

A New Index AGR-PLR Score (APS) for Patients with Esophageal Squamous Cell Carcinoma Undergoing Radical Esophagectomy

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Purpose: Biomarkers of the systemic inflammatory response and nutritional-related indicators have been used to assess the host anti-tumor immune response and predict prognosis in esophageal squamous cell carcinoma (ESCC). However, a new indicator system combining platelet-to-lymphocyte ratio (PLR) and albumin-globulin ratio (AGR), AGR-PLR score (APS), has not yet been evaluated for the prognosis prediction among ESCC patients.

Methods: A retrospective analysis was performed, including 633 patients with ESCC, comprising 450 in the training cohort and 183 in the validation cohort.

Results: In this study, we found that the overall survival time among patients with an APS of 2 was significantly shorter than that among patients with an APS of 1, and the survival time of patients with an APS of 1 was significantly shorter than that of patients with an APS of 0. Multivariate analysis showed that the APS was an independent prognostic factor for patients with ESCC. The APS demonstrated better prognostic accuracy and effectiveness for ESCC patients than either PLR or AGR alone. In addition, a new prediction nomogram was established according to tumor grade, APS, and tumor, node, metastasis (TNM) stage. Compared with the traditional 8th version of TNM staging system, this nomogram demonstrated improved sensitivity and specificity for the prediction of 3- and 5-year survival.

Conclusion: APS is a novel independent prognostic indicator for the radical resection of ESCC and a potential biomarker for monitoring the therapeutic response.

Keywords: AGR, ESCC, nomogram, prognosis, PLR

Introduction

Esophageal cancer (EC) is one of the most common malignant tumors that affect the digestive system, characterized by high malignancy, strong invasiveness, and poor prognosis, and it is considered among the leading causes of cancer-related death worldwide.¹ In China, esophageal squamous cell carcinoma (ESCC) is the most commonly occurring form of EC, accounting for approximately 90% of all EC cases, whereas esophageal adenocarcinoma is rarer.^{2,3} Currently, clinical treatments for EC include surgical resection and combination treatments of chemotherapy, radiotherapy, and immunotherapy.⁴ However, despite recent advances in the diagnosis and comprehensive treatment of ESCC, the prognosis of ESCC patients remains poor, with a 5-year survival rate of only 10%-30%.⁵ At present, prognosis and treatments for ESCC patients are primarily guided by the tumor, node, metastasis (TNM) staging system. However, differentiated survival rates across ESCC patients with the same TNM stage who receive the same treatment have been

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observed in clinic. Therefore, a new clinical prognostic indicator for ESCC that can be used in tandem with the TNM staging system is urgently necessary to provide effective prognostic predictions and treatment guidance to further limit tumor progression and promote survival among ESCC patients.

Growing evidence indicates that interactions between inflammation and immune responses play key roles in the tumorigenesis, proliferation, progression, and metastasis of malignant tumors.⁶ Systemic inflammatory response biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the monocyte-to-lymphocyte ratio (MLR), have been used to assess the host anti-tumor immune responses and predict prognosis in multiple malignant tumors, including ESCC.^{7,8} Recently, several studies have reported the use of the serum albumin-globulin ratio (AGR), a nutrition-related indicator, to predict prognosis in patients with multiple tumors.^{9,10} However, in ESCC, the AGR-PLR score (APS), a new indicator that combines systemic inflammatory factors with nutritional-related indicators, has not yet been evaluated for prognosis prediction among ESCC patients. Therefore, in this study, we aimed to explore the ability of the APS to predict postoperative prognosis among ESCC patients established a nomogram based on APS and TNM stages to provide better ESCC prognostic predictions.

Materials and Methods

Participants

A retrospective analysis was performed using the clinical pathology data from 450 ESCC who were patients admitted and received surgeries at the First Affiliated Hospital of Soochow University from 2011 to 2015. The analysis results were then confirmed in 183 ESCC who were patients admitted and received surgery from 2016 to 2019. Inclusion criteria included: 1) ESCC confirmed by postoperative pathology; 2) no preoperative chemotherapy, radiotherapy, immunotherapy, or other complementary treatment; 3) no distant metastasis at diagnosis; 4) no severe liver or kidney dysfunction, acute or chronic infection, malnutrition markers detected in the blood or immune system, or other diseases affecting indicators of blood cells, albumin, or coagulation before surgery; 5) received radical resection of EC; and 6) complete data, including clinical pathology, laboratory examination and follow-up. Follow-up studies to determine the postoperative survival status of patients were performed through outpatient or telephone review,

conducted once every 3 months during the first year and once every 6 months starting in the second year after surgery and continuing until December 2019. Overall survival (OS) was defined as the duration between the surgery date and date of death or the last valid follow-up. This study was performed in accordance with the Helsinki Declaration. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. All patients in this study signed informed consent forms.

Peripheral Blood Collection and Related Indicators Calculation

Morning peripheral venous blood samples were collected from ESCC patients 1 week before surgery. Neutrophil, lymphocyte and platelet counts were obtained from routine tests using an automatic blood cell analyzer (Sysmex XN9000, Japan). Serum albumin and globulin levels were detected using an automated biochemical analyzer (Beckman, USA). NLR, MLR, PLR and AGR were calculated according to the following equations: NLR = peripheral blood neutrophil count/peripheral lymphocyte count; PLR = peripheral platelet count/peripheral blood lymphocyte count; MLR = peripheral blood monocyte count/peripheral blood lymphocyte count; and AGR = the absolute value of peripheral albumin/the absolute value of peripheral globulin. The optimal cut-off values for NLR, PLR, MLR, and AGR were determined according to receiver operating characteristic curve (ROC): NLR (NLR \leq 1.36, NLR $>$ 1.36), PLR (PLR \leq 132, PLR $>$ 132), MLR (MLR \leq 0.27, MLR $>$ 0.27), and AGR (AGR \leq 1.75, AGR $>$ 1.75).

Statistical Analysis

The correlation between APS and the clinicopathological parameters of ESCC patients was evaluated using the Chi-square test. Kaplan-Meier analysis were used for survival analysis. Multivariate survival analyses were conducted using the Cox Proportional Risk Model. The predictive efficacies of independent prognostic factors were evaluated and compared using the area under the time-dependent ROC-curve (AUC). The nomogram was established in accordance with the Akaike Information Guidelines. Bootstrap repeat sampling (1000 bootstrap re-samplings) was used for the verification and calibration of the nomogram. All statistical analyses were conducted using SPSS 22.0 (Chicago, IL, USA), Graph Pad Prism 6 (La Jolla, CA, USA) and R 3.0.3 Software (Vienna, Austria). $P < 0.05$ was considered significant.

Results

Correlations Between Systemic Inflammatory Index, Nutritional Index, and ESCC Patient Prognosis

A total of 633 patients with ESCC were included in this study, including 450 in the original cohort and 183 in the validation cohort. The baseline clinical and demographic data for patients in both the original and validation cohorts are displayed in Table 1. In the original cohort, the optimal cut-off values of PLR, NLR, MLR, and AGR for ESCC patient

survival prediction were determined based on the ROC curve, and the results were 132, 1.36, 0.27, and 1.75, respectively. All patients were divided into high-level and low-level groups according to the optimal cut-off values. Using Kaplan-Meier survival analysis, we found that patients with high levels of PLR, NLR, and MLR and low levels of AGR were associated with shorter survival times (Figure 1A–D, all $P < 0.05$). Univariate analysis was subsequently conducted to investigate which clinicopathological variables were associated with postoperative survival among ESCC patients in the original cohort. Tumor grade, TNM stage, PLR, NLR, MLR and AGR were identified as potential to be the risk factors affecting the prognosis of ESCC patients (Table 2). Significant clinicopathological variables identified by the univariate analysis were then incorporated into the multivariate Cox proportional hazard model to determine independent prognostic factors. Tumor grade, TNM stage, PLR, and AGR were identified as independent risk factors affecting the OS of ESCC patients based on the multivariate analysis, whereas NLR and MLR were not identified as independent prognostic factors associated with OS. According to these results, we established the APS system, which combines the PLR and AGR. The APS system included 3 categories (0, 1 and 2), as follows: APS of 0, $PLR \leq 132$ and $AGR > 1.75$; APS of 1, $PLR > 132$ or $AGR \leq 1.75$; APS of 2, $PLR > 132$ and $AGR \leq 1.75$. The correlations between the APS and clinicopathological variables among patients with ESCC are shown in Table 3. APS was associated with PLR, NLR, MLR and AGR, but not with age, sex, grade, location, T stage, N stage, or TNM stage (Table 3). A Kaplan-Meier survival analysis was performed for the established APS system. We found that OS among patients with APS of 2 was significantly shorter than that among patients with APS of 1, and the OS among patients with APS of 1 was significantly shorter than that among patients with APS of 0 (Figure 2A). Multivariate analysis was performed, which showed that APS was an independent prognostic factor for patients with ESCC (Table 2). Further analysis of the AUC predicted the 3- and 5-year survival among ESCC patients in the original cohort. We also found APS was associated with a larger AUC for the estimation of prognosis among ESCC patients compared with those for either PLR or AGR alone (Figure 2B and C). Similar results were obtained in the validation cohort (Figure 2D–F).

Table 1 Clinicopathological Characteristics of ESCC Patients

Characteristic	Original Queue (n=450)		Validation Queue (n=183)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	343	76.4	142	77.6
Female	107	23.6	41	22.4
Age				
≤60	210	46.7	72	39.3
>60	240	53.3	111	60.4
Tumor location				
Upper	30	6.7	8	4.3
Middle	270	60.0	111	60.7
Lower	150	33.3	64	35.0
Histological grade				
Well differentiated	26	5.8	15	8.2
Moderately differentiated	198	44.0	95	51.9
Poorly or not differentiated	226	50.2	73	39.9
T stage				
T1	106	23.5	49	26.8
T2	120	26.7	45	24.6
T3	213	47.3	89	48.6
T4a	11	2.4	0	0.00
N stage				
N0	241	53.6	66	36.1
N1	134	29.8	72	39.3
N2	62	13.8	37	20.2
N3	13	2.9	8	4.4
TNM stage (AJCC, 8th)				
I	78	17.3	38	20.8
II	215	47.8	50	27.3
III	157	34.9	95	52.0

Abbreviations: ESCC, esophageal squamous cell carcinoma; TNM, tumor, node, metastasis; AJCC, American Joint Committee on Cancer.

Nomogram Establishment and Prognosis Performance Assessment

To further investigate the prognostic value of the APS system, we aimed to extract the optimal predictive model

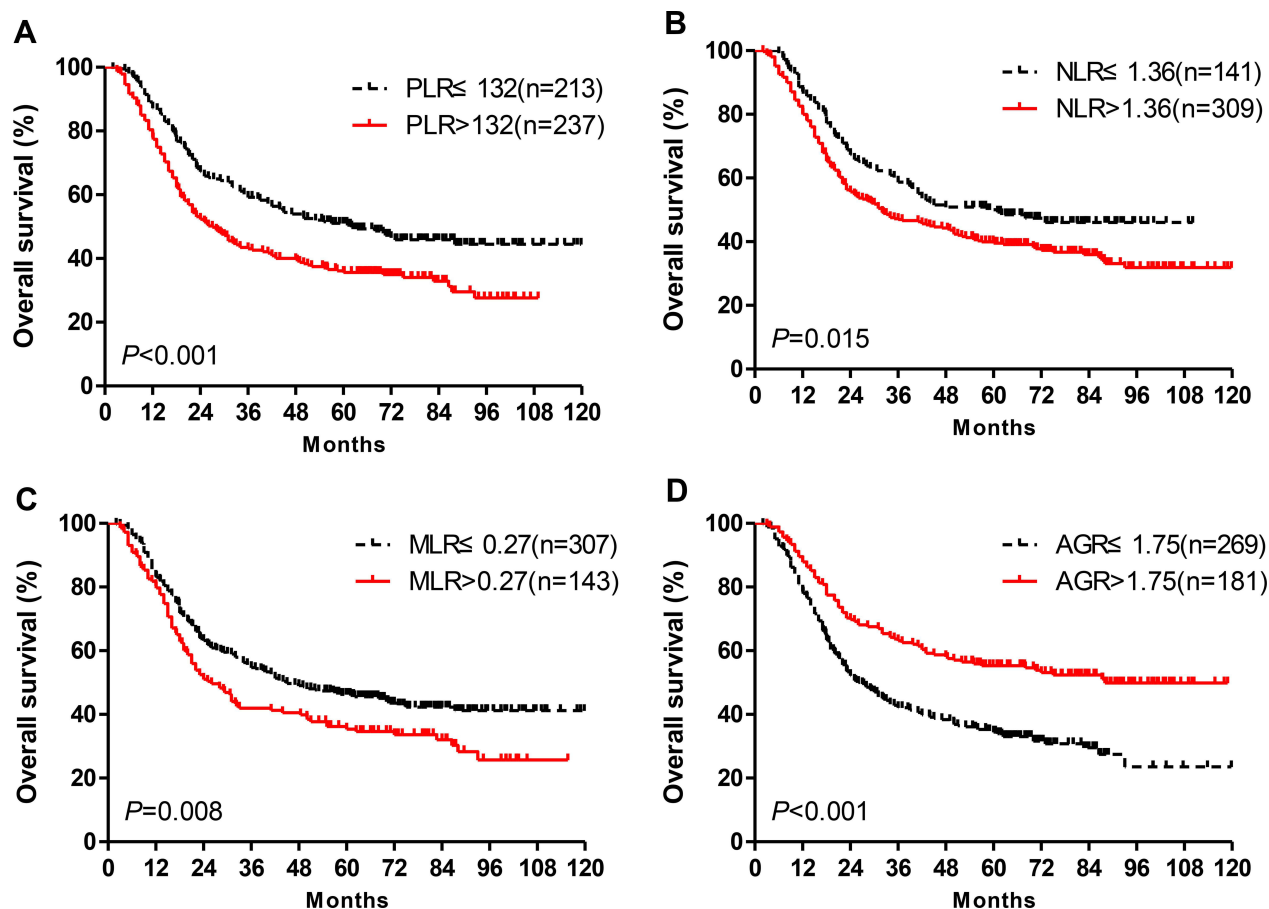


Figure 1 The prognostic significance is based on the PLR (A), NLR (B), MLR (C) and AGR (D) in ESCC patients from the original cohort.

from the original cohort based on the Cox proportional hazard regression modeling method. Subsequently, a nomogram was established, including tumor grade, APS, and TNM stage for the prediction of 3- and 5-year survival among ESCC patients (Figure 3). The C-index of the nomogram was 0.80, which was significantly higher than that of TNM (0.73, $P < 0.001$). The calibrated 3- and 5-year survival rates indicated that the nomogram predictions were highly coordinated with real-world observations (Figure 4A and B). We also investigated differences in the prognostic prediction capabilities between the established nomogram and the traditional TNM staging system using AUC analysis. We found that the AUC of the established nomogram was larger than that for the TNM staging system (Figure 4C and D), indicating that our nomogram was a more accurate method for OS prediction among ESCC patients after surgery.

The established nomogram was then verified in the 183 patients' validation cohort. In the validation cohort, the 3- and 5-year survival rates predicted by the calibrated curve

of the nomogram were consistent with real-world observations (Figure 5A and B). The AUC value for the nomogram was significantly higher than that for the TNM staging system (Figure 5C and D). Collectively, these results demonstrate that the nomogram was more accurate and effective for the prediction of survival among ESCC patients than existing methods.

Discussion

Currently, prognostic prediction and postoperative treatment plan establishment among ESCC patients are based primarily on the TNM staging system. However, due to tumor heterogeneity, differences in the prognosis of ESCC patients within the same TNM stage were observed.¹¹ Some studies have confirmed that the nomogram model based on TNM stage can predict the prognosis of ESCC patients more accurately than TNM stage alone.^{7,12,13} Therefore, autologous prognostic indicators were combined with the TNM staging system to improve prognostic prediction accuracy among ESCC patients. In recent years, accumulating

Table 2 Univariate and Multivariate Cox Regression Analyses for Overall Survival in Patients with ESCC in Original Queue

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex: Male vs Female	0.83 (0.62–1.10)	0.194		
Age: >60 vs ≤60	1.12 (1.00–1.27)	0.050		
Tumor location		0.989		
Middle vs Upper	1.00 (0.62–1.63)	0.994		
Lower vs Upper	0.98 (0.59–1.63)	0.945		
Grade		<0.001*		0.002*
Moderately vs Well	3.64 (1.48–8.92)	0.005*	1.79 (0.70–4.58)	
Poorly vs Well	5.85 (2.40–14.27)	<0.001*	2.63 (1.04–6.72)	
TNM stage (AJCC, 8th)		<0.001*		<0.001*
II vs I	2.86 (1.80–4.54)	<0.001*	2.36 (1.45–3.84)	0.001*
III vs I	5.82 (3.65–9.28)	<0.001*	4.68 (2.87–7.62)	<0.001*
PLR: >132 vs ≤132	1.55 (1.22–1.97)	<0.001*	1.44 (1.11–1.86)	0.006*
NLR: >1.36 vs ≤1.36	1.39 (1.06–1.81)	0.017*	1.11 (0.84–1.46)	0.474
MLR: >0.27 vs ≤0.27	1.39 (1.09–1.78)	0.009*	1.24 (0.95–1.63)	0.108
AGR: >1.75 vs ≤1.75	0.54 (0.42–0.70)	<0.001*	0.54 (0.42–0.71)	<0.001*
APS		<0.001*		<0.001*
1 vs 0	2.12 (1.44–3.12)	<0.001*	2.11 (1.43–3.11)	<0.001*
2 vs 0	3.17 (2.12–4.72)	<0.001*	3.34 (2.24–4.98)	<0.001*

Note: *Represents a statistically difference.

Abbreviations: ESCC, esophageal squamous cell carcinoma; TNM, tumor, node, metastasis; AJCC, American Joint Committee on Cancer; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; AGR, albumin-globulin ratio; APS, AGR-PLR score.

evidence has demonstrated the key roles played by the chronic inflammatory response in tumorigenesis, invasion and metastasis for various tumor types. The associated inflammatory and nutritional indicators in peripheral blood, such as PLR, NLR, MLR and AGR, have been closely associated with the prognosis of patients with various types of tumors.^{7–10} Due to the advantages of high repeatability, high accuracy and low cost associated with the assessment of inflammation indicators in peripheral blood, the contributions of inflammatory and nutrition-related indicators in peripheral blood on tumors prognosis and diagnosis have attracted increasing attention.

Plasma albumin and globulin are two important components of human plasma that have been demonstrated to play important roles during the anti-tumor response.¹⁴ Reductions in plasma albumin levels serve as an indicator of poor nutritional status and the occurrences of chronic inflammatory reactions. In a variety of malignant tumors, including lung, nasopharyngeal and breast cancers, low albumin levels have been demonstrated to serve as an

independent prognostic factor in patients.^{15,16} Plasma globulin is synthesized by immune organs, and the levels of plasma globulin directly reflect the status of inflammatory and immune responses.¹⁷ In the inflammatory microenvironment, plasma globulin levels are promoted by various inflammatory factors. As reported by previous studies, plasma globulin levels are significantly correlated with poor prognosis among patients with malignant tumors.^{18,19} Recently, AGR (calculated as the ratio between albumin and globulin levels in the serum) has been identified as an important indicator for tumors evaluation, including ESCC.^{9,10,20} As reported by Oki et al, the preoperative reduction of AGR levels was associated with poor prognosis, increased tumor infiltration depth, and positive lymph node metastasis in ESCC patients.⁹ Poor OS IN patients with ESCC was found to be associated with low AGR levels.^{10,20} Consistently, in our study, we identified AGR to be an independent prognostic indicator for ESCC patients. Patients with low AGR levels presented with a shorter life span after surgery.

Table 3 Baseline Characteristics for ESCC Patients with APS in Original Queue

Clinical Parameter	APS=0 (86)	APS=1 (222)	APS=2 (142)	χ^2	P
Sex				3.32	0.190
Male	69	161	113		
Female	17	61	29		
Age				1.10	0.576
≤60	47	113	80		
>60	39	109	62		
Histological grade				1.95	0.745
Well differentiated	7	12	7		
Moderately differentiated	40	94	64		
Poorly or not differentiated	39	116	71		
Tumor location				1.26	0.868
Upper	4	17	9		
Middle	54	133	83		
Lower	28	72	50		
T stage				3.26	0.775
T1	22	50	34		
T2	27	54	39		
T3	36	112	65		
T4	1	6	4		
N stage				7.62	0.267
N0	49	122	70		
N1	26	69	39		
N2	10	24	28		
N3	1	7	5		
TNM stage (AJCC, 8th)				1.88	0.758
I	15	39	24		
II	46	104	65		
III	25	79	53		
PLR				231.99	<0.001*
PLR≤132	86	127	0		
PLR>132	0	95	142		
NLR				11.25	0.004*
NLR≤1.36	35	76	30		
NLR>1.36	51	146	112		
MLR				5.07	0.079
MLR≤0.27	59	161	87		
MLR>0.27	27	61	55		
AGR				223.96	<0.001*
AGR≤1.75	0	127	142		
AGR>1.75	86	95	0		

Note: *Represents a statistically difference.

Abbreviations: ESCC, esophageal squamous cell carcinoma; TNM, tumor, node, metastasis; AJCC, American Joint Committee on Cancer; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; AGR, albumin-globulin ratio; APS, AGR-PLR score.

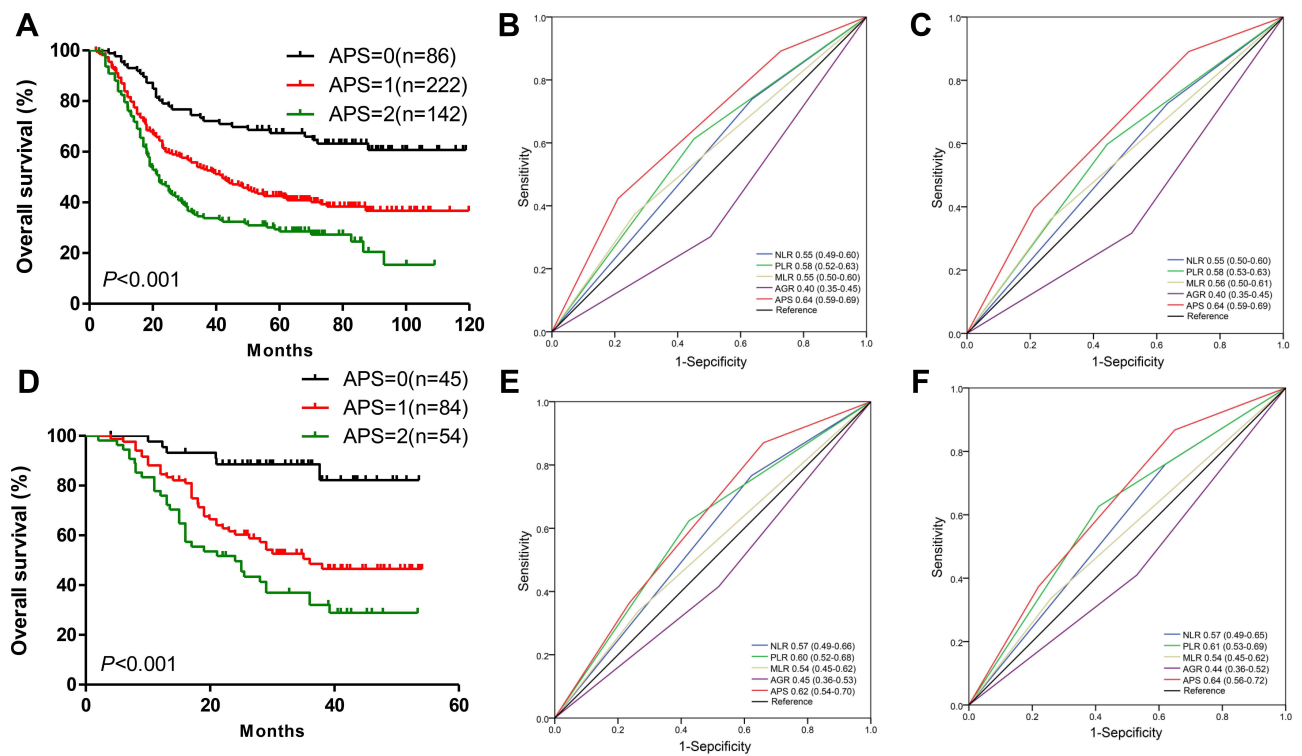


Figure 2 (A) The prognostic significance based on the APS among ESCC patients in the original cohort. (B and C) The predictive ability of the APS in ESCC was compared against the predictive abilities of PLR, NLR, MLR, and AGR by ROC curves in 3-years or 5-year in original cohort. (D) The prognostic significance is based on APS among ESCC patients in validation cohort. (E and F) The predictive ability of the APS in ESCC was compared against the predictive abilities of PLR, NLR, MLR, and AGR by ROC curves for 3-years or 5-year in validation cohort.

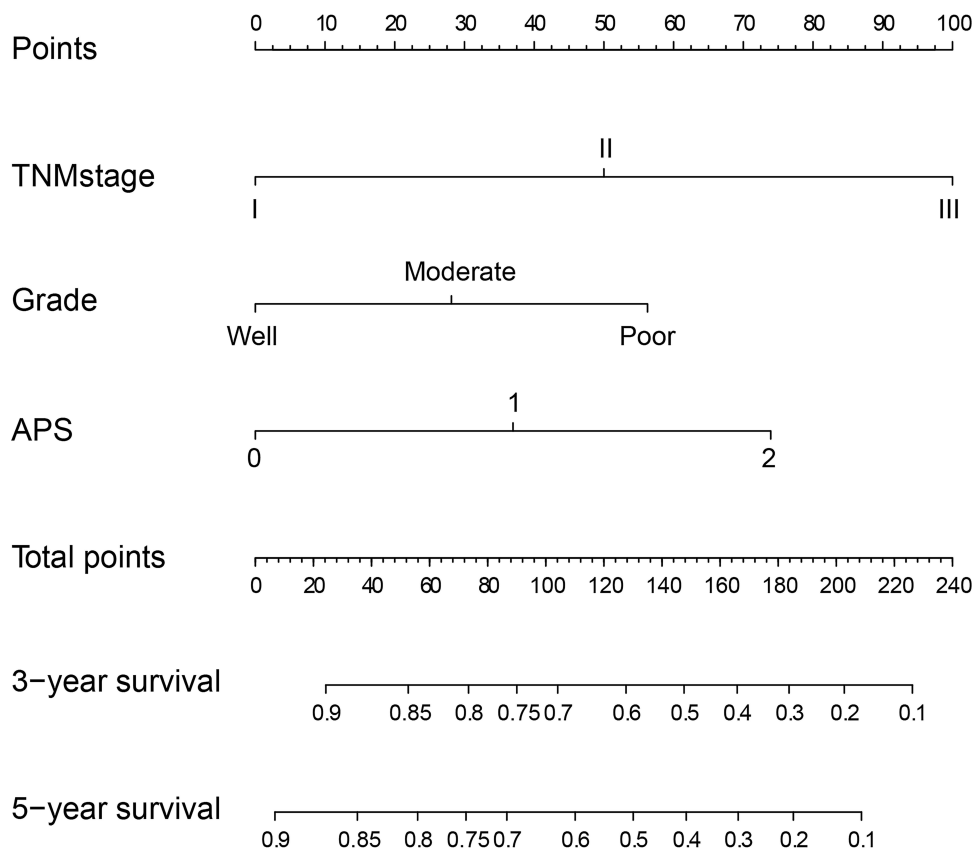


Figure 3 The nomogram integrating APS, TNM stage, and grade for the prediction of the 3- and 5-year survival rates of ESCC patients.

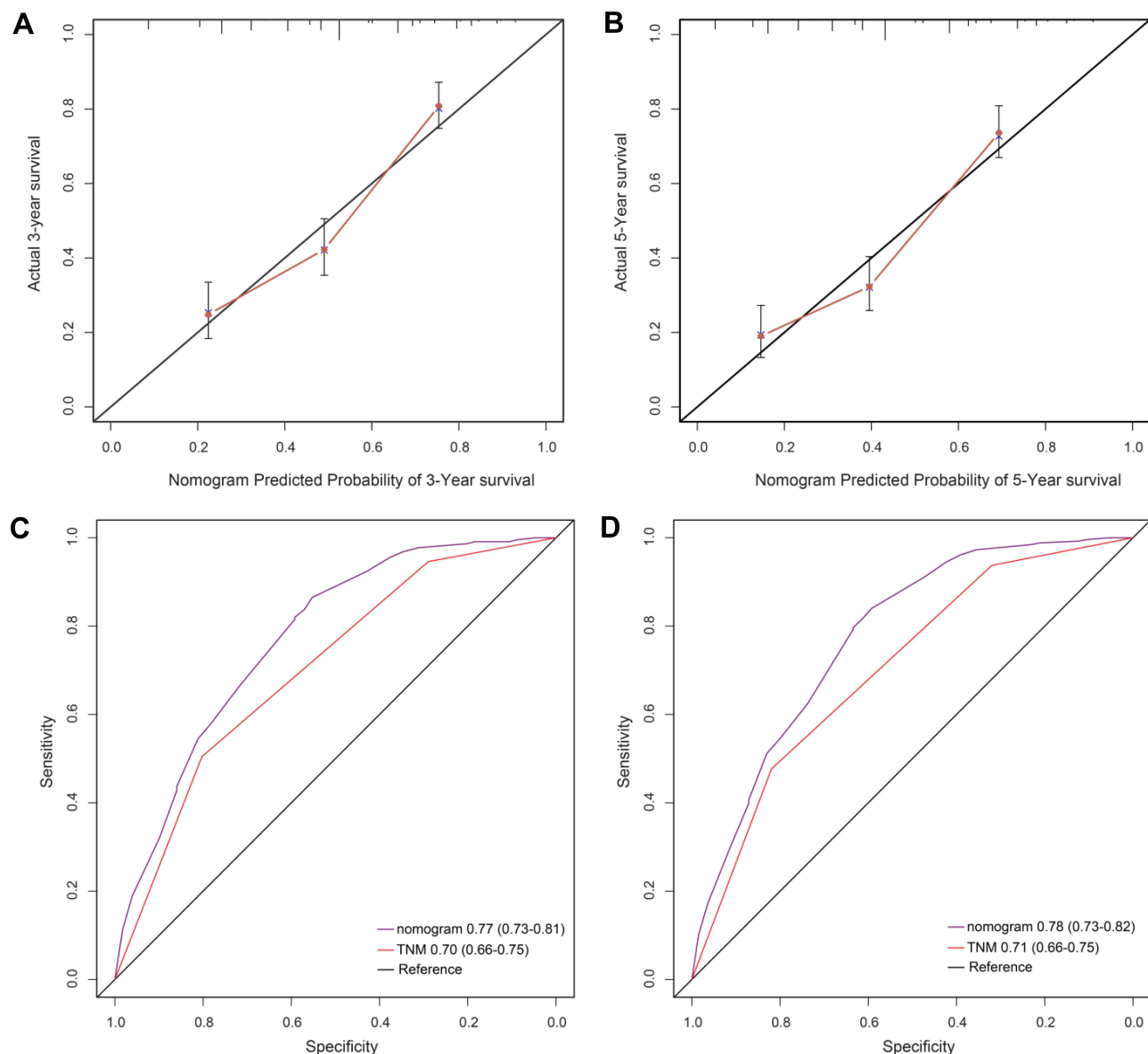


Figure 4 (A) The 3-year survival rate of ESCC patients predicted by the nomogram was highly consistent with the real-world, observed values in the original cohort. (B) The 5-year survival rate of ESCC patients predicted by the nomogram was highly consistent with the real-world, observed values in original cohort. (C) The ability of the nomogram to predict the 3-year survival rate of ESCC patients by ROC analysis, showing that the nomogram has a larger AUC than the TNM staging in original cohort. (D) The ability of the nomogram to predict the 5-year survival rate of ESCC patients by ROC analysis, showing that the nomogram has a larger AUC than TNM staging in original cohort.

Prior to this study, systemic inflammatory indicators including NLR, PLR, and MLR were reported to be key factors associated with ESCC prognosis.^{7,8} Xie et al found that poor survival prognosis among patients with Phase I and II ESCC was associated with high PLR.²¹ This association could potentially be explained by the promotion of tumor proliferation caused by the secretion of PDGF and TGF- β from platelets. Rapid tumor proliferation, in turn, promotes compensatory hyperplasia among platelets. In addition, platelets and neutrophils also promote the adhesion and seeding of distant organs through

the secretion of VEGF.²² In our study, we confirmed that both NLR and MLR were factors associated with ESCC survival, and PLR was identified as an independent prognostic factor for ESCC.

In this study, we established the APS system using PLR and AGR. The APS demonstrated better prognostic accuracy and effectiveness in ESCC patients than either PLR or AGR alone. In addition, a new nomogram for prognostic prediction was established according to tumor grade, APS and TNM stage. Compared with the traditional 8th version of the TNM staging system, this nomogram demonstrated improved

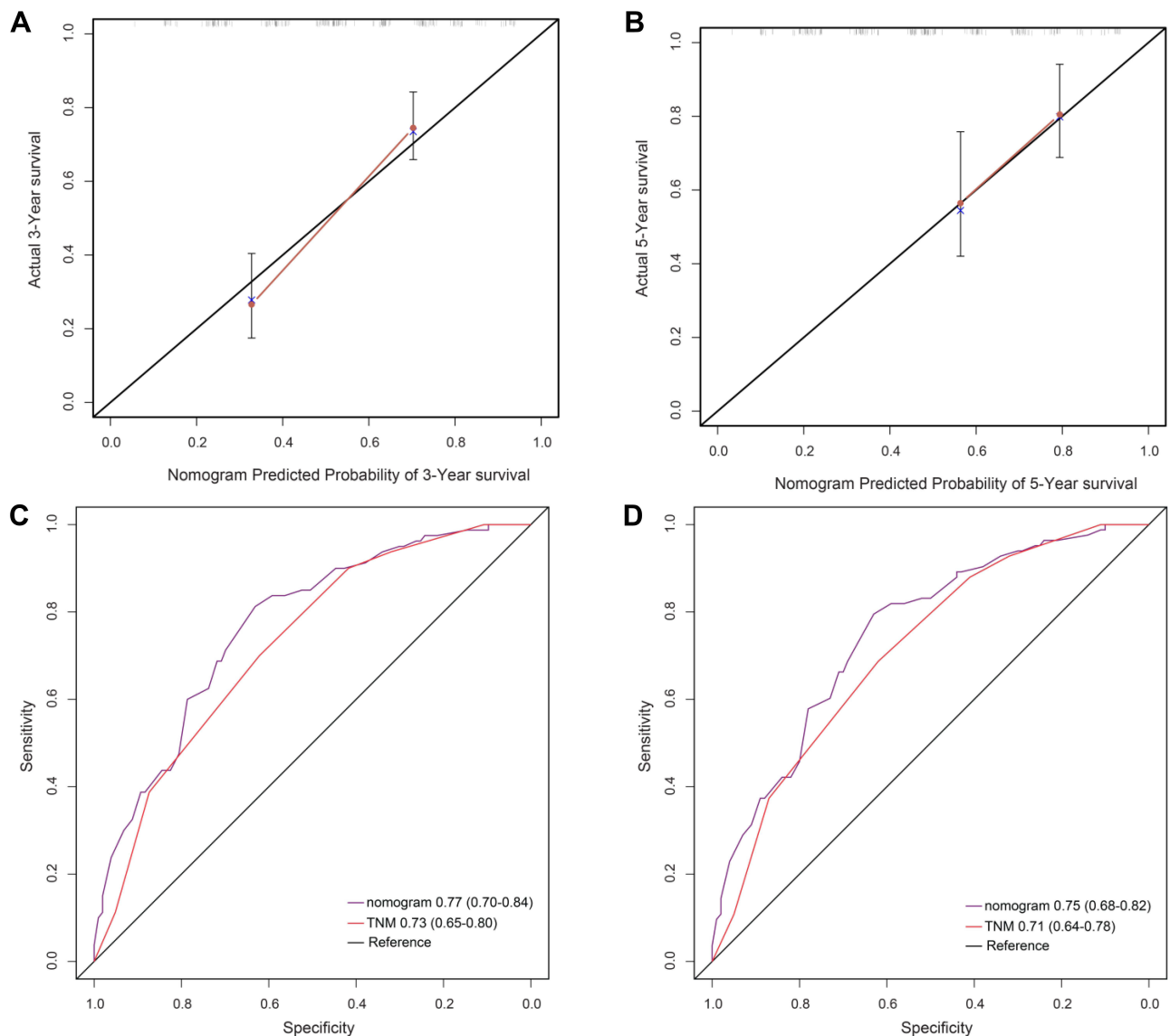


Figure 5 (A) The 3-year survival rate of ESCC patients predicted by the nomogram is highly consistent with the real-world, observed values in the validation cohort. (B) The 5-year survival rate of ESCC patients predicted by the nomogram is highly consistent with the real-world, observed values in the validation cohort. (C) The ability of the nomogram to predict the 3-year survival rate of ESCC patients by ROC analysis, showing that the nomogram has a larger AUC than the TNM staging in validation cohort. (D) The ability of the nomogram to predict the 5-year survival rate of ESCC patients by ROC analysis, showing that the nomogram has a larger AUC than the TNM staging in validation cohort.

sensitivity and specificity for the prediction of the 3- and 5-year survival. This result was subsequently confirmed using a separate validation cohort. As demonstrated by the calibrated nomogram in both the testing and validation cohorts, the predicted survival rate was highly consistent with the real-world observations. Therefore, we believed that APS and the APS-based prognostic nomogram represent promising effective and accurate indicators for survival prediction among ESCC patients.

In our results, we demonstrated the practical values of APS for prognostic prediction in ESCC patients. However,

this result was limited for the following reasons. First, the data used to establish the nomogram were obtained from a single medical institution. Second, as is typical of retrospective studies, the potentials of selection bias, detection bias, and analysis bias are inevitable. Third, the cut-off values used in this study were not further validated. Fourth, the current standard treatment for operable N+ or T3-4 locally advanced ESCC patients is neoadjuvant chemoradiotherapy plus surgery. However, our study includes a part of patients who need neoadjuvant treatment have undergone surgery alone. Our results maybe only suitable

for operable esophageal cancer patients who have not undergone neoadjuvant chemoradiation. Therefore, further validation of the prognostic significance of APS in large-scale prospective studies and across more pathological types of EC patients remains necessary.

Conclusion

APS is a novel independent prognostic indicator among patients after the radical resection of ESCC and serves as a potential biomarker for the monitoring of the therapeutic response. The prognostic nomogram that was established integrating APS was able to objectively and reliably predicted survival among ESCC patients after radical resection, with better performance than the traditional TNM staging system. Therefore, this nomogram could facilitate the distinction among different ESCC patients according to predicted survival outcome and allow for the early establishment of precise and timely individualized treatment strategies.

Code Availability

The authors declare that all data and R scripts supporting the findings of this study are available from the corresponding author upon reasonable request.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Statement

The study protocol was performed in accordance with the guidelines outlined in the Declaration of Helsinki. The Ethics Committee of the First Affiliated Hospital of Soochow University approved the study, and all participants signed informed consent statements.

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Disclosure

The authors declare that they have no competing interests.

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