Original Article

A prognostic nomogram based on lymph node skipping metastases in esophageal squamous cell carcinoma

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Background: At present, the definition of lymph node skipping metastases (NSM) in esophageal squamous cell carcinoma (ESCC) is not uniform, and there were few clinical prognostic models with NSM as a factor. On the other hand, N-staging of ESCC has long been controversial. This study aimed to define NSM in ESCC and investigate its prognostic implications. Meanwhile, according to the cumulative number of cervical, thoracic and abdominal region lymph nodes, a new N-stage was defined and compared with the N-stage of American Joint Committee on Cancer/the Union for International Cancer Control (AJCC/UICC) and Japan Esophageal Society (JES).

Methods: ESCC patients who underwent radical esophagectomy with lymph node metastases (LNM) between January 2012 and December 2022 at Mianyang Central Hospital and West China Hospital of Sichuan University. Patients were grouped into training and external validation cohorts. NSM was defined as any LNM outside the primary tumor region. Meanwhile, this study created a new postoperative pathology N-staging [PN(n)] based on the regional division of LNM to compare with the 8th edition of the AJCC/UICC and the 11th edition of JES N-staging.

Results: There were 232 patients enrolled (training: 161; validation: 71). Cox-regression identified factors that could predict outcomes independently. Kaplan-Meier survival analysis was performed. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC) and calibration plots. Independent risk factors for death included NSM [hazard ratio (HR) =1.5202], age (HR =1.036), T-stage (HR =2.874), and AJCC/UICC N stage (HR =1.9601). Prognostic models for 1-year (AUC: 0.923, 0.985), 3-year (AUC: 0.747, 0.746), and 5-year (AUC: 0.695, 0.713) survival showed high accuracy.

Conclusions: NSM is associated with worse overall survival (OS) in ESCC, and the constructed prognostic model effectively predicts OS for ESCC patients.

Keywords: Esophageal squamous cell carcinoma (ESCC); node skip metastases; nomogram; prognostic model; N stage

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Introduction

Esophageal cancer (EC) has the seventh highest fatality rate among all cancers, with 445,129 additional deaths in 2022 (1). In China, EC ranks fifth in terms of incidence among all cancer types, with 90% of pathological types being esophageal squamous cell carcinoma (ESCC) (2).

EC has an extensive lymphatic drainage system. Lymphatic vessels in the submucosa of the esophagus have abundant longitudinal, transverse, and horizontal traffic (3). This results in lymph node metastases (LNM) which is a frequently observed metastatic route of ESCC (4). In particular, lymph node skipping metastases (NSM) is highly prevalent in ESCC and represents the expansion of cancer invasion, attracting increasing attention over the years. NSM as a particular pattern of LNM was first introduced by Prenzel *et al.* to predict the survival outcomes for patients with EC (5) and directly related to prognosis. But the results of the studies on the prognostic value of NSM in ESCC were inconsistent and even contradictory (6,7). The potential reasons could be the different N staging systems and various NSM definitions in recent studies. Previous research on predictive models related to ESCC includes various factors such as radiological examination results, tumor size, invasion depth, gender, age and others. However, most of these predictive models mainly focus on diagnosis such as predicting specific LNM (8,9). There were few clinical prediction models for ESCC patients that take NSM into consideration. Therefore, this study based on the inconsistent definition and uncertain prognosis of NSM in ESCC in previous studies to redefine NSM and developed a model by analyzing data from two research centers and conducting thorough internal and external validation then predict clinical outcomes.

N stage is a crucial prognostic factor for ESCC. Currently, there are two commonly used N staging systems in ESCC. American Joint Committee on Cancer/the Union for International Cancer Control (AJCC/UICC) N staging system consider the number of metastatic lymph nodes as a determinant of tumor prognosis (10). In contrast, Japan Esophageal Society (JES) N staging system emphasizes the region of LNM (11). Based on controversy persists between the two N staging systems, an increasing number of studies are being conducted to explore how the type of LNM influences prognosis. At present, some studies have reported the modification of N staging (12,13), others including para-respiratory and para-digestive lymph node stations, the positive lymph node metastases rate (LNMR) (the number of metastatic lymph nodes/the number of examined lymph nodes), the number of positive lymph node stations and the proportion of examined lymph node stations (the number of positive lymph node stations/the number of examined lymph node stations) (14,15). This study trying to devise an N staging system that considers the cervix thoracic abdominal region of LNM, with compared analysis of the three N staging systems to assess their influence on ESCC prognosis. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1798/rc).

Highlight box

Key findings

- The new definition of lymph node skipping metastases (NSM) in esophageal squamous cell carcinoma (ESCC) correlates with poorer overall survival.
- Prognostic model incorporating NSM effectively predict ESCC prognosis.
- The quantity of lymph node metastases (LNM) being a more reliable prognostic indicator than the extent of esophageal cancer metastases.

What is known and what is new?

- The definition of NSM in esophageal cancer lacks standardization. N stage is a crucial prognostic factor for ESCC and N stage of ESCC is controversial.
- NSM was defined as any LNM outside the primary tumor region. Our study developed a clinical prediction model incorporating NSM and the model effectively predicts 1-, 3-, 5-year survival for ESCC patients.

What is the implication, and what should change now?

- The definition of NSM in ESCC should be reconsidered.
- The prognosis of redefined NSM for ESCC should be studied further.
- The clinical prognostic model of NSM in ESCC patients should be fully evaluated and applied to the clinic.

Methods

Patients and follow-up methods

This was a two-center retrospective study involving 232 ESCC patients between January 2012 and December 2022 with LNM who underwent esophagectomy with complete lymph node dissection. Patients were divided into training (Mianyang Central Hospital) and external validation (West China Hospital of Sichuan University) cohorts. The following criteria were used for inclusion: (I) primary

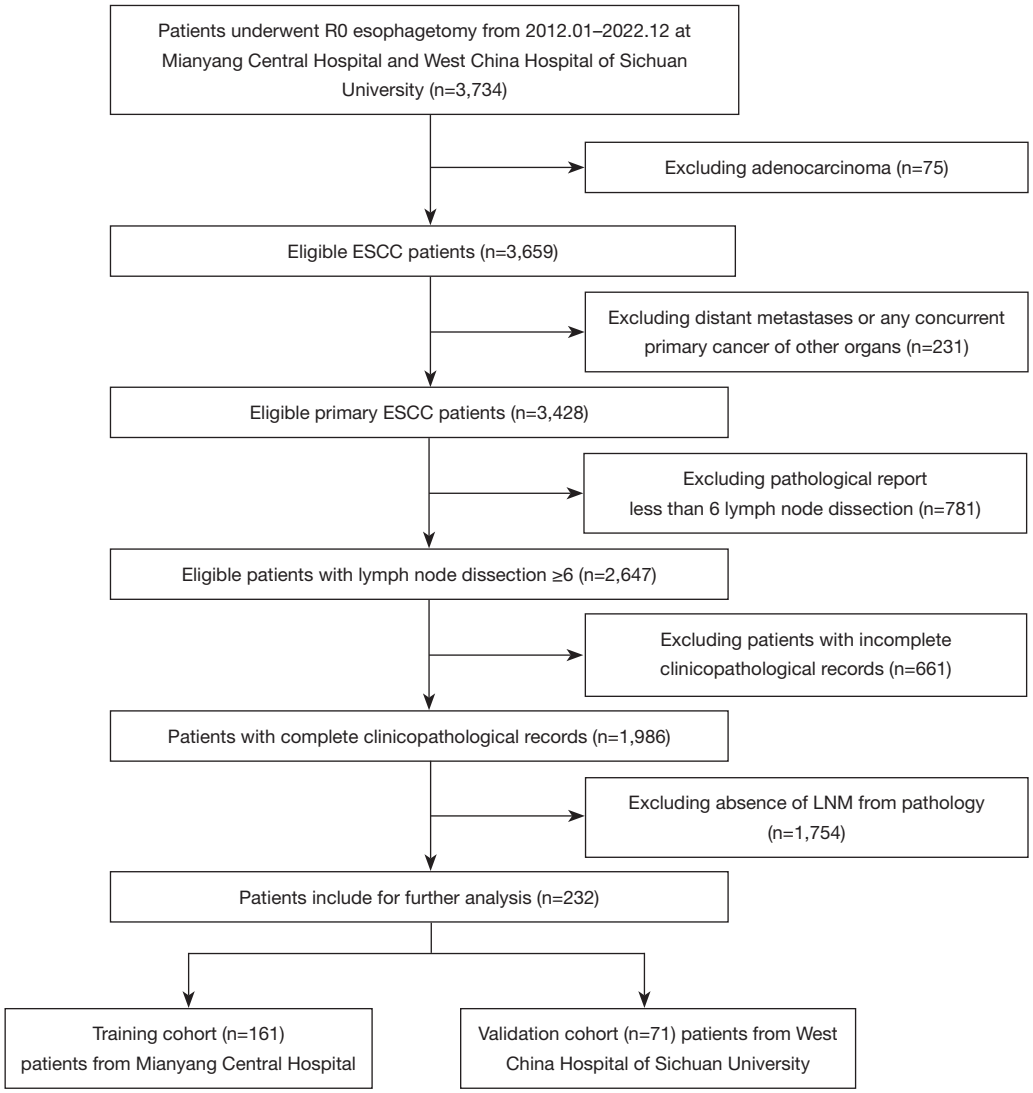

Figure 1 Flow chart for patient inclusion and exclusion. ESCC, esophageal squamous cell carcinoma; LNM, lymph node metastases.

ESCC; (II) patients with no contraindications underwent radical esophagectomy via left (Sweet) or right (McKeown or Ivor-Lewis) esophagectomy approaches depending on the tumor location with at least a two-field (thoracic and abdominal) lymphadenectomy; (III) available pathological results for lymph nodes; and (IV) lymph node dissection ≥6. Out of the 3,734 patients who underwent EC surgery, 75 patients with adenocarcinoma of the esophagus were excluded. Additionally, 231 patients with other metastases or any tumor that coexists with EC, 781 patients with less than 6 lymph nodes, 1,754 patients without LNM based on pathology data, and 661 patients with incomplete clinicopathological records were also excluded. Patients receiving neoadjuvant therapy were excluded. After all the exclusion, a total of 232 patients were finally enrolled in the study. This study adhered to the ethical principles outlined in the Declaration of Helsinki (as revised in 2013), including maintaining participant confidentiality, as well as conducting the research with integrity and respect for the rights of individuals involved. The study was approved by Ethics Committees of Mianyang Central Hospital (No. S202403119-01) and West China Hospital of Sichuan University (No. 20211235). Informed consent for this retrospective study was waived. For a visual representation of the selection process, please refer to *Figure 1*.

Overall survival (OS) was the primary endpoint of

the follow-up. OS was defined as the time from the start of tumor treatment until death from any cause, loss to follow up, or the end of the follow-up period, whichever occurred first.

Data collection

All participants underwent radical esophagectomy combined with lymph node dissection. Common clinical characteristics such as age and sex were recorded. Two experienced pathologists independently evaluated the specimens to determine the pathological diagnosis of ESCC. Data included pathological features, tumor site, tumor differentiation (grading), T stage, AJCC/UICC N stage, state of NSM, vascular infiltration, number of LNM, LNM locations, overall number of resected lymph nodes, LNMR (the proportion of positive lymph nodes in the total number of lymph nodes removed). Patients receiving neoadjuvant therapy were excluded. Specific lymph node sites (cervical, abdominal, subcarinal, and left gastric) were also analyzed for their association with prognosis in previous studies of esophageal cancer. Survival time data, including causes of death and endpoint dates were obtained from each follow-up, the electronic medical records system (EMRS), and in contact with patients or relatives through communication devices. The last follow-up was conducted in December 2023.

Definition

The AJCC/UICC system was used for N staging based on postoperative pathology. LNM was defined based on defined AJCC/UICC N regions, cervical lymph nodes were classified as levels I (medial group), VI, and VII, thoracic lymph nodes were classified as groups 2, 4, 5, 6, 7, 8, and 9, 10, 15. Abdominal lymph nodes were classified as groups 16, 17, 18, 19, 20. NSM was defined as the absence of LNM in the same region as the primary tumor. For example, if the primary tumor was in the thoracic region, but abdominal LNM occurred, it was classified as NSM. If the primary tumor is in the middle thoracis, it is not classified as NSM even if there are LNM in the upper or lower thoracic region. New lymph node staging {new postoperative pathology N-staging [PN(n)]} system was developed. In this system, the presence of one positive lymph node region (cervical, thoracic, or abdominal) was classified as N1, two positive regions as N2, and three positive regions as N3. At PN(n) system, cervical, thoracic and abdominal is according to AJCC/UICC region principle. N staging was also performed according to the region, the difference between PN(n) and JES N staging was that PN(n) not consider the detailed dissection station of LNM but was determined according to the segmentation of the esophagus. All the patients' N stages were restaged according to the JES N staging principles. The AJCC/UICC, JES N staging anatomical location, definitions of NSM and PN(n) staging are shown in the *Tables 1-3*.

Statistical analysis

Statistical analyses were performed using the R programming language (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Survival analysis was conducted using the R packages 'survival' and 'survminer'. The 'survival' package in R was utilized to determine cut-off values for significant continuous variables (age and lymph node detection rate). These continuous variables were then transformed into binomial categorical variables based on the cut-off values.

In the analysis of differences between the training set and the validation set, categorical variables were presented as counts and percentages. Pearson's Chi-squared test or the exact probability method was used to compare the differences between the two cohorts. Quantitative data following a normal distribution was described as mean with standard deviation (SD) and the comparison between the two groups was performed using an independent samples *t*-test. Linear Regression analyzed collinearity analysis of NSM with the other variables. Variance inflation factor (VIF) >5 indicated that there was collinearity between the variables. Continuous variables that did not follow a normal distribution were presented as the interquartile range (IQR), and the Mann-Whitney rank sum test was used to compare independent sample non-parametric tests between the cohorts. $P<0.05$ was considered statistically significant. Since there were no missing values in the entire dataset, there was no need to handle missing values.

Performed univariate analysis by Cox regression, variables with significant differences ($P<0.05$) were included in the multivariate Cox regression model. Based on the results of the Cox multivariate analysis, nomograms were created to forecast an individual's OS at 1-, 3-, and 5-year intervals. This nomogram can convert the correlation coefficients of the Cox proportional risk model into 0–100 points to calculate the total score. The prediction results were obtained by the corresponding relationship between the total score and the probability of outcome events. Log-rank tests were

Table 1 The lymph node anatomic region of ESCC

Region	Mediastinal region	Anatomical boundaries	AJCC/UICC	JES
Cervix lymph nodes	–	Hypopharynx to sternal notch	1R/1L: right/left lower cervical paratracheal nodes	101: cervical paraesophageal lymph nodes
Thoracic lymph nodes	Upper mediastinal	Sternal notch to lower border of azygos vein	2R/2L: right/left upper paratracheal nodes	106recR/106recL: right/left recurrent laryngeal nerve lymph nodes
			8U: upper thoracic paraesophageal lymph nodes	105: upper thoracic paraesophageal lymph nodes
			4R: right lower paratracheal nodes	106: paratracheal lymph nodes
			4L: left lower paratracheal nodes	106tbL: left tracheobronchial lymph nodes
			5: subaortic nodes	113: ligamentum arteriosum lymph nodes (Botallo lymph nodes)
			6: anterior mediastinal nodes	114: anterior mediastinal lymph nodes
	Middle mediastinal	Lower border of azygos vein to inferior pulmonary vein	7: subcarinal nodes	107: subcarinal lymph nodes
			8 M: middle thoracic paraesophageal lymph nodes	108: middle thoracic paraesophageal lymph nodes
			10L/10R: left/right bronchial paratracheal nodes	109L/109R: left/right main bronchus lymph nodes
	Lower mediastinal	Inferior pulmonary vein to esophagogastric junction	8Lo: lower thoracic paraesophageal lymph nodes	110: lower thoracic paraesophageal lymph nodes
			9L/9R: left/right inferior pulmonary ligament nodes	112pulL/112pulR: left/right pulmonary ligament lymph nodes
			15: diaphragmatic nodes	111: supradiaphragmatic lymph nodes
Abdominal lymph nodes	–	Esophagogastric junction to 5 cm below esophagogastric junction	16: paracardial nodes	1/2: right/left paracardial lymph nodes
			17: left gastric nodes	3a: lesser curvature lymph nodes along the branches of the left gastric artery
			18: common hepatic nodes	7: lymph nodes along the left gastric artery
			19: splenic nodes	8a/8p: lymph nodes along the common hepatic artery (anterosuperior/posterior group)
			20: celiac nodes	11p/11d: lymph nodes along the proximal/distal splenic artery
				9: lymph nodes along the celiac artery

AJCC/UICC, American Joint Committee on Cancer/the Union for International Cancer Control; ESCC, esophageal squamous cell carcinoma; JES, Japan Esophageal Society.

Table 2 The definition of NSM

Region	AJCC/UICC	NSM
Cervix lymph nodes	1R/1L: right/left lower cervical paratracheal nodes	Others
Thoracic lymph nodes	2R/2L: right/left upper paratracheal nodes	Others
	8U: upper thoracic paraesophageal lymph node	
	4R: right lower paratracheal nodes	
	4L: left lower paratracheal nodes	
	5: subaortic nodes	
	6: anterior mediastinal nodes	
	7: subcarinal nodes	
	8 M: middle thoracic paraesophageal lymph nodes	
	10L/10R: left/right bronchial paratracheal nodes	
	8Lo: lower thoracic paraesophageal lymph nodes	
	9L/9R: left/right inferior pulmonary ligament nodes	
	15: diaphragmatic nodes	
Abdominal lymph nodes	16: paracardial nodes	Others
	17: left gastric nodes	
	18: common hepatic nodes	
	19: splenic nodes	
	20: celiac nodes	

AJCC/UICC, American Joint Committee on Cancer/the Union for International Cancer Control; NSM, lymph node skipping metastases.

Table 3 The definition of PN(n)

N stage	AJCC/UICC	PN(n)	JES
N1	1–2 regional lymph node metastases	LNM accumulated to 1 anatomic location (for example, it is limited to the thoracic)	Cervix: 101; 106rec
			Upper thoracic: 101; 105; 106rec
			Middle thoracic: 106rec; 108: 1, 2, 3a
			Lower thoracic: 110: 1, 2, 3a, 7, 20
			Abdominal: 110: 1, 2, 3a, 7, 20
N2	3–6 regional lymph node metastases	LNM accumulated to 2 anatomic locations (LNM limited to the thoracic and abdominal)	Cervix: 102; 104; 105
			Upper thoracic: 104; 106tbL; 107; 108; 109
			Middle thoracic: 101; 104; 105; 107; 109; 110; 112aoA; 112pul: 7, 9, 20
			Lower thoracic: 101; 106rec; 107; 108; 109; 112aoA; 112pul: 9
			Abdominal: 111; 112aoA; 112pul: 8a, 9, 11P, 19
N3	More than 7 regional lymph node metastases	LNM accumulated to 3 anatomic locations (thoracic and abdominal cervix)	Cervix: 100
			Upper thoracic: 102mid; 106pre; 106tbR; 110; 112aoA; 112pul: 1, 2, 3a, 7, 20
			Middle thoracic: 106tbL
			Lower thoracic: 111: 8a, 11p; 104; 105; 106tbL
			Abdominal: 106rec; 107; 108; 109: 11d

AJCC/UICC, American Joint Committee on Cancer/the Union for International Cancer Control; LNM, lymph node metastases; JES, Japan Esophageal Society; PN(n), new postoperative pathology N-staging.

conducted on the features selected by univariate analysis, and Kaplan-Meier curves were developed to estimate OS. Hazard ratios (HRs) and 95% confidence interval (CI) were calculated, and forest plots were used to visualize the results of the Cox analysis. Additionally, validation of the nomogram was measured by the area under the receiver operating characteristic (ROC) curve (AUC). Finally, a validation set was utilized to perform ROC verification to evaluate the stability and effectiveness of the model.

Results

Clinicopathological characteristics

Overall, there were 232 patients included in this study, with 202 male and 30 female participants. The age range of the patients was 42 to 70 years, with a cut-off at 62 years. The training cohort consisted of 161 patients, and an external validation cohort consisted of 71 patients. In all cohorts, the most frequently occurring T stage was T3, accounting for 105 cases (45.3%). T4 was the second most common T stage, with 52 cases (22.4%). T2 accounted for 48 cases (20.7%), while T1 accounted for 27 cases (11.6%). According to the AJCC/UICC N stage, 73 patients (31.4%) were classified as N1 stage, 69 (29.7%) as N2 stage, and 90 (38.9%) as N3 stage. The JES N stage distribution was as follows: 64 (27.6%) for N1, 124 (53.4%) for N2, 37 (15.9%) for N3, and 7 (3.1%) for N4. The majority of cases originated from the thoracic esophagus (n=167; 72.0%), followed by the abdominal region (n=61; 27.99%). Regarding tumor grade, 88 patients (37.9%) had G1, 106 (45.7%) had G2, and 38 (16.4%) had G3. Additionally, 102 patients (43.9%) had NSM. In our developed PN(n) staging system, the distribution of cases was as follows: PN(n) N1, 145 cases (62.5%); PN(n)N2, 84 cases (36.2%); and PN(n)N3, 3 cases (1.3%), with an average LNMR of 24%. The Cut-off for LNMR was 0.06. The median number of lymph node dissection stations was 5.5 (range, 4–7) based on the 25th and 75th quantiles. The median numbers of positive and examined lymph nodes in both cohorts were 3 (range, 1–14) and 26 (range, 6–45), respectively. The most commonly affected lymph node stations were 7, 8, 16, and 17. Collinearity analysis of NSM with the other variables showed VIF ranging from 1.054–1.294, excluded correlation with NSM and age, T-stage, LNMR, number of lymph node dissected stations, PN(n), JES N stage, AJCC/UICC N stage. Detailed baseline patient information and the differences between the two cohorts were summarized in *Table 4*. No significant differences were observed between the training and validation cohorts (P>0.05).

Risk factors for prognosis

Age, T stage, AJCC/UICC N stage, NSM and LNMR were all significantly associated with OS in the univariate analysis (P<0.05), while PN(n)N2 (P=0.22) and PN(n)N3 (P=0.99) were no significance. Multivariate analysis revealed significant associations between OS and age, T stage, AJCC/UICC N stage, and NSM. The HR (95% CI) of age was 1.0360 (1.0056–1.0673), indicating that with each 1-unit increase in age, the risk of death increased by 3.6%. The HR (95% CI) of the T4 stage was 2.8740 (1.1496–7.1848), meaning the risk of death in the T4 stage group was 1.874 times higher than in the T1 stage group, using T1 as the baseline. The HR (95% CI) of AJCC/UICC N2 was 1.9601 (1.1028–3.4840), indicating a 96.01% increased risk of death in the N2 population compared to the N1 population. The HR (95% CI) for NSM was 1.5202 (1.0227–2.2598), with a 52% higher risk of death compared to those without NSM. PN(n) stage was not a risk factor for prognosis in either univariate or multivariate analysis. Detailed multivariate and univariate analyses for the training cohort were presented in *Table 5*. Independent risk factors were illustrated in the multivariate forest plot (*Figure 2*).

OS

The median follow-up duration was 57 months. Since the median survival time of some variables was not obtained, the description of OS uses the mean survival time. In the training cohort, the mean OS for T1, T2, T3, and T4 was 68, 49.2, 36.5, and 27.7 months, respectively. The mean OS for the AJCC/UICC N1, N2, and N3 stages was 62.7, 33.9, and 28.4 months, respectively. The mean survival time for individuals with NSM was 30.6 months, compared to 51 months for those without NSM. The mean survival time for individuals with LNMR >0.06 was 36.7 months, while it was 73.2 months for those with LNMR ≤0.06. The mean survival time was 49.2 months for individuals age ≤62 years compared to 31.6 months for those age >62 years. The Kaplan-Meier survival curves for independent risk factors were shown in *Figure 3A-3E*.

Prognostic models for patients with ESCC

A nomogram was constructed based on Cox analysis of

Table 4 Basic clinical information of patients with ESCC

Variables	All cohorts	Training cohort	Validation cohort	P value
Gender				0.16
Male	202 (87.1)	144 (89.4)	58 (81.7)	
Female	30 (12.9)	17 (10.6)	13 (18.3)	
Age (years)	60.65±7.75	62.58±7.73	60.56±9.23	0.09
T stage				0.44
T1	27 (11.6)	18 (11.2)	9 (12.7)	
T2	48 (20.7)	38 (23.6)	10 (14.1)	
T3	105 (45.3)	70 (43.5)	35 (49.3)	
T4	52 (22.4)	35 (21.7)	17 (23.9)	
AJCC/UICC N				0.19
N1	73 (31.4)	51 (31.7)	22 (31.0)	
N2	69 (29.7)	53 (32.9)	16 (22.5)	
N3	90 (38.9)	57 (35.4)	33 (46.5)	
JES N				0.85
N1	64 (27.6)	43 (26.7)	21 (29.6)	
N2	124 (53.4)	85 (52.8)	39 (54.9)	
N3	37 (15.9)	28 (17.4)	9 (12.7)	
N4	7 (3.1)	5 (3.1)	2 (2.8)	
Grading				0.11
G1	88 (37.9)	54 (33.5)	34 (47.9)	
G2	106 (45.7)	78 (48.4)	28 (39.4)	
G3	38 (16.4)	29 (18.0)	9 (12.7)	
Location				0.13
Upper	4 (0.01)	4 (2.5)	0 (0.0)	
Middle	167 (72.0)	110 (68.3)	57 (80.3)	
Lower	61 (27.99)	47 (29.2)	14 (19.7)	
NSM				0.51
NSM(–)	130 (56.1)	93 (57.8)	37 (52.1)	
NSM(+)	102 (43.9)	68 (42.2)	34 (47.9)	
PN(n)				0.21
N1	145 (62.5)	98 (60.9)	47 (66.2)	
N2	84 (36.2)	62 (38.5)	22 (31.0)	
N3	3 (1.3)	1 (0.6)	2 (2.8)	
LNMR	0.19 [0.09, 0.34]	0.21 [0.09, 0.37]	0.18 [0.10, 0.30]	0.17
Number of lymph node dissection stations	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]	0.46

Data are presented as n (%), median [IQR] or mean ± SD. AJCC/UICC, American Joint Committee on Cancer/the Union for International Cancer Control; ESCC, esophageal squamous cell carcinoma; IQR, interquartile range; JES, Japan Esophageal Society; LNMR, lymph node metastases rate; NSM, lymph node skipping metastases; NSM(–), without lymph node skipping metastases; NSM(+), with lymph node skipping metastases; PN(n), new postoperative pathology N-staging; SD, standard deviation.

Table 5 Univariate and multivariate analyses of overall survival in the training cohort

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>62.58 *vs.* ≤62.58 years)	1.0543 (1.0257–1.0838)	<0.001	1.0360 (1.0056–1.0673)	0.02
T stage (baseline T1)				
T2	2.1588 (0.8736–5.3345)	0.10	1.7090 (0.6767–4.3164)	0.26
T3	3.2427 (1.3826–7.6053)	0.007	2.2497 (0.9216–5.4915)	0.08
T4	4.4390 (1.8268–10.7867)	0.001	2.8740 (1.1496–7.1848)	0.02
AJCC/UICC N (baseline N1)				
N2	2.6427 (1.5376–4.5420)	<0.001	1.9601 (1.1028–3.4840)	0.02
N3	3.1643 (1.8687–5.3582)	<0.001	2.1938 (1.2664–3.8005)	0.005
NSM	1.9235 (1.3121–2.8197)	0.001	1.5202 (1.0227–2.2598)	0.04
PN(n) [baseline PN(n)1]				
PN(n)2	1.2722 (0.8664–1.8680)	0.22	–	–
PN(n)3	0.0000 (0.0000–Inf)	0.99	–	–
LNMR	2.9730 (1.2416–7.1188)	0.02	2.2812 (0.9528–5.4617)	0.06

AJCC/UICC, American Joint Committee on Cancer/the Union for International Cancer Control; CI, confidence interval; HR, hazard ratio; Inf, infinity; LNMR, lymph node metastases rate; NSM, lymph node skipping metastases; PN(n), new postoperative pathology N-staging.

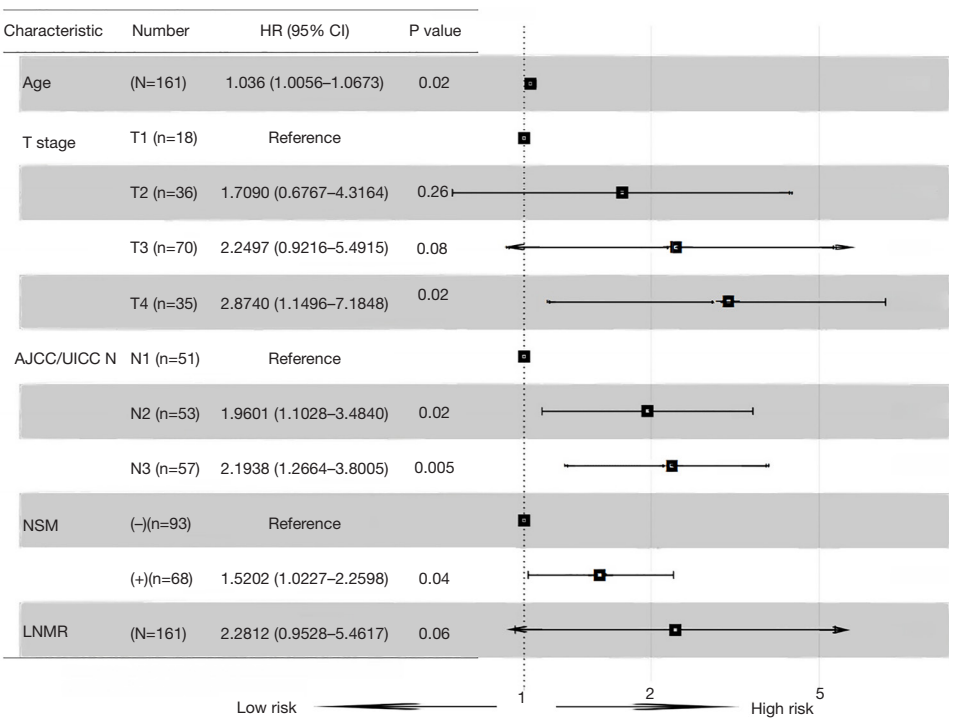

Figure 2 Multifactorial forest plot of independent prognostic factors. AJCC/UICC, American Joint Committee on Cancer and the Union for International Cancer Control; CI, confidence interval; HR, hazard ratio; LNMR, lymph node metastases rate; NSM, lymph node skipping metastases; NSM(–), without lymph node skipping metastases; NSM(+), with lymph node skipping metastases.

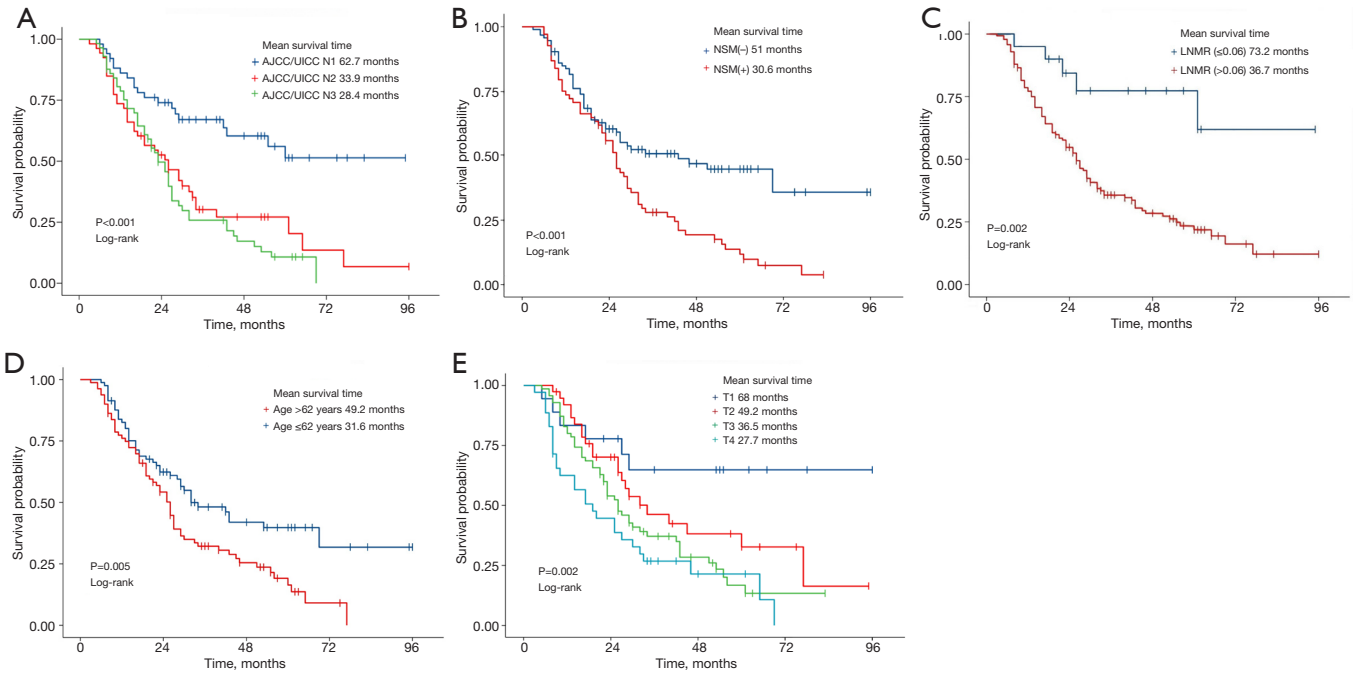

Figure 3 K-M curve for AJCC/UICC N stage, NSM, LNMR, age and AJCC/UICC T stage. (A) K-M for AJCC/UICC N stage and median survival time of N1, N2, N3. (B) K-M for NSM and median survival time for NSM and without NSM. (C) K-M for LNMR and median survival time for LNMR >0.06 and LNMR ≤0.06. (D) K-M for age and median survival time for age >62 years and age ≤62 years. (E) K-M for AJCC/UICC T stage and median survival time for T1, T2, T3, T4. AJCC/UICC, American Joint Committee on Cancer and the Union for International Cancer Control; K-M, Kaplan-Meier; LNMR, lymph node metastases rate; NSM, lymph node skipping metastases; NSM(–), without lymph node skipping metastases; NSM(+), with lymph node skipping metastases.

independent risk factors, including age, NSM, T stage and AJCC/UICC N stage (*Figure 4*). By adding up the scores at each variable point on the nomogram, the risk of death at 1 year, 3 years and 5 years for individual patients could be calculated. ROC curves and calibration plots were constructed to present the performance of the model. Internal validation was performed using bootstrapping (1,000 resampling) to avoid potential overfitting. The AUC and 95% CI in the training cohort at 1-, 3-, and 5-year were 0.923 (0.8760–0.9679), 0.747 (0.6654–0.8286), and 0.695 (0.5689–0.8202), respectively. Calibration plots for the model at 1 year, 3 years, and 5 years all closely align with the diagonal line, indicating that the model's prediction performance is well aligned with the actual situation.

Next, external validation was conducted using the ROC curve and AUC to further validate the stability of the model and its predictive effect. The AUC and 95% CI in the validation cohort were as follows: 0.985 (0.9631–1.00), 0.746 (0.6176–0.874), and 0.713 (0.54–0.8857). The AUC of the validation cohort at 1 year was a little higher than that of the training cohort. However, this difference was not statistically significant at the 5% significance level. Please refer to the ROC curves of the two cohorts and their validation in *Figure 5A,5B*. The calibration curves of 1 year, 3 years, and 5 years were shown in *Figure 6A-6C*. The AUC value and 95% CI for the two cohorts were presented in *Table 6*.

Discussion

In this retrospective cohort study, we defined NSM and investigated the effects of NSM on prognosis in ESCC which demonstrate that patients with NSM have poorer OS. To achieve this, this study created a prediction model that could estimate the OS of ESCC patients. Calibration curves showed that our model fit well in two cohorts. Our intention was for this model to guide clinical practice and emphasize the prognostic significance of NSM. We also compared the AJCC/UICC N staging system with the JES N staging system and concluded that the AJCC/UICC N

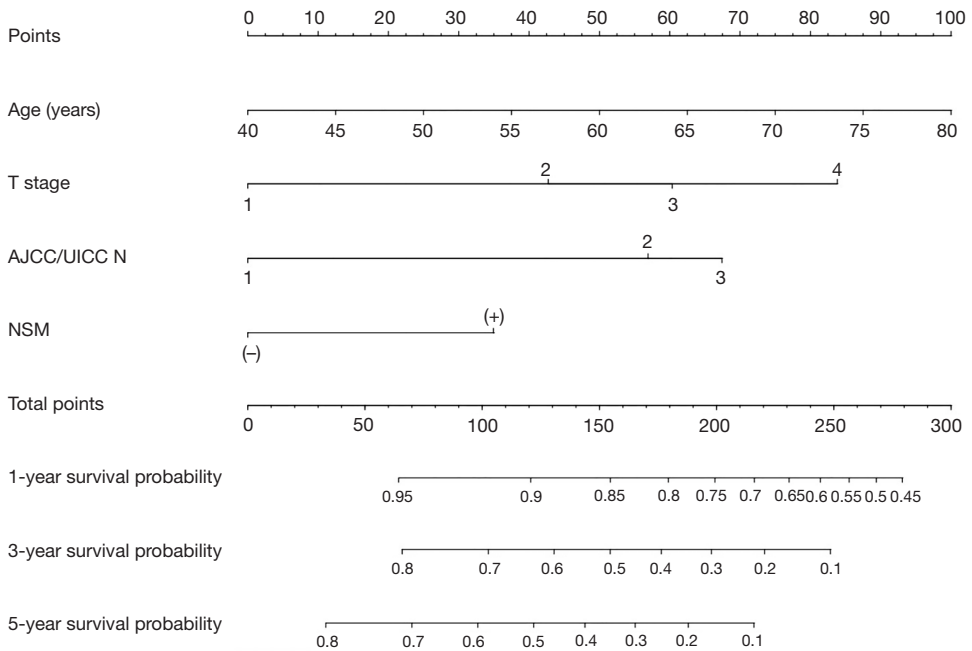

Figure 4 Nomogram for predicting survival in ESCC patients based on NSM, T stage, and AJCC/UICC N stage. AJCC/UICC, American Joint Committee on Cancer and the Union for International Cancer Control; ESCC, esophageal squamous cell carcinoma; NSM, lymph node skipping metastases; NSM(–), without lymph node skipping metastases; NSM(+), with lymph node skipping metastases.

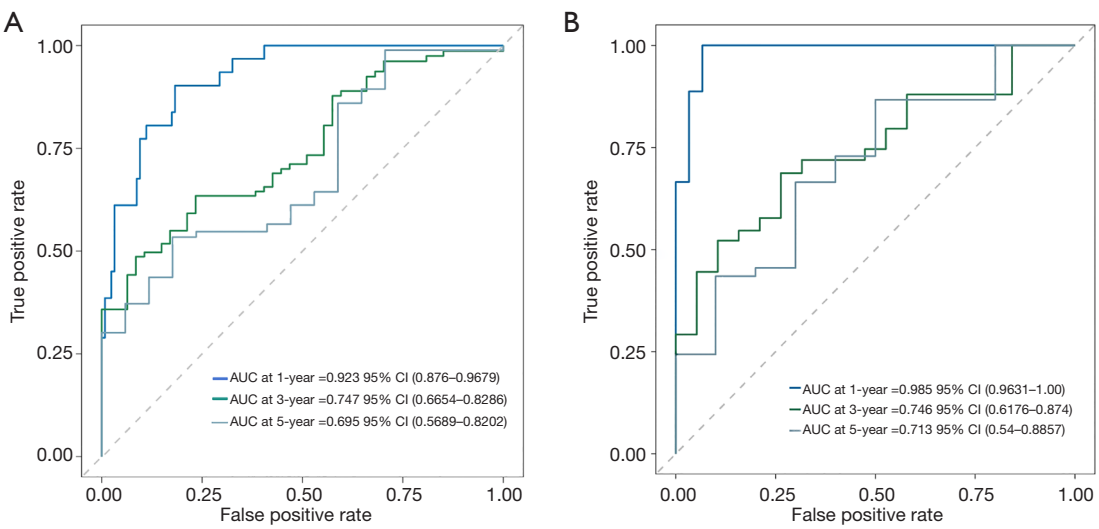

Figure 5 ROC curves for the training cohort (A) and the validation cohort (B). The AUC and 95% CI in the training cohort at 1-, 3-, and 5-year were 0.923 (0.876–0.9679), 0.747 (0.6654–0.8286), and 0.695 (0.5689–0.8202). The AUC and 95% CI in the validation cohort were as follows: 0.985 (0.9631–1.00), 0.746 (0.6176–0.874), and 0.713 (0.54–0.8857). AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic.

staging system was an important factor affecting prognosis.

LNM in ESCC is a crucial factor in determining treatment strategies and predicting prognosis (16). NSM as a specific type with significant prognostic implications has been observed in multiple tumors (17). In clinical practice, NSM is often defined as nodal metastases that occur outside

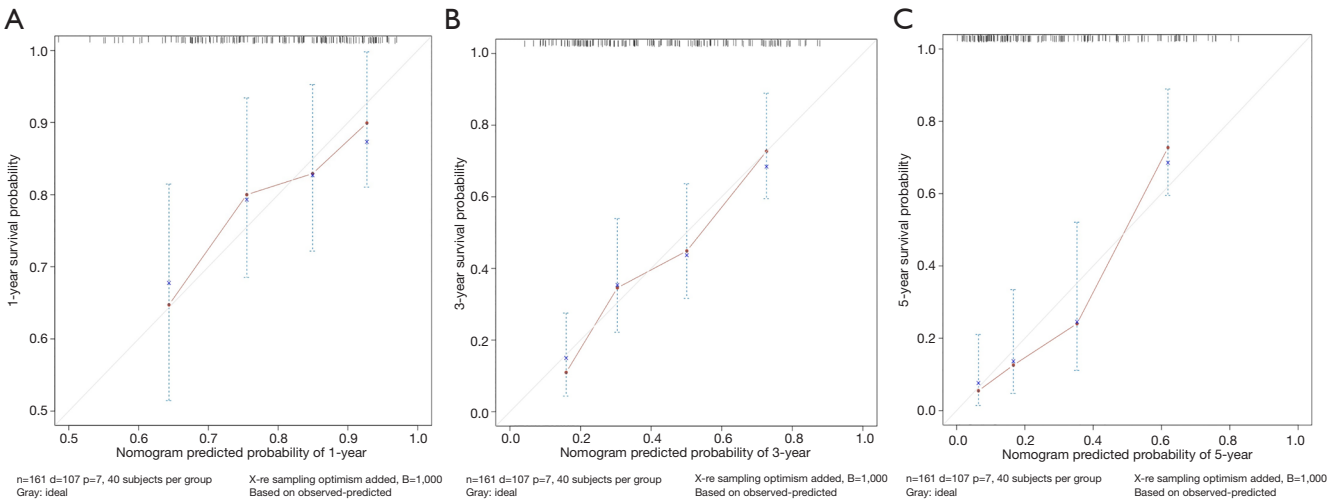

Figure 6 Calibration plots for model at 1 year (A), 3 years (B), 5 years (C). The calibration plots for the model at 1-, 3-, and 5-year all closely align with the diagonal line, indicating that the model's prediction performance is well aligned with the actual situation.

Table 6 ROC curve AUC in the training and validation cohort

Survival time	Training cohort		Validation cohort	
	AUC	95% CI	AUC	95% CI
1-year	0.923	0.876–0.9679	0.985	0.9631–1.00
3-year	0.747	0.6654–0.8286	0.746	0.6176–0.874
5-year	0.695	0.5689–0.8202	0.713	0.54–0.8857

AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic.

the nodal drainage area of the primary tumor. However, the precise definition varies across different tumors, especially in ESCC. For example, NSM may involve no first-station metastases and direct metastases to the second, third or contralateral lymph nodes with an incidence of less than 0.6% (18,19). In contrast, in NSCLC that NSM refers to a discontinuous tumor behavior that results in metastases to the mediastinal lymph nodes (6). Similarly, in gastric cancer, NSM involves extraperigastric lymph nodes without perigastric LNM, with an incidence of approximately 11% (20). The definition of NSM in esophageal cancer lacks standardization (7), with current criteria being categorized into three main systems: the JES criteria, the AJCC criteria, and anatomical compartments (5). According to the JES criteria, lymph nodes in the cervical region, mediastinum, and abdominal cavity were numbered and named systematically, categorized into four sub-stations (1, 2, 3, and 4) relative to the primary tumor. NSM refers to the occurrence of metastases in lymph nodes 2, 3, and 4, while the sentinel lymph node remains free from metastases (21,22). The AJCC guidelines define NSM similarly, specifically designating each segmental esophageal para-lymph node as the primary lymph node station. On the other hand, the anatomical compartment criterion defines NSM as the occurrence of metastases in distant regional lymph nodes while there is an absence of metastases in adjacent regional lymph nodes (23). Meanwhile, according to the AJCC/UICC N region boundaries, regional LNM is defined within the specific regions of the primary tumor, whereas NSM is defined as metastases occurring in regions distinct from those of the primary tumor. This study used a completely different definition of NSM from the previous ones, and found the effect of NSM on prognosis of ESCC. It is more likely suggested that NSM may be regarded as an indicator of poor prognosis in the future ESCC.

Previous research has shown a wide range in the occurrence of NSM in ESCC, with estimates ranging from 20% to 73.6% (17,24,25). In our study, we found that

43.9% of patients exhibited NSM which is consistent with previous findings. However, the prognostic impact of NSM in ESCC remains uncertain. He *et al.* found no statistically significant difference in OS between patients with NSM and those without NSM. However, they did find that patients with NSM at N2 had significantly worse OS than those without NSM (P=0.001) (26). On the other hand, Li *et al.* reported a high prevalence of NSM in thoracic esophageal cancer, which was significantly associated with poor survival outcomes (27). Additionally, study on abdominal LNM in thoracic esophageal cancer have shown that patients with positive abdominal lymph nodes have shorter OS and progression-free survival than those with negative abdominal lymph nodes (28), further contributing to the body of research on the prognosis of esophageal cancer influenced by NSM. A study indicated neoadjuvant therapy modifies the frequency and distribution of nodal metastases (29). Overall, our study indicates that patients with NSM have a shorter OS. A key factor contributing to the significant variance in NSM incidence rates is the differing definitions of NSM among researchers.

The nomogram provides an easy-to-understand visual representation for estimating the risk based on patient characteristics, making it applicable in the field of oncology and medical prognosis (30). Nomogram clearly represent the complex results of the Cox regression. The model based on preoperative neutrophil lymphocyte ratio (preNLR), N-stage, p53 and tumor diameter had excellent performance for OS of patients with ESCC with AUC of 0.785 (95% CI: 0.662–0.908) (31). Lin *et al.* constructed a prediction model enrolled 256 patients that 160 in the training cohort and 96 in the validation cohort based gender, clinical T stage, clinical N stage and primary gross tumor volume for patients with upper thoracic presented favorable prognostic efficacy in the both training and validation cohorts, with C-index of 0.622, 0.713, and AUC value of 0.709, 0.739, respectively (32). A prognostic nomogram constructed by Duan *et al.* enrolled 95 patients in the primary cohort and 55 patients in the validation cohort included the infiltration of cytotoxic T lymphocytes ($CD8^+$)/forkhead box protein P3 ($Foxp3^+$)/$CD33^+$ cells and the programmed cell death ligand 1 (PD-L1) to predicted OS with previously untreated patients with ESCC after esophagectomy calibration curves showed the C-index for predicting OS was 0.844 (95% CI: 0.707–0.981) in the internal validation and 0.772 (95% CI: 0.617–0.927) in the external validation cohort (33). There were few clinical prognostic models with NSM as a factor included AJCC/UICC and JES N stage. In our study, the calibration curves also demonstrate the consistency of the model. The 1-year AUC was 0.923 (95% CI: 0.8760–0.9679) for the training cohort and 0.985 (95% CI: 0.9631–1.00) for the validation cohort. Although the variables included in our model differ from those in previous studies, the 1-year predictive possibility appears to be better than that of the ESCC predictive models for esophageal cancer established by other variables. Notably, patients with NSM had shorter OS times compared to those without. Three-year (AUC of training cohort: 0.747; AUC of validation cohort: 0.746) and 5-year (AUC of training cohort: 0.695; AUC of validation cohort: 0.713) predictive accuracy gradually decreases. The reason for the decline in predictive ability over time could have been caused by tumor progresses over time and is associated with receiving further treatment. In future studies, it is further proved that more variables such as immunotherapy, PD-L1, vascular tumor emboli, and neutrophil lymphocyte ratio (NLR), PN(n) are related to NSM, and it is more necessary to build a clinical prediction model of ESCC with more variables.

In summary, this study compared the AJCC/UICC N staging system and the JES N staging system and identified the AJCC/UICC N stage as the only independent risk factor affecting the survival of patients with ESCC. Meanwhile, this study proposed a new staging system that divides the cervix, thorax, and abdomen into segments: N1 denotes lymph node involvement in one region, N2 indicates involvement in two regions, and N3 indicates involvement in three regions. This approach builds upon previous research, such as the study by An *et al.* (34), which classified patients with EC who had undergone 3-field lymphadenectomy into four groups based on the extent of lymph node involvement: no LNM, metastases in one field, metastases in two fields, and metastases in all three fields. Significant differences in 5-year survival rates were observed among these groups. Similarly, for non-surgical patients with ESCC, Hu *et al.* categorized esophageal lymphatic drainage into neck and chest lymph nodes which classified patients into N0 (no involvement in any region), N1 (involvement of a single region), N2 (involvement of two regions), and N3 (involvement of three regions). The revised staging system they implemented also showed predictive value (35). However, in this study PN(n) stage was not a risk factor for ESCC prognosis.

Studies on ESCC N staging have also focused on the metastatic lymph node ratio, the number of positive lymph

node stations, and the positive lymph node station ratio (14,36,37). These studies have provided the basis and advantages of their corresponding staging systems. Several studies have shown that the number of lymph nodes samples can impact both the accuracy of the nodal staging as well as survival. Tian *et al.* indicated that examining ≥14 and 18 lymph nodes could improve the prognostic prediction performance of the N stage (38) with T1–2 EC. Other research recommended harvesting at least 21 lymph nodes to acquire accurate staging and long-term survival information for patients with declared node-negative disease using the right thoracic approach (39). In this study, according to inclusion and exclusion criteria, patients with at least 6 lymph nodes were included without the upper limit on the number of lymph nodes harvested. Perhaps the upper limit on the number of lymph nodes harvested should also be taken into account in future studies.

Our study also identified T stage and age as independent risk factors for an unfavorable prognosis in ESCC. These findings align with traditional prognostic indicators for esophageal cancer, clinical guidelines, and extensive research (40,41).

There are a few limitations to the current study that need to be acknowledged. Firstly, it was a retrospective study, which means that there may be some selection bias that cannot be avoided. We only selected patients with ESCC for this study, Whether the conclusions of this study are applicable to other carcinoma needs further research. Secondly, there is a chance of inaccuracies in the reassessment of JES N staging because the lymph node stations were initially identified during surgery using the 8th AJCC/UICC N staging system, based on the information in the pathology reports. Thirdly, in this study, patients were collected according to strict inclusion and exclusion criteria, resulting in a small sample size. And prospective studies with larger sample sizes are needed to verify whether the results are applicable to all populations.

Conclusions

The new definition of NSM in ESCC correlates with poorer OS, and prognostic model incorporating NSM effectively predict ESCC prognosis. The predictive model provides an effective basis for evaluating the 1-, 3-, and 5-year OS of patients. The quantity of LNM being a more reliable prognostic indicator than the extent of esophageal cancer metastases. The definition of NSM could serve as an extra point of reference in developing future guidelines for N staging.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study adhered to the ethical principles outlined in the Declaration of Helsinki (as revised in 2013), including maintaining participant confidentiality, as well as conducting the research with integrity and respect for the rights of individuals involved. The study was approved by Ethics Committees of Mianyang Central Hospital (No. S202403119-01) and West China Hospital of Sichuan University (No. 20211235). Informed consent for this retrospective study was waived.

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