Henan 450052, China

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[†]These authors contributed equally to this work and share first authorship.

ABSTRACT

BACKGROUND

The controlling nutritional status (CONUT), prognostic nutritional index (PNI), neutrophil-to-lymphocyte * platelet ratio (NLPR) and aggregate index of systemic inflammation (AISI) are new parameters that reflect the immune-nutritional status of patients with some cancers.

PURPOSE

To establish and validate competing risk nomogram prediction models for overall survival (OS) and progression-free survival (PFS) in esophageal cancer (EC) patients and compare them with the American Joint Committee on Cancer (AJCC) staging system.

METHODS

A total of 647 EC patients who received radical surgery (RS) treatment in The First Affiliated Hospital of Zhengzhou University from August 5, 2012, to August 1, 2017, were enrolled and randomly divided into a training cohort (456 cases) and a validation cohort (191 cases). The Lasso Cox regression model was used for data reduction and feature selection. The baseline variables of the training cohort were used to construct nomograms based on univariate and multivariate Cox models. The index of concordance (C-index), time-dependent receiver operating characteristic (ROC) curves, time-dependent area under curve (AUC) and calibration curves were used to evaluate the discrimination and calibration of the nomograms, and decision curve analysis (DCA) was used to evaluate the net benefit of the nomograms. The relative integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated to evaluate the improvement in predictive accuracy of our new model compared with the AJCC staging system. Finally, the relationship between CONUT, PNI, NLPR and AISI and prognostic survival was explored according to risk plot, time-dependent AUC, Kaplan-Meier and restricted cubic spline (RCS).

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RESULTS

Based on the multivariate analysis for OS in the training cohort, nomograms with 9 variables, including CONUT, NLPR, and AISI, were established. Time-dependent ROC, time-dependent AUC, calibration curves, and DCA showed that the 1-year, 2-years, and 3-years OS and PFS probabilities predicted by the nomograms were consistent with the actual observations. The C-index, NRI, and IDI of the nomograms showed better performance than the AJCC staging system alone. Moreover, risk plot, time-dependent AUC, and Kaplan–Meier showed that higher CONUT, NLPR, and AISI scores and lower PNI were associated with poorer prognosis, and there was a nonlinear relationship between them and survival risk.

CONCLUSION

CONUT, NLPR and AISI can be used as clinical prognostic indicators for EC patients. In addition, the nomogram models, including CONUT, NLPR, and AISI, have better prognostic value than the AJCC staging system alone, which is helpful to guide the clinical decision-making of EC patients to adjust the treatment plan and follow-up strategy.

KEYWORDS

Esophageal cancer; Aggregate index of systemic inflammation; Neutrophil-to-lymphocyte * platelet ratio; Controlled nutritional status score; Overall survival; Progression-free survival; Nomogram; Restricted cubic spline

ABBREVIATIONS

CONUT	:	Controlling Nutritional Status
PNI	:	Prognostic Nutritional Index
NLPR	:	Neutrophil-To-Lymphocyte * Platelet Ratio
AISI	:	Aggregate Index of Systemic Inflammation
OS	:	Overall Survival
PFS	:	Progression Free Survival
EC	:	Esophageal Cancer
AJCC	:	American Joint Committee on Cancer
C-index	:	Index of Concordance
ROC	:	Receiver Operating Characteristic
DCA	:	Decision Curve Analysis
IDI	:	Integrated Discrimination Improvement
NRI	:	Net Reclassification Improvement
RCS	:	Restricted Cubic Spline
RS	:	Radical Surgery
CTCs	:	Circulating Tumor Cells
EMT	:	Epithelial Mesenchymal Transition

INTRODUCTION

EC is the seventh most common malignant tumor in the world and the fourth leading cause of cancer-related death in China [1]. Due to the lack of typical symptoms, it is often at an advanced stage when initially diagnosed. Despite advances in neoadjuvant chemotherapy and adjuvant chemoradiotherapy, the prognosis of patients with EC

remains poor, and surgery remains the most important treatment [2-4]. Although the AJCC staging system is valuable in predicting prognosis and determining treatment strategies, patients with the same tumor stage may experience completely different disease progression. Therefore, it is still necessary to find more valuable prognostic factors in EC.

An increasing number of studies have shown that the nutritional status of patients is an important factor in determining the success or failure of cancer treatment [5]. The systemic nutritional status is an important component of the tumor microenvironment and plays an important role in tumor growth, progression and metastasis [6]. Patients with malignant tumors are often malnourished due to poor appetite, the consumption of nutrients by the tumor, adverse treatment reactions and other reasons [7,8]. Malnutrition further reduces tolerance to treatment and ultimately affects recurrence and survival, leading to death [9,10]. In addition, malnutrition may affect the quality of life of patients with malignant tumors [11]. Therefore, strategies to improve the nutritional status of patients with malignant tumors are urgently needed. As the first step in screening nutritional status screening, the PNI and CONUT are particularly important for evaluating the nutritional status of tumor patients [12].

According to recent studies, the preoperative inflammatory response may be related to tumor progression and metastasis and has important predictive and prognostic value for various types of cancer [13,14]. Systemic inflammatory markers, such as the NLPR and AISI [15], have been proposed to reflect the balance between cells promoting tumor inflammation and cells with antitumor immune functions (such as cytotoxic T lymphocytes), which are equal to certain specific markers of the host immune status.

In recent years, nomograms have been widely used in oncology as a method with high accuracy for survival [16-19]. Favorable prognostic models based on nomograms have been constructed for several cancers, including breast [20], prostate [21], colon [22], and intrahepatic cholangiocarcinoma [23]. For the first time, we developed and validated a nomogram combining CONUT, NLPR, AISI, clinicopathological variables, and hematologic indicators to predict 1-year, 2-years, and 3-years OS and PFS in EC patients and compared its prognostic value with the AJCC staging system. The results of this study may provide clinicians with more personalized and comprehensive information prospects.

MATERIALS AND METHODS

Study Population

A total of 647 EC patients who received radical surgery (RS) for the first time at The First Affiliated Hospital of Zhengzhou University from August 5, 2012, to August 1, 2017, were enrolled. At the same time, the clinical data of the patients were collected, including age, sex, blood test results (blood routine, blood coagulation, inflammatory markers, liver function test, etc.) One week before RS, postoperative pathological examination results (tumor location and size, histological type and grade, etc.), and postoperative adjuvant therapy.

The exclusion criteria were as follows: (1) Perioperative death occurred; (2) Lost to follow-up; (3) Received radiotherapy; (4) Complicated with infection, autoimmune diseases and blood system-related diseases; (5) Complicated with other malignant tumors within 5 years; and (6) Received emergency surgery.

Follow-Up

All patients were followed according to the standard schedule after the EC operation. The patients were followed up every 3 months - 4 months for 2 years, including chest CT, routine blood tests and tumor marker

analysis. The patients were followed up every 6 months after 2 years until 5 years after the operation. Enhanced CT and gastroscopy of the chest, abdomen and pelvis were performed once a year. The last follow-up time was January 1, 2022.

Definition

The clinicopathological stages were classified in accordance with the eighth edition of the AJCC TNM staging system. Tumor size was defined as the maximum diameter of postoperative gross pathology. RS was defined as complete resection with a negative margin under a microscope. OS was defined as the time interval from the date of the operation to the date of death from any cause. PFS was defined as the period from the date of randomization to the earliest date of disease recurrence, namely, local recurrence or distant metastasis.

Calculation

The following calculations were performed: PNI = 10 × albumin concentration (g/L) + 0.005 × lymphocyte count (/mm^3); NLPR = neutrophil/ (lymphocyte × platelet) count; and AISI = (neutrophil × platelet × monocyte)/ lymphocyte count. In addition, the method used to calculate the CONUT score is shown in detail in Table 1.

Parameters	Normal	Mild	Moderate	Severe
ALB (g/L)	≥35.00	34.90-30.00	29.90-25.00	< 25.00
Score	0	2	4	6
T-CHO (mg/dL)	≥180.00	140.00-179.99	100.00-139.99	< 100.00
Score	0	1	2	3
Lymph (×109/L)	≥1.60	1.20-1.59	0.80-1.19	< 0.80
Score	0	1	2	3

Table 1: CONUT scoring criteria.

Study Design and Statistical Analysis

The study design is shown in Figure 1. The patient cohort of The First Affiliated Hospital of Zhengzhou University was used as the training cohort to construct nomogram models including CONUT, NLPR and AISI, and the internal validation of the model was carried out in the training cohort.

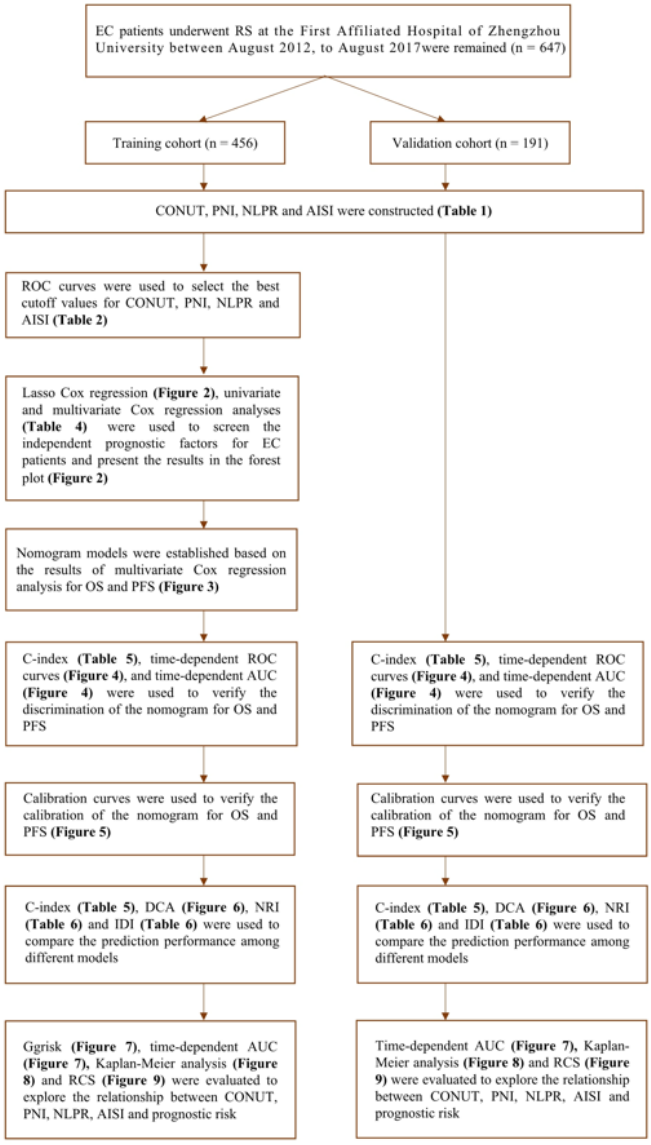

Figure 1: Flow chart of the study design.

In the training cohort, the ROC curves and the maximum value of Youden index (Youden index = sensitivity + specificity -1) were used to determine the best thresholds of CONUT, PNI, NLPR, AISI and other detection indicators to predict OS. The factors with $P < 0.05$ were further included in the multivariate Cox regression analysis to screen the independent risk factors related to survival. Multivariate Cox regression was performed using the mixed, forward, backward, and stepwise methods, and the

AIC values of the four models were calculated and compared using ANOVA. Finally, factors with a $P < 0.05$ in multivariate analysis were selected to construct two nomogram models based on OS and PFS.

Subsequently, the internal validation of the model and the comparison between the models were carried out. The C-index, time-dependent ROC and time-dependent AUC were used to evaluate the discrimination ability. If the C-index and AUC values were between 0.5-0.6, 0.6-0.7 or greater than 0.8, the prediction performance of the model was considered to be poor, fair or good, respectively. Calibration curves were used to evaluate the calibration ability (1000 bootstrap resampling times), and the 45-degree line was used as the optimal model to compare the predictive ability of the nomograms for 1-year, 2-years, and 3-years OS and PFS with the actual OS and PFS. At the same time, DCA assessed the net benefit of the nomograms in a clinical context. The clinical benefit and utility of the NRI and IDI in evaluating the nomogram models compared with AJCC TNM staging alone further demonstrated the superiority of our models. If NRI >0, it indicated positive improvement, indicating that the predictive ability of the new model was improved compared with that of the old model. If NRI <0, it indicates a negative improvement, indicating a decrease in the predictive power of the new model.

Risk plot was used to show the differences in the distribution of population proportion, survival time and research indicators between the high- and low- risk groups. Time-dependent AUC was used to assess the effect of variables changing over time on survival and recurrence. Kaplan–Meier analysis was used to describe the distribution of OS and PFS between the high and low groups, and the log rank test was used to compare the differences in OS and PFS between the two groups. We are also flexitively modeled the association between CONUT, PNI, NLPR, and AISI, and the risk of death and recurrence using RCS with four nodes at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles.

SPSS 26.0 and RStudio 4.2.1 software were used for data analyses. The differences between the two groups were compared, and the categorical variables were compared by $\chi 2$ test. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Study Population Characteristics

According to the inclusion criteria, 647 EC patients were finally included. The included data were randomly divided into a training cohort (n = 456) and a validation cohort (n = 191) at a ratio of 7:3. The median follow-up time was 25.330 months, 24.900 months in the training cohort and 25.600 months in the validation cohort.

The optimal sensitivity, specificity and cutoff values for CONUT, PNI, NLPR, AISI and other indexes were obtained by performing an ROC curve analysis, and these data are shown in detail in Table 2. Then, we divided the aforementioned indicators into high and low groups according to the cutoff values for each variable.

The patients were mainly <65-years old, male, without neoadjuvant therapy, without comorbidities, treated with chemotherapy, pathological grade II, Tis+T1+T2 stage, N0+N1 stage, M0 stage, lower esophagus, without vascular invasion, without nerve invasion, and with a tumor size ≥3 cm. Table 3 summarizes the demographic and clinicopathological characteristics of these EC patients. In the whole population, training cohort and validation cohort, there were no significant differences in demographic and clinical characteristics between the training cohort and validation cohort, which were comparable ($P > 0.05$).

Parameters	Cutoff value	Sensitivity	Specificity	AUC	95% CI	P value
CONUT	3.5	0.552	0.98	0.786	0.739 ~ 0.834	< 0.001
PNI	56.925	0.88	0.695	0.8	0.757 ~ 0.844	< 0.001
NLPR	0.007	0.682	0.9	0.821	0.778 ~ 0.864	< 0.001
AISI	199.604	0.596	1	0.803	0.758 ~ 0.848	< 0.001
RBC (×1012/L)	4.056	0.96	0.515	0.711	0.652 ~ 0.769	< 0.001
Hct (L/L)	0.358	0.638	0.98	0.865	0.826 ~ 0.904	< 0.001
WBC (×109/L)	6.305	0.382	0.7	0.511	0.428 ~ 0.594	0.798
Neut (×109/L)	3.215	0.628	0.94	0.798	0.750 ~ 0.845	< 0.001
Mono (×109/L)	0.405	0.645	0.88	0.787	0.739 ~ 0.834	< 0.001
PDW (fL)	14.9	0.581	1	0.768	0.722 ~ 0.815	< 0.001
Pct (%)	0.216	0.323	0.86	0.572	0.491 ~ 0.652	0.098
MPV (fL)	9.75	0.318	0.84	0.582	0.500 ~ 0.664	0.057
TP (g/L)	65.85	0.98	0.581	0.769	0.722 ~ 0.816	< 0.001
GLOB (g/L)	24.25	0.635	0.96	0.794	0.751 ~ 0.837	< 0.001
PA (mg/L)	208.5	0.579	0.82	0.709	0.639 ~ 0.780	< 0.001
LDL (mmol/L)	2.535	0.618	0.92	0.75	0.697 ~ 0.802	< 0.001
Fib (g/L)	3.085	0.608	0.98	0.819	0.775 ~ 0.863	< 0.001
PCT (ng/mL)	0.022	0.904	0.8	0.779	0.687 ~ 0.872	< 0.001
TAP (μm2)	114.048	0.788	1	0.863	0.831 ~ 0.896	< 0.001
Hb (g/L)	126.5	0.82	0.463	0.632	0.567 ~ 0.696	< 0.001
CRP (mg/L)	0.91	0.869	0.64	0.807	0.746 ~ 0.868	< 0.001
RDW (%)	13.4	0.594	0.9	0.711	0.649 ~ 0.774	< 0.001

Table 2: Diagnostic value of parameters.

Variables	Whole population	Training cohort	Validation cohort	P value
	[cases (%)]	[cases (%)]	[cases (%)]	
Age (y)				0.146
< 65	368 (56.9)	251 (55.0)	117 (61.3)	
≥ 65	279 (43.1)	205 (45.0)	74 (38.7)	
Sex				0.239
Female	212 (32.8)	143 (31.4)	69 (36.1)	
Male	435 (67.2)	313 (68.6)	122 (63.9)	
Neoadjuvant therapy				0.808
No	511 (79.0)	359 (78.7)	152 (79.6)	
Yes	136 (21.0)	97 (21.3)	39 (20.4)	
Comorbidity				0.831
No	451 (69.7)	319 (70.0)	132 (69.1)	
Yes	196 (30.3)	137 (30.0)	59 (30.9)	
Treatment methods				0.11
NC	90 (13.9)	55 (12.1)	35 (18.3)	
Chemotherapy	419 (64.8)	302 (66.2)	117 (61.3)	
Combination therapy	138 (21.3)	99 (20.4)	39 (21.7)	
Histologic subtypes				0.853
ESCC	608 (94.0)	428 (93.9)	180 (94.2)	
Others	39 (6.0)	28 (6.1)	11 (5.8)	
Histologic grade				0.618
III	141 (21.8)	97 (21.3)	44 (23.0)	
II	337 (52.1)	235 (51.5)	102 (53.4)	
I	169 (26.1)	124 (27.2)	45 (23.6)	
T stage				0.955
Tis+T1+T2	350 (54.1)	247 (54.2)	103 (53.9)	
T3+T4	297 (45.9)	209 (45.8)	88 (46.1)	
N stage				0.745
N0+N1	551 (85.2)	387 (84.9)	164 (85.9)	
N2+N3	96 (14.8)	69 (15.1)	27 (14.1)	
M stage				0.956
M0	640 (98.9)	451 (98.9)	189 (99.0)	
M1	7 (1.1)	5 (1.1)	2 (1.0)	

Tumor location				0.249
Upper	123 (19.0)	92 (20.2)	31 (16.2)	
Middle	219 (33.8)	146 (32.0)	73 (38.2)	
Lower	305 (47.1)	218 (47.8)	87 (45.5)	
Vascular invasion				0.944
No	516 (79.8)	364 (79.8)	152 (79.6)	
Yes	131 (20.2)	92 (20.2)	39 (20.4)	
Nerve invasion				0.417
No	550 (85.0)	391 (85.7)	159 (83.2)	
Yes	97 (15.0)	65 (14.3)	32 (16.8)	
Tumor size (cm)				0.22
< 3	281 (43.4)	191 (41.9)	90 (47.1)	
≥ 3	366 (56.6)	265 (58.1)	101 (52.9)	
CONUT				0.785
< 3.500	330 (51.0)	231 (50.7)	99 (51.8)	
≥ 3.500	317 (49.0)	225 (49.3)	92 (48.2)	
PNI				0.584
< 56.925	400 (61.8)	285 (62.5)	115 (60.2)	
≥ 56.925	247 (38.2)	171 (37.5)	76 (39.8)	
NLPR				0.912
< 0.007	246 (38.0)	174 (38.2)	72 (37.7)	
≥ 0.007	401 (62.0)	282 (61.8)	119 (62.3)	
AISI				0.514
< 199.604	309 (47.8)	214 (46.9)	95 (49.7)	
≥ 199.604	338 (52.2)	242 (53.1)	96 (50.3)	
RBC (×1012/L)				0.164
< 4.056	288 (44.5)	211 (46.3)	77 (40.3)	
≥ 4.056	359 (55.5)	245 (53.7)	114 (59.7)	
Hct (L/L)				0.633
< 0.358	282 (43.6)	196 (43.0)	86 (45.0)	
≥ 0.358	365 (56.4)	260 (57.0)	105 (55.0)	
WBC (×109/L)				0.433
< 6.305	412 (63.7)	286 (62.7)	126 (66.0)	
≥ 6.305	235 (36.3)	170 (37.3)	65 (34.0)	
Neut (×109/L)				0.909
< 3.215	280 (43.3)	198 (43.4)	82 (42.9)	
≥ 3.215	367 (56.7)	258 (56.6)	109 (57.1)	
Mono (×109/L)				0.688
< 0.405	270 (41.7)	188 (41.2)	82 (42.9)	
≥ 0.405	377 (58.3)	268 (58.8)	109 (57.1)	
PDW (fL)				0.918
< 14.900	313 (48.4)	220 (48.2)	93 (48.7)	
≥ 14.900	334 (51.6)	236 (51.8)	98 (51.3)	
Pct (%)				0.297
< 0.216	459 (70.9)	318 (69.7)	141 (73.8)	
≥ 0.216	188 (29.1)	138 (30.3)	50 (26.2)	
MPV (fL)				0.162
< 9.750	463 (71.6)	319 (70.0)	144 (75.4)	
≥ 9.750	184 (28.4)	137 (30.0)	47 (24.6)	
TP (g/L)				0.783
< 65.850	334 (51.6)	237 (52.0)	97 (50.8)	
≥ 65.850	313 (48.4)	219 (48.0)	94 (49.2)	
GLOB (g/L)				0.183
< 24.250	289 (44.7)	196 (43.0)	93 (48.7)	
≥ 24.250	358 (55.3)	260 (57.0)	98 (51.3)	
PA (mg/L)				0.232
< 208.500	291 (45.0)	212 (46.5)	79 (41.4)	
≥ 208.500	356 (55.0)	244 (53.5)	112 (58.6)	
LDL (mmol/L)				0.15
< 2.535	297 (45.9)	201 (44.1)	96 (50.3)	
≥ 2.535	350 (54.1)	255 (55.9)	95 (49.7)	

Fib (g/L)				0.915
< 3.085	296 (45.7)	208 (45.6)	88 (46.1)	
≥ 3.085	351 (54.3)	248 (54.4)	103 (53.9)	
PCT (ng/mL)				0.181
< 0.022	104 (16.1)	79 (17.3)	25 (13.1)	
≥ 0.022	543 (83.9)	377 (82.7)	166 (86.9)	
TAP (μm2)				0.355
< 114.048	200 (30.9)	136 (29.8)	64 (33.5)	
≥ 114.048	447 (69.1)	320 (71.6)	127 (66.5)	
Hb (g/L)				0.757
< 126.500	277 (42.8)	197 (43.2)	80 (41.9)	
≥ 126.500	370 (57.2)	259 (56.8)	111 (58.1)	
CRP (mg/L)				0.292
< 0.910	114 (17.6)	85 (18.6)	29 (15.2)	
≥ 0.910	533 (82.4)	371 (81.4)	162 (84.8)	
RDW (%)				0.811
< 13.400	296 (45.7)	210 (46.1)	86 (45.0)	
≥ 13.400	351 (54.3)	246 (53.9)	105 (55.0)	

Table 3: Demographic and clinical characteristics of patients with EC. (n = 647).

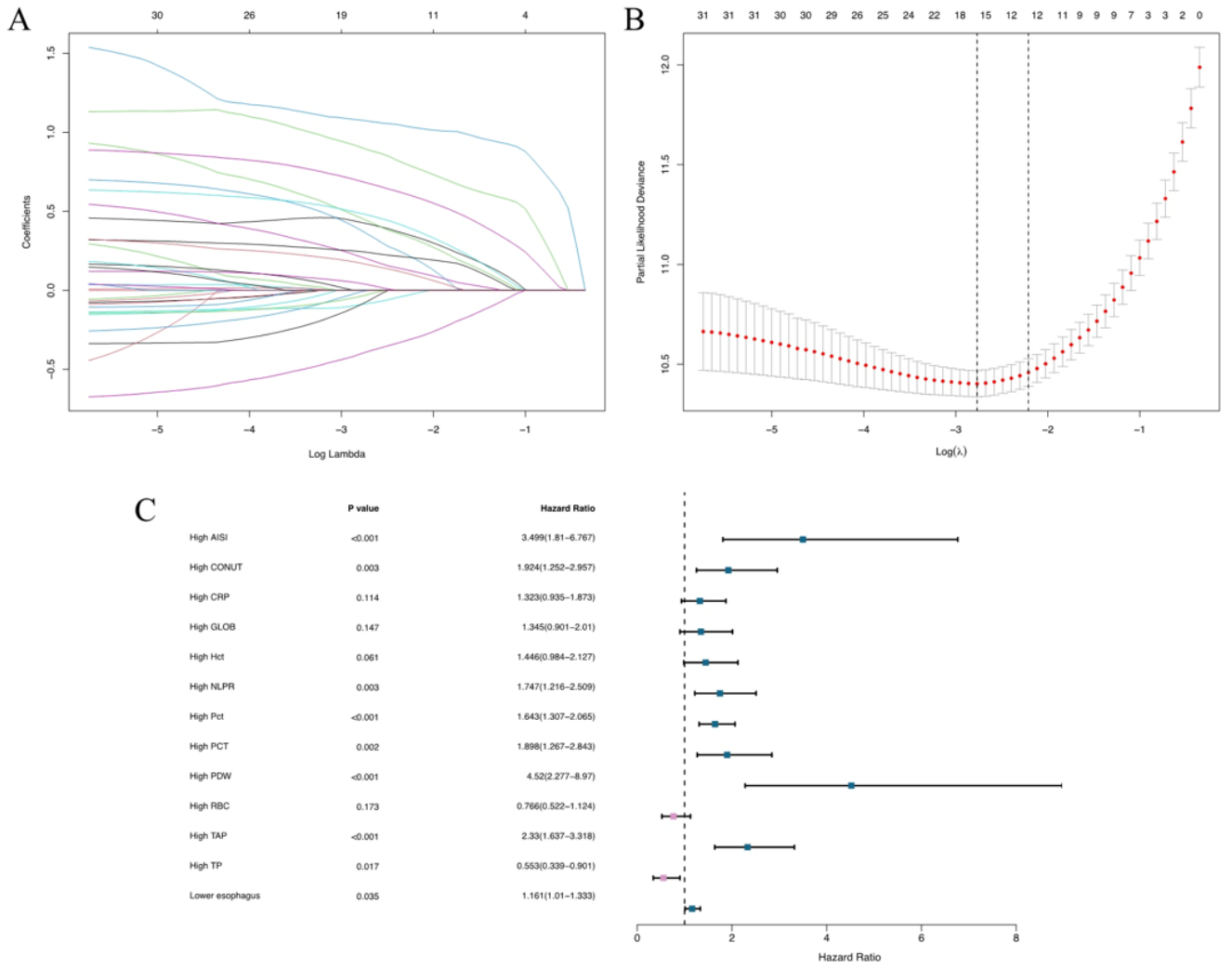

Figure 2: A,B) Determination of the number of factors by the LASSO analysis; **C)** The forest plot of the HR of high CONUT, NLPR, and AISI with OS in patients with EC.

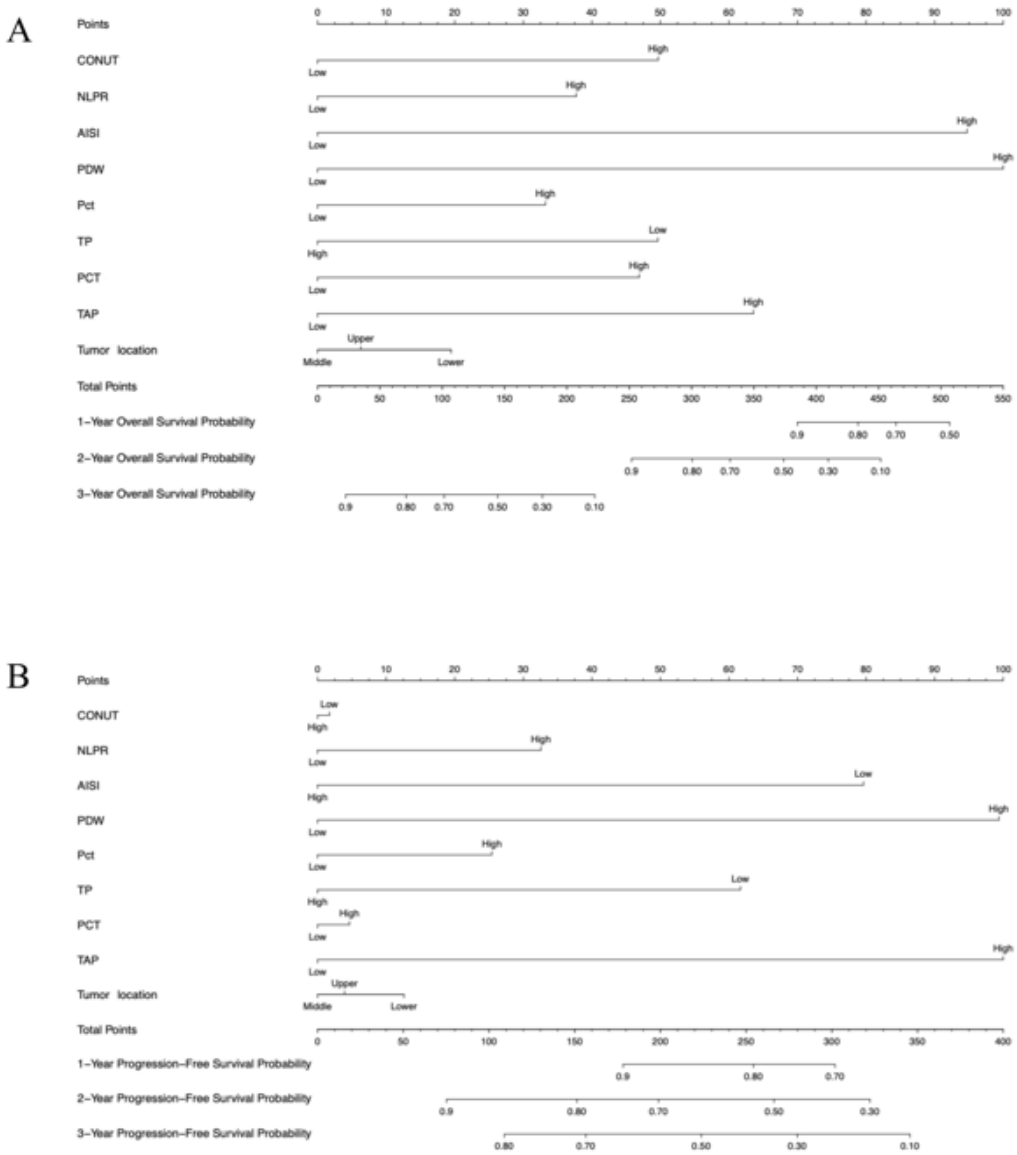

Figure 3: Nomogram models of EC patients: **A)** For predicting the 1-year, 2-years, and 3-years OS rates and **B)** 1-year, 2-years, and 3-years PFS rates. To predict the 1-year, 2-years, and 3-years OS and PFS rates of EC patients, locate the patient's AISI on the "AISI" axis. Draw a straight line up to the "point" axis to determine the points for "AISI". Repeat the process for each of the remaining axes, drawing a straight line each time to the "point" axis. Add the points received from each variable and locate this point on the "total point" axis. A straight line is drawn down from the "total point" axis to the "1-year OS and PFS", "2-years OS and PFS", and "3-years OS and PFS" axis to determine the 1-year, 2-years, and 3-years OS and PFS rates of EC patients.

Univariate and Multivariate Cox Regression Analyses

Through the LASSO Cox regression model (Figure 2), 16 indicators related to OS were screened and put into the univariate Cox regression model. Univariate Cox regression analysis showed that tumor location, CONUT, NLPR, AISI, RBC, Hct, PDW, Pct, TP, GLOB, PCT, TAP, and CRP were associated with OS ($P < 0.05$). The above indicators were included in the multivariate Cox regression analysis, which was performed using the mixed regression method, forward regression method, backward regression method and stepwise method, and the AIC values of the four models were 3693.035, 3693.035, 3692.968 and 3692.968, respectively. The ANOVA function showed that there was no difference among the four multivariate Cox regression models ($P \geq 0.05$). The results showed the hazard

rate (HR). A forest plot was generated to visualize the results of the multivariate Cox regression analysis (Figure 2).

Nomogram Establishment

According to the analysis of the multivariate Cox regression model, we found that 9 factors exerted significant effects on OS, and thus, we used these variables to build nomograms. These nomograms were then used to assess the risk of death (Figure 3) and recurrence (Figure 3) at 1-year, 2-years and 3-years after RS. From the nomograms, we found that NLPR, AISI, PDW, and TAP were the main factors affecting the prognosis. Among these significant independent variables, each subtype was assigned a score on the rating scale. The total score of the independent prognostic factors projected to the lowest level represents the probabilities of 1-year, 2-years, and 3-year OS and PFS. Generally, the higher the total score of the nomogram was, the greater the risk of recurrence was.

Nomogram Validation and Evaluation

The C-index, time ROC, and time-dependent AUC were used to evaluate the discrimination of the nomograms. The C-indexes based on OS and PFS were 0.824 and 0.708 in the training cohort, and 0.799 and 0.692 in the validation cohort, respectively (Table 5). The AUCs of 1-year, 2-years, and 3-years OS and PFS in the training group were 0.864, 0.980, and 0.915 (Figure 4A) and 0.745, 0.756, and 0.728 (Figure 4C), respectively, and those in the validation group were 0.810, 0.985, and 0.924 (Figure 4B) and 0.743, 0.784, and 0.687 (Figure 4D), respectively. The time-dependent AUCs for predicting OS over 8 years were all >0.8 (Figure 4E and Figure 4F), and those for PFS were >0.7 (Figure 4G and Figure 4H), indicating favorable discrimination of the nomograms.

The nomograms were internally validated by 1000 bootstrap resamples. Calibration curves showed admirable agreement between the predicted and actual 1-year, 2-years, and 3-years OS and PFS probabilities (Figure 5).

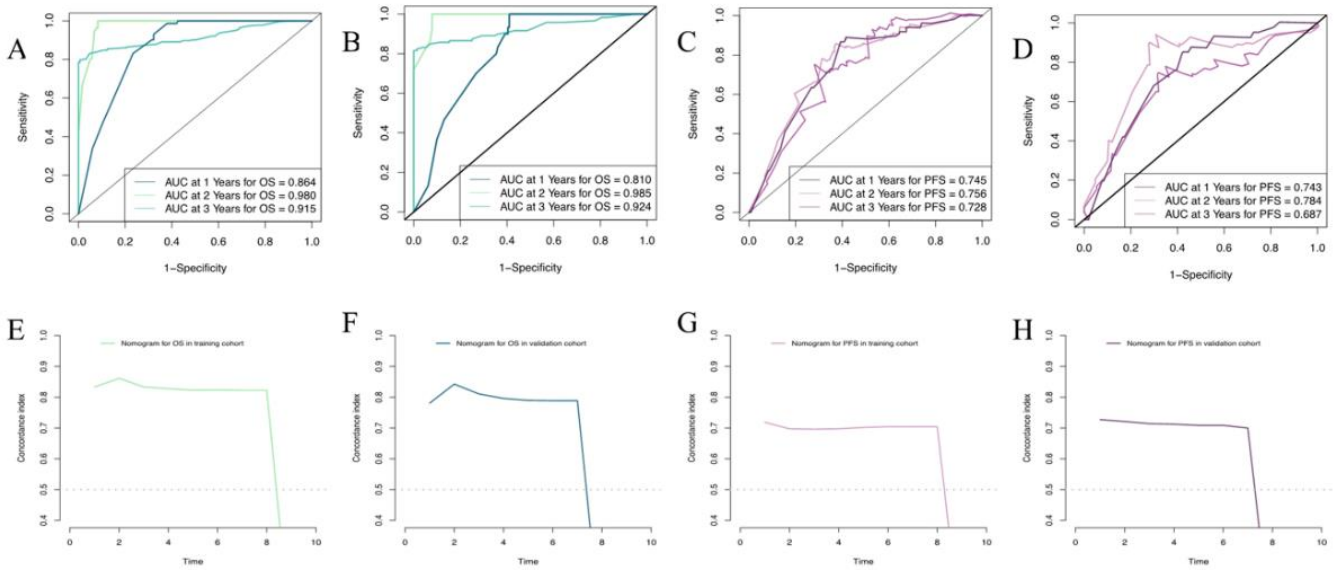

Figure 4: The prognostic performance of nomograms in patients with EC. The time-dependent ROC curves of nomograms: **A)** For OS in training cohort; **B)** For OS in validation cohort; **C)** For PFS in training cohort; **D)** For PFS in validation cohort. The time-dependent AUC curves of nomograms **E)** For OS in training cohort; **F)** For OS in validation cohort; **G)** For PFS in training cohort; **H)** For PFS in validation cohort.

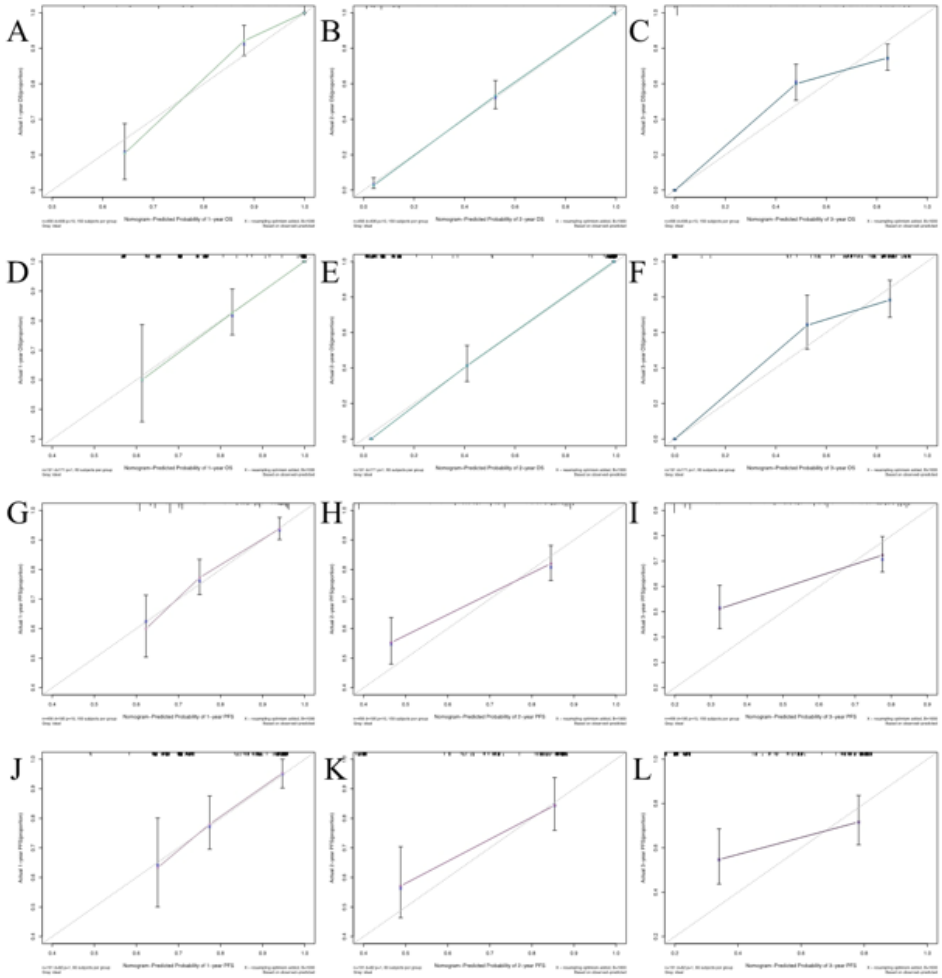

Figure 5: Calibration curves of nomograms. Calibration curves of the nomogram in training cohort: **A)** 1-year OS, **B)** 2-years OS, **C)** 3-years OS; Calibration curves of the nomogram in validation cohort: **D)** 1-year OS, **E)** 2-years OS, **F)** 3-years OS; Calibration curves of the nomogram in training cohort: **G)** 1-year PFS, **H)** 2-years PFS, **I)** 3-years PFS; Calibration curves of the nomogram in validation cohort: **J)** 1-year PFS, **K)** 2-years PFS, **L)** 3-years PFS. The X-axis represents the model-predicted survival, and the Y-axis represents actual survival. The bar represents 95% CI measured by Kaplan-Meier analysis, and the dotted line represents the ideal reference line.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (y)	1.054	0.78 ~ 1.154	0.599			
T stage	1.093	0.752 ~ 1.113	0.374			
Tumor location	0.837	1.05 ~ 1.358	0.007	1.161	1.010 ~ 1.333	0.035
CONUT	0.079	9.825 ~ 16.297	< 0.001	1.924	1.252 ~ 2.957	0.003
NLPR	0.187	4.277 ~ 6.700	< 0.001	1.747	1.216 ~ 2.509	0.003
AISI	0.032	22.448 ~ 43.635	< 0.001	3.499	1.810 ~ 6.767	< 0.001
RBC (×1012/L)	8.319	0.095 ~ 0.152	< 0.001	0.766	0.522 ~ 1.124	0.173
Hct (L/L)	0.158	5.059 ~ 7.877	< 0.001	1.446	0.984 ~ 2.127	0.061
WBC (×109/L)	0.856	0.956 ~ 1.428	0.128			
PDW (fL)	0.049	15.236 ~ 27.064	< 0.001	4.52	2.277 ~ 8.970	< 0.001
Pct (%)	0.484	1.672 ~ 2.549	< 0.001	1.643	1.307 ~ 2.065	< 0.001
TP (g/L)	9.859	0.080 ~ 0.128	< 0.001	0.553	0.339 ~ 0.901	0.017
GLOB (g/L)	0.145	5.451 ~ 8.670	< 0.001	1.345	0.901 ~ 2.010	0.147
PCT (ng/mL)	0.195	3.658 ~ 7.190	< 0.001	1.898	1.267 ~ 2.843	0.002
TAP (μm2)	0.162	4.711 ~ 8.077	< 0.001	2.33	1.637 ~ 3.318	< 0.001
CRP (mg/L)	0.275	2.711 ~ 4.875	< 0.001	1.323	0.935 ~ 1.873	0.114

Table 4: Univariate and multivariate Cox analyses on variables for the prediction of OS of EC patients.

Parameters	Training cohort		Validation cohort	
	C-index	95% CI	C-index	95% CI
The nomogram for OS	0.824	0.808 ~ 0.840	0.799	0.774 ~ 0.824
The AJCC criteria-based tumor staging for OS	0.517	0.490 ~ 0.544	0.507	0.460 ~ 0.554
The nomogram for PFS	0.708	0.675 ~ 0.741	0.692	0.639 ~ 0.745
The AJCC criteria-based tumor staging for PFS	0.532	0.493 ~ 0.571	0.539	0.514 ~ 0.564

Table 5: C-index of the nomograms and AJCC criteria-based tumor staging alone in survival prediction for EC patients.

Clinical Value of the Nomograms Compared with AJCC Criteria-Based Tumor Staging

In the training cohort, both were based on OS (0.824 *vs.* 0.517) and PFS (0.708 *vs.* 0.532); In the validation cohort, the C-index of the nomograms was higher than that of the AJCC staging system alone, both based on OS (0.799 *vs.* 0.507) and PFS (0.692 *vs.* 0.539) (Table 4 and Table 5).

DCA validated the clinical value of the models and their impact on practical decision making. In both the training and validation cohorts, the net benefit of the nomograms was greater than that of the AJCC staging system for both OS and PFS (Figure 6), indicating a substantial net benefit of the nomogram in predicting survival at 1-year, 2-years, and 3-years.

In the training cohort, the NRIs for 1-year, 2-years, and 3-year OS were 0.541, 0.912, and 0.653, respectively, and those for PFS were 0.388, 0.536, and 0.283, respectively. The NRIs of 1-year, 2-years, and 3-years OS in the validation cohort were 0.509, 0.913, and 0.762, respectively, and those for PFS were 0.534, 0.649 and 0.227, respectively. Similarly, the IDIs for 1-year, 2-years, and 3-years OS were 0.206, 0.825, and 0.590, respectively, and those for PFS were 0.131, 0.301, 0.320, respectively. The IDIs of 1-year, 2-years, and 3-years OS in the validation cohort were 0.176, 0.828, and 0.646, respectively, and those for PFS were 0.138, 0.378 and 0.385, respectively. Therefore, the results of the IDI and NRI showed that the nomograms in this study had statistically higher predictive power for OS and PFS than the AJCC staging system (Table 6).

Index	Training cohort			Validation cohort		
	Estimate	95% CI	P value	Estimate	95% CI	P value
NRI (*vs.* the AJCC criteria-based tumor staging)						
For 1-year OS	0.541	0.407 ~ 0.741		0.509	0.295 ~ 0.971	
For 2-year OS	0.912	0.864 ~ 1.252		0.913	0.864 ~ 1.439	
For 3-year OS	0.653	0.490 ~ 0.804		0.762	0.610 ~ 0.899	
For 1-year PFS	0.388	0.260 ~ 0.730		0.534	0.062 ~ 0.819	
For 2-year PFS	0.526	0.312 ~ 0.833		0.649	0.254 ~ 1.365	
For 3-year PFS	0.283	0.154 ~ 0.549		0.227	0.019 ~ 0.985	
IDI (vs. the AJCC criteria-based tumor staging)						
For 1-year OS	0.206	0.128 ~ 0.273	< 0.001	0.176	0.107 ~ 0.308	< 0.001
For 2-year OS	0.825	0.769 ~ 0.867	< 0.001	0.828	0.691 ~ 0.886	< 0.001
For 3-year OS	0.59	0.515 ~ 0.658	< 0.001	0.646	0.534 ~ 0.742	< 0.001
For 1-year PFS	0.131	0.076 ~0.187	< 0.001	0.138	0.058 ~ 0.254	< 0.001
For 2-year PFS	0.301	0.211 ~ 0.398	< 0.001	0.378	0.233 ~ 0.515	< 0.001
For 3-year PFS	0.32	0.217 ~0.414	< 0.001	0.385	0.251 ~ 0.520	< 0.001

Table 6: NRI and IDI of the nomograms and AJCC criteria-based tumor staging alone in survival prediction for EC patients.

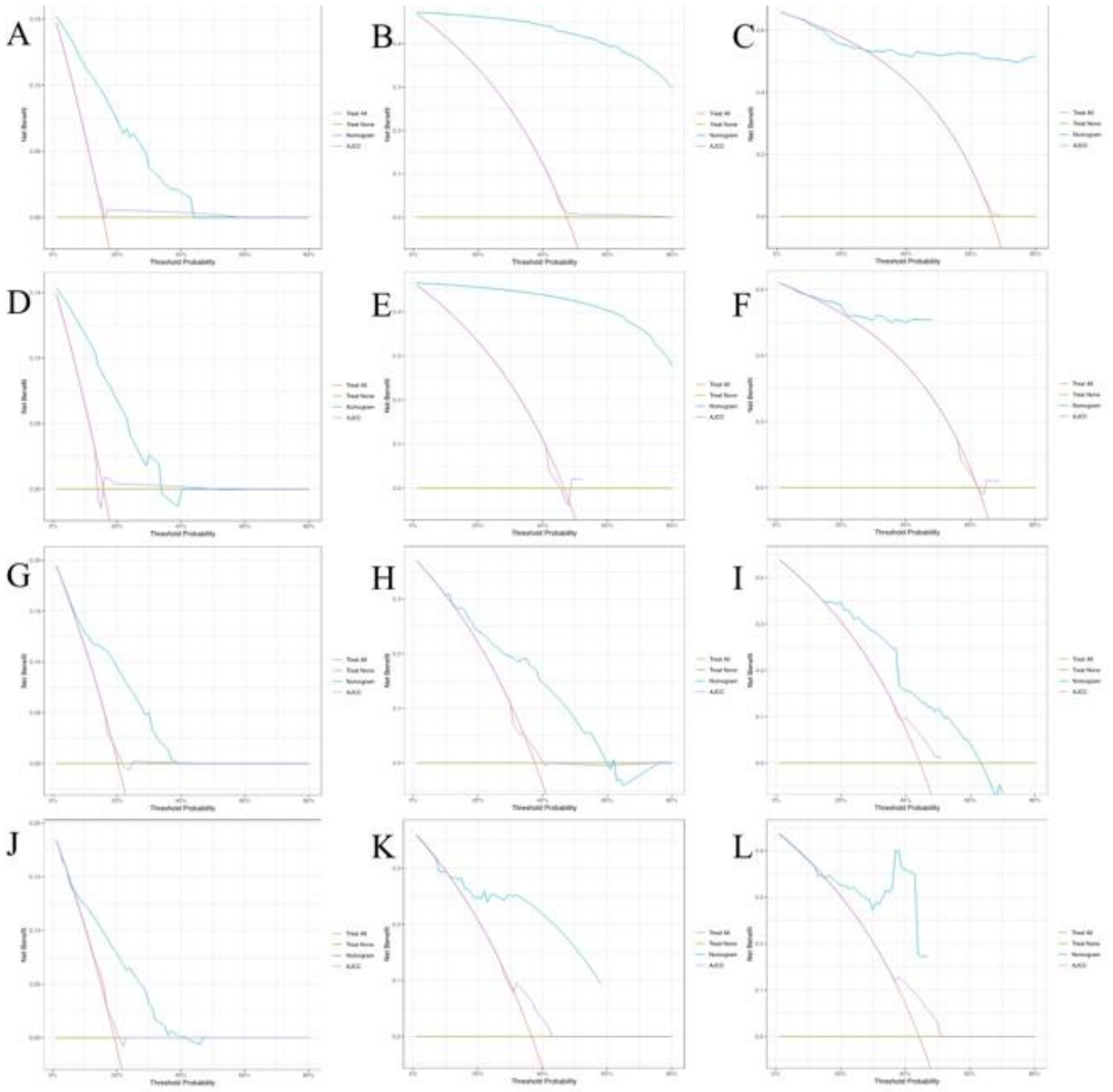

Figure 6: DCA curves of the nomograms and the AJCC criteria-based tumor staging. The DCA curves were plotted based on: **A)** 1-year OS, **B)** 2-years OS, **C)** 3-years OS in training cohort; **D)** 1-year OS, **E)** 2-years OS, **F)** 3-years OS in validation cohort; **G)** 1-year PFS, **H)** 2-years PFS, **I)** 3-years PFS in training cohort; **J)** 1-year PFS, **K)** 2-years PFS, **L)** 3-years PFS in validation cohort.

Survival Analyses

To further explore the influence of variables on EC prognosis, we plotted scatter plots of indicator expression in different samples along with corresponding OS (Figure 7).

For predicting OS over 7 years, the time-dependent AUCs of CONUT, PNI, NLPR and AISI were all >0.8 in both the training cohort (Figure 7D) and validation cohort (Figure 7E) and >0.7 in the training cohort (Figure 7F) and validation cohort (Figure 7G) for predicting PFS over 7 years.

By performing a Kaplan-Meier assessment, as was shown in Figure 8, we determined the relationship between CONUT, PNI, NLPR, and AISI and OS/PFS; Encouragingly, all results were statistically significant (P <0.001). For patients with lower CONUT, NLPR, and AISI

and a higher PNI, the survival curves were apparently better than those of patients with the opposite results.

Taking CONUT, PNI, NLPR and AISI as the variables of RCS, as shown in Figure 9, the nonlinear correlation P <0.001 of the above variables indicated that there were nonlinear relationships between them and the hazard ratios of OS and PFS.

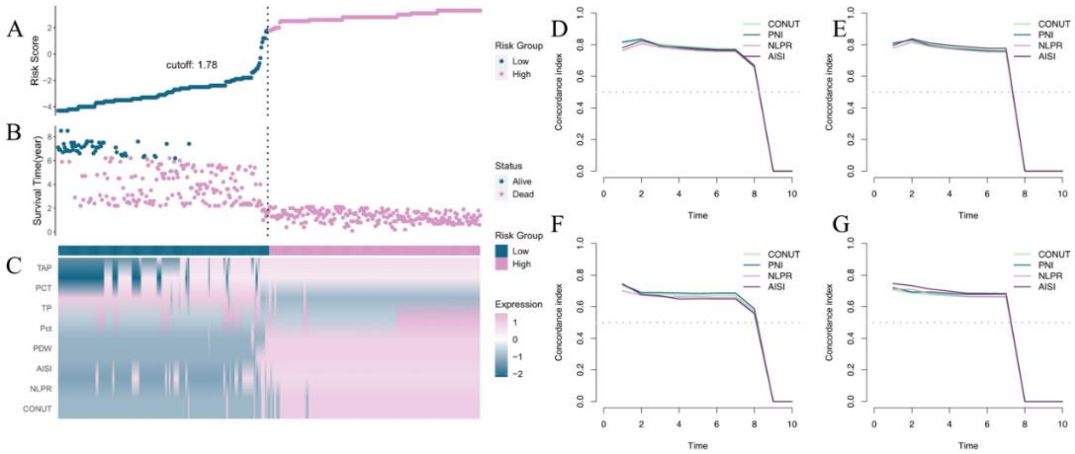

Figure 7: Relationship between the survival status/ risk score rank and survival time (year)/risk score rank and the prognostic performance of CONUT, PNI, NLPR, and AISI in patients with EC. **A)** The distribution of risk score; **B)** The survival duration and status of EC patients; **C)** A heatmap of CONUT, NLPR, and AISI in the classifier. The time-dependent AUC curves of CONUT, PNI, NLPR, and AISI; **D)** for OS in training cohort, **E)** for OS in validation cohort, **F)** for PFS in training cohort, **G)** for PFS in validation cohort.

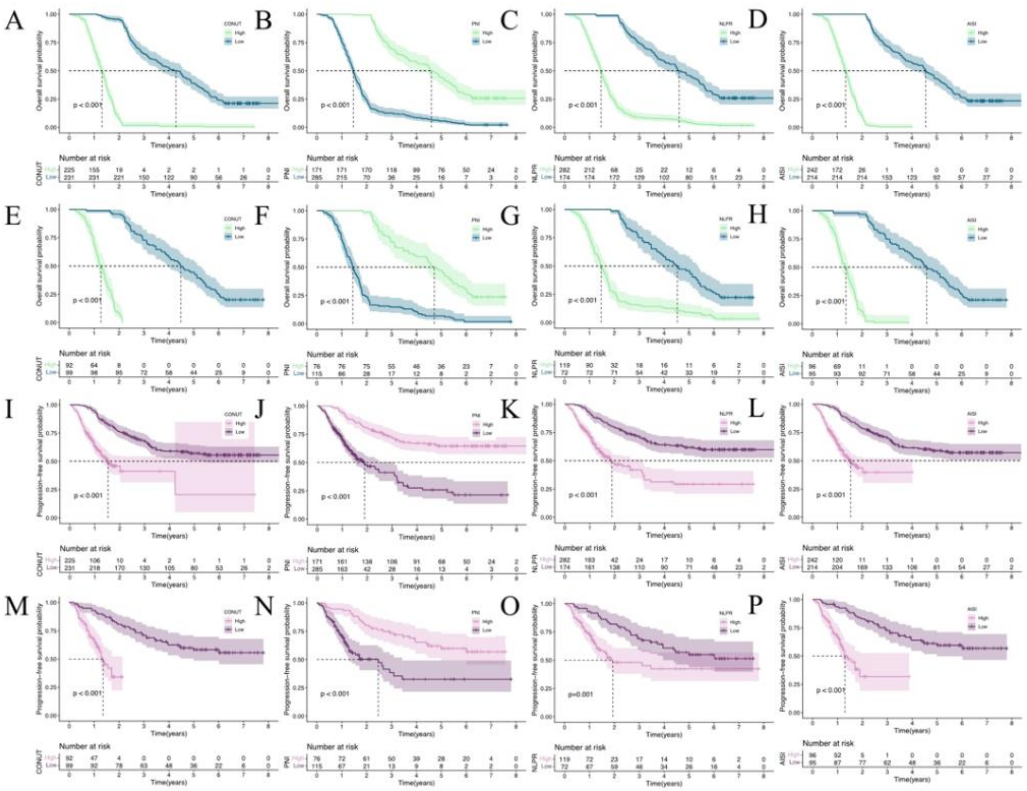

Figure 8: Kaplan-Meier curves for risk stratification. Kaplan-Meier plots for OS in training cohort between: **A)** CONUT, **B)** PNI, **C)** NLPR, **D)** AISI risk score groups; for OS in validation cohort between **E)** CONUT, **F)** PNI, **G)** NLPR, **H)** AISI risk score groups; for PFS in training cohort between **I)** CONUT, **J)** PNI, **K)** NLPR, **L)** AISI risk score groups; for PFS in validation cohort between **M)** CONUT, **N)** PNI, **O)** NLPR, **P)** AISI risk score groups.

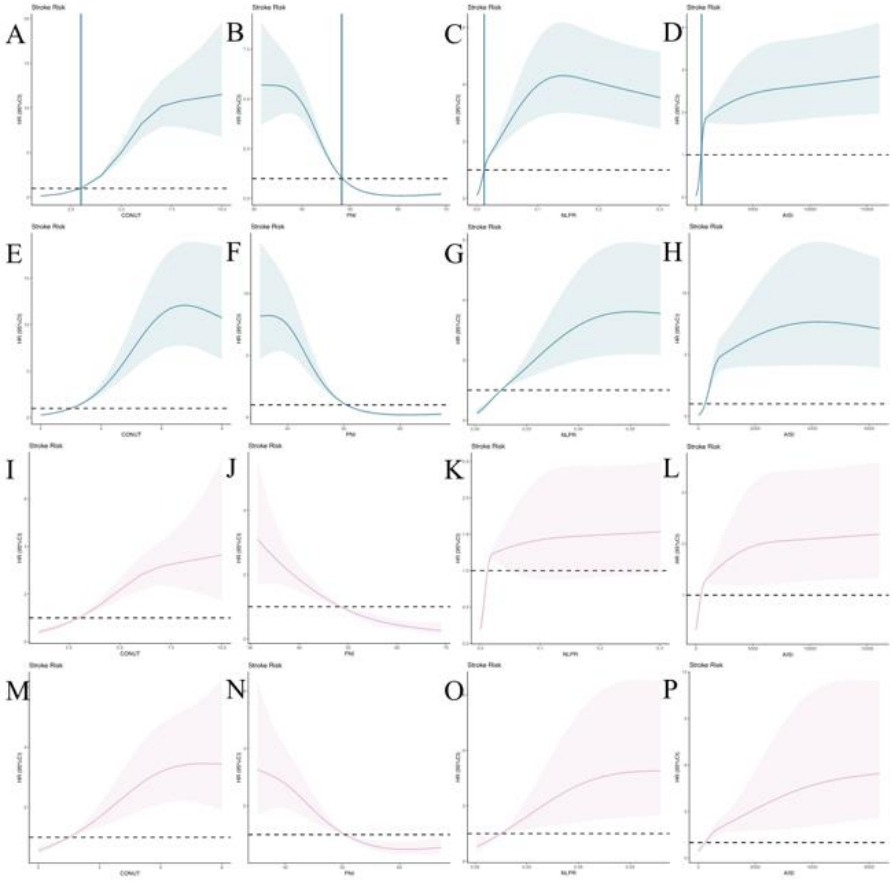

Figure 9: Association between CTC, INNS, TAP and HR for OS and PFS using RCS regression models in patients with EC. **A)** CONUT, **B)** PNI, **C)** NLPR, **D)** AISI and OS in training cohort; **E)** CONUT, **F)** PNI, **G)** NLPR, **H)** AISI and OS in validation cohort; **I)** CONUT, **J)** PNI, **K)** NLPR, **L)** AISI and PFS in training cohort; **M)** CONUT, **N)** PNI, **O)** NLPR, **P)** AISI and PFS in validation cohort. (Unadjusted covariable).

DISCUSSION

In this study, the data of 647 EC patients from The First Affiliated Hospital of Zhengzhou University were retrospectively analyzed. Cox regression analyses were used to screen 9 variables, including CONUT, NLPR, and AISI, to construct OS and PFS prediction models for EC patients, which were visualized as nomograms. The C-index, time-dependent ROC and time-dependent AUC were used to evaluate the performance of the nomograms, which showed that the models had favorable discrimination. The calibration curves of the new nomograms matched commendably with the standard curves in both the training and validation cohorts. In addition, the NRI and IDI at 1-year, 2-years, and 3-years showed a positive improvement effect of the nomograms, and the DCA curves showed that the nomograms produced a net benefit. Therefore, the models proposed in this study have good prediction accuracy and perform better than the traditional AJCC staging system due to the combination of CONUT, NLPR, AISI and traditional predictors. Because different patients have different clinicopathological characteristics, the prognosis prediction results of different patients by these models are not the same. Such a prediction shows that the results are undoubtedly very interesting and more convincing than simply telling the patient whether the risk of recurrence is "high" or "low" and, at the same time, can be used as an important reference for the subsequent development of personalized treatment options for the patients.

In the nomogram we constructed for OS, the weight of AISI was relatively high, and NLPR also had a significant effect. To date, few studies have confirmed that NLPR and

AISI are independent predictors of a poor prognosis for patients with EC. However, we explain the prognostic value of NLPR and AISI using the theories described below. First, the number of neutrophils increases in both the tumor microenvironment and the whole body, which is usually associated with a poor prognosis for patients with solid cancer [23]. As a component of the inflammatory response, neutrophils not only inhibit the immune system by inhibiting the cytolytic activity of immune cells (such as lymphocytes, activated T cells and natural killer cells) [24,25] but also activate endothelial cells and parenchymal cells to increase the adhesion of circulating tumor cells and promote distant metastasis [26]. Second, platelets may act as a protective "cloak" for circulating tumor cells (CTCs), protecting them from immune-mediated damage. Platelet and endothelial cell adhesion proteins may also promote metastasis by increasing tumor cell extravasation [27]. Third, lymphocytes secrete various cytokines, such as IFN-γ and TNF-α, to prevent tumor growth and improve the prognosis of patients with cancer [28]. In conclusion, NLPR and AISI should be objective indicators that reflect the balance between host inflammation and the immune response.

In addition, we could also see the value of CONUT in our prediction model. Recently, the CONUT score was reported to be a prognostic factor for the survival of patients with different types of cancer, including colorectal cancer [29,30], gastric cancer [31], EC [34,35], hepatocellular carcinoma [36], intrahepatic cholangiocarcinoma [37] and lung cancer [38]. Not surprisingly, the CONUT score can be used as a prognostic factor for the OS of patients with various types of cancer because its components reflect tumor progression. First, serum albumin is a marker of nutritional status and is reported to be associated with tumor necrosis because proinflammatory cytokines reduce albumin synthesis [39]. Second, the total cholesterol concentration is associated with tumor progression because tumor tissue reduces the plasma cholesterol concentration and calorie intake. Third, the total number of lymphocytes reflects the immune state. Due to the insufficient immune response of the host to cancer cells, a low peripheral blood lymphocyte count is related to a poor prognosis for patients with several cancers [40].

The significant influence of TAP and PDW in nomograms was evident, regardless of the prediction models based on OS or PFS. Most studies of the association between PDW and malignancy have shown that high PDW is significantly associated with poor prognosis [41-45]. PDW can sensitively reflect the changes in platelet volume associated with pseudopod formation and shape changes during platelet activation, and its elevation is considered an indicator of platelet activation [46]. Upon activation, platelets are able to release particles containing a variety of pro-tumor factors, which can promote tumor cell growth and proliferation, angiogenesis, and epithelial mesenchymal transition (EMT) [47,48]. Soviet scholars Kostyantin A and Galakhin discovered the TAP. In the process of metabolism, cancer cells can release complex abnormal glycoproteins and calcium histone proteins that constitute TAP [49]. In essence, TAP is the result of cancer cell glycosylation changes, which can indirectly reflect the amount and degree of cell cancerization. Upregulation of TAP expression has been observed in various tumor types, such as breast cancer, ovarian cancer, colon cancer, endometrial cancer, gastric cancer, and lung cancer [50-58]. TAP significantly affects the occurrence, development and metastasis of tumors, making it an important indicator of tumor prognosis. However, the role of TAP in the occurrence and development of ESCC remains unclear and needs further study. However, while these indicators are commonly measured in clinical examinations, they are often overlooked and deserve more attention given their importance in the aforementioned studies and the present results.

Our study has several limitations. First, this study was a retrospective study that only included two nutritional indexes and two inflammatory indexes. We did not further explore the pathways and molecular mechanism through which the nutritional and inflammatory factors indicated by peripheral blood CONUT, PNI, NLPR and AISI scores participate in the occurrence and development of EC. Second, this study was a small sample retrospective study, and a large-sample prospective study is needed for further exploration. Although we performed internal validation of the nomogram models, external validation in other populations is needed. Third, in similar studies, the cutoff values for CONUT, PNI, NLPR and AISI were different [59]. Although our findings were consistent with previous observations, our conclusions are not easy to verify in another independent cohort due to the lack of standardized cutoff values for these factors. The cutoff values of CONUT, PNI, NLPR and AISI determined by the highest Youden index were 3.500, 56.925, 0.007 and 199.604 in our study, respectively. Similarly, we can also calculate cutoff values by RCS, which were 3.000, 48.273, 0.012 and 486.181. According to the results, the cutoff values obtained by the two methods are not exactly the same. Therefore, we must conduct prospective studies to determine the appropriate threshold value. Fourth, cytogenetic research is currently at the forefront of the treatment of EC patients; however, obtaining cytogenetic data is not easy in our clinical practice and requires more input and support. Therefore, in further studies, we will consider this indicator and other factors to construct more advanced prediction models. In general, although this study has some similarities with previous studies, it is actually a continuation and sub distillation of previous studies and is also in line with the current research trend of constantly searching for new prognostic indicators to improve the predictive performance of models to provide accurate prognostic assessment and personalized treatment for patients.

CONCLUSION

In summary, we explored the prognostic value of CONUT, PNI, NLPR, and AISI in EC patients and explored their nonlinear relationships with survival and recurrence HR. In addition, nomogram models related to OS and PFS were established based on CONUT, NLPR, AISI and traditional classical predictors. With these models, we can predict EC patients' recurrence more accurately and better manage the prognosis of patients.

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AUTHORS' CONTRIBUTIONS

Study design: FW. Conducting the experiments: HKW and XL. Data collection: YLY. Data analysis: XL and JXX. Data interpretation: HKW. Drafting the manuscript: HKW and QW. FW takes full responsibility for the integrity of the data analysis. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

DECLARATIONS

Ethical Approval and Consent to Participate

The study followed the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Scientific Research and Clinical Trial of the First Affiliated Hospital of Zhengzhou University (Approval Identifier: KY-2022-0362). All patients provided written informed consent for the collection and publication of their medical information at the first visit to our center, which was filed in their medical records, and the ethics committees approved this consent procedure.

Consent for Publication

Consent to publish has been obtained from all authors.

Competing Interests

The authors have no competing interests to declare.

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