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ORIGINAL RESEARCH

Association of Naples Prognostic Score with Survival in Patients with Inoperable Esophageal Squamous Cell Carcinoma Undergoing Chemoradiotherapy Combined with Immunotherapy

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Objective: This study aimed to determine whether the Naples Prognostic Score (NPS) is an independent predictor of overall survival (OS) and progression-free survival (PFS) in patients with unresectable esophageal squamous cell carcinoma (ESCC) undergoing chemoradiotherapy combined with immunotherapy.

Materials and Methods: We analyzed 139 patients with inoperable ESCC undergoing chemoradiotherapy combined with immunotherapy between January 2020 and November 2024. We systematically evaluated the associations between NPS categories and clinical features across these cohorts. Kaplan-Meier analysis was employed to generate survival curves stratified by NPS. Univariate and multivariate Cox models assessed NPS as an independent predictor of OS and PFS for risk stratification.

Results: Stratification analysis based on the NPS revealed distinct survival outcomes: the median OS was 23 months for Group 0, 17.5 months for Group 1, and 11 months for Group 2. The corresponding PFS durations were 19.5 months (Group 0), 15 months (Group 1), and 9 months (Group 2), respectively. The prognostic value of NPS was confirmed by receiver operating characteristic (ROC) curve analysis, which yielded an area under the curve (AUC) of 0.701 ($P < 0.05$). Importantly, multivariate Cox regression analysis established NPS as an independent prognostic factor for both OS (HR: 2.404; 95% CI: 1.411–4.095; $P < 0.01$) and PFS (HR: 2.203; 95% CI: 1.321–3.674; $P = 0.02$). These results highlight the clinical significance of NPS in prognostic assessment and treatment strategy formulation for patients with inoperable ESCC.

Conclusion: The NPS has been demonstrated to be a reliable prognostic tool in unresectable ESCC. It provides a practical framework for baseline risk stratification at diagnosis to identify high-risk patients who may benefit from intensified nutritional support, closer surveillance, or enrollment in novel immunotherapy trials, thereby guiding personalized treatment and optimizing resource use.

Keywords: naples prognostic score, predictive values, inoperable ESCC, chemoradiotherapy, immunotherapy

Introduction

Esophageal cancer is the eighth most prevalent malignancy worldwide and the sixth leading cause of cancer-related mortality.[1] Owing to nonspecific early symptoms and a lack of effective screening, the majority of patients with esophageal squamous cell carcinoma (ESCC) are diagnosed at a locally advanced stage (T3-4) or with regional nodal disease that is not amenable to resection.[2] For these locally advanced, unresectable cases, concurrent chemoradiotherapy combined with immunotherapy has been established as the standard therapeutic paradigm; nevertheless, long-term outcomes remain suboptimal, with 5-year survival rates languishing at just 35.8%.[3] In this therapeutic milieu, the ability

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to robustly identify prognostically distinct patient subsets to guide individualized management constitutes a critical and as yet unmet clinical imperative.

Accumulating evidence underscores the pivotal role of systemic inflammation in cancer initiation, progression, and metastasis. Clinically accessible inflammatory biomarkers-including absolute peripheral blood cell counts (neutrophils, leukocytes, lymphocytes, and monocytes) and derived ratios including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have demonstrated prognostic relevance in predicting overall survival (OS) in cancer patients.[4] Furthermore, nutritional status has emerged as a critical determinant of oncological outcomes. Established nutritional indices, including the Prognostic Nutritional Index (PNI), Controlling Nutritional Status (CONUT) and modified Glasgow Prognostic Score (mGPS), have been demonstrated to be reliable predictors of cancer prognosis.[5,6]

The Naples Prognostic Score (NPS), a novel composite metric integrating inflammatory and nutritional parameters, has emerged as a robust prognostic tool in oncology. This composite metric incorporates key indicators including serum albumin levels, total cholesterol concentrations, NLR, and LMR, comprehensively evaluating systemic inflammatory status and nutritional homeostasis. Its clinical validity has been established across various malignancies such as colorectal cancer,[7] endometrial cancer,[8] and esophageal cancer.[9] However, within the cohort of patients with unresectable ESCC, and specifically under the contemporary dual-modality regimen of concurrent chemoradiotherapy combined with immunotherapy, the prognostic relevance of the NPS remains inadequately characterized. This study targets that unmet need by delivering the first systematic appraisal of NPS prognostic performance in the context of this therapeutic paradigm.

Patients and Methods

Study Population

This retrospective cohort analysis evaluated 139 patients with inoperable ESCC who underwent definitive chemoradiotherapy combined with immunotherapy at Weifang People's Hospital between January 2020 and November 2024. The inclusion criteria were as follows: (1) histopathological or cytologically confirmed ESCC; (2) absence of distant metastatic lesions; (3) no prior antitumor therapy (including chemotherapy, radiotherapy, or targeted agents); and (4) availability of complete pretreatment laboratory and radiographic data. The exclusion criteria comprised: (1) active inflammatory or infectious diseases at baseline evaluation; (2) documented malignancies at other anatomical sites; and (3) severe comorbidities (eg, autoimmune disorders, end-stage organ failure) that significantly compromise immune function or nutritional status.

This study received approval from the Ethics Committee of Weifang People's Hospital, Shandong Second Medical University (approval number: KYLL20250508-3). As a retrospective analysis, the requirement for written informed consent was waived in accordance with institutional guidelines. The research strictly followed the principles set forth in the Declaration of Helsinki. All patient medical data were anonymized and managed securely to maintain confidentiality.

Data Collection

Prior to initiating chemoradiotherapy combined with immunotherapy, all patients underwent comprehensive laboratory evaluations, including complete blood count (CBC) and biochemical profiling. These results were obtained from the database of Weifang People's Hospital to ensure data accuracy and reliability. Utilizing the Clinical Information System (CIS), a series of key variables were extracted from the electronic medical records of each participant. The dataset encompassed 23 variables: sex, age at diagnosis, Karnofsky Performance Status (KPS) score, smoking status, alcohol consumption, tumor location, histologic differentiation, clinical stage, T-stage, N-stage, tumor size, total cholesterol (TC), NLR, LMR, serum albumin levels, carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA19-9), Squamous Cell Carcinoma Antigen (SCC); Cytokeratin 19 Fragment (CYFRA), systemic immune-inflammation index (SII), PNI, progression-free survival (PFS) and OS. These variables were systematically collected in accordance with standardized oncological research protocols to evaluate clinical characteristics, therapeutic interventions, and prognostic outcomes.

Procedures of Treatment

The treatment protocol entailed 5–6 weeks of intensity-modulated radiation therapy (IMRT) in conjunction with systemic chemotherapy, employing either fluorouracil combined with cisplatin or paclitaxel combined with carboplatin, administered concurrently with immunotherapy. Prior to radiotherapy initiation, all participants underwent baseline diagnostic chest CT imaging. Contrast-enhanced high-resolution CT imaging facilitated the delineation of personalized radiation targets based on individual tumor morphology. Radiation doses were administered at 50–60 Gy in daily fractions of 1.8–2.0 Gy, delivered five times per week. Two board-certified radiation oncologists conducted independent verification of all treatment plans through dual-review quality control protocols.

Definitions and Grouping in NPS, PNI and SII

The NPS consolidates four biomarkers: serum albumin (≥4 g/dL), total cholesterol (>180 mg/dL), NLR<2.96, and LMR>4.44. For each parameter meeting the predefined threshold, 0 points are assigned; deviations from these criteria result in 1 point. Patients are stratified into three prognostic tiers based on cumulative scores: 0 points (low-risk), 1–2 points (intermediate-risk), and 3–4 points (high-risk). The relevant critical values and grouping methods were all derived from relevant literature.[10–12] The PNI is equal to the sum of serum albumin level (in g/L) and lymphocyte count ($\times 10^9$/L) multiplied by 5. Receiver operating characteristic (ROC) curve analysis based on PFS was used to determine the optimal cutoff value for the PNI. This identified a critical value of 55.58, allowing for the stratification of patients into two groups: PNI ≥55.58 (no nutritional risk) and PNI<55.58 (nutritional risk). Similarly, the SII is defined as platelet count × neutrophil count / lymphocyte count ($\times 10^9$/L). Using PFS based ROC analysis, we established thresholds of <594.4 $\times 10^9$/L for favorable prognosis and ≥594.4 $\times 10^9$/L for poor prognosis, highlighting the dynamic relationship between systemic inflammation and survival outcomes. By integrating both nutritional and inflammatory biomarkers, these indices refine risk stratification accuracy, offering clinicians practical, noninvasive tools to tailor therapeutic strategies in oncology.

Follow-Up

PFS was defined as the time from randomization to the first occurrence of tumor progression or death from any cause, whichever came first. OS was measured from the date of initial diagnosis until death from any cause. During the first three years, patients received structured follow-up evaluations every three months, which were then conducted every six months for the subsequent two years, and annually after five years. The follow-up data were rigorously extracted from our institution's medical records and verified prior to November 2024.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 8.4.3. Associations between categorical variables and correlations between categorical data and the NPS were evaluated using Chi-square tests, as appropriate. ROC curves were generated to assess the prognostic discriminative capacity and comparative performance of the scoring systems. Survival distributions were visualized using the Kaplan-Meier analyses, with intergroup prognostic disparities analyzed using Log rank tests. Variables demonstrating statistical significance ($P<0.05$) in univariate analyses were subsequently integrated into multivariate analyses using Cox proportional hazards regression models to identify independent prognostic determinants. A threshold of $P<0.05$ was established to denote statistical significance.

Results

Patient Characteristics

Between January 2020 and November 2024, a total of 139 patients with inoperable ESCC underwent chemoradiotherapy combined with immunotherapy (Figure 1). The cohort comprised 56 females (40.3%) and 83 males (59.7%), with 94 patients (67.6%) aged >60 years and 45 patients (32.4%) ≤60 years. Tumor distribution analysis revealed 95 cases (68.3%) in the upper/middle esophagus and 44 cases (31.7%) in the lower esophagus. Disease staging demonstrated 24 patients (17.3%) in stage II–III and 115 patients (82.7%) in stage IV. During follow-up, 87 patients (62.6%) developed

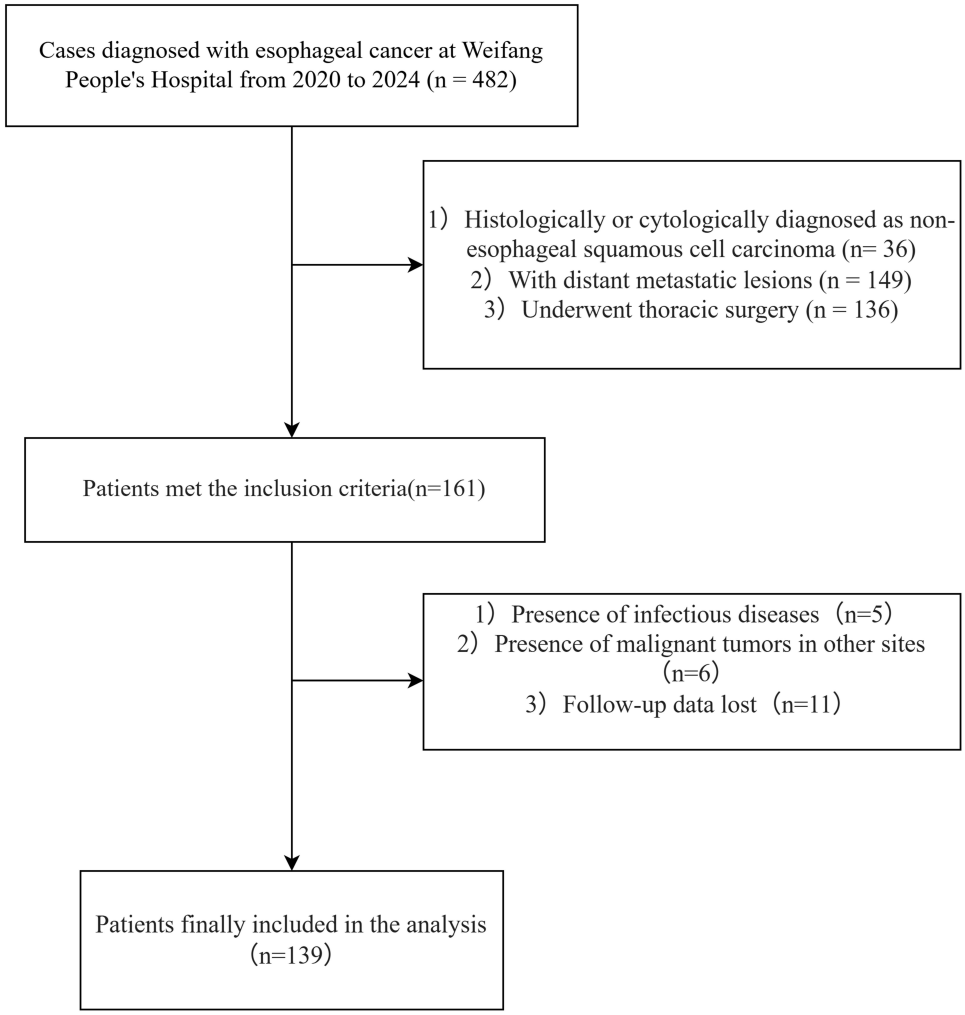

Figure 1 Screening Flowchart.

disease recurrence or metastasis, with 62 patients (44.6%) succumbing to the disease. Comprehensive demographic, clinical, and baseline laboratory parameters are detailed in Table 1.

Associations Between NPS and Clinicopathological Parameters of ESCC Patients

Based on the NPS classification system, patients were stratified into three prognostic groups: Group 0 (n=26, 18.7%), Group 1 (n=60, 43.2%), and Group 2 (n=53, 38.1%) (Table 2). Comparative analysis revealed no statistically significant

Table 1 Clinicopathological Variables in Inoperable ESCC Patients

Variable	N (%)
Age (years)	
≤60	45 (32.4)
>60	94 (67.6)
Gender	
Female	56 (40.3)
Male	83 (59.7)

(*Continued*)

Table 1 (Continued).

Variable	N (%)
KPS performance status	
90-100	95 (68.3)
80-90	44 (31.7)
Smoking	
No	44 (31.7)
Yes	95 (68.3)
Alcohol abuse	
No	57 (41)
Yes	82 (59)
Histological grade	
Well or Moderated	16 (11.5)
Poorly	123 (88.5)
Tumor location	
Lower	44 (31.7)
Upper or middle	95 (68.3)
Tumor size (cm)	
<5cm	92 (66.2)
≥5cm	47 (33.8)
TNM stage	
II–III	24 (17.3)
IV	115 (82.7)
T stage	
T1-2	7 (5)
T3-4	132 (95)
Lymph node metastasis	
N0-1	77 (55.4)
N2-3	62 (44.6)
CEA	
Normal	134 (96.4)
High	5 (0.36)
CA199	
Normal	131 (94.2)
High	8 (0.58)
SCC	
Normal	102 (73.4)
High	37 (26.6)
CYFRA	
Normal	122 (87.8)
High	17 (12.2)
NPS	
0,1	86 (61.9)
2	53 (38.1)
NLR	
Low	73 (52.5)
High	66 (47.5)
LMR	
Low	1 (0.1)
High	138 (99.9)

(*Continued*)

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Table 1 (Continued).

Variable	N (%)
SII	
Low	56 (40.3)
High	83 (59.7)
PNI	
Low	128 (92.1)
High	11 (7.9)

Abbreviations: KPS, Karnofsky Performance Status; CEA, Carcinoembryonic Antigen; CA199, Cancer Antigen 19–9; SCC, Squamous Cell Carcinoma Antigen; CYFRA, Cytokeratin 19 Fragment; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-inflammation Index, PNI, Prognostic Nutritional Index.

Table 2 Association of the NPS with the Clinicopathological Variables

Variable	NPS			P value
	Group 0 (n=26)	Group 1 (n=60)	Group 2 (n=53)	
Age (years)				0.742
≤60	10 (38.5)	18 (30)	17 (32.1)	
>60	16 (61.5)	42 (70)	36 (67.9)	
Gender				0.625
Female	1 (3.8)	6 (10)	5 (9.4)	
Male	25 (96.2)	54 (90)	48 (90.6)	
KPS performance status				0.359
90-100	17 (65.4)	38 (63.3)	40 (75.5)	
80-90	9 (34.6)	22 (36.7)	13 (24.5)	
Smoking				0.359
No	9 (34.6)	22 (36.7)	13 (24.5)	
Yes	17 (65.4)	38 (63.3)	40 (75.5)	
Alcohol abuse				0.705
No	10 (38.5)	27 (45)	20 (37.7)	
Yes	16 (61.5)	33 (55)	33 (62.3)	
Histological grade				0.464
Well or Moderated	3 (11.5)	9 (15)	4 (7.5)	
Poorly	23 (88.5)	51 (85)	49 (92.5)	
Tumor location				0.141
Lower	4 (15.4)	21 (35)	19 (35.8)	
Upper or middle	22 (84.6)	39 (65)	34 (64.2)	
Tumor size (cm)				0.529
<5cm	17 (65.4)	37 (61.7)	38 (71.7)	
≥5cm	9 (34.6)	23 (38.3)	15 (28.3)	
TNM stage				0.289
II–III	24 (92.3)	47 (78.3)	44 (83)	
IV	2 (7.7)	13 (21.7)	9 (17)	
T stage				0.026
T1-2	4 (15.4)	2 (3.3)	1 (1.9)	
T3-4	22 (84.6)	58 (96.7)	52 (98.1)	

(*Continued*)

Table 2 (Continued).

Variable	NPS			P value
	Group 0 (n=26)	Group 1 (n=60)	Group 2 (n=53)	
Lymph node metastasis				0.320
N0-1	15 (57.7)	29 (48.3)	33 (62.3)	
N2-3	11 (42.3)	31 (51.7)	20 (37.3)	
CEA				0.989
Normal	25 (96.2)	58 (96.7)	51 (96.2)	
High	1 (3.8)	2 (3.3)	2 (3.8)	
CA199				0.721
Normal	24 (92.3)	56 (93.3)	51 (96.2)	
High	2 (7.7)	4 (6.7)	2 (3.8)	
SCC				0.515
Normal	18 (69.2)	47 (78.3)	37 (69.8)	
High	8 (30.8)	13 (21.7)	16 (30.2)	
CYFRA				0.471
Normal	21 (80.8)	54 (90)	47 (88.7)	
High	5 (19.2)	6 (10)	6 (11.3)	

Abbreviations: KPS, Karnofsky Performance Status; CEA, Carcinoembryonic Antigen; CA199, Cancer Antigen 19–9; SCC, Squamous Cell Carcinoma Antigen; CYFRA, Cytokeratin 19 Fragment; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-inflammation Index; PNI, Prognostic Nutritional Index.

differences across these groups regarding baseline characteristics, including age, gender, smoking history, alcohol consumption, KPS score, tumor location, tumor size, histological grade, TNM stage, or serum tumor markers (CEA, SCC, CYFRA and CA19-9 levels; all P>0.05).

NPS System Parameter and ROC Analyses

Figure 2 displays the ROC curves comparing the prognostic performance of the NPS, NLR, SII, and PNI. The analysis demonstrated that NPS exhibited superior discriminatory power, with an AUC of 0.701 (95% CI: 0.604–0.797; P<0.001). The sensitivity, specificity, and F1 score assessing the stratification prediction ability for patient survival were 59%, 77%, and 65.5%, respectively. By comparison, NLR, SII, and PNI showed relatively weaker predictive performance, with

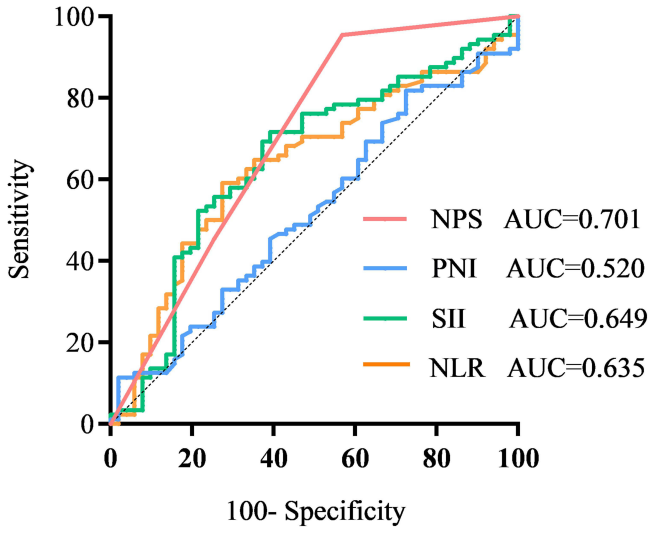

Figure 2 ROC curve analysis to evaluate the predictive value of NPS and other inflammation-related markers in patients with unresectable ESCC.
Abbreviations: ROC, Receiver operating characteristic curve; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation Index; PNI, Prognostic Nutritional Index.

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AUC values of 0.635 (P=0.007), 0.649 (P=0.004), and 0.520 (P=0.693), respectively. Evaluation of additional inflammation-associated prognostic markers yielded the following AUC values: lymphocyte count (0.580, P = 0.115), neutrophil count (0.703, P < 0.001), monocyte count (0.664, P = 0.001), serum albumin (0.462, P = 0.460), and total cholesterol (0.408, P = 0.070) (Table 3). Notably, given the suboptimal stability of neutrophil and monocyte-based parameters, the NPS emerged as the most robust predictive tool in this clinical context.

Univariate Analyses of Prognostic Factors for OS and PFS in Inoperable ESCC Patients

Univariate analysis of clinical pathological variables and inflammation-related prognostic scoring systems revealed that tumor location (P=0.005) and NPS (P<0.001) were significantly associated with OS, while NPS (P<0.001), NLR (P<0.001), and SII (P=0.01) were significantly associated with PFS (Table 4 and Table 5). We found no significant correlation between OS or PFS and age, KPS) score, tumor size, clinical staging, differentiation, PNI, serum CEA, SCC, CYFRA, and CA19-9 (all P>0.05). Kaplan-Meier analysis was performed to compare PNI, SII, NLR, and NPS. For OS, the survival curves among NPS score groups exhibited a significant separation trend (P<0.001), indicating that this scoring system has significant stratified predictive value for OS (Figure 3A). The survival curves of NLR groups displayed a statistical difference (P=0.046), with the low NLR group showing better median OS (Figure 3B). There were no significant differences observed for PNI and SII (PNI: P=0.423; SII: P=0.403) (Figure 3C and D). In terms of PFS, only PNI showed no statistical significance (P=0.252, Figure 4).

Multivariate Analyses of Prognostic Factors for OS and PFS in Inoperable ESCC Patients

To further investigate the prognostic value of NPS in patients with unresectable ESCC, variables with significance (P < 0.05) in univariate analysis were included in a multivariate Cox regression analysis (Table 6). The results demonstrated that NPS served as an independent prognostic factor for both OS (HR: 2.404; 95% CI: 1.411–4.095; P<0.001) and PFS (HR: 2.203; 95% CI: 1.321–3.674; P=0.002). Additionally, tumor location was identified as an independent predictor of OS (P=0.015).

Discussion

The establishment of a reliable prognostic prediction system is essential for guiding risk stratification and treatment strategies in patients with inoperable ESCC. The analysis of systemic inflammation and nutritional status provides a valuable approach to assessing their association with prognosis. This study is the first to demonstrate a significant correlation between NPS and the prognosis of patients with inoperable ESCC. Compared to other traditional prognostic scoring systems, NPS exhibits superior predictive accuracy.

The interplay between inflammation and tumorigenesis has long been the focus of extensive investigation by the scientific community. Studies have confirmed its crucial role in the occurrence and progression of tumors,[13] which can

Table 3 Comparison of the Area Under the Curve Values of Inflammation-Related Prognostic Scoring Systems

Variables	Median (Range)	AUC	95% CI	P value
NLR	2.767 (0.683–9.913)	0.635	0.54–0.731	0.008
SII	666.913 (166.045–3175.519)	0.649	0.552–0.746	0.004
PNI	49.550 (29.400–77.600)	0.520	0.604–0.797	0.692
Lymphocyte	1.560 (0.560–4.100)	0.580	0.481–0.680	0.115
Neutrophil	4.430 (1.470–12.800)	0.703	0.614–0.791	<0.001
Monocyte	0.410 (0.030–1.740)	0.664	0.569–0.759	0.001
Serum albumin (mg/dL)	41.200 (21.100–72.400)	0.462	0.363–0.561	0.460
Total cholesterol (mg/dL)	188.000 (88.000–424.000)	0.408	0.313–0.502	0.070

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation Index; PNI, Prognostic Nutritional Index.

Table 4 Univariate Analyses of Clinicopathological Variables for OS and PFS in Inoperable ESCC Patients

Variables	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)			0.395			0.658
≤60	Reference	0.469–1.348		Reference	0.576–1.417	
>60	0.796			0.903		
Gender			0.714			0.479
Female	Reference	0.475–2.961		Reference	0.588–3.098	
Male	1.186			1.350		
KPS performance status			0.054			0.369
90–100	Reference	0.315–1.011		Reference	0.518–1.276	
80-90	0.565			0.813		
Smoking			0.616			0.114
No	Reference	0.671–		Reference	0.884–2.326	
Yes	1.147	1.959		1.434		
Alcohol abuse			0.932			0.176
No	Reference	0.618–1.691		Reference	0.873–2.097	
Yes	1.022			1.353		
Histological grade			0.139			0.467
Well or Moderated	Reference	0.578–3.602		Reference	0.419–1.490	
Poorly	1.443			0.790		
Tumor location			0.005			0.087
Lower	Reference	0.290–0.798		Reference	0.443–1.056	
Upper or middle	0.481			0.684		
Tumor size (cm)			0.602			0.943
<5cm	Reference	0.688–1.905		Reference	0.634–1.527	
≥5cm	1.145			0.948		
TNM stage			0.139			0.794
II–III	Reference	0.864–2.854		Reference	0.606–1.923	
IV	1.570			1.080		
T stage			0.526			0.337
T1-2	Reference	0.385–6.479		Reference	0.555–5.578	
T3-4	1.579			1.759		
Lymph node metastasis			0.842			0.898
N0-1	Reference	0.639–1.732		Reference	0.638–1.483	
N2-3	1.052			0.973		
CEA			0.727			0.605
Normal	Reference	0.190–3.185		Reference	0.477–3.564	
High	0.778			0.605		
CA199			0.484			0.669
Normal	Reference	0.555–3.468		Reference	0.332–2.030	
High	1.387			0.821		
SCC			0.745			0.212
Normal	Reference	0.515–1.608		Reference	0.448–1.196	
High	0.910			0.732		
CYFRA			0.127			0.365
Normal	Reference	0.165–1.251		Reference	0.345–1.479	
High	0.454			0.715		

Abbreviations: OS, Overall Survival; PFS, Progression-Free Survival; Unresectable ESCC, Unresectable Esophageal Squamous Cell Carcinoma; KPS, Karnofsky Performance Status; CEA, Carcinoembryonic Antigen; CA199, Cancer Antigen 19–9; SCC, Squamous Cell Carcinoma Antigen; CYFRA, Cytokeratin 19 Fragment; NPS, Naples Prognostic Score.

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Table 5 Univariate Analyses of Inflammation-Related Prognostic Scoring Systems for OS and PFS in Inoperable ESCC Patients

Variables	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
NPS Group			<0.001			<0.001
0.1	Reference	1.456–4.221		Reference	1.759–4.177	
2	2.479			2.711		
NLR			0.052			<0.001
Low	Reference	0.995–2.730		Reference	1.422–3.355	
High	1.649			2.184		
LMR			0.598			0.507
Low	Reference	0.081–4.262		Reference	0.003–155,578.266	
High	0.587			20.559		
SII			0.412			0.010
Low	Reference	0.736–2.111		Reference	1.156–2.928	
High	1.247			1.840		
PNI			0.433			0.267
Low	Reference	0.640–2.833		Reference	0.751–2.812	
High	1.347			1.453		

Abbreviations: OS, Overall Survival; PFS, Progression-Free Survival; Unresectable ESCC, Unresectable Esophageal Squamous Cell Carcinoma; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-inflammation Index; PNI, Prognostic Nutritional Index.

accelerate pathological processes through mechanisms including the enhancement of tumor cell proliferation,[14] migration,[15] invasion,[16] and the upregulation of angiogenesis mediated by vascular endothelial growth factor (VEGF).[17] Particularly, neutrophils, lymphocytes, and monocytes significantly impact the tumor microenvironment

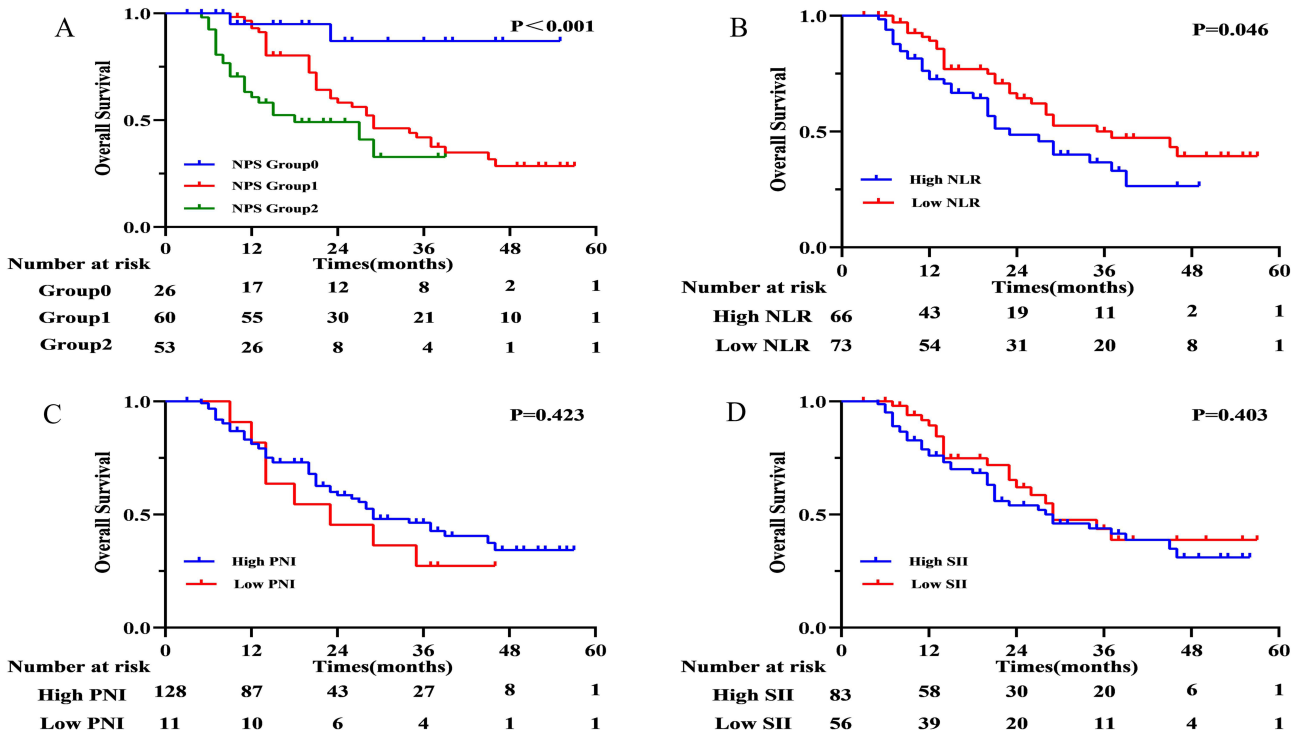

Figure 3 Kaplan-Meier curves for OS among the NPS 0, 1, 2 groups (**A**), high NLR group vs low NLR group (**B**), high PNI group vs low PNI group (**C**), and high SII group vs low SII group (**D**) in patients with unresectable ESCC.

Abbreviations: OS, Overall Survival; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; SII, Systemic Immune-inflammation Index; ESCC, Esophageal Squamous Cell Carcinoma.

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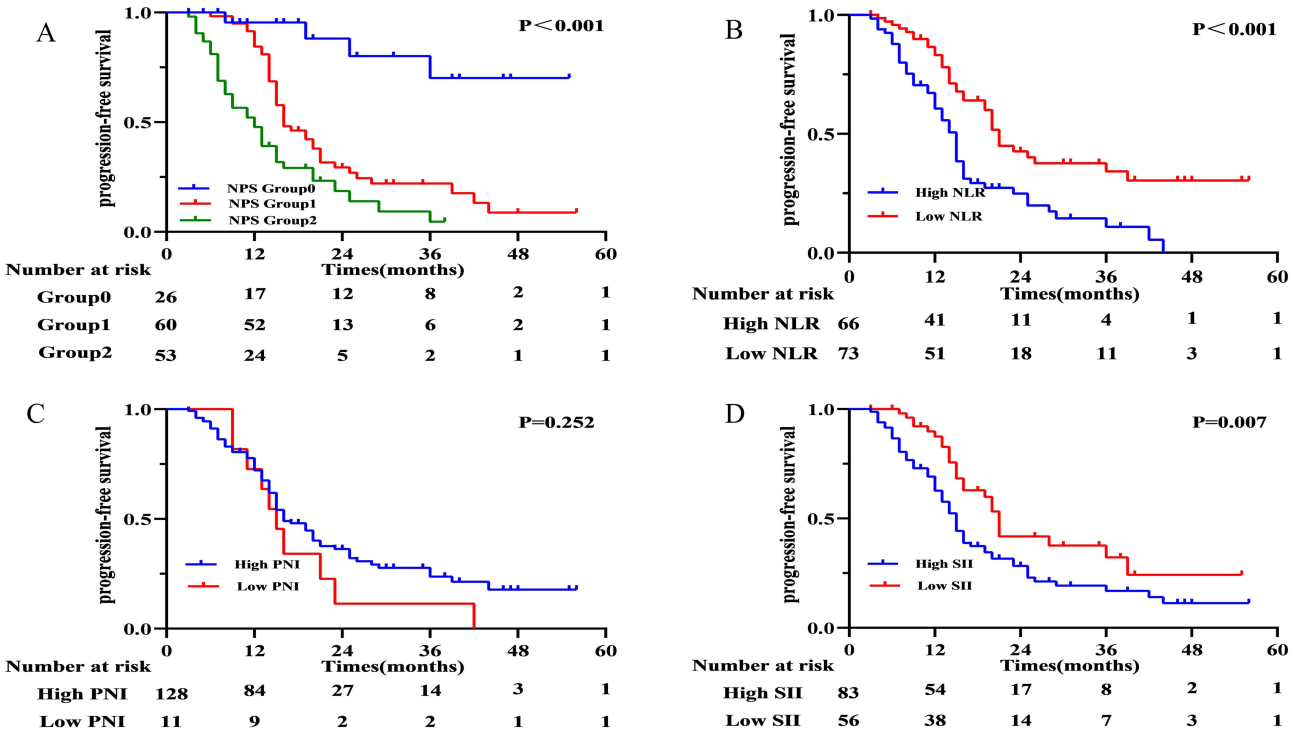

Figure 4 Kaplan-Meier curves for PFS among the NPS 0, 1, 2 groups (**A**), high NLR group vs low NLR group (**B**), high PNI group vs low PNI group (**C**), and high SII group vs low SII group (**D**) in patients with unresectable ESCC.

Abbreviations: PFS, Progression-Free Survival; NLR, Neutrophil-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; SII, Systemic Immune-inflammation Index; ESCC, Esophageal Squamous Cell Carcinoma.

and its developmental processes. The NLR and LMR serve as inflammation-related indicators associated with cancer, participating in the immune responses involved in tumor initiation and progression, and have been shown to hold significant prognostic value in various malignancies.[18,19] They are closely linked to cancer-related inflammation and immune responses, playing a crucial role.[4,20,21] Neutrophils promote tumor angiogenesis by secreting VEGF and release inflammatory mediators to aid in the proliferation and metastasis of cancer cells.[22] They are recruited to the tumor

Table 6 Multivariate Analyses of Prognostic Factors for OS and PFS in Inoperable ESCC Patients

Variables	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
NPS Group			<0.001			0.002
0.1	Reference	1.411–4.095		Reference	1.321–3.674	
2	2.404			2.203		
NLR						0.380
Low				Reference	0.732–2.264	
High				1.287		
SII						0.221
Low				Reference	0.821–2.351	
High				1.389		
Tumor location			0.007			
Lower	Reference	0.299–0.825				
Upper or middle	0.497					

Abbreviations: OS, Overall Survival; PFS, Progression-Free Survival; Unresectable ESCC, Unresectable Esophageal Squamous Cell Carcinoma; NPS, Naples Prognostic Score; NLR, Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-inflammation Index.

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microenvironment through adhesion molecule-1, where they help circulating tumor cells (CTCs) achieve immune evasion by encapsulating them.[23,24] Additionally, lymphocytes are central to anti-tumor immunity. They inhibit cancer cell invasion, proliferation, and migration by activating cytotoxic responses while precisely identifying and eliminating tumor cells through immune surveillance.[25–27] Tumor-associated macrophages derived from monocytes are associated with poor prognosis in various cancers. These macrophages enhance tumor angiogenesis, inflammatory responses, and microenvironment remodeling by secreting substances such as M2 macrophage-related anti-tumor factors, thereby promoting tumor progression and inducing immune suppression.[28,29] Taken together, a systemic inflammatory state can orchestrate an immunosuppressive tumor microenvironment by recruiting myeloid-derived suppressor cells, promoting M2 macrophage polarization, and inducing formation of neutrophil extracellular traps, thereby contributing to resistance to immune checkpoint inhibitors.[30–32]

In summary, a high NLR reflects excessive neutrophil infiltration together with lymphocyte depletion. Tumor-associated neutrophils not only promote angiogenesis but can further differentiate into myeloid-derived suppressor cells (MDSCs) that potently inhibit cytotoxic T-cell activity.[33] Concurrent lymphopenia directly undermines immune surveillance and effector antitumor responses. A low LMR denotes lymphocyte loss alongside monocytosis; these monocytes can give rise to tumor-associated macrophages (TAMs) that exacerbate T-cell exhaustion and facilitate tumor invasion. Collectively, patients identified by a high NPS are likely to harbor an immunosuppressive "cold-tumor" microenvironment. This phenotype may help to identify, in clinical practice, those patients who are less likely to benefit from immune-based therapies and to inform the development of more precise, individualized immunotherapeutic strategies.

Furthermore, the biochemical mechanisms underlying the prognostic influence of NPS involve serum albumin and total cholesterol levels. Systemic inflammation or stress triggers hepatic production of acute-phase proteins, while increased interstitial fluid and subsequent consumption contribute to decreased albumin levels. This reduction not only reflects malnutrition but also signifies a sustained systemic inflammatory state. Studies have demonstrated that hypoalbuminemia can impair free radical scavenging, accelerate apoptosis in normal cells, and promote tumor progression-factors closely linked to adverse clinical outcomes.[34,35] Research by Chen et al further confirmed a significant association between low cholesterol levels and poor prognosis in ESCC patients.[36] The potential mechanisms may include reduced membrane fluidity due to hypocholesterolemia, which weakens surface receptor signaling and compromises the ability of immune-active cells to effectively recognize and eliminate cancer cells.[37,38] Thus, total cholesterol levels serve as a critical prognostic indicator for assessing overall survival in these patients.

NPS establishes a multidimensional predictive model by integrating four categories of inflammatory and nutritional indicators, offering a more objective reflection of patients' inflammatory and nutritional status compared to other systemic inflammatory scores. Yu Qiu et al demonstrated that elevated NPS is associated with poor prognosis in breast cancer,[39] while Gennaro et al further confirmed its prognostic utility in colorectal cancer.[7] Similarly, Li Qing et al identified NPS as an independent prognostic factor in operable endometrial cancer.[8] Moreover, multiple studies have highlighted NPS as a significant prognostic marker in various malignancies, including gastric cancer,[40] upper urinary tract urothelial carcinoma,[41] pancreatic cancer,[42] and hepatocellular carcinoma.[12] However, clinical data on the NPS scoring system for inoperable ESCC remain limited. In this study, we established NPS as an important independent prognostic factor for inoperable ESCC. Higher NPS scores correlated with worse PFS and OS in ESCC patients undergoing chemoradiotherapy combined with immunotherapy, aligning with prior findings. Our results indicate that NPS is a readily applicable and comprehensive predictive tool, capturing patients' systemic inflammatory and nutritional status across multiple dimensions. ROC analysis revealed that NPS exhibits a superior AUC compared to other prognostic indicators, including the PNI, SII, serum albumin, total cholesterol, NLR, and LMR. Furthermore, we developed a novel predictive model based on NPS, reinforcing its role as a robust independent prognostic marker. These findings underscore the clinical utility of NPS, particularly its advantage in identifying high-risk patients with increased likelihood of recurrence or mortality. Moreover, the NPS may inform individualized care: high-risk (Group 2) patients could merit intensified nutrition, closer monitoring, and novel immunotherapy combinations, whereas low-risk (Group 0) patients may be managed with standard therapy. By integrating multiple laboratory parameters, NPS

outperforms single biomarkers in prognostic stratification and has important implications for personalizing treatment in unresectable ESCC.

This study has several limitations that should be acknowledged. First, the retrospective nature of the study, the modest sample size from a single center, the relatively short follow-up period, and the absence of an independent external validation cohort may limit the generalizability of our findings. Second, potential confounding factors-including dyslipidemia, medication history, and nutritional interventions-could influence inflammatory and nutritional markers. Third, despite implementing strict inclusion criteria, the study design constraints mean that laboratory parameters (such as serum albumin and total cholesterol levels) may remain susceptible to selection bias and various sources of interference. Finally, despite standardized protocols, variation in chemotherapy regimens and individual responses to immunotherapy may have introduced unmeasured confounding that affected survival outcomes.

Conclusion

In conclusion, the NPS constitutes a practical and clinically applicable scoring system that can effectively predict prognosis and enable risk stratification in patients with unresectable ESCC. Elevated NPS scores correlate with reduced OS and PFS. By comprehensively incorporating multiple laboratory parameters, the NPS system outperforms individual biomarkers in prognostic prediction. These findings suggest the NPS can stratify baseline risk before combined chemoradiotherapy and immunotherapy: high-NPS patients may need intensified nutritional support, closer monitoring, or combination strategies, while low-NPS patients may be suitable for standard regimens. Prospective, multicenter validation is required.

Data Sharing Statement

The datasets are available from the first corresponding author, Jianwen Li on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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