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ORIGINAL RESEARCH

Naples Prognostic Score as a Novel Prognostic Prediction Tool for Resectable Locally Advanced Esophageal Squamous Cell Carcinoma After Neoadjuvant Therapy

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Purpose: Esophageal squamous cell carcinoma (ESCC) is a highly invasive malignancy with poor prognosis, especially in its locally advanced stages. Recent studies have highlighted the role of inflammation and nutrition in cancer prognosis. The Naples prognostic score (NPS), which integrates inflammatory and nutritional markers, has demonstrated prognostic value in various cancers. However, its applicability in patients with resectable locally advanced ESCC after neoadjuvant therapy remains unexplored. This study aimed to evaluate the prognostic value of the NPS in predicting overall survival (OS) and progression-free survival (PFS) in these patients.

Patients and Methods: A retrospective study was conducted on 175 patients with locally advanced ESCC who underwent neoadjuvant therapy followed by surgical resection at Fujian Medical University Union Hospital between 2016–2020. Patients were grouped by NPS scores (0,1–2,3-4). Survival analysis was performed using the Kaplan-Meier method, and the predictive accuracy of NPS was evaluated using receiver operating characteristic (ROC) curves. Cox proportional hazards regression models were used to identify independent prognostic factors for OS and PFS.

Results: Significant differences in OS (p=0.0025) and PFS (p=0.0018) were observed across the three NPS groups. Multivariable Cox regression analysis confirmed that patients with higher NPS scores (NPS group 2) had significantly worse OS (HR = 2.768, 95% CI: 1.239–6.183, p = 0.013) and PFS (HR = 3.345, 95% CI: 1.574–7.109, p = 0.002). The area under the curve (AUC) for NPS was 0.63 for OS and 0.67 for PFS, indicating moderate predictive value.

Conclusion: The NPS is a simple and effective prognostic tool for assessing survival outcomes in patients with resectable locally advanced ESCC following neoadjuvant therapy. Its integration into clinical practice may aid in better stratification and treatment decision-making for these patients.

Keywords: NPS score, esophageal squamous cell carcinoma, neoadjuvant therapy, prognostic assessment, overall survival, progression-free survival

Introduction

Esophageal cancer remains a significant global health challenge, ranking as the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide.[1,2] Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two primary histological subtypes. While EAC predominates in developed countries, ESCC is more prevalent in developing regions, particularly in East Asia and Africa.[3] Despite

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advances in diagnosis and treatment, the prognosis for patients with locally advanced ESCC remains poor, with a five-year survival rate below 30%. The current standard of care for locally advanced ESCC involves neoadjuvant therapy followed by surgical resection. Neoadjuvant therapy, as an essential component of the contemporary multidisciplinary treatment model for esophageal cancer, has evolved to include various approaches such as concurrent chemoradiotherapy, chemotherapy alone, immunotherapy, and combinations of immunotherapy. However, even with rigorous multimodal treatment, recurrence rates remain high, and long-term survival outcomes are still suboptimal.

In a retrospective study investigating neoadjuvant treatment protocols for locally advanced esophageal cancer, the results indicated that neoadjuvant chemoradiotherapy (CRT) significantly improves pathological response compared to chemotherapy (CT), though it may not enhance survival outcomes.[4] In contrast, the CROSS trial, which exemplifies the neoadjuvant concurrent chemoradiotherapy model, demonstrated that this approach can achieve an impressive pathological complete response (pCR) rate of nearly 50%.[5] As research progresses, the treatment of esophageal cancer is entering the era of precision medicine, with increasing applications of immunotherapy and targeted therapies in neoadjuvant settings. In one study, camrelizumab combined with chemotherapy exhibited significant antitumor activity in locally advanced esophageal squamous cell carcinoma undergoing neoadjuvant treatment.[6] However, there remains controversy regarding neoadjuvant treatment protocols for esophageal cancer, with ongoing prospective clinical trials such as KEYNOTE-585.[7] The strategy of integrating immunotherapy as part of neoadjuvant treatment, in conjunction with chemotherapy and radiation therapy, is still in a critical exploratory phase characterized by robustly designed clinical trials.[8] Therefore, identifying reliable prognostic markers is crucial for optimizing treatment strategies and improving patient outcomes.

In recent years, increasing attention has been directed toward the role of systemic inflammation and nutritional status in cancer progression and prognosis.[9] Several inflammation and nutrition-based prognostic scores such as lymphocyte/monocyte ratio (LMR), systemic immunoinflammatory index (SII), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), prognostic nutritional index (PNI), have been explored in various malignancies, including ESCC.[10–13] These scores have demonstrated potential in predicting survival outcomes, but their predictive accuracy and clinical utility remain inconsistent. The Naples Prognostic Score (NPS) is a composite prognostic model incorporating both inflammatory and nutritional markers, namely serum albumin (sAlb), total cholesterol (T-cho), NLR, and lymphocyte-to-monocyte ratio (LMR). First introduced by Galizia et al for predicting outcomes in colorectal cancer patients, the NPS has since been validated in other malignancies, including gastric and pancreatic cancers.[14] Its strength lies in its ability to reflect both the inflammatory state and the nutritional reserves of the patient, factors known to influence tumor progression and patient survival. To date, however, the NPS has not yet been applied to patients with resectable locally advanced ESCC following neoadjuvant therapy. Given the established role of inflammation and nutrition in cancer prognosis, we hypothesize that the NPS could serve as a valuable prognostic tool in this patient population. This study aims to evaluate the prognostic value of the NPS in predicting overall survival (OS) and progression-free survival (PFS) in patients with resectable locally advanced ESCC who have undergone neoadjuvant therapy.

Materials and Methods

Study Design and Protocol

This retrospective study is based on data collected from our single-center. We declare that this study has been approved by the Ethics Committee of Fujian Medical University Union Hospital (Approval No. 2024KY155). Due to the retrospective nature of the research, we applied for a waiver of informed consent. We declare that all patient data were anonymized and securely stored using encryption measures. The research process strictly adhered to the principles of the Declaration of Helsinki. All procedures were conducted in strict accordance with relevant guidelines and regulations. The primary objective of this study is to evaluate the role of NPS scores in assessing survival in resectable esophageal cancer after neoadjuvant therapy.

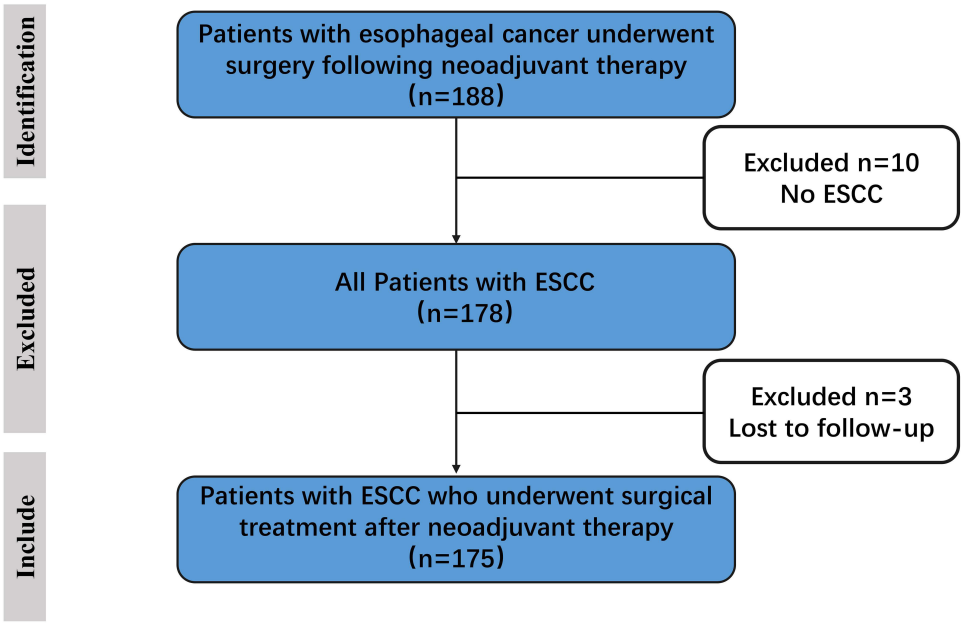

Figure 1 Study flow chart.

Patients Selection Settings

In this study, 188 patients with locally advanced esophageal cancer who attended the Department of Thoracic Surgery of Fujian Medical University Union Hospital between January 2016 and October 2020 were retrospectively selected as study subjects. After excluding ten patients with non-esophageal squamous cell carcinoma, three patients were not able to return for follow-up examinations and further treatment after surgery. All attempts to contact these patients were unsuccessful, leading to their exclusion from the study. Data for all patients were obtained from the electronic medical record system, ultimately including 175 patients with locally advanced unresectable esophageal squamous cell carcinoma (ESCC), comprising 147 men and 28 women (Figure 1).

The Inclusion and exclusion criteria were as follows: (1) patients diagnosed with ESCC by endoscopic pathology were included, while those with esophageal adenocarcinoma and other special pathological types of esophageal cancer were excluded, as different pathological types require different neoadjuvant treatments, potentially biasing nutritional assessments; (2) all patients were diagnosed with locally advanced unresectable ESCC, received preoperative neoadjuvant therapy, and subsequently underwent surgery, specifically thoraco-laparoscopic combined with cervical, thoracic, and abdominal three-incision esophagectomy. Patients who did not receive adjuvant therapy post-surgery were excluded to prevent survival bias; (3) laboratory data had to be obtained within seven days before surgery, as data beyond this period might not accurately reflect the preoperative nutritional status, causing bias. Patients who recently took medications affecting lab results or those with missing data were excluded; (4) Patients with concurrent or prior other malignancies or diseases affecting nutritional reserves were excluded to ensure the accuracy of preoperative Naples prognostic score (NPS); and (5) Patients lost to follow-up were excluded to ensure data accuracy and objectivity.

Follow-Up Investigation

All included patients were regularly followed up starting from the day of neoadjuvant therapy initiation. During preoperative neoadjuvant therapy, telephone follow-ups were conducted every 2–3 weeks. Postoperatively, follow-ups were monthly for the first year and every three months thereafter. During follow-ups, clinical data and laboratory results were collected, including survival status, recurrence, metastasis, quality of life, and adverse reactions.

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Outcome Data, Measures And definitions

Patient Characteristics

All patients underwent preoperative neoadjuvant therapy and were evaluated for potential tumor resectability, followed by radical surgery. Perioperative baseline characteristics included age, sex, tumor location, tumor size, tumor grade, and chemotherapy regimen. Postoperative assessments included surgical radicality, complications, serum albumin and cholesterol levels, complete blood count (including neutrophil, lymphocyte, and monocyte counts and percentages), NLR, and LMR. Additionally, postoperative pathological differentiation and ypTNM staging of the tumor were collected.

NPS Scores

Preoperative blood samples were drawn by experienced nurses, collecting serum ALB and TC levels, lymphocyte count, neutrophil count, and monocyte count from complete blood count and biochemical tests. According to Galizia et al, a scoring system was utilized based on the following criteria: a score of 0 was assigned if ALB ≥4.0 mg/dL, TC >180 mg/dL, NLR ≤2.96, and LMR >4.44. A score of 1 was assigned if any of these conditions were not met. The NPS score was the sum of the individual scores. Patients were categorized into three groups based on their NPS scores: those with an NPS score of 0 were classified into the NPS0 group, those with an NPS score of 1–2 were classified into NPS1 group, and those with an NPS score of 3–4 were classified into NPS3 group. (Figure 2) The distribution of patients according to different NPS scores and groupings is illustrated in the bar chart (Figure 2).

Outcomes

The primary outcomes of this study was overall survival (OS) and progression-free survival (PFS). OS was defined as the interval from the date of surgery to the date of death from any cause. PFS was defined as the interval from the date of surgery to the date of confirmed tumor recurrence or metastasis.

Neoadjuvant Therapy

All patients received neoadjuvant chemotherapy consisting of a taxane-based regimen combined with a platinum agent prior to surgery. The specific regimen included paclitaxel (175 mg/m²) and cisplatin (75 mg/m²) administered for 2 to 4 cycles, with each cycle repeating every three weeks. After 2 cycles, an evaluation of treatment efficacy was conducted, and surgery was performed within three weeks following the completion of neoadjuvant chemotherapy.

Surgical Technique And perioperative Care

All patients underwent thoraco-laparoscopic three-incision esophagectomy. Intraoperatively, frozen pathology sections of the right recurrent laryngeal nerve lymph nodes were examined to decide on three-field lymph node dissection. All included patients had negative right recurrent laryngeal nerve lymph nodes and underwent two-field lymph node dissection.

Patients were instructed on deep breathing, effective coughing, and expectoration exercises. They were also encouraged to engage in appropriate physical activity to enhance lung tolerance for surgery.

Postoperatively, a 22 Fr chest tube and an 8 Fr pigtail drain were placed in the right thoracic cavity. The chest tube was removed after satisfactory lung re-expansion was confirmed on postoperative day 1 chest X-ray, and the pigtail drain was removed when drainage was less than 100 mL/24 hours. A 22 Fr abdominal drain was placed and removed when drainage was less than 100 mL/24 hours. An 8 Fr subcutaneous neck drain was typically removed within 24–48 hours postoperatively. All patients received jejunostomy tubes for postoperative enteral nutrition support.

All patients underwent a full cycle of adjuvant therapy postoperatively, consistent with the preoperative neoadjuvant therapy regimen.

Statistical Analysis

The comparison of categorical data was performed using Pearson's chi-square test or Fisher's exact probability method, while the comparison of continuous data was conducted using independent samples *t*-test or Mann–Whitney *U*-test. The

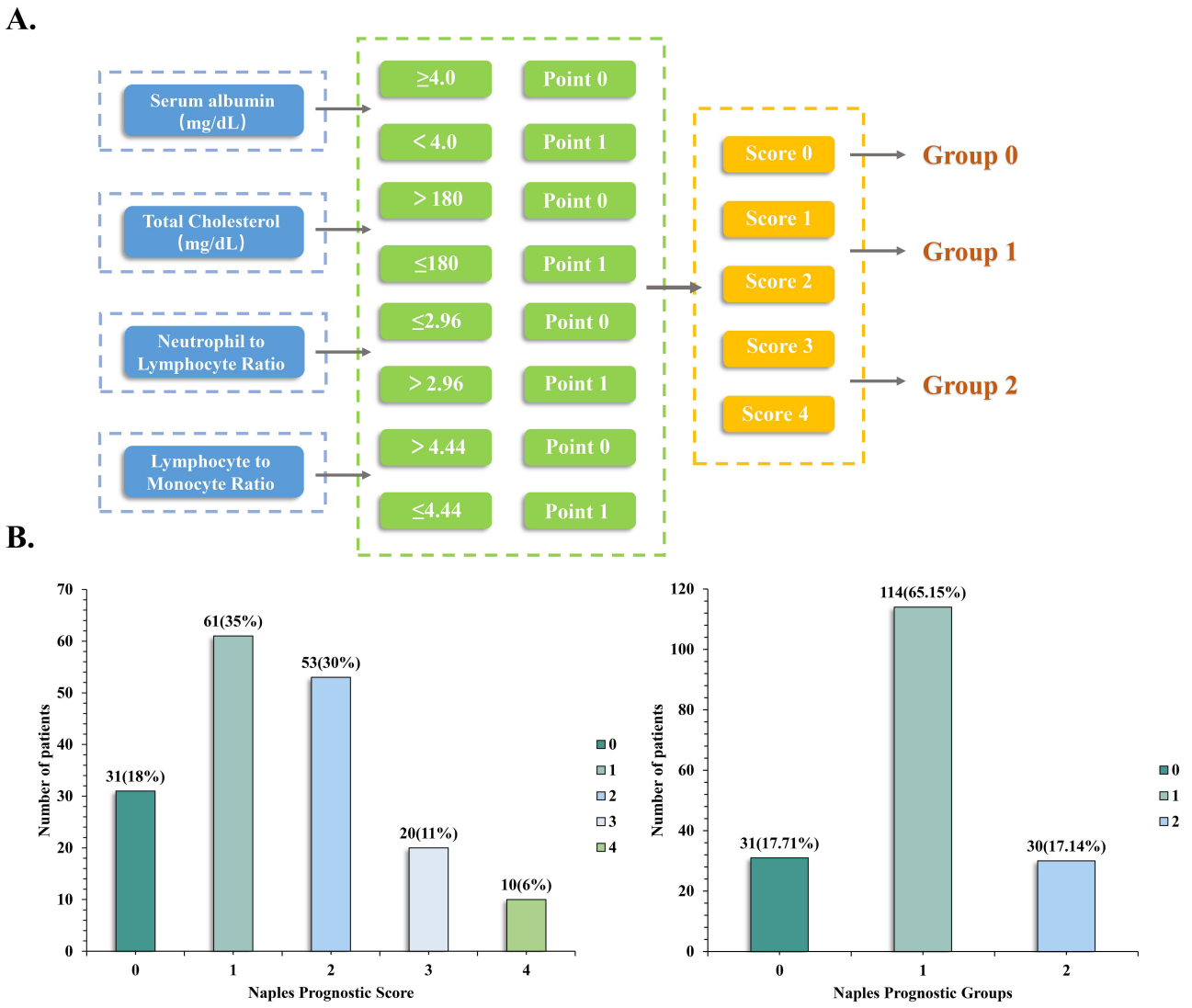

Figure 2 (**A**) Definition and grouping criteria of NPS. (**B**) Patient distribution in accordance with the NPS scores and the NPS groups.

primary outcome of this study was overall survival (OS), defined as the interval between the date of surgery and the date of death. The secondary outcome was progression-free survival (PFS), defined as the interval between the date of surgery and the date of diagnosis of tumor progression. Univariate and multivariable Cox proportional hazards regression models were used to identify variables associated with OS and PFS. Hazard ratios (HR) and 95% confidence intervals (CI) for OS and PFS were then calculated. Survival analysis was conducted using the Kaplan-Meier method, with survival time comparisons performed using the Log rank test. To assess the discriminative power of the prognostic scoring system, time-dependent receiver operating characteristic (ROC) curves were plotted. Differences in the area under the curve (AUC) were compared. With higher AUC values indicated better predictive ability. All statistical analyses were conducted by SPSS version 22.0.0 and R version 4.3.2. Statistical significance was set at $P<0.05$.

Result

Patient Characteristics

Between January 2016 and October 2020, a total of 188 patients were diagnosed with stage II or III locally advanced ESCC were enrolled in the study. All patients received preoperative neoadjuvant chemotherapy, followed by surgery and subsequent adjuvant therapy. After applying exclusion criteria (10 patients with non-squamous cell carcinoma and 3

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patients lost to follow-up), the final cohort consisted of 175 patients (Figure 1), including 147 males (84.0%) and 28 females (16.0%). Patients were stratified into three groups based on their NPS score: NPS group 0 comprised 31 patients (17.71%), with an average age of 58.19±7.264 years (median=60, IQR=52-64) and an average BMI of 22.68±3.17 (median=22.23, IQR=20.34–24.00). NPS group 1 included 114 patients (65.14%), with an average age of 60.16±7.33 years (median=62, IQR=54-65) and an average BMI of 21.79±2.93 (median=21.62, IQR=19.80–23.45). NPS group 2 consisted of 30 patients (17.15%), with an average age of 58.6±7.88 years (median=59, IQR=53-66) and an average BMI of 21.79±2.80 (median=21.47, IQR=20.44–22.93). There were no significant differences among the three groups in terms of age (P=0.319), BMI (P=0.314), hypertension (P=0.575), diabetes (P=0.07), tumor location (P=0.555), postoperative ypT stage (P=0.611), postoperative ypN stage (P=0.232), or postoperative ypM stage (P=0.097). However, 3 groups were statistically significant differences in gender (P=0.003) and degree of tumor differentiation (P=0.001) (Table 1).

Table 1 Baseline Characteristics of Patients With Esophageal Cell Carcinoma

Characteristics	Total (N=175)	Naples Prognostic Score Group			P-value
		NPS0 (N=31)	NPS1 (N=114)	NPS2 (N=30)	
Age					
Mean±SD	59.54±7.42	58.19±7.26	60.16±7.33	58.6±7.88	0.319
Median (IQR)	60(54–65)	60(52–64)	62(54–65)	59(53–66)	
BMI					
Mean±SD	21.95±2.96	22.68±3.17	21.79±2.93	21.79±2.80	0.314
Median (IQR)	21.87(20.07–23.45)	22.23(20.34–24.00)	21.62(19.80–23.45)	21.47(20.44–22.93)	
Gender					
Male	147(84.00%)	21(67.70%)	96(84.20%)	30(100%)	0.003
Female	28(16.00%)	10(32.30%)	18(15.80%)	0(0%)	
Hypertension					
Absent	142(81.14%)	26(83.90%)	90(78.90%)	26(86.70%)	0.575
Present	33(18.86%)	5(16.10%)	24(21.10%)	4(13.30%)	
Diabetes					
Absent	172(98.29%)	29(93.50%)	113(99.10%)	30(100%)	0.07
Present	3(1.71%)	2(6.50%)	1(0.90%)	0(0%)	
Main tumor location					
Upper	16(9.14%)	5(16.10%)	8(7.00%)	3(10.00%)	0.555
Middle	102(58.29%)	18(58.10%)	68(59.60%)	16(53.30%)	
Low	57(32.57%)	8(25.8%)	38(33.30%)	11(36.70%)	
Tumor differentiation					
Well	54(30.86%)	19(61.30%)	28(24.60%)	7(23.30%)	0.001
Moderate	83(47.43%)	7(22.60%)	63(55.30%)	13(43.30%)	
Poor	38(21.71%)	5(16.10%)	23(20.20%)	10(33.30%)	
ypT stage					
T_{0-2}	70(40%)	10(32.26%)	48(42.11%)	12(40.00%)	0.611
T_{3-4}	105(60%)	21(67.74%)	66(57.89%)	18(60.00%)	
ypN stage					
N_0	85(48.57%)	18(58.06%)	50(43.86%)	17(56.67%)	0.232
N_{1-3}	90(51.43%)	13(41.94%)	64(56.14%)	13(43.33%)	
ypM stage					
M_0	174(99.43%)	30(96.77%)	114(100%)	30(100%)	0.097
M_1	1(0.57%)	1(3.23%)	0(0)	0(0)	
Neutrophil-to-lymphocyte ratio					
Mean±SD	2.68±2.44	1.62±0.60	2.33±1.73	2.19±1.04	<0.0001
Median (IQR)	2.03(1.47–2.03)	1.53(1.20–2.09)	1.97(1.48–2.65)	1.99(1.20–2.93)	

(*Continued*)

Table 1 (Continued).

Characteristics	Total (N=175)	Naples Prognostic Score Group			P-value
		NPS0 (N=31)	NPS1 (N=114)	NPS2 (N=30)	
Lymphocyte-to-monocyte ratio					
Mean±SD	3.98±1.84	5.91±1.50	3.93±1.58	5.10±3.96	<0.0001
Median (IQR)	3.75(2.73–4.84)	5.41(4.81–6.45)	3.71(2.89–4.44)	3.43(2.81–6.58)	
Serum albumin (mg/dL)					
Mean±SD	42.23±6.58	43.84±2.37	42.70±7.12	38.77±6.36	<0.0001
Median (IQR)	41.80(39.00–44.10)	43.80(41.30–45.20)	42.10(38.98–44.03)	38.90(35.50–40.88)	
Total cholesterol (mg/dL)					
Mean±SD	5.35±1.33	6.17±1.37	5.44±1.24	4.18±0.77	<0.0001
Median (IQR)	5.07(4.44–6.15)	5.94(5.14–6.83)	5.16(4.66–6.13)	4.21(3.65–4.45)	
Naples Prognostic Score					
0	31(17.70%)	31(100%)	-	-	-
1	61(34.90%)	-	61(53.50%)	-	
2	53(30.30%)	-	53(46.50)	-	
3	20(11.40%)	-	-	20(66.70%)	
4	10(5.70%)	-	-	10(33.30%)	

Preoperative NPS and Postoperative Outcomes

NPS Groups and Survival Outcomes

We divided the patients into three groups according to their NPS scores and performed survival analysis. The Log rank test method showed that there was a significant difference in three-year OS among the three groups (Log-rank P=0.0025) (Figure 3). The median OS value was 48 months, while three-year OS rates of 83.87% for the NPS0 group, 75.44% for the NPS1 group, and 36.67% for the NPS2 groups. Univariate and multivariable Cox regression analyses were conducted to examine the clinicopathological factors associated with OS. The Cox regression model identified ypN and NPSgroup2 as significant prognostic factors for OS. Multivariable analysis confirmed that the NPSgroup2 was an independent risk factor for OS (Table 2). PFS was also analyzed, and the Log rank test showed a significant difference in PFS among the three groups (Log-rank P=0.0018) (Figure 3). The median PFS was 48 months, with three-year PFS rate of 80.65%, 70.18%, and 43.33% for the NPS0, NPS1, and NPS2 groups, respectively. Further univariate and multivariable regression analyses were performed for PFS. The Cox regression model indicated that tumor hypodifferentiation, ypT stage, ypN stage, and NPSgroup2 were significant prognostic factors for PFS. Multivariable analysis confirmed that NPSgroup2 was an independent risk factor for PFS (Table 3).

Subgroup Analysis

We further performed a subgroup analysis by dividing into 2 groups based on the ypT staging after neoadjuvant therapy, ypT0-2 and ypT3-4. In the ypT0-2 subgroup, no significant differences in OS (Log-rank P=0.2236) or PFS (Log-rank P=0.1893) were observed among the NPS0, NPS1, and NPS2 groups. Conversely, in the ypT3-4 subgroup, significant differences were found in OS (Log-rank P=0.0011) and PFS values (Log-rank P=0.00035) among the NPS0, NPS1, and NPS2 groups (Figure 4).

Predictive Accuracy of the NPS Score

We performed a subject working curve (ROC) analysis to evaluate the predictive value of the NPS score for OS and PFS. The analysis demonstrated that the NPS score is a good predictor of resectable esophageal squamous cell carcinoma after neoadjuvant therapy. The area under the curve (AUC) was 0.63 for OS and 0.67 for PFS. NLR, LMR, sAlb, and T-Cho were categorized into scores of 0 and 1 as shown in Figure 2, and ROC analysis was performed to assess the predictive value of these different scores for OS and PFS.

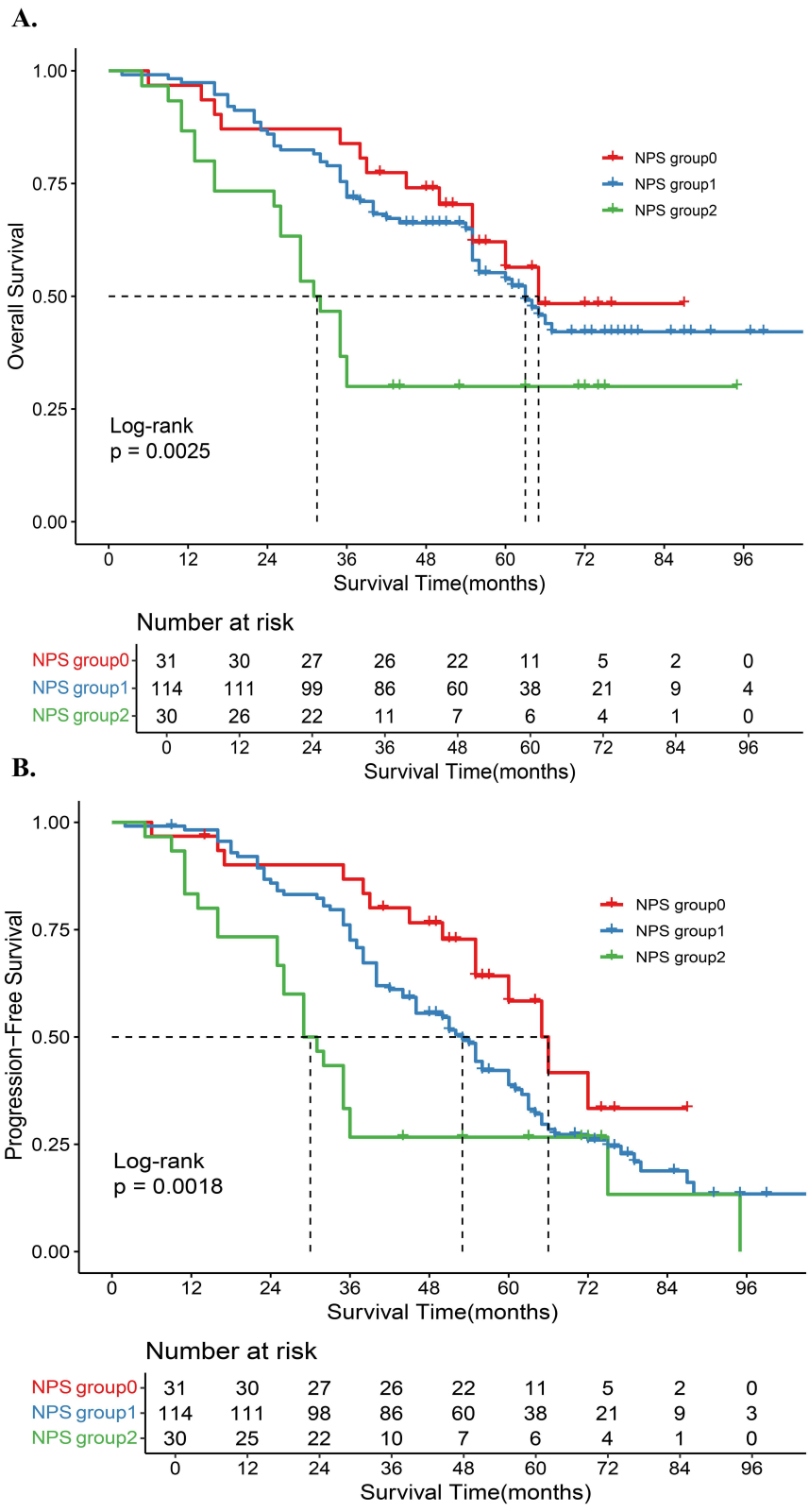

Figure 3 Overall survival (OS) and progression-free survival (PFS) in patients with resectable esophageal squamous cell carcinoma after neoadjuvant therapy, stratified by NPS groups (0, 1, and 2). (**A**) OS according to NPS groups; (**B**) PFS according to NPS groups.

Table 2 Clinicopathological Features of OS and Univariate and Multifactorial Analysis

Characteristics	Total (N=175)	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age							
≤60	79(45.12%)	Reference			Reference		
>60	96(54.86%)	1.170	0.770–1.778	0.462	0.861	0.552–1.342	0.508
Gender							
Male	147(84.00%)	Reference			Reference		
Female	28(16.00%)	1.229	0.682–2.215	0.493	1.067	0.561–2.028	0.843
Hypertension							
Absent	142(81.14%)	Reference			Reference		
Present	33(18.86)	1.219	0.699–2.126	0.485	0.759	0.419–1.375	0.363
Diabetes							
Absent	172(98.29%)	Reference			Reference		
Present	3(1.71)	1.132	0.279–4.602	0.862	1.854	0.429–8.022	0.409
BMI							
<22	92(52.57%)	Reference			Reference		
≥22	83(47.43%)	0.900	0.592–1.370	0.624	1.358	0.860–2.145	0.190
Main tumor location							
Upper	16(9.14%)	Reference			Reference		
Middle	102(58.29%)	1.606	0.687–3.755	0.274	1.621	0.678–3.877	0.277
Low	57(32.57%)	1.979	0.830–4.715	0.124	2.035	0.822–5.038	0.125
Tumor differentiation							
Well	54(30.86%)	Reference			Reference		
Moderate	83(47.43%)	1.073	0.654–1.762	0.779	1.107	0.650–1.866	0.708
Poor	38(21.71%)	1.075	0.601–1.924	0.807	1.034	0.545–1.965	0.918
ypT stage							
T0-2	70(40.00%)	Reference			Reference		
T3-4	105(60.00%)	1.462	0.940–2.275	0.092	1.372	0.839–2.246	0.208
ypN stage							
N0	85(48.57%)	Reference			Reference		
N1-3	90(51.43%)	1.599	1.041–1.2455	0.032	1.436	0.907–2.275	0.123
ypM stage							
M0	174(99.43%)	Reference			Reference		
M1	1(0.57%)	1.657	0.230–11.934	0.616	1.526	0.183–12.706	0.696
NPS Group							
0	31(17.71%)	Reference			Reference		
1	114(65.14%)	1.211	0.661–2.220	0.535	1.209	0.606–2.411	0.590
2	30(17.14%)	2.662	1.328–5.336	0.006	2.768	1.239–6.183	0.013

Compared to other assessed hematological biomarkers, the AUC of NPS in relation to the NLR, LMR, sAlb, and T-Cho was found to be the highest for both OS and PFS (Figure 5).

Discussion

Our study is the first to apply the NPS score as a prognostic tool in patients with resectable locally advanced ESCC who have undergone neoadjuvant therapy. The results demonstrated that higher NPS scores were significantly associated with poorer overall survival (OS) and progression-free survival (PFS). Specifically, patients in the NPS2 group showed

Table 3 Clinicopathological Features of PFS and Univariate and Multifactorial Analysis

Characteristics	Total (N=175)	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	P value	HR	95% CI	P value
Age							
≤60	79(45.12%)	Reference			Reference		0.777
>60	96(54.86%)	1.063	0.741–1.526	0.739	1.057	0.720–1.552	
Gender							
Male	147(84.00%)	Reference			Reference		0.760
Female	28(16.00%)	0.810	0.490–1.338	0.411	1.089	0.6321.875	
Hypertension							
Absent	142(81.14%)	Reference			Reference		0.266
Present	33(18.86)	0.855	0.533–1.369	0.513	0.749	0.450–1.246	
Diabetes							
Absent	172(98.29%)	Reference			Reference		0.979
Present	3(1.71)	0.654	0.160–2.674	0.555	1.020	0.240–4.337	
BMI							
<22	92(52.57%)	Reference			Reference		0.215
≥22	83(47.43%)	1.099	0.764–1.579	0.612	1.281	0.866–1.894	
Main tumor location							
Upper	16(9.14%)	Reference			Reference		
Middle	102(58.29%)	1.786	0.857–3.722	0.122	1.618	0.760–3.442	0.212
Low	57(32.57%)	2.192	1.033–4.652	0.041	1.940	0.893–4.214	0.094
Tumor differentiation							
Well	54(30.86%)	Reference			Reference		
Moderate	83(47.43%)	1.108	0.729–1.683	0.631	1.005	0.642–1.573	0.983
Poor	38(21.71%)	0.909	0.546–1.515	0.715	0.791	0.451–1.388	0.415
ypT stage							
T0-2	70(40.00%)	Reference			Reference		0.112
T3-4	105(60.00%)	1.149	1.024–2.167	0.037	1.400	0.925–2.120	
ypN stage							
N0	85(48.57%)	Reference			Reference		0.077
N1-3	90(51.43%)	1.505	1.048–2.163	0.027	1.415	0.963–2.081	
ypM stage							
M0	174(99.43%)	Reference			Reference		0.716
M1	1(0.57%)	1.267	0.176–9.098	0.814	1.473	0.182–11.916	
NPS Group							
0	31(17.71%)	Reference			Reference		
1	114(65.14%)	1.698	0.962–2.995	0.068	1.708	0.912–3.201	0.095
2	30(17.14%)	3.061	1.577–5.943	<0.001	3.345	1.574–7.109	0.002

markedly worse outcomes compared to the NPS0 and NPS1 groups. These findings suggest that the NPS score could serve as a simple, effective, and clinically valuable prognostic marker in this patient population.

Neoadjuvant therapy has become the standard treatment for locally advanced esophageal cancer, but its optimal modality and efficacy remain debated, particularly across different pathological subtypes.[15,16] A meta-analysis showed that neoadjuvant chemoradiotherapy improved the three-year survival rate in esophageal squamous cell carcinoma (ESCC), but offered no added benefit over chemotherapy alone in esophageal adenocarcinoma, where chemotherapy may avoid the adverse effects of radiotherapy.[17] However, outcomes remain inconsistent. One retrospective study found better clinical and pathological response rates with chemoradiotherapy compared to chemotherapy, though no significant differences in overall survival (OS) or progression-free survival (PFS) were noted. Similarly, a prospective study of 264 patients reported no significant OS difference between neoadjuvant radiotherapy and chemotherapy. These findings

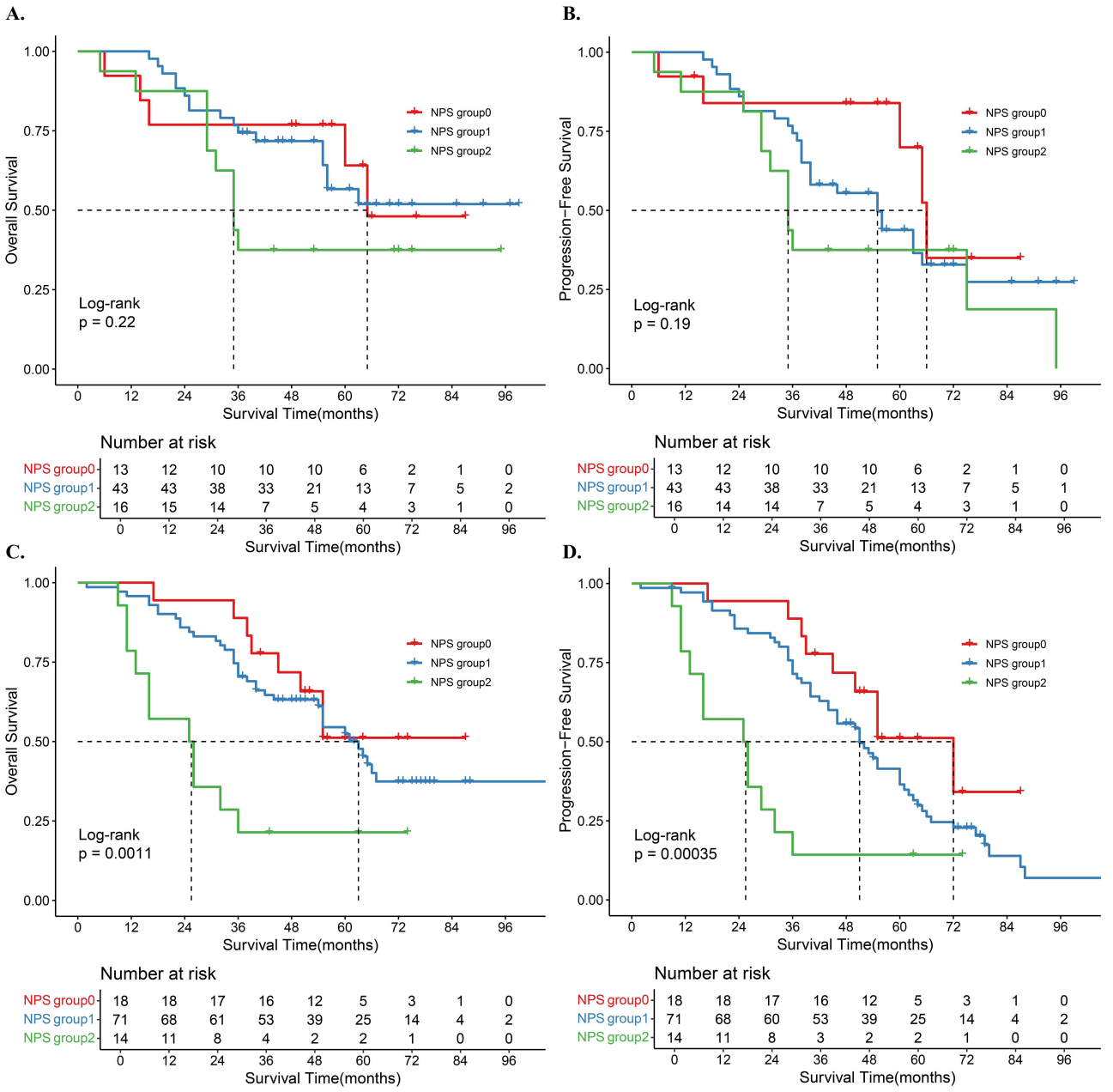

Figure 4 Subgroup analysis of overall survival (OS) and progression-free survival (PFS) in NPS groups (0, 1 and 2), stratified by ypT stage. (**A**) OS of ypT0-2 stage patients; (**B**) PFS of ypT0-2 stage patients; (**C**) OS of ypT3-4 stage patients; (**D**) PFS of ypT3-4 stage patients.

underscore the complexity of esophageal cancer treatment and the need for reliable prognostic models to guide treatment decisions.[15]

Inflammation and nutritional status are increasingly recognized as critical determinants of cancer prognosis. Previous studies have explored the prognostic value of various inflammation- and nutrition-based biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), in patients with ESCC. However, the predictive accuracy of these individual markers has been inconsistent across studies.[18–21] Our study builds on this body of research by integrating these factors into a composite score, the NPS, which has been previously validated in colorectal and gastric cancers.[14,22–25] The moderate predictive ability of the NPS, as indicated by the area under the curve (AUC) values of 0.63 for OS and 0.67 for PFS, aligns with these previous findings and underscores the utility of combining multiple prognostic factors into a single score. In the context of

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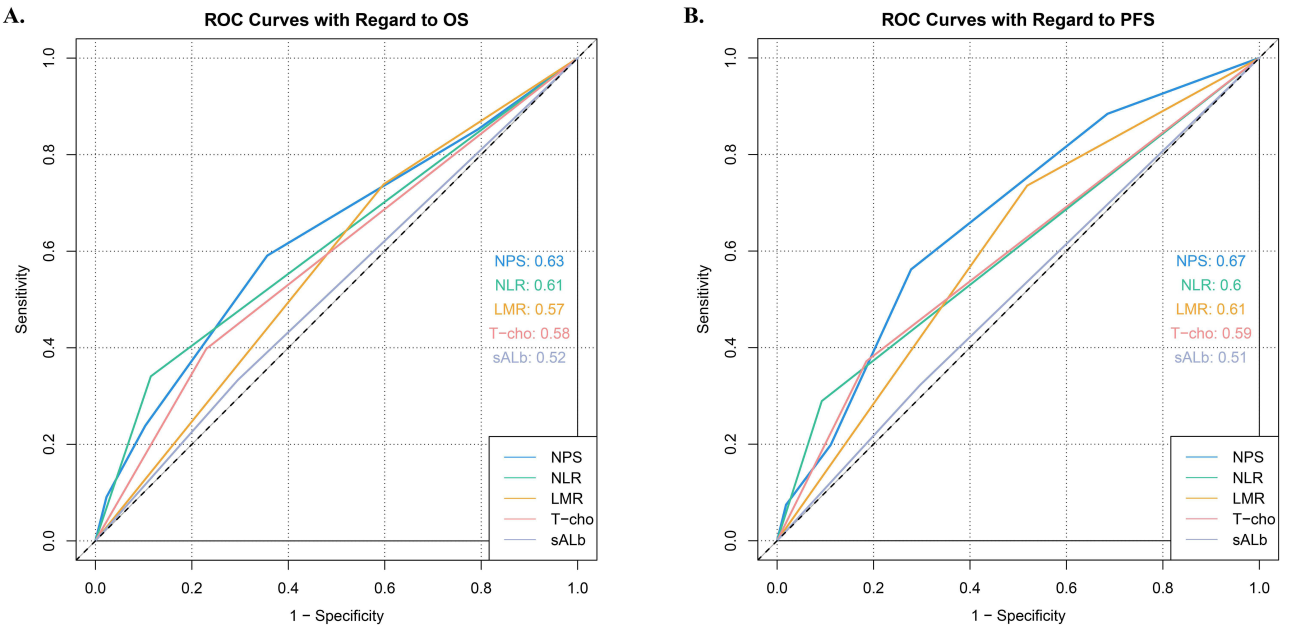

Figure 5 ROC curves revealing the discriminatory power of peripheral blood markers for predicting (**A**) OS and (**B**) PFS.

esophageal cancer, other composite scores, such as the systemic immune-inflammation index (SII) and Glasgow Prognostic Score (GPS), have also been shown to predict outcomes.[26,27] However, our results suggest that the NPS, with its inclusion of nutritional markers (albumin and cholesterol levels) alongside inflammatory indices, may provide a more comprehensive assessment of the patient's overall condition, particularly in malnourished patients, which is common in ESCC.

The clinical implications of our findings are significant. The NPS is a simple, cost-effective tool that relies on routine blood tests, making it easily implementable in clinical practice. Its ability to predict survival outcomes in patients with resectable ESCC after neoadjuvant therapy provides clinicians with a valuable tool for patient stratification. For high-NPS patients, alternative therapeutic strategies, such as more aggressive adjuvant treatments or closer post-surgical follow-up, could be considered to improve long-term outcomes. Furthermore, the NPS could be used in combination with other prognostic factors, such as ypTNM staging and response to neoadjuvant therapy, to develop more comprehensive risk models for ESCC patients. By incorporating both tumor biology (staging) and patient condition (inflammation and nutrition), clinicians could refine their treatment approaches, ultimately personalizing care to maximize survival and minimize recurrence risks.

Despite the promising findings, this study has several limitations. First, as a single-center retrospective study, there is the potential for selection bias. Future multicenter studies with larger, more diverse patient populations are necessary to validate the generalizability of these results. Second, while the NPS showed moderate predictive accuracy, the AUC values suggest that further refinement of the score may be needed to enhance its prognostic power. Additional factors, such as dynamic changes in inflammation and nutritional markers over time, could potentially improve the score's predictive ability. Finally, the study's follow-up period, while sufficient for intermediate-term outcomes, may not capture the full range of survival outcomes, especially for patients with long-term survival. Extended follow-up in future studies would provide a more comprehensive understanding of the long-term prognostic value of the NPS in ESCC.

Future research should focus on prospective, multicenter studies to validate the NPS in larger cohorts of ESCC patients. Additionally, exploring the role of dynamic changes in NPS before and after neoadjuvant therapy could provide insights into its utility in monitoring treatment response and adjusting therapeutic strategies. Integration of NPS with other novel biomarkers, such as immune checkpoint inhibitors or molecular markers, may further enhance its prognostic value and provide a more holistic understanding of patient outcomes in ESCC.

Conclusion

This study demonstrates that the NPS is a simple and effective tool for predicting survival outcomes in patients with resectable locally advanced ESCC following neoadjuvant therapy. Patients with higher NPS scores, particularly those in the NPS2 group, had significantly poorer OS and PFS, highlighting the potential of NPS as an independent prognostic marker. Given its reliance on routine clinical data, the NPS can be easily integrated into clinical practice into preoperative assessments to help stratify patients based on their risk and guide personalized treatment strategies.

Data Sharing Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, 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 author(s) report no conflicts of interest in this work.

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