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## Retrospective Cohort Study

# Prediction of lymph node metastasis in early gastric signet-ring cell carcinoma: A real-world retrospective cohort study

Jia-Jia Yang, Xiao-Yong Wang, Rui Ma, Mei-Hong Chen, Guo-Xin Zhang, Xuan Li

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## Abstract

### BACKGROUND

Signet-ring cell carcinoma (SRCC) was previously thought to have a worse prognosis than other differentiated gastric cancer (GC), however, recent studies have shown that the prognosis of SRCC is related to pathological type. We hypothesize that patients with SRCC and with different SRCC pathological components have different probability of lymph node metastasis (LNM).

### AIM

To establish models to predict LNM in early GC (EGC), including early gastric SRCC.

### METHODS

Clinical data from EGC patients who had undergone gastrectomy at the First Affiliated Hospital of Nanjing Medical University from January 2012 to March 2022 were reviewed. The patients were divided into three groups based on type: Pure SRCC, mixed SRCC, and non-signet ring cell carcinoma (NSRC). The risk factors were identified through statistical tests using SPSS 23.0, R, and EmpowerStats software.

### RESULTS

A total of 1922 subjects with EGC were enrolled in this study, and included 249 SRCC patients and 1673 NSRC patients, while 278 of the patients (14.46%) presented with LNM. Multivariable analysis showed that gender, tumor size,



depth of invasion, lymphovascular invasion, ulceration, and histological subtype were independent risk factors for LNM in EGC. Establishment and analysis using prediction models of EGC showed that the artificial neural network model was better than the logistic regression model in terms of sensitivity and accuracy (98.0% *vs* 58.1%,  $P = 0.034$ ; 88.4% *vs* 86.8%,  $P < 0.001$ , respectively). Among the 249 SRCC patients, LNM was more common in mixed (35.06%) rather than in pure SRCC (8.42%,  $P < 0.001$ ). The area under the ROC curve of the logistic regression model for LNM in SRCC was 0.760 (95%CI: 0.682-0.843), while the area under the operating characteristic curve of the internal validation set was 0.734 (95%CI: 0.643-0.826). The subgroups analysis of pure types showed that LNM was more common in patients with a tumor size  $> 2$  cm (OR = 5.422,  $P = 0.038$ ).

## CONCLUSION

A validated prediction model was developed to recognize the risk of LNM in EGC and early gastric SRCC, which can aid in pre-surgical decision making of the best method of treatment for patients.

**Key Words:** Early gastric cancer; Signet-ring cell carcinoma; Lymph node metastasis; Nomogram; Prediction model

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**Core Tip:** By establishing and comparing prediction models of lymph node metastasis (LNM) in early gastric cancer, we found that artificial neural network model was better than logistic regression model in sensitivity and accuracy. Among 249 signet-ring cell carcinoma (SRCC) patients, LNM was more common in mixed than in pure SRCC. A validated prediction model was also developed to recognize the risk for LNM in early gastric SRCC, which can be used to help make decisions regarding treatment of patients before performing surgery.

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## INTRODUCTION

According to the latest global cancer statistics, gastric cancer is considered to be the fifth leading type of cancer and the fourth leading cause of cancer-related deaths worldwide[1]. However, the progression of diagnostic methods has led to early gastric cancer (EGC) being more easily detectable[2]. Our previous study revealed that the rate of EGC diagnosis was 10.0%, while the rate of lymph node metastasis (LNM) in EGC was 12.3%[3]. EGC can be treated using surgical therapy with a 5-year survival rate of 80%-100%[4], and can also be resected *via* endoscopic resection, which is recommended as an effective method of treatment for EGC. Endoscopic submucosal dissection (ESD) can effectively improve the prognosis of patients[5]. Clinical decision of endoscopic *vs* surgical resection for EGC relies on the accurate assessment of the risk of LNM[6]. LNM mainly depends on tumor size, depth of invasion, and histological type[7].

Signet ring cell carcinoma (SRCC) is a common histological type with dismal prognosis[8] that predominantly consists of cells with poor cohesiveness with the predominance of cells in the signet ring. Among gastric cancer cases, the incidence of SRCC has increased and is reported to vary from 8.7% to 23.4%[9-11], while the behavior of SRCC in gastric cancer is controversial. In advanced gastric cancer, SRCC is considered to be a more severe invasive type with a higher level of peritoneal dissemination and a similar or worse prognosis than non-signet ring cell carcinoma (NSRC)[5,12,13]. However, it has been reported that the behavior of early SRCC may be equivalent to, or more favorable than other types of EGC due to its lower probability of LNM[14,15], suggesting that less invasive surgery is suitable. In addition, only few reports have been published on risk factors for LNM in early SRCC and the clinicopathological differences between pure and mixed SRCC.

Therefore, the objectives of this research study were to: (1) To identify the factors that can predict LNM in EGC to establish suitable models; and (2) to investigate the differences between pure and mixed SRCC to identify factors that can predict LNM in EGC with a signet-ring cell histology.

## MATERIALS AND METHODS

### Patients

We examined the retrospective clinical information of patients who had undergone surgery at the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, from January 2012 to March 2022. A total of 1922 patients were enrolled. The eligibility criteria used is illustrated in the flow diagram shown in [Figure 1](#). Standard gastrectomy was the principal surgical procedure performed with a curative intent. Only patients who did not receive preoperative therapy were included in the study. The exclusion criteria were as follows: (1) pT2-4 gastric cancer identified using histopathological examination after radical gastrectomy; (2) high-grade dysplasia of the gastric mucosa; (3) a lack of lymphadenectomy; (4) cancer treated using neoadjuvant chemotherapy; (5) multiple gastric cancers; and (6) stump gastric cancer.

### Gross and histopathological evaluation

All resected tumors samples made into 2-mm-thick slices, stained with hematoxylin and eosin (H&E) and immunohistochemical staining, and assessed by qualified pathologists at the institution using World Health Organization (WHO) diagnostic criteria. Based on this, the patients were divided into 3 groups: (1) Pure SRCC (p-SRCC), which is defined as having a predominant component (> 50%) isolated carcinoma cells containing intracytoplasmic mucin16; (2) mixed SRCC (m-SRCC), which is defined as adenocarcinoma with a minor component (10-50%) of isolated carcinoma cells containing intracytoplasmic mucin; and (3) NSRC. Identification of risk factors associated with LNM in patients with EGC were conducted by comparing the clinicopathological characteristics of the patients and the gross findings of cancer lesions, including the age and gender, tumor size, location and macroscopic type, lymphovascular invasion (LVI), LNM, depth of invasion, perineural invasion, histological type, and ulceration during surgery. The patients were also divided into 5 macroscopic type groups: Protruded (I), elevate (IIa), flat (IIb), depressed (IIc), and excavated (III). As for the location of lesion, we divided the stomach into five sections: cardia, fundus, body, antrum, and angle.

LNM was determined based on the indications for ESD recommended by the Japanese Gastric Cancer Association. Based on the guidelines for ESD and endoscopic mucosal resection for EGC (2<sup>nd</sup> edition) [16], the absolute indications for endoscopic treatment are as follows: (1) Differentiated intramucosal carcinoma with a maximum diameter of  $\leq 2$  cm and without ulcerative lesions; (2) differentiated intramucosal carcinoma with a maximum diameter of  $> 2$  cm and without ulcerative lesions; (3) cT1a with a diameter of  $\leq 3$  cm and ulceration [UL (+)]; and (4) undifferentiated intramucosal carcinoma with a maximum diameter of  $\leq 2$  cm and without ulcerative lesions. The terminology used in this study is based on the Japanese classification of gastric carcinoma.

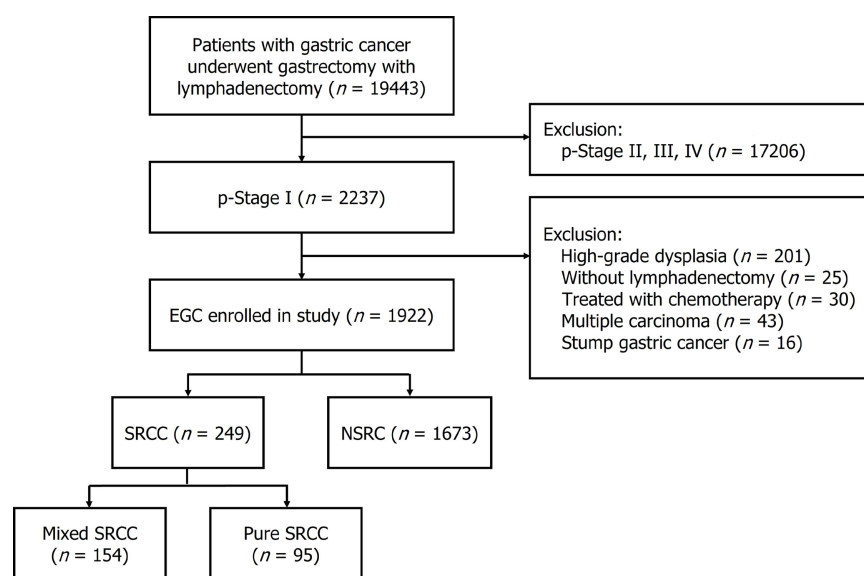
### Development of a predictive model for LNM

Variables that are significantly associated with LNM ( $P < 0.05$ ) were identified as candidate variables for the artificial neural network (ANN) model and multivariate logistic regression (LR). A random sample of 75% of all EGC patients were assigned to the training set, while the remaining 25% were used as internal validation of the LR model. The cut-off value was determined using ROC curves, which were then used to evaluate the discriminatory ability of the model. Then, a backward step-down selection process, with a maximum threshold of  $P < 0.05$ , was used for the final LR model selection of the nomogram. Bootstrapping using 2000 replications was conducted for internal validation.

In the ANN model, a total of 13 neural nodes were used as input layers. There were five neural nodes in the hidden layer, while the hyperbolic tangent transfer function was adopted. Two of the neural nodes in the output layer were LNM or not. The softmax transfer function was used as the transfer function. All samples were randomly assigned to the training group and the verification group at a ratio of 7:3. The training group was used to train the neural network. The verification group was used to evaluate the final neural network, and to construct the topological hierarchical structure of the neural network model. The final neural network fitting results were represented using the normalized importance percentage graph and a bar diagram was drawn. Finally, the area under the operating characteristic curve (AUC) of the recipients of the two models were calculated to compare and evaluate diagnostic accuracy using the chi-square test.

### Statistical analysis

Continuous variables were converted to binary variables, and the cut-off point of age was determined by maximizing the sum of sensitivity and specificity after spline smoothing, which was found to be 65 years. Categorical variables are displayed as a percentage. Univariable analysis was performed to identify risk factors associated with LNM using various statistical tests, including the student *t*-test, Chi-square test, or the Fisher exact test. Multivariable analysis only included variables with a  $P < 0.05$  in the univariate analysis. The results are shown as an odds ratio (OR), 95% confidence interval (CI), and a *P* value. The multivariate LR model was used to identify independent factors associated with LNM. Calibration of the model was assessed using the Hosmer-Lemeshow nomogram and ROC curve goodness-of-fit test. R (<http://www.R-project.org>) and EmpowerStats software ([www.empowerstats.com](http://www.empowerstats.com))



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**Figure 1** Flow diagram showing the study design and population. EGC: Early gastric cancer; SRCC: Signet ring cell carcinoma; NSRC: Non-signet ring cell carcinoma.

powerstats.com, X&Y solutions, Inc. Boston, MA, United States) was used to determine the nomogram and ROC curve. The ANN model and further statistical analyses were performed using IBM SPSS Statistics for Windows v.23.0 software. A *P* value of < 0.05 was used to indicate statistical significance.

## RESULTS

### Clinicopathological features of patients with EGC

Among the 1922 patients enrolled, 249 patients were with SRCC and 1673 patients were with NSRC, and their outcomes are reported in [Figure 1](#). The clinicopathological characteristics of SRCC and NSRC are described in [Table 1](#). For patients with SRCC, the mean age was  $53.14 \pm 10.03$ , the male-to-female ratio was 1.15:1 (133/116), and the mean lesion size was  $2.14 \pm 1.43$  cm. For patients with NSRC, the mean age was  $57.01 \pm 11.78$ , the male-to-female ratio was 2.85:1 (1238/435), and the mean lesion size was  $1.89 \pm 1.22$  cm. When the patients were divided into five groups based on location, a majority of the EGCs were found to be in the gastric antrum and angle ( $n = 1189$ , 61.86%). There was a significant difference in SRCC and NSRC ( $P < 0.001$ ) based on location. Most tumors were depressed (IIc), followed by flat (IIb) and elevated (IIa), protruded and excavated, which were in the minority, but no statistical significance was found based on macroscopic type between SRCC and NSRC ( $P = 0.105$ ). Mucosa invasion occurred in 59.84% of ( $n = 149$ ) SRCC, while submucosa invasion was observed more often in NSRC ( $n = 865$ , 51.70%). LVI was identified in 136 patients, among which 18 were diagnosed with SRCC and 118 were NSRC. LNM was identified in 278 patients, in which 62 were SRCC patients and 216 were NSRC patients. A total of 22 EGCs occurred with perineural invasion, of which 7 were SRCC and 15 were NSRC. Ulceration was identified in 701 patients, in which 74 (29.72%) were diagnosed with SRCC and 627 (37.48%) with NSRC. Overall, these results showed significant differences in age, gender, tumor size, LNM, depth of invasion, perineural invasion, tumor location, and ulceration between SRCC and NSRC.

### Risk factors of LNM in EGC as shown through the univariate and multivariate analyses

In the univariate analysis, LNM was significantly associated with age ( $P = 0.015$ ), gender ( $P < 0.001$ ), tumor size ( $P < 0.001$ ), macroscopic type ( $P = 0.008$ ), depth of invasion ( $P < 0.001$ ), LVI ( $P < 0.001$ ), perineural invasion ( $P < 0.001$ ), tumor location ( $P = 0.001$ ), ulceration ( $P < 0.001$ ) and histological subtype ( $P < 0.001$ ). The multivariable analysis showed that being female (OR = 1.912,  $P < 0.001$ ), tumor size ( $> 2$  cm) (OR = 1.875,  $P = 0.001$ ), submucosal invasion (OR = 3.340,  $P < 0.001$ ), LVI (OR = 6.682,  $P < 0.001$ ), the presence of ulcers (OR = 1.695,  $P = 0.001$ ), and the pathological pattern of mixed SRCC (OR = 4.595,  $P < 0.001$ ) were independent predictors of LNM in EGC ([Table 2](#)).

### Comparison of clinical models of LNM in EGC

The LR model nomogram revealed that LVI had the greatest impact on scoring, followed by histological subtype and depth of invasion. The effects of gender, tumor size, and ulceration on model performance



Table 1 Clinical characteristics in patients with early gastric cancer

	SRCC <i>n</i> = 249, <i>n</i> (%)	NSRC <i>n</i> = 1673, <i>n</i> (%)	<i>P</i> value
Age (yr)	53.14 ± 10.03	57.01 ± 11.78	< 0.001
≤ 65	161 (64.66)	634 (37.90)	
> 65	88 (35.34)	1039 (62.10)	
Gender			< 0.001
Male	133 (53.41)	1238 (74.00)	
Female	116 (46.59)	435 (26.00)	
Location			< 0.001
Cardia	11 (4.42)	235 (14.05)	
Fundus	5 (2.01)	143 (8.55)	
Body	43 (17.27)	296 (17.69)	
Antrum	129 (51.81)	641 (38.31)	
Angle	61 (24.50)	358 (21.40)	
Macroscopic type			0.105
Protruded (0-I)	3 (1.20)	27 (1.61)	
Elevated (0-IIa)	11 (4.42)	128 (7.65)	
Flat (0-IIb)	52 (20.88)	353 (21.10)	
Depressed (0-IIc)	178 (71.49)	1076 (64.32)	
Excavated (0-III)	5 (2.01)	89 (5.32)	
Tumor size (cm)	2.14 ± 1.43	1.89 ± 1.22	0.001
≤ 2	139 (55.82)	1124 (67.18)	
> 2	110 (44.18)	549 (32.82)	
Ulceration			0.027
UL (-)	175 (70.28)	1046 (62.52)	
UL (+)	74 (29.72)	627 (37.48)	
Depth of invasion			0.001
M	149 (59.84)	808 (48.30)	
SM	100 (40.16)	865 (51.70)	
LVI			1
Absence	231 (92.77)	1555 (92.95)	
Presence	18 (7.23)	118 (7.05)	
Perineural invasion			0.041
Absence	242 (97.19)	1658 (99.10)	
Presence	7 (2.81)	15 (0.90)	
LNM			< 0.001
Absence	187 (75.10)	1457 (87.09)	
Presence	62 (24.90)	216 (12.91)	

SRCC: Signet-ring cell carcinoma; NSRC: Non-signet ring cell carcinoma; LVI: Lymphovascular invasion; LNM: Lymph node metastasis; M: Mucosal; SM: Submucosal; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.

**Table 2 Logistic regression analysis of the risk factors of lymph node metastasis in early gastric cancer**

	LNM		Univariate	Multivariate analysis		
	Present	Absent	P value	OR	95%CI	P value
Total	278	1644				
Age			0.015			
≤ 65	135	660				
> 65	143	984				
Gender			< 0.001			
Male	160	1211		1		
Female	118	433		1.912	1.392-2.626	< 0.001
Location			0.001			
Cardia	17	229				
Fundus	9	139				
Body	45	294				
Antrum	141	629				
Angle	66	353				
Macroscopic type			0.008			
Protruded (0-I)	9	21				
Elevated (0-IIa)	16	123				
Flat (0-IIb)	37	368				
Depressed (0-IIc)	201	1053				
Excavated (0-III)	15	79				
Tumor size (cm)			< 0.001			
≤ 2	134	1129		1		
> 2	144	515		1.875	1.260-2.417	0.001
Ulceration			< 0.001			
UL (-)	134	1087		1		
UL (+)	144	557		1.695	1.246-2.306	0.001
Depth of invasion			< 0.001			
M	54	903		1		
SM	224	741		3.34	2.156-5.174	< 0.001
LVI			< 0.001			
Absence	199	1587		1		
Presence	79	57		6.682	4.358-10.245	< 0.001
Perineural invasion			< 0.001			
Absence	262	1638				
Presence	16	6				
Histological type						
Pure SRCC	8	87	< 0.001	1		< 0.001
NSRC	216	1457		2.619	1.454-3.598	0.894
Mixed SRCC	54	100		4.595	2.654-6.954	< 0.001

SRCC: Signet-ring cell carcinoma; NSRC: Non-signet ring cell carcinoma; M: Mucosal; SM: Submucosal; LVI: Lymphovascular invasion; LNM: Lymph

node metastasis; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.

were also significant. Each level of the variable was summed using the total score based on the point scale and was positioned on the total score scale to determine the corresponding LNM probability for each patient (Figure 2). This predictive model demonstrated that the AUC was 0.797 with 95%CI: 0.776-0.818. Following 2000 bootstrap repetitions, the AUC of the internal validation in the training set was 0.816 (95%CI: 0.794-0.839).

We also established an ANN model and assessed its ability by comparing it with a traditional LR model to predict the risk of LNM in EGC patients (Figure 3) presents the structure of the established ANN model and was influenced by 6 significant predictors: Gender, tumor size, submucosal invasion, LVI, histological type and ulceration, and histological type revealed the greatest impact on scoring, followed by the depth of invasion and LVI, while ulceration accounted for the least but still exerted a significant effect. The predictive model demonstrated an AUC of 0.878 with a 95%CI of 0.862-0.893.

In addition, differences between ANN and the multivariate LR model were further compared based on sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and AUC according to the actual rate of LNM confirmed pathologically. Table 3 shows the classification distribution of the two models. The sensitivity and accuracy of the ANN model (96.4% *vs* 58.3%,  $P = 0.034$ , 88.2% *vs* 86.7%,  $P < 0.001$ ) and the AUC (0.878 *vs* 0.797,  $P < 0.001$ ; 0.899 *vs* 0.816,  $P < 0.001$ ; respectively) were better than that of the multivariate LR model in the training and validation sets (Figure 4). The specificity (88.0% *vs* 88.8%,  $P < 0.001$ ) and positive predictive value (19.4% *vs* 27.7%,  $P < 0.001$ ) was inferior to that of the multivariate LR model. There was no difference in the negative predictive value between the two groups (99.9% *vs* 96.7%,  $P = 0.202$ ). The comparisons of the diagnostic assessment are listed in Table 4.

#### Comparison of the clinicopathological features of pure SRCC and mixed SRCC

As shown in Table 5, differences in the clinicopathological characteristics between pure SRCC (p-SRCC) and mixed SRCC (m-SRCC) patients were significant based on the following factors: (1) Age was younger in the p-SRCC (73.68%) patients than in the m-SRCC (59.09%) group ( $P = 0.037$ ); (2) m-SRCC patients were more likely to show invasion into the SM layer, compared with p-SRCC (49.35% *vs* 25.26%,  $P < 0.001$ ); (3) LVI resulted in a significantly higher proportion of cases in the m-SRCC (11.69% *vs* 0.00%,  $P = 0.002$ ) group; (4) LNM was much more frequent in the m-SRCC group (35.06% *vs* 8.42%,  $P < 0.001$ ) than in the p-SRCC group. We also found that ulcers were more likely to be present in the m-SRCC group than in the p-SRCC group, although the difference was not statistically significant. There were no significant differences in the other characteristics between the p-SRCC and m-SRCC groups.

#### Risk factors for LNM in early SRCC as shown by the univariate and multivariate analyses

The univariate analyses demonstrated that the depth of invasion (M and SM), histological type and LVI differed significantly between patients with and without LNM in early SRCC patients. More frequent ulceration was observed in LNM positive SRCC patients, although the difference was not statistically significant. Based on the stepwise multivariate analysis, the significant independent risk factors for LNM in early SRCC were SM invasion (OR = 2.615,  $P = 0.008$ ), LVI (OR = 14.903,  $P = 0.001$ ), and a pathological pattern of mixed SRCC (OR = 1.982,  $P = 0.043$ ). The independent risk factors are listed in Table 6. In addition, we also performed a risk analysis for LNM in SRCC limited to the mucosa and in SRCC with different histological types (p-SRCC and m-SRCC). In SRCC limited to the mucosa (Table 7), histological type ( $P = 0.010$ ) and LVI ( $P = 0.016$ ) were significantly different between patients with and without LNM, and the multivariate analysis showed that the pathological pattern of mixed SRCC (OR = 4.557,  $P = 0.023$ ) was an independent predictor of LNM. In m-SRCC (Table 8), the univariate analyses showed that depth of invasion (M and SM) ( $P = 0.004$ ) and LVI ( $P < 0.001$ ) were risk factors for LNM, and that LVI (OR = 16.173,  $P = 0.001$ ) was a significant independent risk factor for LNM. In p-SRCC, the analyses showed that patients with a tumor size that exceeded 2 cm ( $P = 0.014$ ) and submucosal infiltration ( $P = 0.045$ ) were at a greater risk of LNM, indicating that tumor size  $> 2$  cm (OR = 5.422,  $P = 0.038$ ) is a significant independent risk factor for LNM (Table 8).

#### Clinical model of LNM in early SRCC

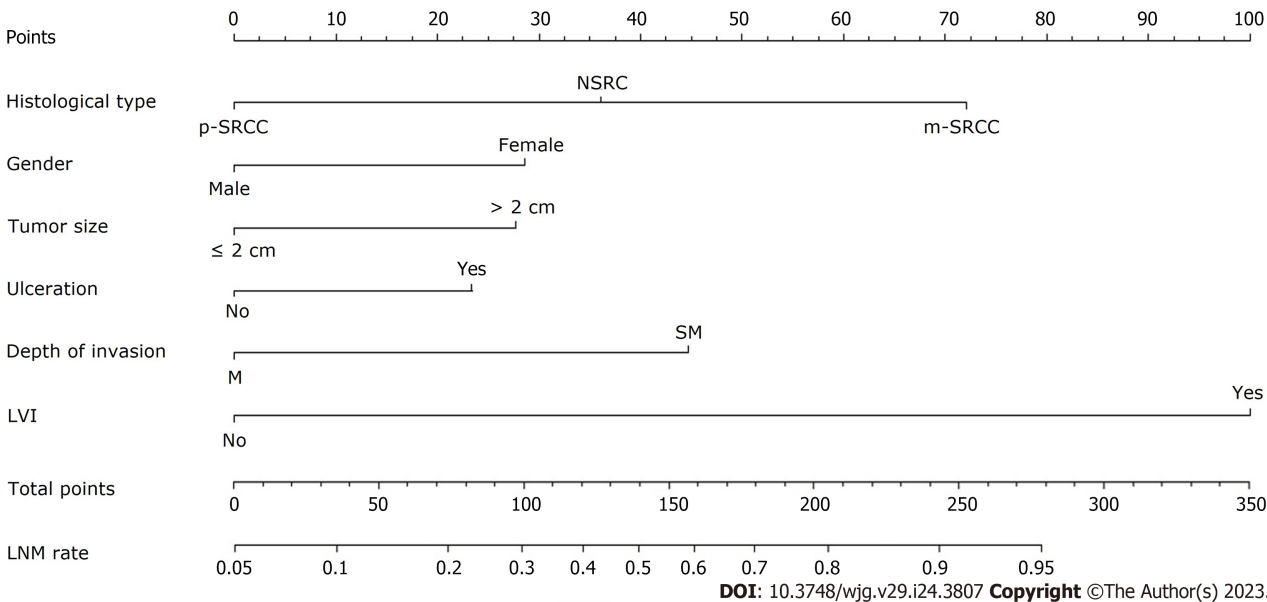
A preoperative predictive nomogram containing important risk factors related to early gastric SRCC LNM was constructed based on the LR model. All parameters of the clinicopathological risk factors of LNM in early gastric SRCC in the univariate analysis were included in the multivariable analysis. The nomogram revealed that LVI had the greatest impact on scoring, followed by invasion depth, and histological subtype (Figure 5). The equation stepwise selected prediction model from observed data included total risk points of LNM =  $-3.24513 + 0.93264 \times \text{DEPTH} + 2.86614 \times \text{LVI} + 0.42064 \times \text{HISTOLOGICAL}$ . This predictive model demonstrated an area under the curve (AUC) of 0.760 with a 95%CI of 0.682-0.843 (Figure 6A), while the AUC of internal validation was 0.734 (95%CI: 0.643-0.826) (Figure 6B). In the calibration plots, the bias-corrected line was calculated using 2000 bootstrapping

Table 3 The Classification of the artificial neural network model and logistic regression model				
Models	Predicted results	Pathological diagnosis		
		+	-	Percent correct
LR	+	77	55	58.3%
	-	201	1589	88.8%
	Percent correct	27.7%	96.7%	86.7%
ANN	+	54	2	96.4%
	-	224	1642	88.0%
	Percent correct	19.4%	99.9%	88.2%

LR: Logistic regression; ANN: Artificial neural network.

Table 4 Comparison of artificial neural network model and logistic regression model for predicting lymph node metastasis			
Diagnostic Index	LR model, (% , 95%CI)	ANN model (% , 95%CI)	P value
Sensitivity	58.3% (48.6-67.1%)	96.4% (87.8-99.9%)	0.034
Specificity	88.8% (87.2-90.4%)	88.0% (86.4-89.6%)	< 0.001
PPV	27.7% (22.3-33.9%)	19.4% (14.9-25.2%)	< 0.001
NPV	96.7% (95.6-97.5%)	99.9% (99.6-1.000%)	0.202
Accuracy	86.7% (85.1-88.2%)	88.2% (86.8-89.8%)	< 0.001
AUC	0.797 (0.776-0.818)	0.878 (0.862-0.893)	< 0.001

PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve.



**Figure 2** Nomogram for predicting lymph node metastasis in early gastric cancer patients. The factors of histological type, gender, tumor size, ulceration, depth of invasion and lymphovascular invasion were included in the model. p-SRCC: Pure signet-ring cell carcinoma; NSRC: Non-signet ring cell carcinoma; m-SRCC: Mixed signet-ring cell carcinoma; M: Mucosal; SM: Submucosal; LVI: Lymphovascular invasion; LNM: Lymph node metastasis.

iterations were indistinguishable and nearly approached the ideal line, while the 95%CI of the prediction model was also relatively accurate (Figure 6C). Therefore, the predictive power of the model was found to be good.

Table 5 Clinical characteristics in patients with pure signet-ring cell carcinoma and mixed signet-ring cell carcinoma

Variable	Pure SRCC	Mixed SRCC	P value
	n = 95, n (%)	n = 154, n (%)	
Age (yr)			0.037
≤ 65	70 (73.68)	91 (59.09)	
> 65	25 (26.32)	63 (40.91)	
Gender			0.131
Male	46 (48.42)	87 (56.49)	
Female	49 (51.58)	67 (43.51)	
Location			0.255
Cardia	4 (4.21)	7 (4.55)	
Fundus	2 (2.11)	3 (1.95)	
Body	13 (13.68)	30 (19.48)	
Antrum	51 (53.68)	78 (50.65)	
Angle	25 (26.32)	36 (23.38)	
Macroscopic type			0.152
Protruded (0-I)	1 (1.05)	2 (1.30)	
Elevated (0-IIa)	5 (5.26)	6 (3.90)	
Flat (0-IIb)	23 (24.21)	29 (18.83)	
Depressed (0-IIc)	65 (68.42)	113 (73.38)	
Excavated (0-III)	1 (1.05)	4 (2.60)	
Tumor size (cm)			0.126
≤ 2	60 (63.16)	79 (51.30)	
> 2	35 (36.84)	75 (48.70)	
Ulceration			0.051
UL (-)	75 (78.95)	100 (64.94)	
UL (+)	20 (21.05)	54 (35.06)	
Depth of invasion			< 0.001
M	71 (74.74)	78 (50.65)	
SM	24 (25.26)	76 (49.35)	
LVI			0.002
Absence	95 (100.00)	136 (88.31)	
Presence	0 (0.00)	18 (11.69)	
Perineural invasion			0.420
Absence	94 (98.95)	148 (96.10)	
Presence	1 (1.05)	6 (3.90)	
LNM			< 0.001
Absence	87 (91.58)	100 (64.94)	
Presence	8 (8.42)	54 (35.06)	

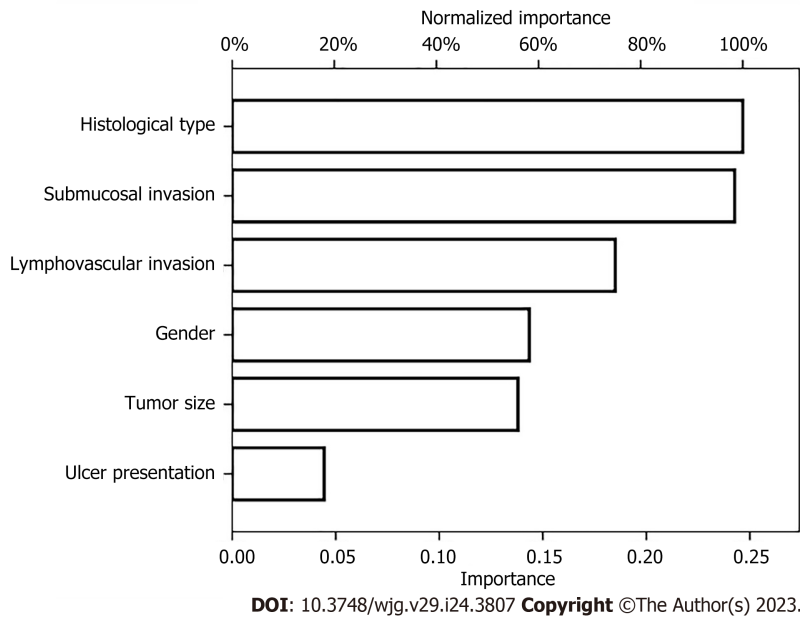
SRCC: Signet-ring cell carcinoma; M: Mucosal; SM: Submucosal; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.



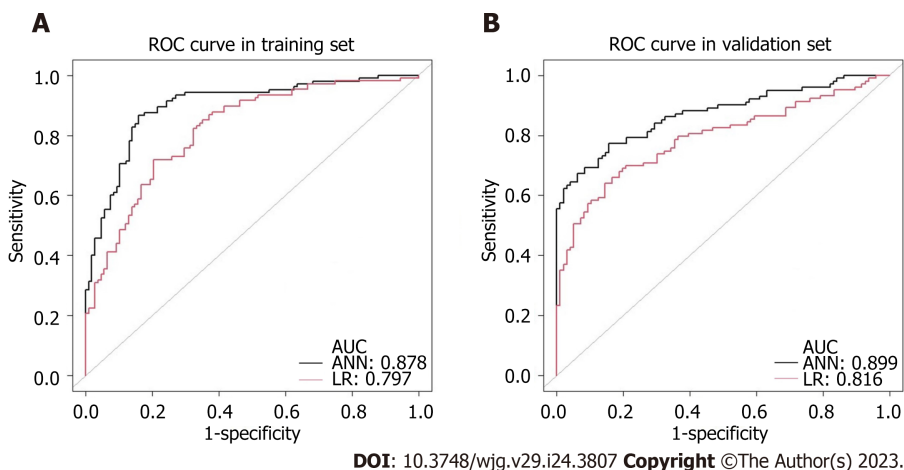
**Table 6 Logistic regression analysis of the risk factors of lymph node metastasis in signet-ring cell carcinoma**

	LNM		Univariate	Multivariate analysis		
	Present	Absent	P value	OR	95%CI	P value
Total	62	187				
Age			0.617			
≤ 65	41	120				
> 65	21	67				
Gender			0.639			
Male	32	101				
Female	30	86				
Location			0.544			
Cardia	2	9				
Fundus	1	4				
Body	10	33				
Antrum	33	96				
Angle	16	45				
Macroscopic type			0.209			
Protruded (0-I)	0	3				
Elevated (0-IIa)	1	10				
Flat (0-IIb)	13	39				
Depressed (0-IIc)	46	132				
Excavated (0-III)	2	3				
Tumor size (cm)			0.351			
≤ 2	30	109				
> 2	32	78				
Ulceration			0.06			
UL (-)	37	128				
UL (+)	25	46				
Depth of invasion			< 0.001			
M	20	129		1		
SM	42	58		2.615	1.282-5.334	0.008
LVI			< 0.001			
Absence	46	185		1		
Presence	16	2		14.903	3.143-70.680	0.001
Perineural invasion			0.146			
Absence	58	184				
Presence	4	3				
Histological type			< 0.001			
Pure SRCC	8	87		1		
Mixed SRCC	54	100		1.982	0.923-4.237	0.043

SRCC: Signet-ring cell carcinoma; M: Mucosal; SM: Submucosal; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.



**Figure 3 Artificial neural network model for predicting lymph node metastasis in early gastric cancer patients.** This model consists of six parameters: histological type, submucosal invasion, lymphovascular invasion, gender, tumor size and ulcer presentation.



**Figure 4 Receiver-operating characteristic curves of the established models for predicting lymph node metastasis in early gastric cancer.** The black and the red curve represent the development data of the artificial neural network and logistic regression model, respectively. A: Comparison of receiver-operating characteristic (ROC) plot in the training set, the area under the curve (AUC) was 0.878 vs 0.797,  $P < 0.001$ ; B: Comparison of ROC plot in the validation set, the AUC was 0.899 vs 0.816,  $P < 0.001$ . ROC: Receiver-operating characteristic; AUC: Area under the curve; ANN: Artificial neural network; LR: Logistic regression.

### Positive LNM results in early SRCC based on the indications for ESD

In the p-SRCC group, the LNM rate of patients with an expanded indication was 2.44% (1/41), and that of patients out of indication was 12.96% (7/54). In the m-SRCC group, the LNM rate in patients with an expanded indication was 16.13% (5/31), and in patients out of indication was 36.59% (45/123). The LNM rate between the expanded indication and out of indication patients in the m-SRCC group was statistically significantly different ( $P = 0.048$ ), while there was no statistical difference in the p-SRCC group ( $P = 0.132$ ). Among all 228 patients, the LNM rate between the expanded indication (6/72, 8.33%) and the out of indication (52/177, 29.38%) patients was statistically significantly different ( $P = 0.001$ ) (Table 9).

## DISCUSSION

As the fifth most common type of cancer worldwide, gastric cancer is a significant threat to human

**Table 7 Logistic regression analysis of the risk factors of lymph node metastasis in signet-ring cell carcinoma limited in mucosal**

	LNM		Univariate	Multivariate analysis		
	Present	Absent	P value	OR	95%CI	P value
Total	20	129				
Age			0.195			
≤ 65	10	80				
> 65	10	49				
Gender			0.306			
Male	9	77				
Female	11	52				
Tumor size (cm)			0.123			
≤ 2	8	78				
> 2	12	51				
Macroscopic type			0.209			
Protruded (0-I)	0	2				
Elevated (0-IIa)	0	7				
Flat (0-IIb)	4	27				
Depressed (0-IIc)	15	91				
Excavated (0-III)	1	2				
LVI			0.016			
Absence	18	129				
Presence	2	0				
Perineural invasion			-			
Absence	20	129				
Presence	0	0				
Location			0.688			
Cardia	1	6				
Fundus	0	3				
Body	3	23				
Antrum	11	66				
Angle	5	31				
Ulceration			1			
UL (-)	15	101				
UL (+)	3	28				
Histological type			0.01			
Pure SRCC	3	66		1		
Mixed SRCC	17	63		4.557	1.235-16.820	0.023

SRCC: Signet-ring cell carcinoma; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.

health. Recently, its incidence (mainly of the intestinal type) has declined in Asia, which may be associated with an increase in focus on and treatment using *Helicobacter pylori* in Asia. However, the incidence of SRCC is rising and needs more attention. The biological behavior of a case is very important when assessing whether ESD is feasible or not. However, the characteristics of early gastric SRCC, including LNM, clinicopathological features and prognosis, are still disputable[9,10,12].

Table 8 Logistic regression analysis of the risk factors of lymph node metastasis in pure and mixed signet-ring cell carcinoma

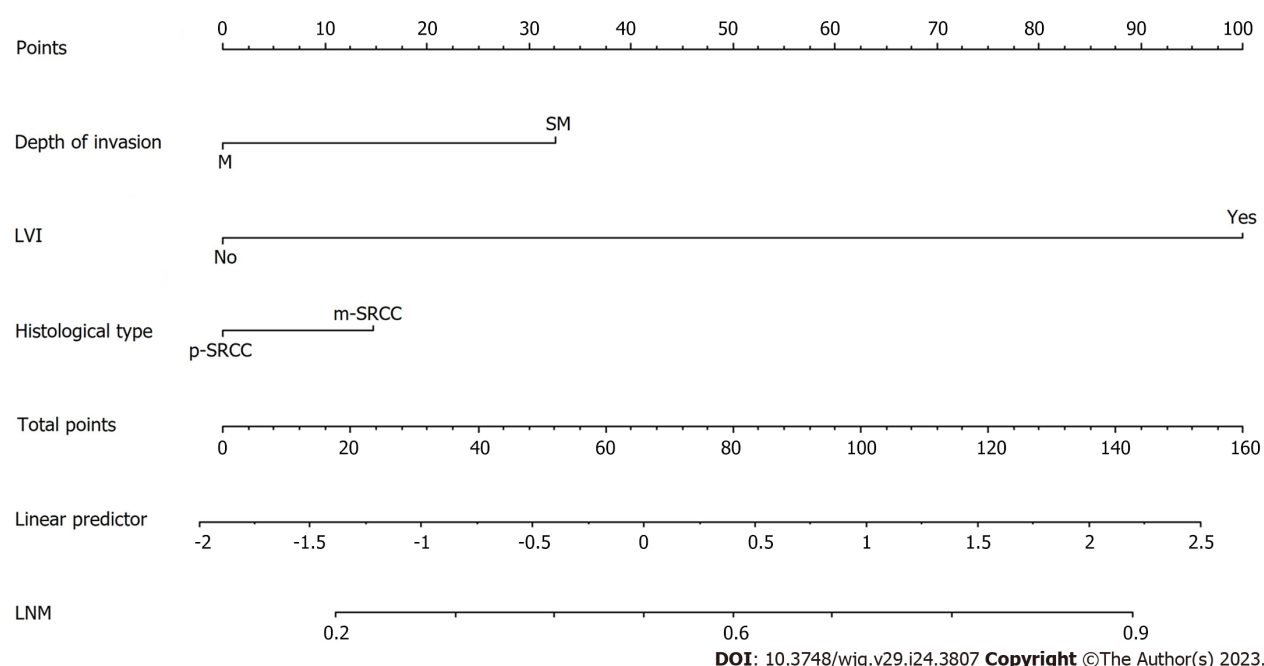
	LNM				Univariate		Multivariate analysis	
	Present		Absent		P value		OR, 95%CI, P value	
	Pure	Mixed	Pure	Mixed	Pure	Mixed	Pure	Mixed
Total	8	54	87	100				
Age					1	1		
≤ 65	7	33	58	63				
> 65	1	21	29	37				
Gender					1	0.377		
Male	3	29	39	62				
Female	5	25	48	38				
Location					0.706	0.412		
Cardia	0	2	4	5				
Fundus	0	1	2	2				
Body	1	9	12	21				
Antrum	5	28	46	50				
Angle	2	14	23	22				
Macroscopic type					0.788	0.314		
Protruded (0-I)	0	0	1	2				
Elevated (0-IIa)	0	1	5	5				
Flat (0-IIb)	3	10	20	19				
Depressed (0-IIc)	4	42	61	71				
Excavated (0-III)	1	1	0	3				
Tumor size (cm)					0.014	0.751		
≤ 2	4	26	56	53			1	
> 2	4	28	31	47			5.422 (1.095-26.856), 0.038	
Ulceration					1	0.189		
UL (-)	6	31	69	69				
UL (+)	2	23	18	31				
Depth of invasion					0.045	0.004		
M	3	17	70	59				1
SM	5	37	17	41				2.395 (0.891-4.998), 0.054
LVI					-	< 0.001		
Absence	8	38	87	98				1
Presence	0	16	0	2				16.173 (4.085-76.619), 0.001
Perineural invasion					1	0.376		
Absence	8	50	86	98				
Presence	0	4	1	2				
Mixed component						0.458		
Differentiated	-	1	-	7				
Undifferentiated	-	30	-	58				
Mixed	-	23	-	35				

M: Mucosal; SM: Submucosal; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; UL (-): Ulcer or ulcer scar is absent; UL (+): Ulcer or ulcer scar is present.

**Table 9 Lymph node metastasis in early gastric signet-ring cell carcinoma according to therapeutic criteria**

	Meet expanded ESD indication			Beyond expanded ESD indication			P value
	Total	LNM (+)	LNM (-)	Total	LNM (+)	LNM (-)	
p-SRCC	41	1	40	54	7	47	0.132
m-SRCC	31	5	26	123	45	78	0.048
Total	72	6	66	177	52	125	0.001

ESD: Endoscopic submucosal dissection; p-SRCC: Pure signet-ring cell carcinoma; m-SRCC: Mixed signet-ring cell carcinoma; LNM: Lymph node metastasis.

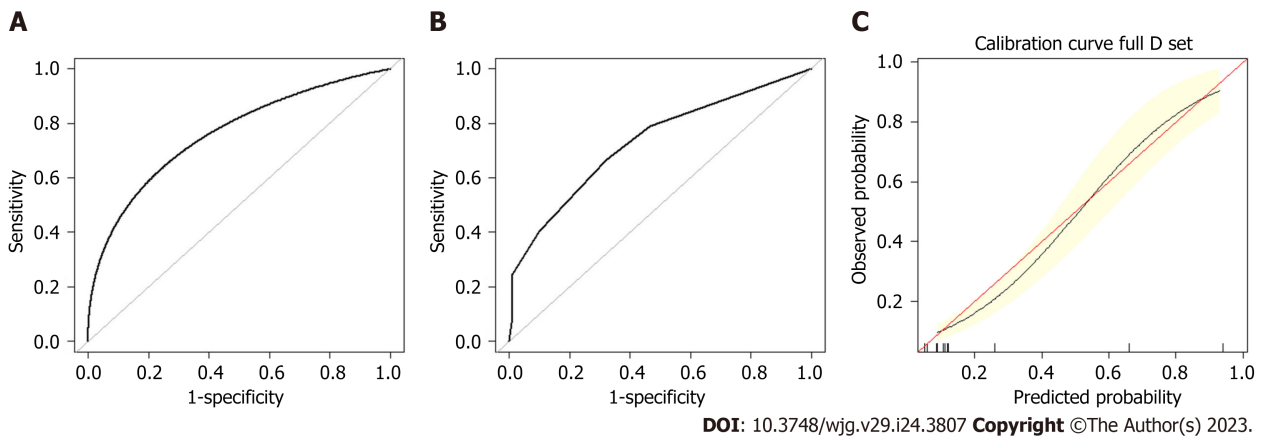


**Figure 5 Nomogram for predicting lymph node metastasis in early signet-ring cell carcinoma patients.** The factors of histological type, depth of invasion and lymphovascular invasion were included in the model. M: Mucosal; SM: Submucosal; LVI: Lymphovascular invasion; p-SRCC: Pure signet-ring cell carcinoma; m-SRCC: Mixed signet-ring cell carcinoma; LNM: Lymph node metastasis.

Numerous reports have identified SRCC as an independent predictor of poor prognosis due to its specific characteristics, such as the high incidence of LNM, as well as the high rate of peritoneal carcinomatosis[17,18], and low sensitivity to chemotherapy[19], especially as the vast majority of these tumors are diagnosed at an advanced stage. Several studies have reported that tumors with a diameter > 2 cm, submucosal infiltration, and lymphatic vascular infiltration are risk factors and independent risk factors for LNM in early gastric SRCC[19]. Huh *et al*[11] and Japanese Gastric Cancer Association[20] showed that the LNM rate was higher in early mixed SRCC than in early pure SRCC, and that mixed SRCC was more aggressive than pure SRCC. To reach an agreement on the treatment options for EGC and early gastric SRCC, these aspects need to be further explored.

A previous study found that being male, age, depressed type, submucosal invasion, LVI, and tumor location were independent risk factors for LNM in EGC[3]. Oh *et al*[21] demonstrated that in patients with EGC without LVI, a tumor size of > 3 cm, submucosal invasion, and undifferentiated histological type were significant risk factors for LNM. In our research study, the incidence of LNM was 14.46%, which is similar to that of previous studies[9,10,13,22-24], and we found that patients of EGC in younger ( $\leq 60$ ), female, tumor size >2cm, with elevated macroscopic type, submucosal invasion, LVI, perineural invasion, tumor located in the gastric antrum and angle, ulceration, and a pathological pattern of mixed SRCC are more likely to have LNM, and all factors were statistically different. In the multivariate





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**Figure 6 Assessment of the nomogram for predicting lymph node metastasis in the training set and validation set.** A: Receiver-operating characteristic receiver-operating characteristic (ROC) plot in the training set. The area under the curve (AUC) of the ROC was 0.760 (95%CI: 0.682-0.843); B: ROC plot in the validation set. The AUC of the ROC was 0.734 (95%CI: 0.643-0.826); C: Calibration plot in the training set. After 2000 repetitions, the bootstrap-corrected calibration curve (black line) lay close to the ideal reference line (red line), which demonstrated a perfect agreement between the predicted and actual outcomes (mean absolute error 0.012).

analysis, being female, tumor size of > 2 cm, with submucosal invasion, LVI, ulceration, and mixed SRCC were independent predictors of LNM in EGC.

Since SRCC shows different clinicopathological and biological characteristics, compared to NSRC, there are only a few studies that have previously reported on it. Therefore, we analyzed the clinicopathological and biological characteristics of SRCC, including pure-SRCC, mixed-SRCC, and SRCC limited to the mucosa in our research. By comparing the clinicopathological features of patients with NSRC and SRCC, we observed that patients with SRCC were of a younger age, were usually female, and showed fewer lesions in the upper section of the stomach with remarkable statistics differences. With respect to the risk factors for LNM in SRCC, our findings demonstrated that patients with a mixed type, submucosal invasion, and higher LVI are more likely to experience LNM. At the same time, we found that the mixed type was the only independent risk factor for LNM in patients with SRCC limited to the mucosa, which is consistent with the multivariable analysis of LNM in patients with mixed SRCC. In addition, the LNM rate in m-SRCC patients with an expanded ESD indication had a higher LNM rate than p-SRCC patients, and the difference was statistically significant. Therefore, for early gastric m-SRCC patients, caution should be exercised when selecting ESD treatment when the lesion exceeds the mucosal layer. For early gastric m-SRCC patients, a tumor size of > 2 cm was independent risk factor for LNM.

At present the predictive probability of LNM has not been clearly defined, and the clinical diagnosis of gastric LNM in EGC is still challenging. Quantitative predictive models are beneficial for both clinicians and patients in making more objective decisions regarding treatment options. The optimal threshold depends on the extent to which the patient or clinician rejects the risk. It is widely known that LR is a simple machine learning algorithm used for binary classification tasks. Neural networks are similar to a LR and can be referred to as a generalized LR. The neural network has advantages over LR models: the hidden layers facilitate the discovery of more complex and non-linear associations of variables. In our research study, we established two models: the ANN and LR model (nomogram) of LNM in EGC, and the LR model (nomogram) of LNM in early gastric SRCC patients. The ANN model and LR model both showed satisfactory performance through internal cross-validation. The methods of assessing diagnostic test accuracy were further used for model comparison. Then, we found that the ANN model of LNM in EGC performed better than the LR model with a significantly higher level of sensitivity, accuracy, and AUC. There were also some differences in the proportion of each risk factor in these two models of EGC. In the nomogram, LVI was dominant, and it was assigned 100 points; while in the ANN, the histological subtype was the most important risk factor, and it was assigned 100%. In addition, we established a nomogram of LNM in early gastric SRCC. In the nomogram, LVI was assigned 100 points; while, submucosal invasion was assigned 32.5 points, and mixed type SRCC was assigned 15 points. The potential of LNM gradually increased along with point accumulation. Our nomogram could predict the potential of LNM in every individual patient, which may help clinicians make informed and customized decisions that guide clinical treatment. Since only a few independent risk factors of LNM were obtained from the multivariate analysis, the ANN model cannot be further established in SRCC patients.

Our ANN and nomogram may serve as effective tools for predicting the incidence of LNM in Chinese patients with EGC, including early gastric SRCC, which may lead to improved selection of appropriate treatments methods. However, there are still several limitations in our study. Firstly, we utilized single-center, retrospective data to build and validate the predictive model. Secondly, we confirmed the

predictability of the model only using internal validation. However, it is necessary to conduct external validation to demonstrate the accuracy of these models. Thirdly, only a limited number of participants were included in this study, which may lead to a statistical analysis bias. Finally, we did not develop a specific cut-off value for LNM for each of the different methods of treatment available for patients with EGC or early gastric SRCC. Hence, further multicenter, large-sample clinical studies that can help establish additional risk factors for LNM in EGC or early gastric SRCC are still necessary.

## CONCLUSION

In conclusion, we constructed an ANN model and a nomogram to predict the probability of LNM in patients with EGC. The ANN model was better than the LR model nomogram in terms of sensitivity and accuracy. We constructed a nomogram for LNM in SRCC as well. These models can be used not only for preoperative evaluation to determine whether standard radical gastrectomy is needed for patients with EGC or early gastric SRCC patients at a high risk of LNM, but also for intraoperative evaluation to determine whether radical lymphadenectomy is necessary.

## ARTICLE HIGHLIGHTS

### Research background

Signet-ring cell carcinoma (SRCC) has shown discriminative biological characteristics compared with adenocarcinoma, and the behavior of SRCC in gastric cancer is controversial. In this study, we recognize the risk of lymph node metastasis (LNM) in early gastric SRCC, which can aid in pre-surgical decision making of the best method of treatment for patients.

### Research motivation

At present the predictive probability of LNM has not been clearly defined, and the clinical diagnosis of gastric LNM in early gastric cancer (EGC) and early gastric SRCC is still challenging. Quantitative predictive models are beneficial for both clinicians and patients in making more objective decisions regarding treatment options.

### Research objectives

We aimed to establish models to predict LNM in EGC, including early gastric SRCC, which can aid in pre-surgical decision making of the best method of treatment for patients.

### Research methods

We examined the retrospective large-sample clinical information of patients who had undergone surgery, by comparing the clinicopathological features of patients with non-signet ring cell carcinoma and SRCC. Variables that are significantly associated with LNM were identified as candidate variables for the artificial neural network (ANN) model and multivariate logistic regression.

### Research results

Our ANN and nomogram may serve as effective tools for predicting the incidence of LNM in Chinese patients with EGC, including early gastric SRCC, which may lead to improved selection of appropriate treatments methods.

### Research conclusions

With respect to the risk factors for LNM in SRCC, our findings demonstrated that patients with a mixed type, submucosal invasion, and higher LVI are more likely to experience LNM. At the same time, we found that the mixed type was the only independent risk factor for LNM in patients with SRCC limited to the mucosa, which is consistent with the multivariable analysis of LNM in patients with mixed SRCC.

### Research perspectives

Further multicenter, large-sample clinical and randomized controlled studies that can help establish additional risk factors for LNM in EGC or early gastric SRCC are still necessary.

## FOOTNOTES

**Author contributions:** Yang JJ, Wang XY, Ma R and Chen MH contributed equally to this work; Yang JJ and Wang XY designed the research study and performed the research; Ma R and Chen MH contributed new reagents and analytic tools; Yang JJ, Wang XY, Ma R and Chen MH analyzed the data and wrote the manuscript; all authors have read and

approve the final manuscript.

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