

The Prognostic Significance of Sarcopenia and the Neutrophil-to-Lymphocyte Ratio in Elderly Patients with Esophageal Squamous Cell Carcinoma

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Objective: To evaluate the correlation between systemic inflammation markers and sarcopenia in elderly patients with esophageal squamous cell carcinoma (ESCC) and their prognostic value.

Materials and Methods: The clinical data of 121 elderly patients with ESCC were collected. The skeletal muscle area at the level of the third lumbar vertebrae (L3) was measured by computed tomography (CT), and then the skeletal muscle index (SMI) was calculated. The neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index (PNI) and Geriatric Nutritional Risk Index (GNRI) were calculated according to laboratory standards. Univariate and multivariate Cox proportional hazards models were used to determine prognostic factors for overall survival (OS).

Results: A total of 121 elderly ESCC patients were enrolled. Among them, 65 patients had sarcopenia. NLR, PNI and GNRI are significantly related to sarcopenia. The OS of ESCC patients with sarcopenia and/or $NLR > 2.24$ was significantly worse.

Conclusion: PNI, GNRI, NLR and sarcopenia were significantly related. Sarcopenia and NLR are independent prognostic factors for elderly ESCC, and when combined have better prognostic value.

Keywords: esophageal squamous cell carcinoma, sarcopenia, neutrophil-to-lymphocyte ratio, survival, nutrition

Introduction

Esophageal cancer is a highly aggressive malignancy. Its incidence rate and mortality rate are very high, ranking ninth and sixth in the world, respectively.¹ The prognosis of patients with esophageal cancer is poor, and the 5-year survival rate is only 18%.² The main pathological types of esophageal carcinoma include esophageal squamous cell carcinoma (ESCC) and adenocarcinoma. At present, surgical treatment is still the main treatment for ESCC. With the gradual progress of population ageing, the number of elderly patients with ESCC is gradually increasing. The treatment of elderly patients with ESCC is an important challenge. Therefore, the prognostic evaluation of elderly patients with ESCC is very important to guide the treatment plan and follow-up strategy.

The progressive growth of tumors in ESCC patients often causes the mechanical obstruction of the esophagus as well as symptoms of progressive

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dysphagia, which leads to reduced nutritional intake in ESCC patients, and then leads to cachexia.³ Many studies have focused on the nutritional status of cancer patients. The Geriatric Nutritional Risk Index (GNRI) is a simplified screening tool based on serum albumin and body weight that can be used to assess nutrition-related risks.⁴ The prognostic nutritional index (PNI) is calculated by the serum albumin concentration and the total number of peripheral blood lymphocytes.⁵ Sarcopenia is a manifestation of body cachexia, which is mainly manifested as a gradual decline in the strength and quality of skeletal muscle.⁶ Because the early symptoms of esophageal cancer are often not considered, most patients can only take in liquid or are unable to eat before going to the doctor, which also causes their nutritional status to be poor. We also found that systemic inflammation is a risk factor for sarcopenia.⁷ Sarcopenia has been used as a predictor of poor prognosis in many gastrointestinal malignancies.⁸ The reduction in skeletal muscle mass measured by computed tomography (CT) is considered to be the gold standard for the diagnosis of sarcopenia.⁹

Complete blood cell count is an easy and inexpensive test in clinical treatment. The systemic inflammatory response is considered to play an important role in the occurrence and development of cancer.¹⁰ The systemic inflammatory response of cancer patients shows significant changes.^{11–13} Studies have confirmed that lymphocyte and platelet count, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and neutrophil-to-lymphocyte ratio (NLR) are related to the prognosis of many cancers.^{14–16}

The purpose of this study was to explore the relationship between preoperative systemic inflammation, GNRI, PNI and sarcopenia in elderly ESCC patients and to evaluate their correlation with the prognosis of ESCC patients.

Materials and Methods

Study Population and Design

From September 2013 to August 2017, 121 elderly patients with ESCC were recruited from the First Affiliated Hospital of Guangxi Medical University (Nanning, China). The inclusion criteria were as follows: (a) ESCC proved by pathology; (b) McKeown or Ivor-Lewis esophagectomy; (c) no distant metastasis found in preoperative examination; (d) age ≥ 65 years; and (e) complete clinical and follow-up data. The exclusion criteria were as follows:

(a) the presence of other malignant tumors; (b) incomplete resection (R1 and R2); and (c) patients with systemic infections and blood diseases. Preoperative blood test results, including complete blood count, albumin, etc., were collected. All blood samples were sent to the same laboratory for analysis. A complete blood count and measurement of height and weight were performed one week before surgery, and then the values of neutrophils (N), platelets (P), monocytes (M), lymphocytes (L) and red blood cell distribution width (RDW), NLR as N/L, MLR as M/L, PLR as P/L were recorded.¹⁷ The PNI was calculated using the following formula: $10 \times \text{serum albumin value (g/dl)} + 0.005 \times \text{total lymphocyte count in the peripheral blood (per mm}^3\text{)}$.⁵ Body mass index (BMI) was calculated as the square of weight (kg)/height (m²). GNRI was calculated as follows: $\text{GNRI} = 1.489 \times \text{serum albumin (g/dl)} + 41.7 \times \frac{\text{weight}}{\text{ideal body weight}}$.⁴ We use the 8th edition of the American Joint Committee on Cancer (AJCC) TNM grading system to stage patients after surgery. The study was conducted in accordance with the Declaration of Helsinki. All patients in the study provided written informed consent, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical College, and the Ethical approval number was 2021 (KY-E-045).

Skeletal Muscle Tissue Measurement

An enhanced CT scan of the abdomen of the patient during the week before treatment was used to collect two consecutive images at the third lumbar vertebrae (L3) level. L3 skeletal muscles include the paraspinal muscles, psoas major, rectus abdominis, internal oblique, external oblique, and transverse abdominal muscles.¹⁸ The skeletal muscle index (SMI) was calculated as the square of the skeletal muscle area (cm²)/height (m²). Sarcopenia was defined as the sex-specific cut-off value of L3 SMI $\leq 52.4 \text{ cm}^2/\text{m}^2$ for males and $\leq 38.5 \text{ cm}^2/\text{m}^2$ for females, which correlates with mortality determined by optimal stratification.¹⁹

Follow-Up

The deadline for follow-up was December 1, 2020. The patients were followed up through outpatient follow-up visits or telephone interviews. Overall survival (OS) was defined as the time from surgery to the last follow-up or death from any cause.

Statistical Analysis

All statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA), and graphs were drawn using GraphPad Prism version 5.0 (GraphPad software, Inc., La Jolla, CA, USA) and R version 4.0.2 (<https://www.r-project.org/>). The time-dependent receiver operating characteristic (ROC) curve was used to determine the clinical index cut-offs, optimal sensitivity, specificity and area under the curve (AUC). Logistic regression analysis was used to evaluate the relationship between sarcopenia and systemic inflammation indicators. Kaplan-Meier analysis was performed to construct survival curve. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate Cox proportional hazards regression models. According to the results of univariate and multivariate Cox regression analysis, a clinical prediction model nomogram was constructed, and then the calibration curve and concordance index (C index) were used to evaluate the prediction accuracy of the nomogram. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Patients and Tumors

A total of 121 patients with ESCC were enrolled. The clinical characteristics of the patients are shown in Table 1. The median age was 69 years (65–86 years and 70.34 ± 4.57 years). Sixty-five patients (53.7%) had sarcopenia. We constructed the ROC curves (Figure 1A) to determine the cut-off value, sensitivity, specificity and AUC value, which were 92.9, 82.8%, 45.6%, and 0.640 (95% CI = 0.541–0.740) for GNRI; 43.35, 85.9%, 44.9%, and 0.648 (95% CI = 0.550–0.747) for PNI; and 22.49, 35.9%, 80.7%, and 0.556 (0.453–0.659) for BMI in 121 elderly ESCC patients.

Systemic Inflammation Markers

The cut-off value, sensitivity, specificity and AUC value of systemic inflammation markers were determined according to the ROC curve (Figure 1B). The cut-off value, sensitivity, specificity and AUC in our cohort were 2.24, 91.2%, 54.7% and 0.714 (95% CI = 0.620–0.808) for NLR; 0.135, 35.1%, 78.1% and 0.594 (95% CI = 0.493–0.695) for RDW; 129.65, 96.5%, 53.1% and 0.820 (95% CI = 0.747–0.892) for PLR; and 0.295, 94.7%, 40.6% and 0.635 (95% CI = 0.534–0.735) for MLR.

Correlation Between Sarcopenia and Clinical Features

We conducted logistic regression analysis on the clinical and pathological characteristics of sarcopenia and patients and systemic inflammation indicators to confirm the relationship between them (Table 2). We found that GNRI (OR = 0.436, 95% CI = 0.194–0.982, $P = 0.045$), PNI (OR = 0.418, 95% CI = 0.182–0.957, $P = 0.039$), and NLR (OR = 3.750, 95% CI = 1.762–7.979, $P = 0.001$) were significantly related to sarcopenia.

Survival Analysis and Risk Factors for OS

The follow-up period ended on December 1, 2020. A total of 57 patients died. The median follow-up period was 39.0 months (range, 1–82). Univariate Cox analysis (Table 3) showed that lymphatic metastasis, cancer embolus, degree of differentiation, tumor depth, sarcopenia, GNRI, PNI, MLR, PLR and NLR were significantly related to OS. We performed multivariate Cox analysis on the statistically significant indicators in the univariate Cox analysis (Table 3). We found that sarcopenia and NLR were independent prognostic factors for elderly patients with ESCC.

Survival analysis showed that patients with sarcopenia had significantly lower OS than those without sarcopenia ($P < 0.0001$, Figure 2A), and patients with a high NLR had a significantly lower OS than patients with a low NLR ($P < 0.0001$, Figure 2B). According to the presence of sarcopenia and the NLR value (> 2.24 or ≤ 2.24), we divided the 121 elderly ESCC patients into four subgroups: sarcopenia/NLR > 2.24 , sarcopenia/NLR ≤ 2.24 , no muscle loss symptoms/NLR > 2.24 and no sarcopenia/NLR ≤ 2.24 . We found that compared with patients in the other groups, the OS of patients with sarcopenia/NLR > 2.24 was significantly worse ($P < 0.0001$, Figure 3A). We combined the two subgroups and established the sarcopenia and NLR (SNLR) group to evaluate the combined prognostic value of SNLR in elderly ESCC patients, defined as follows: no sarcopenia or NLR ≤ 2.24 was assigned 0 points (N=35); sarcopenia or NLR > 2.24 was assigned 1 point (N=41); and both sarcopenia and NLR > 2.24 was assigned two points (N=45). Survival analysis showed that patients with an SNLR score of 0 had a significantly longer OS than patients with a score of 1 or 2 ($P < 0.0001$, Figure 3B).

Table 1 Baseline Characteristics of Patients and Tumors

Characteristics	All Patients	Sarcopenia	Nonsarcopenia	P
	N=121	N=65	N=56	
Age				0.959
≤70	71	38	33	
>70	50	27	23	
Gender				0.847
Male	96	52	44	
Female	25	13	12	
BMI				0.084
≤22.49	87	51	36	
>22.49	34	14	20	
Cancer embolus				0.088
Yes	18	13	5	
No	103	52	51	
Perineural invasion				0.785
Yes	12	6	6	
No	109	59	50	
Smoke				0.326
Yes	42	20	22	
No	79	45	34	
Alcohol drinking				0.905
Yes	49	26	23	
No	72	39	33	
Lymphatic metastasis				0.161
Yes	58	35	23	
No	63	30	33	
Differentiation				0.092
Poor	32	20	12	
Moderately	52	22	30	
Well	37	23	14	
Tumor depth				0.885
T1	16	10	6	
T2	39	20	19	
T3	64	34	30	
T4	2	1	1	

Note: Bold values indicate statistically significant values.

Abbreviation: BMI, body mass index.

Survival Prediction Nomogram Model

Based on the results of multivariate Cox analysis, we established a nomogram for elderly ESCC patients (Figure 4A). The results showed that NLR had the greatest impact on OS, followed by lymphatic metastasis, sarcopenia and tumor depth. At the same time, we evaluated the prognostic value of sarcopenia and NLR combined. We constructed nomograms integrating SNLR, lymphatic

metastasis and tumor depth (Figure 4B). We found that SNLR was the most important factor for OS, followed by lymphatic metastasis and tumor depth. We used the Coxph method to calculate two nomograms, which had accuracy values of 0.759 and 0.761. By establishing a 5-year OS model for the two nomograms (Figure 5A–B), we found that there was a consistency between the predicted survival probabilities and the actual survival probabilities.

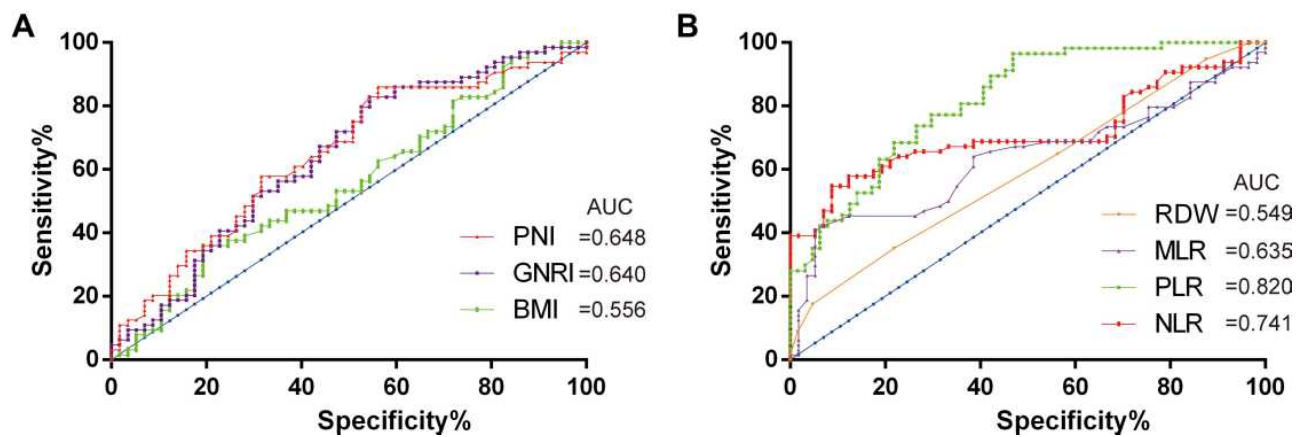


Figure 1 The receiver-operating characteristic (ROC) curves for (A) GNRI, BMI and PNI; (B) Inflammation index.

Abbreviations: AUC, area under the curve; BMI, body mass index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; MLR, monocyte-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio, RDW, red blood cell distribution width.

Discussion

Many studies have confirmed that sarcopenia and systemic inflammation are related to the prognosis of

Table 2 Association Between Clinical Parameters and Sarcopenia

Characteristics	OR (95% CI)	P
Gender(Male)	1.091(0.452–2.634)	0.847
Age(>70)	1.019(0.493–2.107)	0.959
Smoke(Yes)	0.687(0.324–1.457)	0.327
Alcohol drinking(Yes)	0.957(0.462–1.980)	0.905
BMI(>22.49)	0.494(0.221–1.106)	0.086
Lymphatic metastasis(Yes)	1.674(0.813–3.446)	0.162
Cancer embolus(Yes)	2.550(0.848–7.671)	0.096
Perineural invasion(Yes)	0.847(0.257–2.793)	0.847
Differentiation(Poor)	1.630(0.712–3.728)	0.247
Tumor depth(T3+T4)	0.941(0.459–1.929)	0.868
Reflux esophagitis	1.419(0.692–2.911)	0.339
GNRI(>92.9)	0.436(0.194–0.982)	0.045
PNI(>45.35)	0.418(0.182–0.957)	0.039
MLR(>0.295)	1.341(0.618–2.911)	0.458
RDW(>0.135)	2.240(0.974–5.151)	0.058
PLR(>129.65)	1.950(0.927–4.103)	0.078
NLR(>2.24)	3.750(1.762–7.979)	0.001

Note: Bold values indicate statistically significant values.

Abbreviations: BMI, body mass index; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; GNRI, Geriatric Nutritional Risk Index; PNI, Prognostic nutritional index; RDW, red blood cell distribution width.

various cancers. At present, with the ageing of the world's population, the proportion of elderly people is gradually increasing. The ageing process is related to a decline in skeletal muscle mass, and elderly individuals are more likely to suffer from sarcopenia.²⁰ Some studies have shown that sarcopenia is not an independent prognostic factor after neoadjuvant treatment for esophageal cancer.²¹ However, other studies have confirmed that for elderly patients with ESCC, sarcopenia is an independent prognostic factor after neoadjuvant chemotherapy.²² Therefore, the role of sarcopenia in neoadjuvant therapy still needs further research. Some studies have confirmed the relationship between sarcopenia and the prognosis of patients with ESCC,^{23–25} while other studies have confirmed the relationship between systemic inflammation and the prognosis of patients with ESCC. However, these studies did not explore the relationship between sarcopenia and systemic inflammation. Therefore, the relationship between sarcopenia and systemic inflammation and its prognostic role in elderly ESCC patients are still unclear. Whether there is a correlation between sarcopenia and systemic inflammation and its prognostic value are unclear. Therefore, it is necessary to study the prognostic value of sarcopenia and systemic inflammation in elderly patients with ESCC. Through research, we can confirm that NLR and sarcopenia are independent prognostic factors for elderly ESCC patients, sarcopenia is significantly related to NLR, and a higher NLR may cause sarcopenia. Through the joint survival analysis of sarcopenia and NLR, we found that ESCC patients with sarcopenia and high NLR had poor OS. By combining

Table 3 Univariate and Multivariate Analyses of Overall Survival (OS) in the Eligible Patients

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P	HR(95% CI)	P
Gender(Male)	0.783(0.428–1.432)	0.427		
Age(>70)	1.302(0.771–2.197)	0.323		
Smoke(Yes)	0.921(0.531–1.598)	0.769		
Alcohol drinking(Yes)	0.765(0.447–1.311)	0.330		
BMI(>22.49)	0.519(0.269–1.003)	0.051		
Lymphatic metastasis(Yes)	3.482(1.969–6.159)	<0.001	2.050(1.112–3.778)	0.021
Cancer embolus(Yes)	2.600(1.393–4.852)	0.003	1.164(0.565_2.397)	0.681
Perineural invasion(Yes)	0.929(0.371–2.327)	0.875		
Differentiation(Poor)	1.879(1.082–3.262)	0.025	1.647(0.897–3.086)	0.119
Tumor depth(T3+T4)	2.053(1.182–3.566)	0.011	1.451(0.806–2.614)	0.215
Sarcopenia(Yes)	3.885(2.088–7.226)	<0.001	2.344(1.211–4.536)	0.011
GNRI(>92.9)	0.399(0.236–0.674)	0.001	0.638(0.284–1.432)	0.276
PNI(>45.35)	0.369(0.218–0.623)	<0.001	0.911(0.418–1.986)	0.814
MLR(>0.295)	2.198(1.138–4.249)	0.019	1.170(0.546–2.507)	0.686
RDW(>0.135)	1.686(0.978–2.905)	0.060		
PLR(>129.65)	3.015(1.592–5.709)	0.001	1.364(0.633–2.942)	0.428
NLR(>2.24)	5.304(2.673–10.523)	<0.001	2.366(1.024–5.464)	0.044

Note: Bold values indicate statistically significant values.

Abbreviations: BMI, body mass index; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; GNRI, Geriatric Nutritional Risk Index; PNI, Prognostic nutritional index; RDW, red blood cell distribution width.

sarcopenia and NLR, we found that elderly ESCC patients with an SNLR score of 0 had a significantly better prognosis. Through the nomogram, we found that

sarcopenia had a greater impact on the OS of elderly ESCC patients, and SNLR had the greatest impact on the OS of elderly ESCC patients. Surgery is still the first

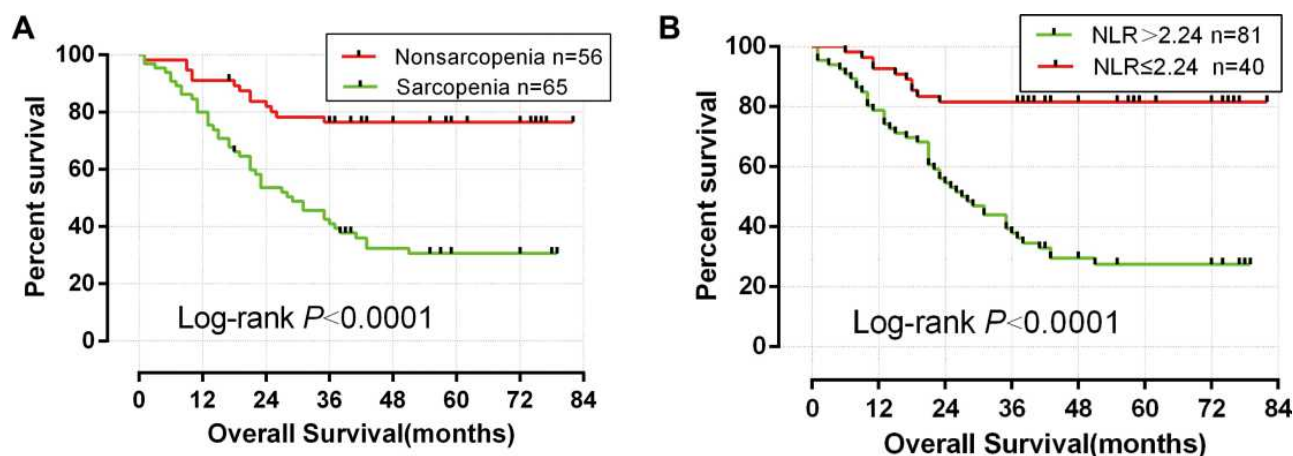


Figure 2 Kaplan-Meier survival curve of overall survival in patients: (A) Sarcopenia; (B) NLR. **Abbreviation:** NLR, neutrophil-lymphocyte ratio.

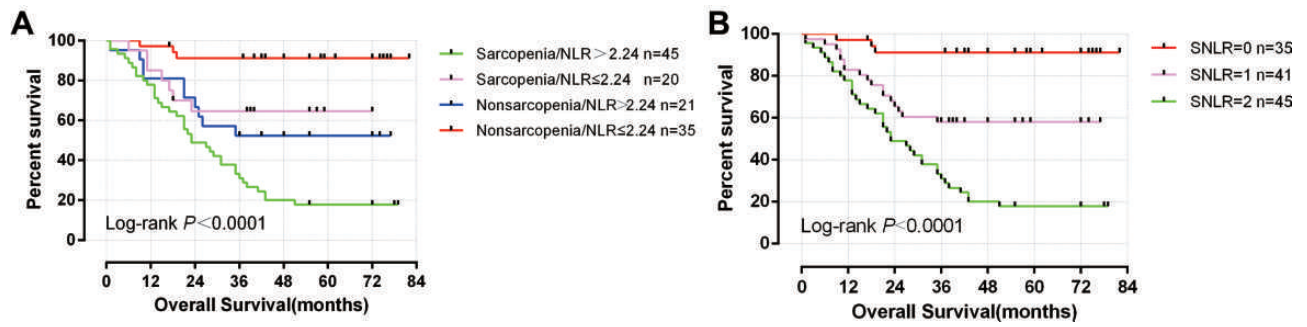


Figure 3 Kaplan–Meier survival curve of overall survival in patients: **(A)** Sarcopenia and NLR; **(B)** SNLR. **Abbreviations:** NLR, neutrophil-lymphocyte ratio; SNLR, sarcopenia and the neutrophil-lymphocyte ratio.

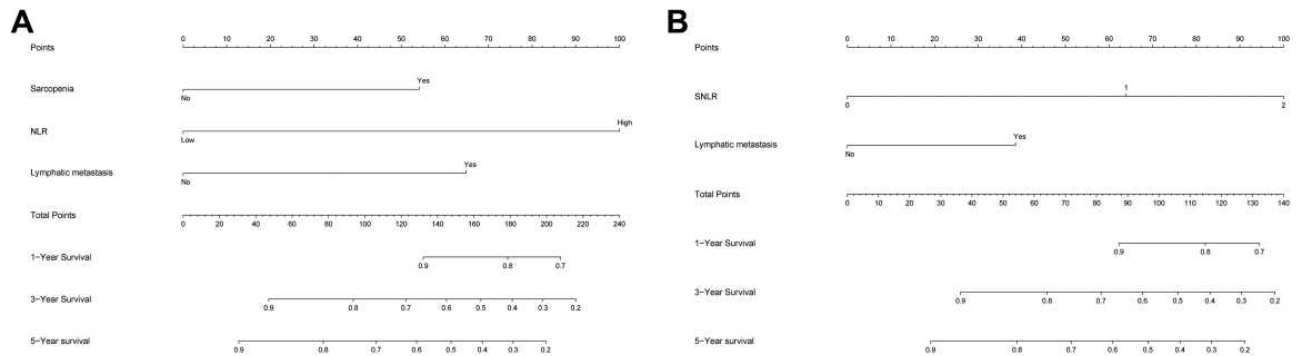


Figure 4 Nomogram for esophageal squamous cell carcinoma. The points identified on the top scale for each independent covariate were added to determine the estimated overall survival and the probability of 1-, 3- and 5-year survival. **(A)** non-SNMR-based nomogram of overall survival. **(B)** SNMR-based nomogram of overall survival. **Abbreviations:** NLR, neutrophil-lymphocyte ratio; SNLR, sarcopenia and the neutrophil-lymphocyte ratio.

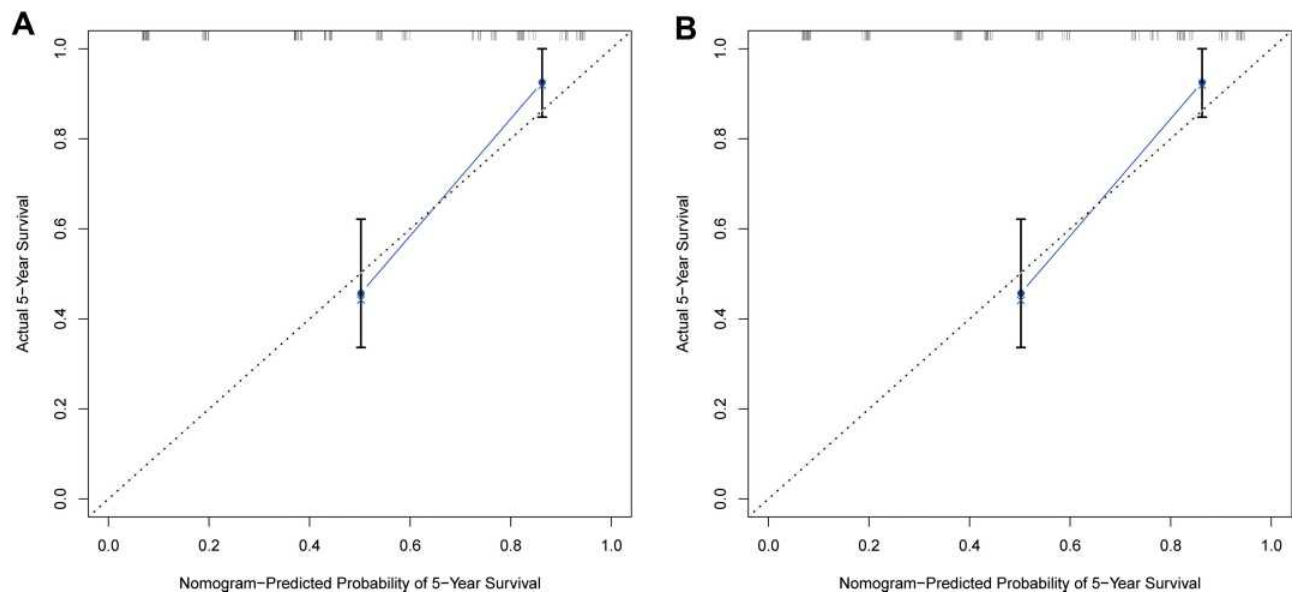


Figure 5 The calibration plot for 5-year survival of **(A)** non-SNLR and **(B)** SNLR. The X-axis presents the predicted probability and the Y-axis shows the actual probability.

choice for the treatment of resectable esophageal cancer. In today’s ageing population, our findings have important clinical significance.

For elderly patients with ESCC, due to the special characteristics of this population, elderly ESCC patients are prone to complications and sarcopenia during

surgery.²⁶ Therefore, the lack of nutrition in the elderly patients with ESCC is a problem worthy of attention. Due to the characteristics of mechanical obstruction in the esophagus caused by esophagus cancer, the incidence of malnutrition in patients with esophageal cancer is significantly higher.²⁷ A previous study found that ESCC patients with a lower GNRI had a significantly worse prognosis,^{28,29} and another study found that a low PNI was significantly associated with poor prognosis in ESCC patients.³⁰ However, in ESCC patients undergoing radical resection of esophageal cancer, the negative effects of surgery and subsequent treatment will further aggravate the original sarcopenia. Although in this study, GNRI and PNI were not independent prognostic factors for ESCC patients, sarcopenia was significantly related to PNI and GNRI. ESCC patients with low PNI and GNRI are more likely to develop sarcopenia. At the same time, sarcopenia has been indicated to have a variety of adverse effects in patients, including a decreased ability to live independently³¹ and an increased chance of accidental falls and fractures.³² These are all factors that lead to poor prognosis in elderly ESCC patients with sarcopenia. Therefore, in the treatment of elderly ESCC patients, a personalized and adequate treatment plan is very important.

Previous studies have found that skeletal muscle can secrete interleukin 15 (IL-15).³³ IL-15 can bind to natural killer (NK) lymphocytes with high affinity through a variety of signaling pathways and protect NK cells from apoptosis by upregulating bcl-2 to ensure the normal development and survival of NK cells.³⁴ Elderly ESCC patients with sarcopenia have a significant decrease in skeletal muscle mass, which will lead to a decrease in IL-15 secretion, resulting in a decline in the antitumor ability of the immune system, leading to tumor progression and ultimately a poor prognosis.

The relationship between sarcopenia and systemic inflammation is very close. Skeletal muscle tissue secretes numerous proinflammatory factors, such as TNF- α and IL-6, leading to the progression of systemic inflammation.³⁴ However, certain proinflammatory factors can promote the decomposition of skeletal muscle and inhibit the differentiation of skeletal muscle cells by inflammatory cells and tumor cells, leading to skeletal muscle atrophy.³⁵ This muscle atrophy caused by inflammation further aggravates systemic inflammation, leading to harmful inflammation-related muscle weakness.³⁶ Previous studies have also found that PNI is significantly related to tumor-

infiltrating lymphocytes (TILs). TILs are a special histological feature of human cancer and reflect the individual immune response of tumors.³⁰ Our study also found that in elderly ESCC patients, sarcopenia is significantly related to NLR, and both are independent prognostic factors for ESCC patients. Patients with a higher NLR have more significant sarcopenia. We believe that this is because systemic inflammation induces the release of proinflammatory cytokines and growth factors, which in turn has a catabolic effect on host metabolism³⁷ and ultimately leads to a decrease in skeletal muscle mass.³⁸

Our research has certain limitations. Our study is a retrospective study, and it was only conducted in a single center. It is necessary to conduct further large-scale cohort studies to obtain more specific results and validate our findings.

Conclusion

GNRI, NRI and NLR are significantly associated with sarcopenia. Both sarcopenia and NLR are independent predictors of postoperative OS in elderly ESCC patients, and they have good comprehensive prognostic value. Sarcopenia and NLR are easily obtained clinical indicators.

Acknowledgments

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Disclosure

The authors declare that they have no competing interests.

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