Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The Value of Preoperative Nutritional Status, the Systemic Inflammation Index and A Nomogram for the Prognosis of Patients with Esophageal Cancer After Radical Resection

Huike Wang
the First Affiliated Hospital of Zhengzhou University
Yalan Yang
the First Affiliated Hospital of Zhengzhou University
Xiangrui Meng
the First Affiliated Hospital of Zhengzhou University
Xi Luo
the First Affiliated Hospital of Zhengzhou University
Feng Wang (fengw010@163.com)
the First Affiliated Hospital of Zhengzhou University

Research Article

Keywords: Esophageal cancer, Control nutritional status score (CONUT), Prognostic nutritional index (PNI), Systemic immune-inflammation index (SII), Overall survival (OS), Progression-free survival (PFS), Nomogram.

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1431680/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Background

Controlling nutritional status (CONUT), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are new parameters that reflect the immune-nutritional status in some cancers.

Purpose

To investigate the relationship between preoperative nutritional status and systemic inflammatory indexes on the clinicopathological prognosis of patients with stage I-IV esophageal cancer and to clarify the predictive value of nutritional status and inflammatory indexes on tumor recurrence, metastasis and long-term survival after radical resection.

Methods

The clinical data of 381 patients who underwent radical esophagectomy at the First Affiliated Hospital of Zhengzhou University from August 5, 2013, to August 1, 2021, were analyzed retrospectively. The preoperative clinical characteristics and hematological examination results were collected, the data on nutritional and immune status were analyzed, tumor recurrence and survival were evaluated by telephone follow-up, and overall survival (OS) and progression-free survival (PFS) were calculated. Nutritional data and the immune status, clinical data and survival information were also analyzed.

Results

Analysis of the clinical data of 381 patients with esophageal cancer undergoing radical esophagectomy revealed that preoperative nutritional status was related to preoperative complications, neoadjuvant therapy, TNM stage, tumor location, pathological type, vascular invasion, nerve invasion and regional lymph node metastasis, and the indexes of systemic inflammation were related to neoadjuvant therapy, TNM stage, tumor location, pathological type and nerve invasion. In univariate analysis, vascular invasion, preoperative CONUT, PNI and SII were identified as important factors affecting prognosis. In multivariate analysis, vascular invasion, preoperative CONUT, PNI, and SII were identified as important factors showing an independent correlation with survival time. A nomogram was developed, and the statistically significant influencing factors from the multivariate Cox regression model were included to predict the 2-, 3- and 5-year overall survival rates of patients with lung metastasis from gastric cancer.

Conclusion

CONUT, PNI and SII are independent risk factors for predicting overall survival and recurrence-free survival after radical resection of esophageal cancer. The proposed nomogram prediction model can aid in individualized analysis of the prognosis of these patients.

Introduction

Esophageal cancer (EC) is currently the fifth most common malignant tumor in China and the fourth leading cause of cancer-related death [12]. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two main histological types of esophageal cancer. ESCC is the most common histological type in Chinese patients, accounting for 90% of all cases; EAC occurs in many western countries [13]. Radical esophagectomy combined with neoadjuvant therapy has become a standard treatment for resectable esophageal malignant tumors[4,5].

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 [3]. Systemic nutritional status is an important part of the tumor microenvironment and plays an important role in tumor growth, progression and metastasis [2]. As the first step of nutritional status screening, the prognostic nutritional index (PNI) and controlled nutritional status (CONUT) are particularly important to evaluate the nutritional status of tumor patients [1]. CONUT has many advantages over SGA and comprehensive nutritional assessment. It is easy to use and understand [7] and has acceptable individual variability in patient physique [11].

Patients with malignant tumors are often malnourished due to poor appetite, the consumption of nutrients by the tumor, adverse treatment reactions and other reasons [55,56]. Malnutrition further reduces the tolerance to treatment and ultimately affects recurrence and survival, leading to death [57,58]. In addition, malnutrition can affect the quality of life of patients with malignant tumors [59]. Therefore, strategies to improve the nutritional status of patients with malignant tumors are urgently needed.

Increasing evidence shows that the interaction between cancer cells, the immune system and inflammation plays a crucial role in the occurrence and development of tumors [60]. In recent years, with the application of immunotherapy targeting programmed death 1 (PD1) and programmed death ligand 1 (PD-L1), tumor immunotherapy has been widely applied and has become an important part of comprehensive tumor therapy [61].

Recent studies have shown that the preoperative inflammatory response may be related to tumor progression and metastasis and has important predictive and prognostic value for various types of cancer [14,15,16]. It has been increasingly recognized that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two markers of systemic inflammation, and an increase in these two ratios may indicate a poor prognosis for patients with various solid tumors, including ESCC [17,18,19]. However, these two inflammatory factors integrate only two cell types. The systemic immune-inflammation index (SII) is based on peripheral neutrophil, platelet and lymphocyte counts and has recently been studied as a new prognostic marker [20,21,22].

Materials And Methods

Clinical data

The medical records of 381 patients who underwent radical esophagectomy in the First Affiliated Hospital of Zhengzhou University from August 5, 2013, to August 1, 2021, were collected, follow-up was conducted, and the information of these patients was systematically analyzed. The inclusion criteria were as follows: ① esophageal cancer patients with a primary tumor located in the esophagus by preoperative gastroscopy and pathological examination; ② TNM stage determined according to the 8th edition of TNM stage of the International Alliance for Cancer Control; ③radical surgery (RO); ④ available data from blood tests, including albumin concentration, total cholesterol, platelet count, lymphocyte count and neutrophil count collected before operation; ⑤ no prior radiotherapy; and ⑥ complete medical records. The exclusion criteria were as follows: ① perioperative death; ② lost to follow-up; ③ no available data on the preoperative blood cell count; ④ concurrent infection, autoimmune diseases and blood system-related diseases; ⑤ other malignant tumors within 5 years; and ⑥ emergency surgery. This study conforms to the principles of the Declaration of Helsinki and relevant ethical requirements.

Methods

Relevant patients were selected according to the inclusion and exclusion criteria. All included patients underwent three routine examinations before the operation: liver and kidney function, blood biochemistry, CT or MRI and gastroscopy. Pathological staging was classified according to the 8th edition of TNM staging of the International Union for Cancer Control [8], and tumor classification was based on WHO classification guidelines. Tumor size was defined as the maximum diameter of postoperative gross pathology. R0 resection was defined as complete resection with a negative margin under a microscope.

Follow-up

All patients were followed according to the standard schedule after esophageal cancer operation. The patients were followed up every 3–4 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.

Overall Survival And Relapse-free Survival

Overall survival (OS) was defined as the time interval from the date of operation to the date of death from any cause, and progression-free survival (PFS) was defined as the time interval from the date of operation to the date when disease progression or death occurred from any cause, whichever occurred first. The last follow-up was January 1, 2022. Among the 381 patients with esophageal cancer included in this study, the 1-, 3-, and 5-year survival rates were 81.89% (312/381), 25.20% (96/381), and 10.76% (41/381), respectively.

Calculation Of Conut, Pni, Nlr, Plr And Sii

Since the half-life of albumin is approximately 21 days, the half-life of lymphocytes is more than 2 weeks and the half-life of platelets is approximately 7–9 days, blood samples were obtained within 1 week before radical esophageal surgery. The following calculations were performed: PNI = 10 × Albumin concentration (g/L) + 0.005 × Lymphocyte count (/mm3); (1) albumin concentrations (g/dL) ≥ 3.5, 3.0-3.49, 2.5–2.99 and < 2.5 g/dL were scored as 0, 2, 4 and 6 points, respectively; (2) the total number of lymphocytes ≥ 1600, 1200–1599, 800–1199 and < 800/mm3 were scored as 0, 1, 2 and 3, respectively; (3) total cholesterol concentration (mg/dL) ≥ 180, 140–179, 100–139 and < 100 mg/dL were scored as 0, 1, 2 and 3, respectively. The CONUT score was calculated according to the sum of (1), (2) and (3); NLR = neutrophil count/lymphocyte count. In addition, PLR = platelet count/lymphocyte count; and SII = platelet count × neutrophil count/lymphocyte count.

Statistical analysis:

SPSS 26.0 software was used for data analysis. Combined with the receiver operating characteristic (ROC) curve, the best cutoff values of CONUT, PNI, NLR, PLR and SII were selected to produce the maximum sensitivity and specificity. According to the best cutoff value, patients were divided into high and low groups according to their CONUT, PNI, NLR, PLR and SII scores. Categorical variable data were analyzed by the chi square test. A Cox regression model was used for single-factor analysis and multivariate survival analysis. The nomogram prediction model was established by using the "rms" package in R software. The risk ratio (HR) of the 95% confidence interval (CI) was used to quantify the correlation strength between predictors and survival rate, and the difference was statistically significant (P < 0.05). In OS and PFS analysis, the Kaplan–Meier method was used to draw survival curves and statistical recurrence rate curves.

Results

Selection of the best cutoff value

Combined with the receiver operating characteristic (ROC) curve, the best cutoff values of CONUT, PNI, NLR, PLR and SII were selected. According to the best cutoff value, the patients were divided into the high CONUT group (CONUT ≥ 2, 184 cases, 48.29%, AUC = 0.764, 95% CI: 0.710–0.819, P < 0.001) and low CONUT group (CONIT < 2, 197 cases, 51.71%); high PNI group (PNI ≥ 48, 196 cases, 51.44%, AUC = 0.774, 95% CI: 0.721–0.827, P < 0.001) and low PNI group (PNI < 48, 185 cases, 48.56%); high NLR group (NLR ≥ 2, 201 cases, 52.76%, AUC = 0.725, 95% CI: 0.661–0.788, P < 0.001) and low NLR group (NLR < 2, 180 cases, 47.24%); high PLR group (PLR ≥ 103, 211 cases, 27.03%, AUC = 0.769, 95% CI: 0.712–0.827, P < 0.001) and low PLR group (PLR < 103, 170 cases, 44.62%); and high SII group (SII ≥ 361, 209 cases, 54.86%, AUC = 0.741, 95% CI: 0.682–0.799, P < 0.001) and low SII group (SII < 361, 172 cases, 45.14%)(Table 1).

Table 1
The cut-off values for the parameters.

Parameters	CONUT	PNI	NLR	PLR	SII
Cutoff values	2	48	1	103	361
Sensitivity	53.8%	45.9%	51.2%	60.8%	60.2%
Specificity	100%	54.1%	92.3%	92.3%	92.3%
AUC	0.764	0.774	0.725	0.769	0.741

Controlling Nutritional Status (CONUT) ,Prognostic nutritional index(PNI), Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation index(SII), Area of under curve(AUC).

Relationship Between Conut, Pni, Nlr, Plr, Sii And Clinical Characteristics

The preoperative nutritional status and clinical characteristics of the 381 patients after radical resection of esophageal cancer are shown in Table 2 and Table 3. Through the correlation analysis between clinical characteristics and preoperative PNI, CONUT, NLR, PLR and SII scores, it can be seen that the CONUT score before the operation is related to different preoperative complications (P = 0.021) and neoadjuvant therapy (P < 0.001), TNM stage (P = 0.015), tumor location (P = 0.001), pathological type (P < 0.001), vascular invasion (P = 0.005), nerve invasion (P < 0.001) and regional lymph node metastasis (P = 0.020). The preoperative PNI was correlated with different preoperative complications (P = 0.008), neoadjuvant therapy (P < 0.001), TNM stage (P = 0.006), tumor location (P = 0.007), pathological type (P < 0.001), vascular invasion (P = 0.013), nerve invasion (P = 0.001) and regional lymph node metastasis (P = 0.014). The preoperative

NLR was correlated with different neoadjuvant therapies ($P < 0.001$), TNM stage ($P = 0.026$), tumor location ($P = 0.044$), pathological type ($P = 0.008$) and nerve invasion ($P = 0.038$). The preoperative PLR was correlated with different neoadjuvant therapies ($P < 0.001$), TNM stage ($P = 0.044$), tumor location ($P = 0.007$), pathological type ($P = 0.005$), nerve invasion ($P = 0.005$) and regional lymph node metastasis ($P = 0.022$). The preoperative SII was correlated with different preoperative complications ($P = 0.040$), neoadjuvant therapy ($P < 0.001$), TNM stage ($P = 0.029$), tumor location ($P = 0.042$), pathological type ($P = 0.005$) and nerve invasion ($P = 0.004$).

Table 2
Comparison of baseline clinical characteristics based on CONUT and PNI

Variables	Case(n)	CONUT				PNI			
		CONUT＜2 (n = 197)	CONUT ≥ 2 (n = 184)	χ^2	P value	PNI＜48 (n = 185)	PNI ≥ 48 (n = 196)	χ^2	P value
Age(y)				0.261	0.609			0.045	0.833
＜65	206	109	97			99	107		
≥ 65	175	88	87			86	89		
Gender				0.604	0.437			0.002	0.967
Female	117	57	60			57	60		
Male	264	140	124			128	136		
Comorbidity				5.362	**0.021**			7.083	**0.008**
Yes	141	62	79			81	60		
No	240	135	105			104	136		
Neoadjuvant therapy				15.154	**＜0.001**			20.521	**＜0.001**
Yes	281	162	119			117	164		
No	100	35	65			68	32		
Treatment mode				0.991	0.609			0.531	0.767
No	41	24	17			18	23		
Chemotherapy	233	117	116			116	117		
Combination therapy	107	56	51			51	56		
Grading				2.609	0.271			2.462	0.292
I	63	38	25			25	38		
II	219	112	107			109	110		
III	99	47	99			51	99		
TNM stage				5.911	**0.015**			7.631	**0.006**
III + IV	225	128	97			96	129		
0 + I + II	156	69	87			89	67		
Tumor location				15.149	**0.001**			9.925	**0.007**
Upper	62	46	16			19	43		
Middle	140	68	72			70	70		
Lower	179	83	96			96	83		
Pathological type				16.668	**＜0.001**			16.438	**＜0.001**
squamous cell carcinoma	354	193	161			162	192		
Adenocarcinoma	20	4	16			16	4		
Signet ring cell carcinoma	7	0	7			7	0		
Vascular invasion				7.746	**0.005**			6.210	**0.013**
Yes	115	47	68			67	48		

Controlling Nutritional Status (CONUT), Prognostic nutritional index(PNI).

Variables	Case(n)	CONUT				PNI			
		CONUT≤2 (n = 197)	CONUT ≥ 2 (n = 184)	χ^2	P value	PNI≤48 (n = 185)	PNI ≥ 48 (n = 196)	χ^2	P value
No	266	150	116			118	148		
Nerve invasion				13.906	**≤0.001**			11.728	**0.001**
Yes	81	27	54			53	28		
No	300	170	130			132	168		
Lymph node metastasis				5.434	**0.020**			6.012	**0.014**
Yes	222	126	96			96	126		
No	159	71	88			89	70		
Tumor size (cm)				2.913	0.088			3.189	0.074
≥ 3	143	82	61			61	82		
≤3	238	115	123			124	114		

Controlling Nutritional Status (CONUT), Prognostic nutritional index(PNI).

Table 3
Comparison of baseline clinical characteristics based on NLR, PLR and SII

Variables	Case(n)	NLR				PLR				SII			
		NLR <2 (n = 180)	NLR ≥ 2 (n = 201)	χ^2	P value	PLR <103 (n = 170)	PLR ≥ 103 (n = 211)	χ^2	P value	SII< 361 (n = 172)	SII ≥ 361 (n = 209)	χ^2	P value
Age(y)				0.468	0.494			0.186	0.666			0.043	0.836
<65	206	94	112			94	112			94	112		
≥ 65	175	86	89			76	99			78	97		
Gender				0.004	0.951			0.002	0.964			0.069	0.792
Female	117	55	62			52	65			54	63		
Male	264	125	139			118	146			118	146		
Comorbidity				2.619	0.106			1.593	0.207			4.237	**0.040**
Yes	141	59	82			57	84			54	87		
No	240	121	119			113	127			118	122		
Neoadjuvant				26.917	**< 0.001**			15.155	**< 0.001**			18.025	**< 0.001**
Yes	281	155	126			142	139			145	136		
No	100	25	75			28	72			27	73		
Treatment mode				2.351	0.309			0.811	0.667			0.812	0.666
No	41	24	17			21	20			21	20		
Chemotherapy	233	107	126			102	131			105	128		
Combination	107	49	58			47	60			46	61		
Grading				0.104	0.949			0.192	0.909			0.040	0.980
I	63	29	34			28	35			29	34		
II	219	105	114			96	123			99	120		
III	99	46	53			46	53			44	55		
TNM stage				4.987	**0.026**			4.054	**0.044**			4.764	**0.029**
III + IV	225	117	108			110	115			112	113		
0 + I + II	156	63	93			60	96			60	96		
Tumor location				6.229	**0.044**			10.030	**0.007**			6.345	**0.042**
Upper	62	38	24			39	23			37	25		
Middle	140	65	75			57	83			60	80		
Lower	179	77	102			74	105			75	104		
Pathological type				9.689	**0.008**			10.448	**0.005**			10.795	**0.005**
squamous cell carcinoma	354	175	179			166	188			168	186		
Adenocarcinoma	20	4	16			3	17			3	17		

Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation index(SII).

Variables	Case(n)	NLR				PLR				SII			
		NLR <2 (n = 180)	NLR ≥ 2 (n = 201)	X^2	P value	PLR <103 (n = 170)	PLR ≥ 103 (n = 211)	X^2	P value	SII< 361 (n = 172)	SII ≥ 361 (n = 209)	X^2	P value
Signet ring cell carcinoma	7	1	6			1	6			1	6		
Vascular invasion				0.088	0.766			2.695	0.101			3.152	0.076
Yes	115	53	62			44	71			44	71		
No	266	127	139			126	140			128	138		
Nerve invasion				4.300	**0.038**			7.877	**0.005**			8.471	**0.004**
Yes	81	30	51			25	56			25	56		
No	300	150	150			145	155			147	153		
Regional lymph node metastasis				2.194	0.139			5.233	**0.022**			3.360	0.067
Yes	222	112	110			110	112			109	113		
No	159	68	91			60	99			63	96		
Tumor size (cm)				0.886	0.347			2.345	0.126			0.893	0.345
≥ 3	143	72	71			71	72			69	74		
<3	238	108	130			99	139			103	135		

Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation index(SII).

Analysis Of Risk Factors Between Conut, Pni, Nlr, Plr, Sii And Clinical Characteristics

Univariate analysis showed that CONUT ≥ 2 (HR = 2.316, 95% CI: 1.141-4.700; P = 0.020) and SII ≥ 361 (HR = 1.698, 95% CI: 1.025–2.815; P = 0.040) were important risk factors for poor prognosis. No vascular invasion (HR = 0.567, 95% CI: 0.425–0.758; P < 0.001) and PNI ≥ 48 (HR = 0.031, 95% CI: 0.011–0.090; P < 0.001) were important factors for good prognosis (Table 4). In multivariate analysis, CONUT ≥ 2 (HR = 2.316, 95% CI: 1.141-4.700; P = 0.020) and SII ≥ 361 (HR = 1.657, 95% CI: 1.117–2.458; P = 0.012) were independently correlated with poor survival time. Vascular invasion (HR = 0.594, 95% CI: 0.470–0.751; P < 0.001) and PNI ≥ 48 (HR = 0.025, 95% CI: 0.009–0.071; P < 0.001) were not independently correlated with good survival (Table 4).

Table 4
Univariate analysis and multivariate analysis of factors correlated with OS

Variables	Case(n)	Univariate analysis			multivariate analysis		
		HR	95.0% CI	P value	HR	95.0% CI f	P value
Age(y)							
65	206	1					
≥ 65	175	0.972	0.778–1.215	0.806			
Gender							
Female	117	1					
Male	264	1.102	0.864–1.406	0.433			
Comorbidity							
Yes	141	1					
No	240	0.825	0.646–1.054	0.124			
Neoadjuvant							
Yes	281	1					
No	100	1.261	0.970–1.640	0.083			
Treatment mode							
No	41	1					
Chemotherapy	233	0.901	0.614–1.320	0.591			
Combination	107	0.980	0.647–1.486	0.925			
Grading							
I	63	1					
II	219	1.224	0.884–1.696	0.223			
III	99	1.410	0.968–2.054	0.074			
TNM stage							
III + IV	225	1					
0 + I + II	156	0.789	0.535–1.164	0.233			
Tumor location							
Upper	62	1					
Middle	140	1.046	0.747–1.464	0.794			
Lower	179	1.086	0.774–1.522	0.634			
Pathological type							
squamous cell carcinoma	354	1					
Adenocarcinoma	20	0.763	0.453–1.285	0.309			
Signet ring cell carcinoma	7	1.577	0.699–3.561	0.273			
Vascular invasion							
Yes	115	1			1		

Controlling Nutritional Status (CONUT), Prognostic nutritional index(PNI), Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation index(SII).

Variables	Case(n)	Univariate analysis			multivariate analysis		
		HR	95.0% CI	P value	HR	95.0% CI f	P value
No	266	0.567	0.425–0.758	**<0.001**	0.594	0.470–0.751	**<0.001**
Nerve invasion							
Yes	81	1					
No	300	0.828	0.612–1.120	0.221			
Regional lymph node metastasis							
Yes	222	1					
No	159	0.973	0.668–1.418	0.889			
Tumor size (cm)							
≥ 3	143	1					
<3	238	0.973	0.766–1.236	0.822			
CONUT							
<2	197	1			1		
≥ 2	184	2.316	1.141-4.700	**0.020**	2.277	1.132–4.582	**0.021**
PNI							
<48	185	1			1		
≥ 48	196	0.031	0.011–0.090	**<0.001**	0.025	0.009–0.071	**<0.001**
NLR							
<2	180	1					
≥ 2	201	0.972	0.692–1.364	0.869			
PLR							
<103	170	1					
≥ 103	211	1.223	0.779–1.921	0.382			
SII							
<361	172	1			1		
≥ 361	209	1.698	1.025–2.815	**0.040**	1.657	1.117–2.458	**0.012**

Controlling Nutritional Status (CONUT), Prognostic nutritional index(PNI), Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation index(SII).

Analysis Of Conut, Pni, Nlr, Plr, Sii And Recurrence And Survival Parameters

High CONUT (log rank P < 0.001), low PNI (P < 0.001), high NLR (P < 0.001), high PLR (P < 0.001), and high SII (P < 0.001) scores were independent prognostic factors for shorter OS and PFS times, and the difference was statistically significant (Fig. 2). The median OS duration was 22 months, and the median PFS duration was 13 months. In the patient group with a high CONUT score, OS (15 months vs. 35 months) and PFS (8 months vs. 18 months) were shorter than those with a low CONUT score (Fig. 2.AB). In the group of patients with high PNI scores, OS (35 months vs. 15 months) and PFS (18 months vs. 7 months) were higher than those with low PNI scores (Fig. 2.CD). In the group of patients with high NLR scores, OS (16 months vs. 33 months) and PFS (8 months vs. 17 months) were shorter than those with low NLR scores (Fig. 2.EF). In the group of patients with high PLR scores, OS (16 months vs. 35 months) and PFS (8 months vs. 18 months) were shorter than those with low PLR scores (Fig. 2.GH). In patients with high SII scores, OS (16 months vs. 36 months) and PFS (8 months vs. 19 months) were shorter than those with low SII scores (Fig. 2.IJ).

Nomogram Prediction Of Os At 2, 3 And 5 Years

According to the analysis of the multivariate Cox regression model, we found that vascular invasion, preoperative CONUT, PNI and SII had a significant impact on OS, so we used these variables to build a nomogram. This nomogram was then used to assess the risk of recurrence at 2, 3 and 5 years after esophageal cancer surgery (Fig. 3). By using the correction curve method, the correction curve shows that there is only a limited deviation from the ideal prediction model (Fig. 4), indicating that the predicted value obtained from the nomogram prediction model can well represent the actual value. With this nomogram, the higher the total score is, the greater the risk of recurrence.

Discussion

Increasing evidence shows that the prognosis of cancer is not only related to tumor factors but also related to the patient's systemic state, including their nutritional and immune status [40]. Malnutrition in cancer patients will adversely affect the immune defense system, destroy the natural immune barrier, change cellular and humoral immunity, and hinder the function of macrophages. This in turn leads to susceptibility and intolerance to infection and even resistance to treatment [41]. Therefore, accurate assessment of nutritional status and inflammatory immune status can improve the survival rate of cancer patients [42].

Recently, it has been reported that the CONUT score and PNI are prognostic factors for the survival of patients with different types of cancer, including colorectal cancer [43,44], gastric cancer [45,46,47], esophageal cancer [47,48,49], hepatocellular carcinoma [50], intrahepatic cholangiocarcinoma [51] and lung cancer [52]. It is not surprising that CONUT and PNI can be used as prognostic factors of OS for various types of cancer because their components reflect the 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 [53]. Second, total cholesterol concentration is associated with tumor progression because tumor tissue reduces 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 poor prognosis in several cancers [54]. However, the relationship between the CONUT score and postoperative complications in cancer patients is still controversial [43,45,48,51]. On the other hand, it can be seen from the definitions of CONUT and PNI that CONUT is more comprehensive and systematic than PNI. In fact, relevant studies have confirmed that CONUT has greater prognostic value than PNI [62].

Studies have found that systemic inflammatory factors such as NLR, PLR and SII are independent markers of the prognosis of a variety of cancers, including ESCC [23,24,25,26,27]. Feng J F [24] found that preoperative NLR and PLR are important predictors of OS in ESCC patients, and PLR is a better prognostic index than NLR. Nakamura K [25] and Yutong H [26] believe that an increased NLR is associated with tumor progression and low survival in EC patients. A meta-analysis by Zhao L [28] showed that a higher PLR may be an important predictive biomarker for EC patients. In addition, SII based on neutrophil, platelet and lymphocyte counts has been proven to be an independent prognostic index for patients with hepatocellular carcinoma, lung cancer, colorectal cancer, kidney cancer, prostate cancer and gastric cancer [19][20][29][30][31]. Among them, some potential theories can be used to explain the prognostic value of NLR, PLR and SII. First, the number of neutrophils increases in both the tumor microenvironment and the whole body, which is usually associated with a poor prognosis in patients with solid cancer [32]. As an inflammatory response, it can not only inhibit the immune system by inhibiting the cytolytic activity of immune cells (such as lymphocytes, activated T cells and natural killer cells) [34,35] but also activate endothelial cells and parenchymal cells to enhance the adhesion of circulating tumor cells and promote distant metastasis [33]. Second, platelets can act as a protective "cloak" for circulating tumor cells (CTCs), protecting them from immune damage. Platelet and endothelial cell adhesion proteins may also promote metastasis by increasing tumor cell extravasation [36]. Third, lymphocytes can secrete a variety of cytokines, such as IFN-γ and TNF-α, to prevent tumor growth and improve the prognosis of cancer patients [37]. In conclusion, SII should be a more objective indicator than all other systemic inflammatory indicators (such as NLR and PLR), which can reflect the balance between host inflammation and the immune response.

In this study, the critical values of CONUT, PNI, NLR, PLR and SII were determined to be 2, 48, 2, 103 and 361, respectively. In univariate and multivariate analyses, CONUT, PNI and SII were significant for OS. As independent prognostic factors, NLR and PLR were not significant in multivariate analysis. It was found that high CONUT, low PNI, high SII, high NLR and high PLR were poor prognostic indicators, and the survival, recurrence and metastasis times of these patients were significantly shortened. In addition, the AUCs of CONUT, PNI, and NLR were calculated. The highest AUCs of PLR and SII were 0.764, 0.226, 0.725, 0.769 and 0.741, respectively, indicating their superiority as markers of nutrition and inflammation.

In this study, a nomogram was constructed according to the independent prognostic factors screened by the Cox regression model, and the prognosis of patients with esophageal cancer was predicted and evaluated by the nomogram. The nomogram provides specific scores for each influencing factor, and the occurrence probability of the final outcome can be inferred by adding the scores of each factor. Additionally, the nomogram transforms a complex regression equation into a simple visual graph, which makes the results more readable. Medical staff can predict the prognosis of patients with esophageal cancer more quickly and conveniently using this nomogram, which is conducive to the prevention of disease progression and has high clinical application value.

Our study has several limitations. First, this study was a small sample retrospective study, which only included two nutritional indexes and three inflammatory indexes. We did not further explore the pathway and molecular mechanism through which the nutritional and inflammatory factors mediated by peripheral blood CONUT, PNI, NLR, PLR and SII participate in the occurrence and development of esophageal cancer, and we did not explore how to organically combine the five indexes CONUT, PNI, NLR, PLR and SII to obtain the maximum prognostic value. Second, a large sample prospective study is needed for further exploration and verification. Third, although our findings are consistent with previous observations, it is not easy to verify our conclusions in another independent cohort due to the lack of standardized cutoff values of CONUT, PNI, NLR, PLR and SII. In similar studies, the cutoff values of CONUT, PNI, NLR, PLR and SII were different[38,39].Therefore, we need to conduct prospective research to find an appropriate threshold.

In conclusion, CONUT, PNI and SII can be used as independent influencing factors to evaluate the nutritional and immune status of patients with esophageal cancer as well as their prognosis. These indexes are easy to obtain and suitable for clinical application. In addition, nomograms have high clinical application value and can intuitively predict the prognosis of patients with esophageal cancer, which can help clinicians better formulate or adjust the diagnosis and treatment plans of these patients.

Abbreviations

ESCC: Esophageal squamous cell carcinoma; EC :Esophageal cancer; EAC: Esophageal adenocarcinoma; RO: Radical surgery;PD-1: Programmed death 1; PD-L1: Programmed death ligand 1; WBC: White blood cell; CONUT: Controlling nutritional status; PNI: Prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; 95% CI: 95% Confidence interval.

Declarations

Acknowledgements

We thank all the patients and their families for participating in the study.

Authors' contributions

Study design: FW. Study conduct:HKW and XL. Data collecting: YLY. Data analysis: XL. Data interpretation: XRM and HKW. Draft manuscript: HKW and XL. FW takes full responsibility for the integrity of the data analysis. All authors read and approved the final manuscript.

Funding

This research was supported by the General program of National Natural Science Foundation of China (81672442), the training of young and middle-aged health science and technology innovation talents in Henan Province (leading talents) (yxkc2020017), the key project of medical science and technology in Henan Province (sbgj2020080), the key scientific research project of colleges and universities in Henan Province Sisco msd2020-0289 Cancer Research Fund (key project) (year 2020)(21a320040).

Availability of data and materials

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

Ethics approval and consent to participate

The study follows the principles of the Declaration of Helsinki. 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 declare that they have no competing interests.

References

1. □□□, □□, □□□,□. □□□□□□□□□□□□□□□□□□□□□□□□□□□□[J]. □□□□□□, 2021, 101(06):421-428.
2. Wu X , Jiang Y , Ge H , et al. Predictive value of prognostic nutritional index in patients with oral squamous cell carcinoma[J]. Oral Diseases.
3. Arends J ,Baracos V , Bertz H , et al. ESPEN expert group recommendations for action against cancer-related malnutrition[J]. Clinical nutrition (Edinburgh, Scotland), 2017, 36(5):1187.
4. Ando N , Kato H , Igaki H , et al. A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907)[J]. Annals of Surgical Oncology, 2012, 19(1):68-74.
5. A V G M , B B B F , B B M S F , et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis.[J]. The Lancet Oncology, 2007, 8(3):226-234.
6. José Ignacio de Ulíbarri, Noemí G. P. de Villar, A. González-MadroñoGiménez, et al. CONUT: A tool for Controlling Nutritional Status. First validation in a hospital population[J]. NutriciónHospitalaria, 2005, 20(1):págs. 38-45.
7. José Ignacio de Ulíbarri, Noemí G. P. de Villar, A. González-MadroñoGiménez, et al. CONUT: A tool for Controlling Nutritional Status. First validation in a hospital population[J]. NutriciónHospitalaria, 2005, 20(1):págs. 38-45.
8. Gospodarowicz M K . TNM Classification of Malignant Tumours[M]. Wiley-Blackwell, 2010.
9. Ichikawa H , Miyata G , Miyazaki S , et al. Esophagectomy Using a Thoracoscopic Approach With an Open Laparotomic or Hand-Assisted Laparoscopic Abdominal Stage for Esophageal Cancer: Analysis of Survival and Prognostic Factors in 315 Patients[J]. Annals of Surgery, 2013, 257.
10. Chen P, Han L, Wang C, Jia Y, Song Q, Wang J, Guan S, Tan B, Liu B, Jia W, Cui J, Zhou W, Cheng Y. Preoperative serum lipids as prognostic predictors in esophageal squamous cell carcinoma patients with esophagectomy. Oncotarget. 2017 Jun 20;8(25):41605-41619. doi: 10.18632/oncotarget.15651. PMID: 28404928; PMCID: PMC5522301.
11. Kazuo, Okadome, Yoshifumi, et al. Prognostic Nutritional Index, Tumor-infiltrating Lymphocytes, and Prognosis in Patients with Esophageal Cancer.[J]. Annals of Surgery, 2018.
12. Li N , Dhar S S , Chen T Y , et al. JARID1D Is a Suppressor and Prognostic Marker of Prostate Cancer Invasion and Metastasis[J]. Cancer Research, 2016, 76(4).
13. Mao Y S , He J , Cheng G Y . Current status of surgical management of esophageal cancer in China and the future strategy[J]. Zhonghuazhongliu za zhi [Chinese journal of oncology], 2010, 32(6):401-404.
14. Crusz S M , Balkwill F R . Inflammation and cancer: advances and new agents[J]. Nature Reviews Clinical Oncology, 2015.
15. Singel K L , Segal B H . Neutrophils in the tumor microenvironment: trying to heal the wound that cannot heal[J]. Immunological Reviews, 2016, 273(1).
16. Schreiber R D , Old L J , Dunn G P . The immunobiology of cancer immunosurveillance and immunoediting.
17. Jinming, Zhu, Yingming, et al. Prognostic significance of the lymphocyte-to-monocyte ratio and the tumor-infiltrating lymphocyte to tumor-associated macrophage ratio in patients with stage T3N0M0 esophageal squamous cell carcinoma[J]. Cancer Immunology and Immunotherapy: Other Biological Response Modifications, 2017.
18. Liu J , Feng J , Huang Y . Combination of neutrophil lymphocyte ratio and platelet lymphocyte ratio is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma[J]. Onco Targets Ther, 2013, 6.
19. Liu J S , Huang Y , Yang X , et al. A nomogram to predict prognostic values of various inflammatory biomarkers in patients with esophageal squamous cell carcinoma[J]. American Journal of Cancer Research, 2015, 5(7):2180.
20. Chen J H ,Zhai E T , Yuan Y J , et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer[J]. World Journal of Gastroenterology, 2017.

21. Tomita M ,Ayabe T , Maeda R , et al. Systemic Immune-inflammation Index Predicts Survival of Patients After Curative Resection for Non-small Cell Lung Cancer[J]. In vivo (Athens, Greece), 2018, 32(3):663-667.
22. Hong X , Cui B , Wang M , et al. Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer[J]. Tohoku Journal of Experimental Medicine, 2015, 236(4):297.
23. Noriyuki, Hirahara, Takeshi, et al. Prognostic value of preoperative inflammatory response biomarkers in patients with esophageal cancer who undergo a curative thoracoscopic esophagectomy[J]. BMC Surgery, 2016, 16(1):66-66.
24. Feng J F , Huang Y , Chen Q X . Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma[J]. World Journal of Surgical Oncology, 2014, 12(1):58.
25. Nakamura K , Yoshida N , Baba Y , et al. Elevated preoperative neutrophil-to-lymphocytes ratio predicts poor prognosis after esophagectomy in T1 esophageal cancer[J]. International Journal of Clinical Oncology, 2017, 22(3):1-7.
26. Yutong H ,Xiaoli X , Shumei L , et al. Increased Neutrophil-Lymphocyte Ratio Is a Poor Prognostic Factor in Patients with Esophageal Cancer in a High Incidence Area in China[J]. Archives of Medical Research, 2015, 46(7):557-563.
27. Hirahara N , Matsubara T , Kawahara D , et al. Prognostic significance of preoperative inflammatory response biomarkers in patients undergoing curative thoracoscopic esophagectomy for esophageal squamous cell carcinoma[J]. Eur J Surg Oncol, 2017, 43(2):493-501.
28. Zhang X , Wang Y , Zhao L , et al. Prognostic value of platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis[J]. Int J Biol Markers, 2018:1724600818766889.
29. Fan L , Dong B , Wang R , et al. Systemic Immune-Inflammation Index predicts the combined clinical outcome after sequential therapy with abiraterone and docetaxel for metastatic castration-resistant prostate cancer patients[J]. European Urology Supplements, 2018, 17(2).
30. Cristian L , Umberto B , Lisa D , et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib[J]. Oncotarget, 2016, 9(34):54564-54571.
31. Wang K ,Diao F , Ye Z , et al. Prognostic value of systemic immune.inflammation index in patients with gastric cancer[J]. [illegible], 2017, 36(9).
32. Coffelt S B , MD Wellenstein, Visser K D . Neutrophils in cancer: neutral no more[J]. Nature Reviews Cancer, 2016.
33. LarcoJ ,Wuertz B , Furcht L T . De Larco JE, Wuertz BRK, FurchtLTThe potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res 10: 4895-4900[J]. Clinical Cancer Research, 2004, 10(15):4895-4900.
34. Petrie H T , Klassen L W , Kay H D . Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes[J]. The Journal of Immunology, 1985, 134(1):230-234.
35. El-Hag A , Clark R A . Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system.[J]. Journal of Immunology, 1987, 139(7):2406.
36. Stanger B , Kahn M . Platelets and Tumor Cells: A New Form of Border Control[J]. Cancer Cell, 2013, 24(1):9-11.
37. Ferrone C ,Dranoff G . Dual roles for immunity in gastrointestinal cancers.
38. Hongdian, Zhang, Xiaobin, et al. The predictive value of a preoperative systemic immune-inflammation index and prognostic nutritional index in patients with esophageal squamous cell carcinoma[J]. Journal of cellular physiology, 2019, 234(2):1794-1802.
39. GengY , Shao Y , Zhu D , et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients with Esophageal Squamous Cell Carcinoma: A Propensity Score-matched Analysis[J]. Scientific Reports, 2016, 6(1):39482.
40. Ogino S ,Galon J , Fuchs C S , et al. Cancer immunology–analysis of host and tumor factors for personalized medicine.[J]. Nature Reviews Clinical Oncology, 2011, 8(12):711-9.
41. ChandralR . Nutrition and immunology: from the clinic to cellular biology and back again.[J]. Proceedings of the Nutrition Society, 1999, 58.
42. Santoso J T ,Cannada T , O'Farrel B , et al. Subjective versus objective nutritional assessment study in women with gynecological cancer: a prospective cohort trial[J]. International Journal of Gynecological Cancer, 2010, 14(2):220-223.
43. Tokunaga R , Sakamoto Y , Nakagawa S , et al. CONUT: a novel independent predictive score for colorectal cancer patients undergoing potentially curative resection[J]. International Journal of Colorectal Disease, 2016, 32(1):1-8.
44. Yasuhitol ,Masatsune S , Kiyoshi M , et al. Impact of the Preoperative Controlling Nutritional Status (CONUT) Score on the Survival after Curative Surgery for Colorectal Cancer[J]. Plos One, 2015, 10(7):e0132488.
45. Kuroda D ,Sawayama H , Kurashige J , et al. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection[J]. Gastric Cancer, 2018.

46. Liu X , Zhang D , Lin E , et al. Preoperative controlling nutritional status (CONUT) score as a predictor of long-term outcome after curative resection followed by adjuvant chemotherapy in stage II-III gastric Cancer[J]. Bmc Cancer, 2018, 18(1):699.
47. Zhang Y , Zhang X . Controlling nutritional status score, a promising prognostic marker in patients with gastrointestinal cancers after surgery: A systematic review and meta-analysis[J]. International Journal of Surgery, 2018:S1743919118307659.
48. Yoshida N , Baba Y , Shigaki H , et al. Preoperative Nutritional Assessment by Controlling Nutritional Status (CONUT) is Useful to estimate Postoperative Morbidity After Esophagectomy for Esophageal Cancer[J]. World Journal of Surgery, 2016, 40(8):1910.
49. Toyokawa T , Kubo N , Tamura T , et al. The pretreatment Controlling Nutritional Status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study[J]. BMC Cancer, 2016, 16(1).
50. Norifumi, Harimoto, Tomoharu, et al. Prognostic Significance of Preoperative Controlling Nutritional Status (CONUT) Score in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma.[J]. World journal of surgery, 2017.
51. Miyata T , Yamashita Y I , Higashi T , et al. The Prognostic Impact of Controlling Nutritional Status (CONUT) in Intrahepatic Cholangiocarcinoma Following Curative Hepatectomy: A Retrospective Single Institution Study[J]. World Journal of Surgery, 2017.
52. TakamoriS , Toyokawa G , Taguchi K , et al. The Controlling Nutritional Status Score Is a Significant Independent Predictor of Poor Prognosis in Patients With Malignant Pleural Mesothelioma[J]. Clinical Lung Cancer, 2017:S1525730417300372.
53. MohriY , Inoue Y , Tanaka K , et al. Prognostic Nutritional Index Predicts Postoperative Outcome in Colorectal Cancer[J]. World Journal of Surgery, 2013, 37(11):2688-2692.
54. DolcettiR ,Viel A , Doglioni C , et al. High Prevalence of Activated Intraepithelial Cytotoxic T Lymphocytes and Increased Neoplastic Cell Apoptosis in Colorectal Carcinomas with Microsatellite Instability[J]. American Journal of Pathology, 1999, 154(6):1805-1813.
55. BouleucC , Amélie Anota, Cécile Cornet, et al. Impact on Health-Related Quality of Life of Parenteral Nutrition for Patients with Advanced Cancer Cachexia: Results from a Randomized Controlled Trial[J]. The Oncologist, 2020, 25.
56. UsterA ,Ruehlin M , Mey S , et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial[J]. Clinical Nutrition, 2017:S0261561417302017.
57. U Müller-Richter, Betz C , Hartmann S , et al. Nutrition management for head and neck cancer patients improves clinical outcome and survival[J]. Nutrition Research, 2017:1.
58. Wang J , Yu B , Xie S , et al. Predictive Value of Nutritional Risk Screening 2002 and Prognostic Nutritional Index for Esophageal Cancer Patients Undergoing Definitive Radiochemotherapy[J]. International Journal of Radiation Oncology*Biology*Physics, 2018, 102(3):e42-e43.
59. Furness K , Huggins C E , Hanna L , et al. a process and mechanism of action evaluation of the effect of early and intensive nutrition care, delivered via telephone or mobile application, on quality of life in people with upper gastrointestinal cancer: a study protocol[J].
60. Bader J E , Voss K , Rathmell J C . Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy[J]. Molecular Cell, 2020, 78(6):1019-1033.
61. YarchoanM , Hopkins A , Jaffee E M . Tumor Mutational Burden and Response Rate to PD-1 Inhibition[J]. New England Journal of Medicine, 2017, 377(25):2500.
62. Yangqin, Zheng, Lianmin, et al. Prognostic impact of the Controlling Nutritional Status score following curative nephrectomy for patients with renal cell carcinoma.[J]. Medicine, 2018.
63. [The Influence of Immunity, Nutrition, and Physical Function on the Onset of Pneumonia after Colorectal Cancer Resection].[J]. Gan to Kagaku Ryoho Cancer & Chemotherapy, 2018.

Figures

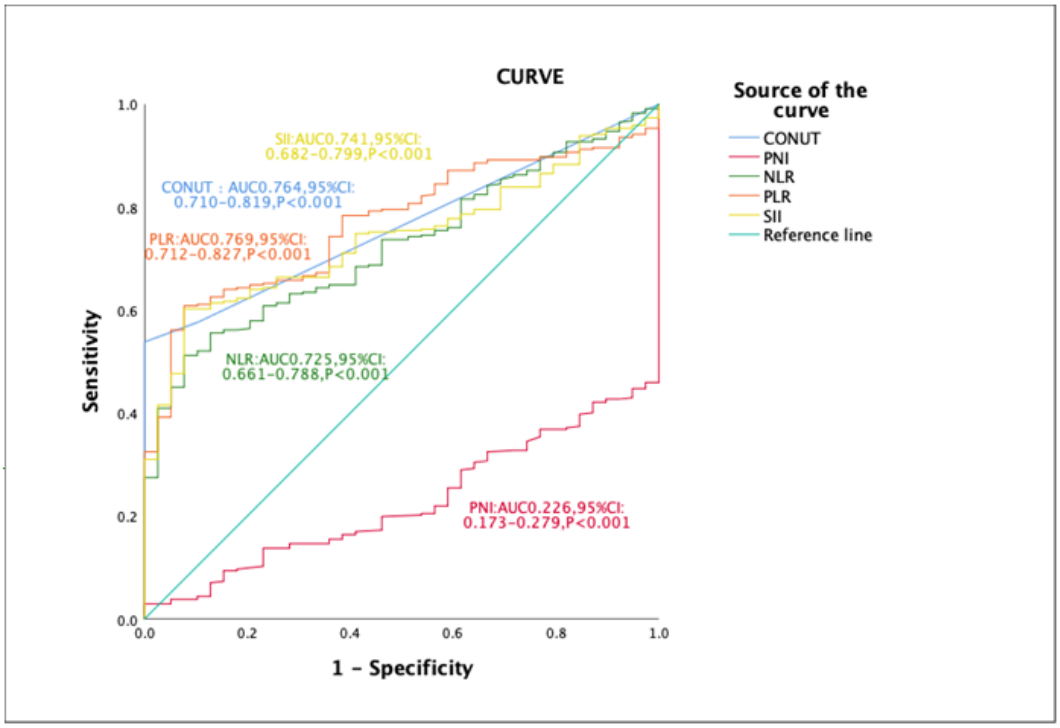

Figure 1

ROC analysis and AUC for sensitivity and specificity of parameters. Receiver operating characteristic(ROC), Area of under curve(AUC) , Controlling Nutritional Status (CONUT), Prognostic nutritional index(PNI), Neutrophil-to-lymphocyte ratio(NLR), Platelet-to-lymphocyte ratio(PLR), Systemic immune-inflammation ind ex(SII).

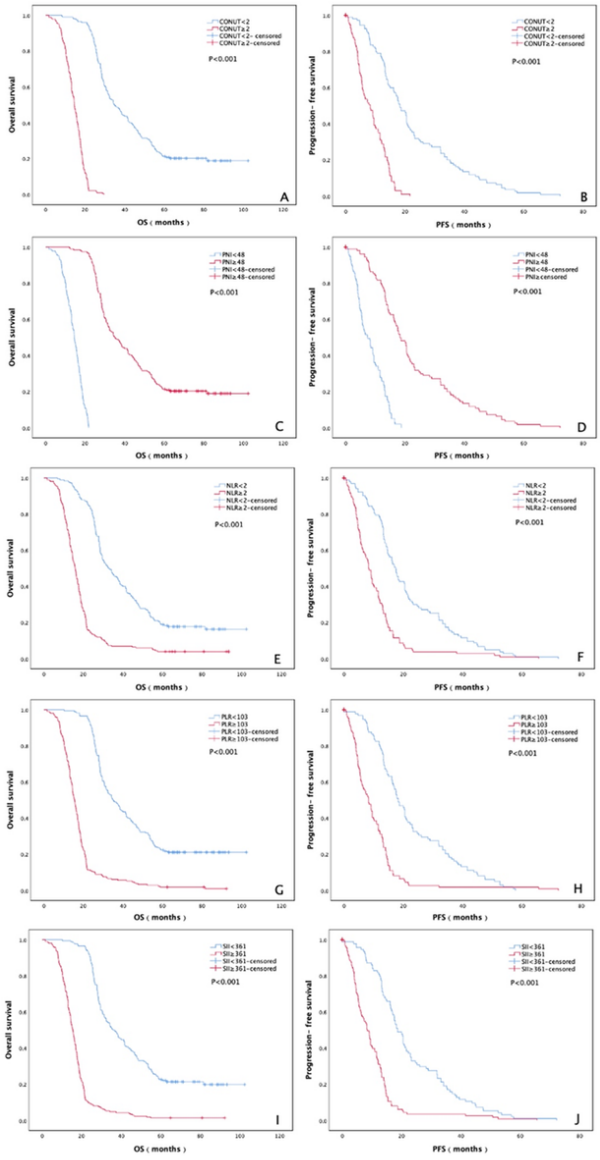

Figure 2

Kaplan-Meier plots of OS according to CONUT、PNI、NLR、PLR、SII.The number at risk was shown below. (A) The CONUT- high group showed a significantly shorter OS compared with the CONUT-low group (14.500VS34.933, log rank P < 0.001).(B) The CONUT-high group showed a significantly shorter PFS compared with the CONUT-low group (8.270VS 18.300, log rank P < 0.001). (C) The PNI-low group showed a significantly shorter OS compared with the PNI- high group (14.500VS 34.933, log rank P < 0.001). (D) The PNI-low group showed a significantly shorter OS compared with the PNI- high group (7.400VS 18.300, log rank P < 0.001). (E) The NLR- high group showed a significantly shorter OS compared with the NLR - low group (15.833VS 32.567, log rank P < 0.001). (F) The NLR - high group showed a significantly shorter PFS compared with the NLR - low group (8.270VS 17.470, log rank P < 0.001). (G) The PLR- high group showed a significantly shorter OS compared with the PLR - low group (15.500VS 34.933, log rank P < 0.001). (H) The PLR - high group showed a significantly shorter PFS compared with the PLR - low group (8.270VS 18.300, log rank P < 0.001). (I) The SII- high group showed a significantly shorter OS compared with the SII - low group (15.500VS 35.800, log rank P < 0.001).(J) The SII - high group showed a significantly shorter PFS compared with the SII - low group (8.430VS 18.630, log rank P < 0.001).

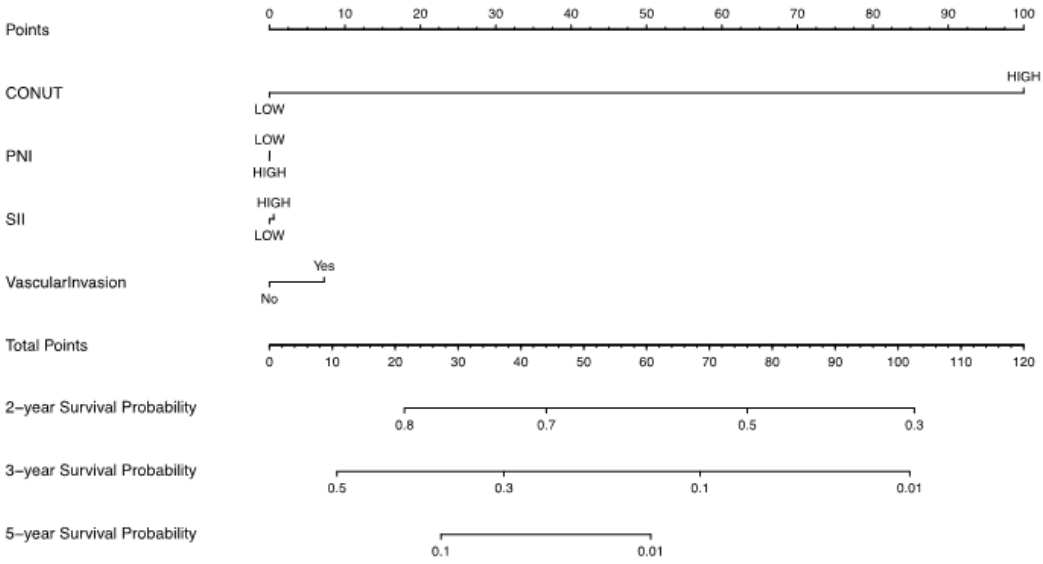

Figure 3

Nomogram predicting recurrence-free survival in patients with esophageal cancer.

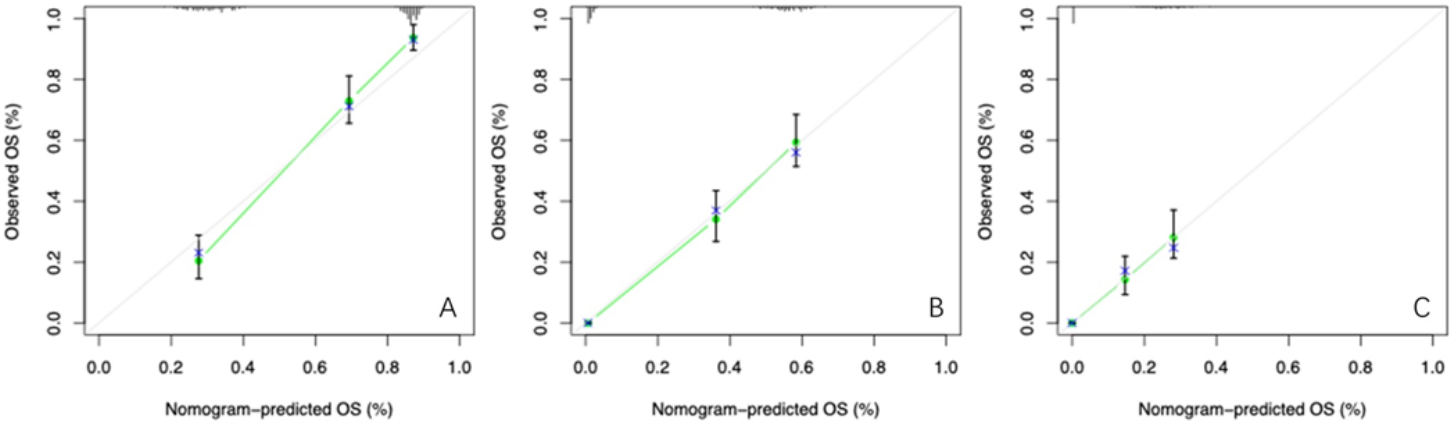

Figure 4

Calibration curves for internal validation of estimating recurrence-free survival in patients with esophageal cancer ,(A)2-year outcome; (B)3-year outcome;(C)5-year outcome.