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ABOUT COVER

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AIMS AND SCOPE

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Development and validation of a nomogram for predicting lymph node metastasis in early gastric cancer

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Abstract

BACKGROUND

Lymph node metastasis (LNM) significantly impacts the treatment and prognosis of early gastric cancer (EGC). Consequently, the precise prediction of LNM risk in EGC patients is essential to guide the selection of appropriate surgical approaches in clinical settings.

AIM

To develop a novel nomogram risk model for predicting LNM in EGC patients, utilizing preoperative clinicopathological data.

METHODS

Univariate and multivariate logistic regression analyses were performed to examine the correlation between clinicopathological factors and LNM in EGC patients. Additionally, univariate Kaplan-Meier and multivariate Cox regression analyses were used to assess the influence of clinical factors on EGC prognosis. A predictive model in the form of a nomogram was developed, and its discrimination ability and calibration were also assessed.

RESULTS

The incidence of LNM in the study cohort was 19.6%. Multivariate logistic regression identified tumor size, location, degree of differentiation, and pathological type as independent risk factors for LNM in EGC patients. Both tumor pathological type and LNM independently affected the prognosis of EGC. The

model's performance was reflected by an area under the curve of 0.750 [95% confidence interval (CI): 0.701-0.789] for the training group and 0.763 (95%CI: 0.687-0.838) for the validation group.

CONCLUSION
A clinical prediction model was constructed (using tumor size, low differentiation, location in the middle-lower region, and signet ring cell carcinoma), with its score being a significant prognosis indicator.

Key Words: Early gastric cancer; Lymph node metastasis; Nomogram; Overall survival; Signet ring cell carcinoma

Core Tip: Early gastric cancer (EGC) refers to adenocarcinoma in which the cancer tissue is limited to the gastric mucosa or submucosa, regardless of tumor size and lymph node metastasis (LNM). It is very important to accurately predict the risk of LNM, and understanding the metastatic status of lymph nodes in EGC is conducive to selecting the appropriate surgical method and improving the overall efficacy of treatment.

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INTRODUCTION

Early gastric cancer (EGC) is characterized by adenocarcinoma confined to the gastric mucosa or submucosa, regardless of tumor size or the presence of lymph node metastasis (LNM). In recent years, advancements in the diagnosis and treatment of gastric cancer in China have led to an increased detection rate of EGC, with a 5-year survival rate exceeding 90%[1]. Despite the generally favorable prognosis of EGC, patients with LNM have a notably lower 5-year survival rate than those without LNM[2]. The standard treatment for EGC patients with LNM currently involves surgical resection accompanied by lymphadenectomy[3]. Moreover, for EGC patients without LNM, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are potential treatment options, contingent upon meeting the procedure's indications[4]. ESD is a favored treatment in EGC, but precise prediction of LNM risk is required before it can be performed. However, current auxiliary tests, including endoscopic ultrasound and computed tomography, exhibit limited accuracy in assessing lymph node status in EGC patients.

To date, numerous studies have investigated the characteristics and patterns of LNM in EGC patients globally; however, there is still no accurate prediction model. Many scholars now view nomograms as efficient instruments for predicting tumor progression and guiding clinical decision-making[5-10]. Prediction models are commonly employed for diagnosis and prognosis evaluation[11,12] and to determine tumor stage, predict recurrence and metastasis risk, estimate patient survival rates[11], and evaluate therapeutic efficacy[12-17]. Global research has extensively explored the use of nomograms for predicting LNM in EGC patients[18-20]. Zhao *et al*[21] developed a nomogram for LNM risk prediction in EGC, incorporating patient sex, year of diagnosis, tumor size, differentiation level, vascular invasion status, and pT stage. Similarly, a nomogram to predict LNM risk in EGC created by Liu *et al*[22] included T stage, computed tomography-detected enlarged lymph nodes, carbohydrate antigen 199 (CA199), histological undifferentiation, and systemic inflammatory response index. Hence, the objective of this study was to develop a new nomogram-based risk model for LNM in EGC patients utilizing preoperative clinicopathological data. This model is intended to predict the likelihood of LNM, a crucial factor in guiding the selection of appropriate surgical approaches in clinical settings.

MATERIALS AND METHODS

Selection criteria and patients

Between January 2010 and April 2019, 1584 EGC patients were admitted to Zhejiang Cancer Hospital, all of whom underwent preoperative biopsy pathology. After the exclusion of 101 patients with a history of preoperative neoadjuvant therapy and 483 patients with incomplete clinical data, 1000 ECG patients were selected for analysis in this study (Figure 1). The inclusion criteria were as follows: (1) Available preoperative endoscopic ultrasound, gastroscopy, and biopsy results; (2) Primary EGC with a pT1 biopsy stage; (3) Complete clinicopathological data; and (4) No prior antitumor treatment before surgery. The exclusion criteria were as follows: (1) Biopsy indicating advanced gastric cancer; (2) History of preoperative neoadjuvant therapy; (3) Incomplete clinical data; (4) Had other concurrent malignant tumors; and (5) Had residual, recurrent, or special gastric tumors (*e.g.*, lymphoma, neuroendocrine tumors, or stromal tumors). This study was designed as a single-center, retrospective investigation and was granted ethical approval by the Hospital

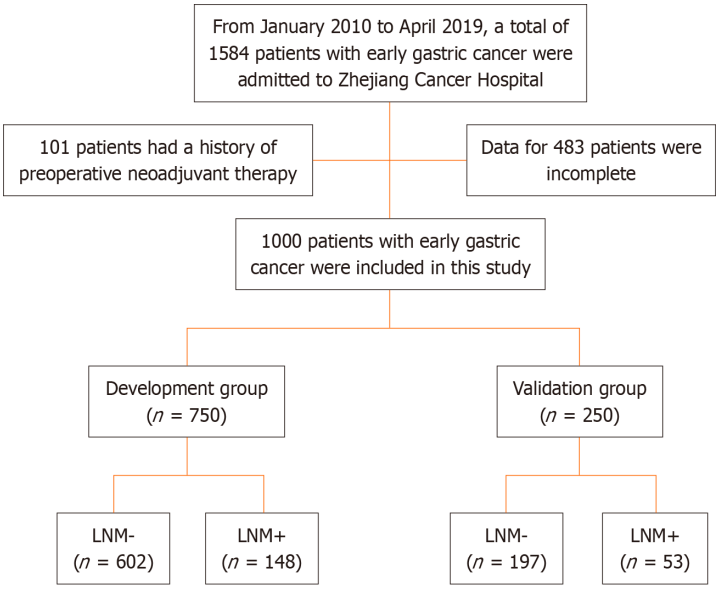

Figure 1 Patient inclusion flowchart showing the number of patients, selection criteria and grouping information. From January 2010 to April 2019, a total of 1584 patients with early gastric cancer were admitted to Zhejiang Cancer Hospital, 101 had undergone preoperative neoadjuvant therapy, 483 had incomplete clinical data, and 1000 patients with early gastric cancer were ultimately included in this study for analysis. LNM: Lymph node metastasis.

Medical Ethics Committee of Zhejiang Cancer Hospital (IRB-2022-371).

Clinicopathological characteristics

According to the "Japanese Gastric Cancer Treatment Guidelines", the influence of clinical factors such as age, sex, body mass index, tumor size, location, differentiation, pathological type, and tumor marker levels on LNM and prognosis was assessed. The demographic and clinicopathological data for both cohorts are summarized in Table 1.

Development of the LNM prediction model

A total of 1000 EGC patients were retrospectively analyzed, and they were randomly allocated to training (n = 750) and validation (n = 250) cohorts at a 7:3 ratio. A nomogram for predicting LNM in EGC patients was then developed and validated. Clinical and pathological data were statistically analyzed using the rms and rmda software packages within SPSS software (Version 25.0, IBM Corp, Armonk, NY, United States) and R 4.2.3 (https://www.r-project.org/). $P < 0.05$ was considered to indicate statistical significance. Categorical data were analyzed using the χ^2 or Fisher exact test. Univariate and multivariate logistic regression models were employed to examine the associations between clinicopathological factors and LNM status in EGC patients. Furthermore, survival data were assessed through univariate Kaplan-Meier analysis and multivariate Cox regression analysis to delineate the impact of various clinical factors on overall survival (OS) in EGC patients. The rms software package was used to construct a nomogram from the multivariate analysis results, and the accuracy of this nomogram was assessed using the Harrell C index and the area under the curve (AUC). The C index which spans from 0.5 to 1.0, reflects the model's ability to differentiate outcomes; a value of 0.5 indicates random chance, while 1.0 indicates perfect discrimination. The AUC, also ranging from 0.5 to 1.0, is a measure of accuracy; an AUC between 0.5 and 0.7 suggests low accuracy, an AUC between 0.7 and 0.9 indicates moderate accuracy, and an AUC above 0.9 suggests high accuracy. Calibration curves and receiver operating characteristic (ROC) curves were used to assess the prediction accuracy and reliability of the model, respectively. Decision curve analysis (DCA) was then used to evaluate the clinical value of the nomogram and other standard clinicopathological parameters.

Follow-up

All patients underwent follow-up examinations every 3 mo for the 1st 2 years after surgery and every 3 mo to 6 mo for 2 years to 5 years after surgery. The follow-up methods included outpatient visits, telephone calls, and other means, with the follow-up period extending until May 2022.

RESULTS

Baseline characteristics

The overall LNM rate in the cohort of EGC patients was 20.1% (201/1000). The patient demographics included 620 males and 380 females, with ages ranging from 20 years to 87 years (median 59). There were 563 patients with a tumor diameter ≤ 2 cm and 437 patients with a tumor diameter > 2 cm. In terms of tumor differentiation, 80 patients had high differentiation, 216 had medium differentiation, and 704 had low differentiation. Anatomically, 86 patients had upper gastric

Table 1 Demographic and clinicopathological data for both cohorts

Factor	Development group		Validation group	
	LNM-, *n* = 602	LNM+, *n* = 148	LNM-, *n* = 197	LNM+, *n* = 53
Age in yr				
≤ 60	340	88	103	38
> 60	262	60	94	15
Sex				
Female	210	68	72	31
Male	392	80	125	22
BMI				
≤ 24	421	100	130	36
> 24	181	48	67	17
Tumor size in cm				
≤ 2	392	47	107	17
> 2	210	101	90	36
Tumor location				
Proximal	66	2	17	1
Middle	96	39	31	20
Distal	440	107	149	32
Differentiation				
Poor	450	136	78	40
Moderate	119	10	77	10
Well	33	2	42	3
Pathological type				
AC	403	67	147	23
SRCC	199	81	50	30
CEA				
Normal	566	136	179	50
Abnormal	36	12	18	3
CA125				
Normal	589	143	194	52
Abnormal	13	5	3	1
CA19-9				
Normal	578	140	190	52
Abnormal	24	8	7	1
CA242				
Normal	589	146	191	52
Abnormal	13	2	6	1
CA72-4				
Normal	549	131	177	45
Abnormal	53	17	20	8

AC: Adenocarcinoma; BMI: Body mass index; CA125: Carbohydrate antigen 125; CEA: Carcinoembryonic antigen; LNM: Lymph node metastasis; SRCC:

Signet ring cell carcinoma.

tumors, 186 had middle gastric tumors, and 728 had lower gastric tumors. Pathologically, there were 640 patients with adenocarcinoma and 360 patients with signet ring cell carcinoma. Among the 750 patients in the training set, 148 (19.7%) had LNM, and in the validation set of 750 patients, 53 (21.2%) had LNM.

Analysis of risk factors for LNM in EGC

Univariate analysis revealed that sex ($\chi^2 = 6.232$, $P < 0.05$), tumor size ($\chi^2 = 54.467$, $P < 0.05$), tumor site ($\chi^2 = 19.260$, $P < 0.05$), tumor differentiation degree ($\chi^2 = 20.501$, $P < 0.05$), and tumor pathological type ($\chi^2 = 23.851$, $P < 0.05$) were significantly associated with LNM in EGC patients (Table 1). Multivariate analysis revealed that tumor size [odds ratio (OR) = 4.430, $P < 0.05$], middle gastric location (OR = 7.568, $P < 0.05$), lower gastric location (OR = 4.479, $P < 0.05$), poor differentiation ($P < 0.05$), moderate differentiation (OR = 0.400, $P < 0.05$), and pathological type (OR = 1.716, $P < 0.05$) were independent risk factors for LNM in EGC patients (Table 2).

Analysis of prognosis in EGC patients

The 3-year survival rate for the 1000 EGC patients in this study was 95.27%. Univariate analyses identified tumor size, differentiation, pathological type, and LNM as prognostic factors for EGC. Multivariate Cox regression analysis confirmed that tumor pathological type and LNM were independent risk factors for the prognosis of EGC patients (Table 3). The 3-year survival rate for EGC patients without LNM was 96.42%, while that for patients with LNM was 90.56%, with a significant difference (Figure 2A). The 3-year survival rate for EGC patients with a tumor diameter ≤ 2 cm was 96.16%, whereas that for patients with a tumor diameter > 2 cm was 94.14%, with a significant difference (Figure 2B). The influence of tumor location on survival time was not statistically significant (Figure 2C). The 3-year survival rates for patients with well-differentiated and poorly differentiated EGC were 95.73% and 95.09%, respectively (Figure 2D), and the 3-year survival rates for early gastric adenocarcinoma and early signet ring cell carcinoma patients were 95.78% and 94.45%, respectively, and these differences were significant (Figure 2E).

Development and validation of predictive models for LNM risk in EGC

Based on the independent predictors of LNM in EGC, a clinical nomogram was developed to predict the risk of LNM in EGC (Figure 3). The predictors included in the nomogram were tumor size, tumor location, degree of tumor differentiation, and tumor pathological type. Figure 4A shows the calibration curve for predicting LNM in EGC patients within the training cohort. The curve demonstrated a strong correlation between the nomogram predictions and the actual outcomes. The AUC of the model was 0.75 [95% confidence interval (CI): 0.701-0.789] (Figure 4B), and the C index for predicting LNM was 0.75.

Validation of the predictive accuracy of the nomogram for LNM in EGC

A validation cohort of 250 EGC patients from the same center was used to further assess the model's suitability and validate the independent risk factors incorporated into the nomogram. Figure 4C shows the agreement of the nomogram calibration curve in predicting the risk of LNM. The AUC of this model was 0.763 (95%CI: 0.687-0.838) (Figure 4D), and the C index for predicting LNM was 0.763. The DCA indicated the strong clinical utility of the model (Figure 5).

DISCUSSION

Currently, the main treatment options for EGC patients are surgical resection and endoscopic resection. Compared to surgical resection, endoscopic resection offers benefits such as reduced trauma and improved postoperative quality of life [22,23], making it the preferred treatment for EGC patients. Nevertheless, due to the inability to perform lymph node dissection with endoscopic techniques, the risk of recurrence following endoscopic resection is greater than that after surgical resection; consequently, EGC patients with LNM still require surgical resection for comprehensive tumor removal. Accurate prediction of LNM risk is crucial, and understanding the metastatic status of lymph nodes in EGC is conducive to choosing the most suitable surgical approach, thereby enhancing treatment effectiveness.

We investigated 13 variables to comprehensively identify risk factors for LNM in EGC patients. We found that tumor size, tumor location, degree of tumor differentiation, and tumor pathological type were independent risk factors for LNM in EGC patients. These factors were incorporated into a predictive model presented as a nomogram. Furthermore, we evaluated the discriminatory ability and calibration of the model, followed by internal validation.

Previous studies with large sample sizes have reported LNM rates in EGC ranging from 16.7% to 25.37%[24,25]. In this study, we found an LNM rate of 20.1% (201/1000) in the entire cohort. The training group exhibited an LNM rate of 19.7%, while the validation group's rate was 21.2%. These findings align with previously reported results. Numerous factors influence LNM in EGC, and the identified risk factors differ across studies. Consistently, the depth of tumor invasion and tumor size are significant predictors of LNM across almost all research[9,21,26,27]. Based on preoperative clinicopathological data, we identified risk factors for LNM in EGC patients, and the results showed that tumor size, tumor location, degree of differentiation and pathological type were independent predictive risk factors for LNM in EGC patients. The study revealed that the LNM rate among patients with tumors ≤ 2 cm was 11.4% (64/563), whereas patients

Table 2 Univariate and multivariate analysis of lymph node metastasis factors in patients with early gastric cancer

Variables	Univariate		Multivariate		
	χ^2	*P* value	OR	95%CI	*P* value
Age in yr	0.431	0.512	NA	NA	NA
Sex	6.232	0.013	0.787	0.525-1.179	0.245
BMI	0.314	0.576	NA	NA	NA
Tumor size in cm	54.467	< 0.001	4.430	2.964-6.620	0.000
Tumor location	19.260	< 0.001	NA	NA	NA
Middle	NA	NA	7.568	1.692-33.857	0.008
Distal	NA	NA	4.479	1.040-19.281	0.044
Differentiation	20.501	< 0.001	NA	NA	NA
Poor	NA	NA	NA	NA	0.015
Moderate	NA	NA	0.400	0.192-0.834	0.015
Well	NA	NA	0.260	0.059-1.154	0.076
Pathological type	23.851	< 0.001	1.716	1.130-2.606	0.011
CEA	0.898	0.343	NA	NA	NA
CA125	0.753	0.385	NA	NA	NA
CA19-9	0.585	0.444	NA	NA	NA
CA242	0.396	0.529	NA	NA	NA
CA72-4	1.010	0.315	NA	NA	NA

BMI: Body mass index; CA125: Carbohydrate antigen 125; CEA: Carcinoembryonic antigen; CI: Confidence interval; NA: Not applicable; OR: Odds ratio; SRCC: Signet ring cell carcinoma.

Table 3 Univariate analysis and multivariate analysis affecting the prognosis of patients with early gastric cancer

Variable	Univariate	Multivariate		
	P value	HR	95%CI	*P* value
Tumor size	0.023	1.288	0.92-1.861	0.177
Tumor location	0.206			
Differentiation	0.022	1.310	0.897-1.913	0.163
Pathological type	0.000	2.357	1.558-3.565	0.000
LNM	0.000	1.817	1.170-2.820	0.008

CI: Confidence interval; HR: Hazard ratio; LNM: Lymph node metastasis.

with tumors > 2 cm had a significantly greater LNM rate of 31.4% (137/437) ($P < 0.05$), consistent with the findings of other researchers. Du *et al*[28] reported that a tumor size ≥ 3.0 cm is an independent risk factor for LNM in EGC patients, with tumors in patients with LNM being notably larger than those in patients without LNM. Previous studies have divided the tumor location into the upper, middle and lower thirds of the stomach. Our multivariate analysis revealed that tumor location is an independent risk factor for LNM in EGC patients ($P < 0.05$). Specifically, tumors in the stomach body, antrum, and pyloric region pose a greater risk of LNM than those in the cardia and gastric fundus. Wang *et al*[19] also found that LNM may be more likely to occur in the lower part of the stomach, and they proposed that this tendency may be related to the occurrence of ulcerated undifferentiated invasive carcinoma or submucosal carcinoma in the antrum, as well as vascular invasion. These conditions, along with other forms of EGC treated with EMR, were not considered in their study. The tumor differentiation level is also a significant risk factor for LNM in EGC patients. In a retrospective study of 503 EGC patients, Zhao *et al*[21] confirmed that the degree of tumor differentiation is an independent risk factor for LNM in EGC, which is consistent with our results. This study's findings indicate that less differentiated tumors have a greater incidence of LNM, with a significant difference among the designated groups ($P <$

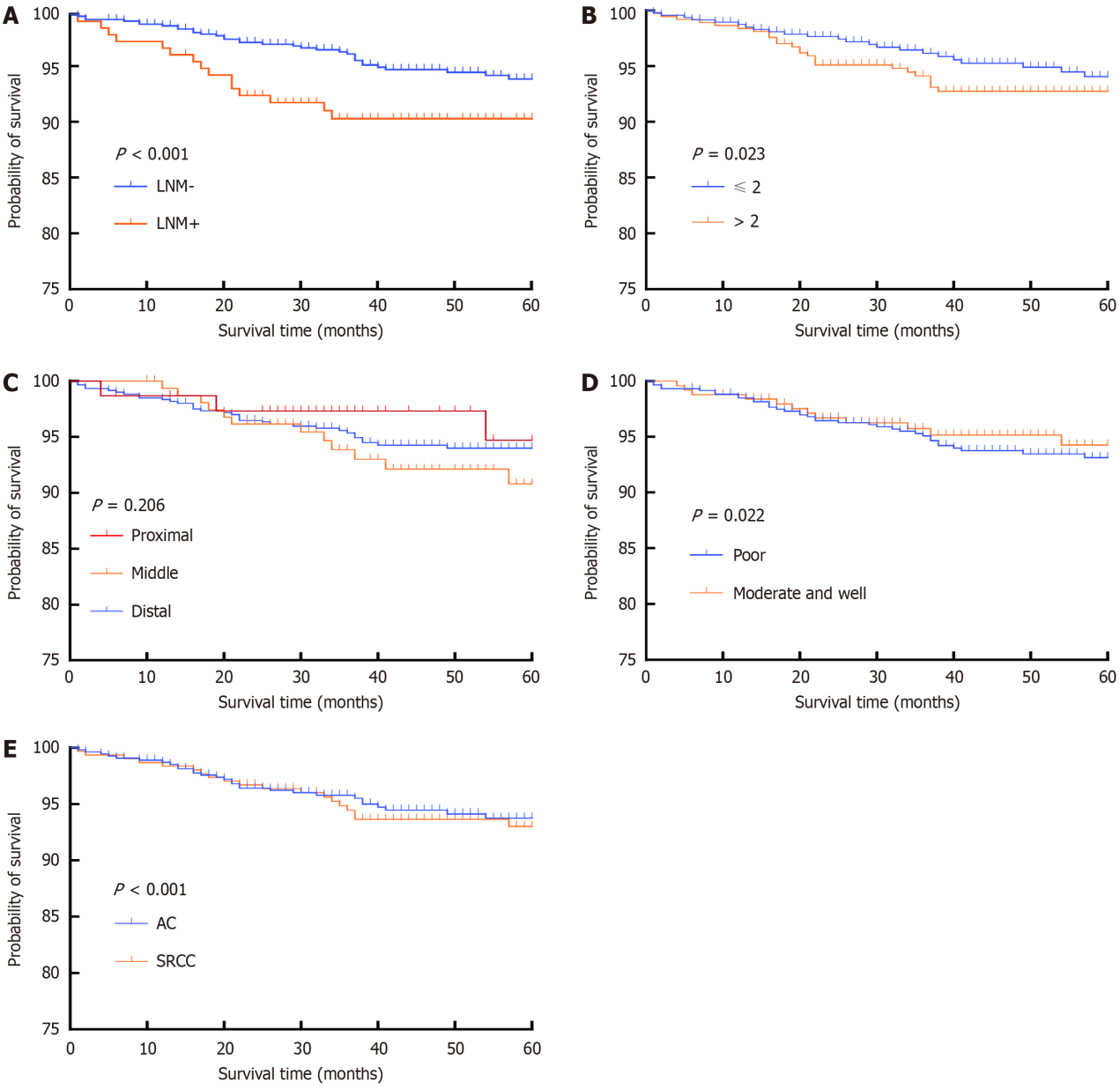

Figure 2 Kaplan-Meier survival curve based on risk factors associated with overall survival. A: Lymph node metastasis (LNM); B: Tumor size; C: Tumor location; D: Degree of differentiation; E: Pathological type. The presence of lymph node metastasis, tumor larger than 2 cm, poor differentiation, and the signet ring cell carcinoma (SRCC) pathological type were all associated with a preferred 3-year overall survival ($P < 0.05$). AC: Adenocarcinoma.

0.05). Signet ring cell carcinoma, a special histopathological type of gastric cancer, typically exhibits features such as poor differentiation, high aggressiveness, early metastasis, rapid disease progression and a poor prognosis. In this study, the LNM rate in gastric adenocarcinoma patients was 14.4% (100/640), while in signet ring cell carcinoma, it was 30.3% (96/360). The LNM rate for early-stage signet ring cell carcinoma was also greater than that for non-signet ring cell carcinoma types.

The risk factors for LNM in EGC patients were included in the survival analysis. The results showed that both pathological type and LNM status significantly influenced the prognosis of EGC, with patients having signet ring cell carcinoma and LNM exhibiting the worst outcomes. Based on the preoperative clinicopathological data, we identified the risk factors for LNM in EGC and developed a nomogram to visualize the risk of LNM. Then, we verified the model's predictive ability using ROC curve analysis. The model achieved an AUC of 0.75 (95%CI: 0.701-0.789) in the training set, and an AUC of 0.763 (95%CI: 0.687-0.838) in the validation set, indicating that the prediction model has a good ability to distinguish whether LNM will occur in EGC. Furthermore, the calibration curve for the model exhibited a strong agreement between the predicted and actual probabilities, demonstrating the model's excellent calibration. This indicates that the model can reliably inform the selection of the most suitable treatment approach. Although numerous studies worldwide have focused on the development of nomograms for predicting LNM in EGC, factors such as depth of tumor invasion, number of metastatic lymph nodes, vascular invasion, lymphangiosarcoma thrombosis, nerve invasion, and other clinicopathological data that can only be obtained after surgery have been incorporated. These models are not suitable for preoperative treatment selection in EGC patients. To the best of our knowledge, this is the first nomogram

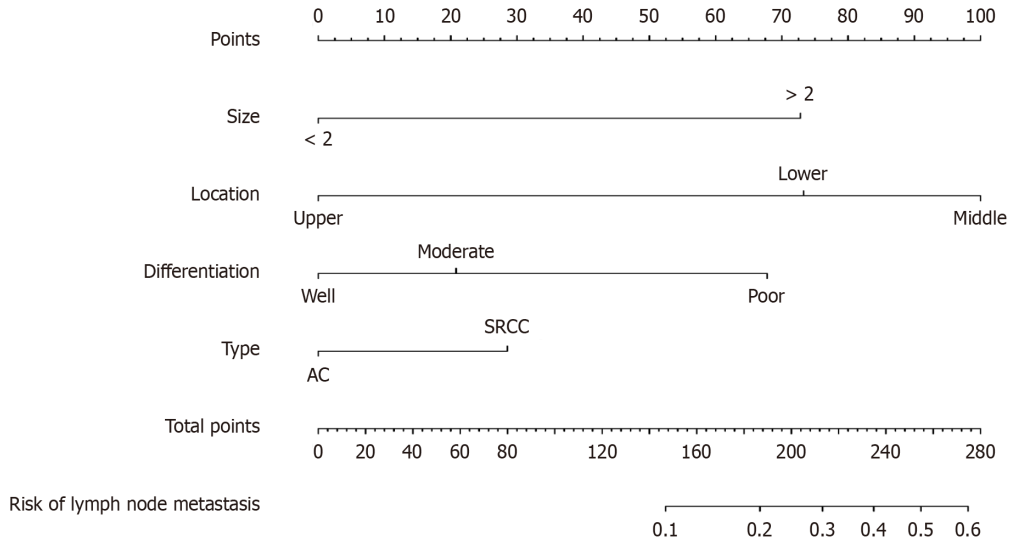

Figure 3 Nomogram including tumor size, tumor location, degree of tumor differentiation, and tumor pathological type. Based on the independent predictors of early gastric cancer lymph node metastasis, a clinical nomogram was developed to predict the risk of lymph node metastasis in early gastric cancer. AC: Adenocarcinoma; SRCC: Signet ring cell carcinoma.

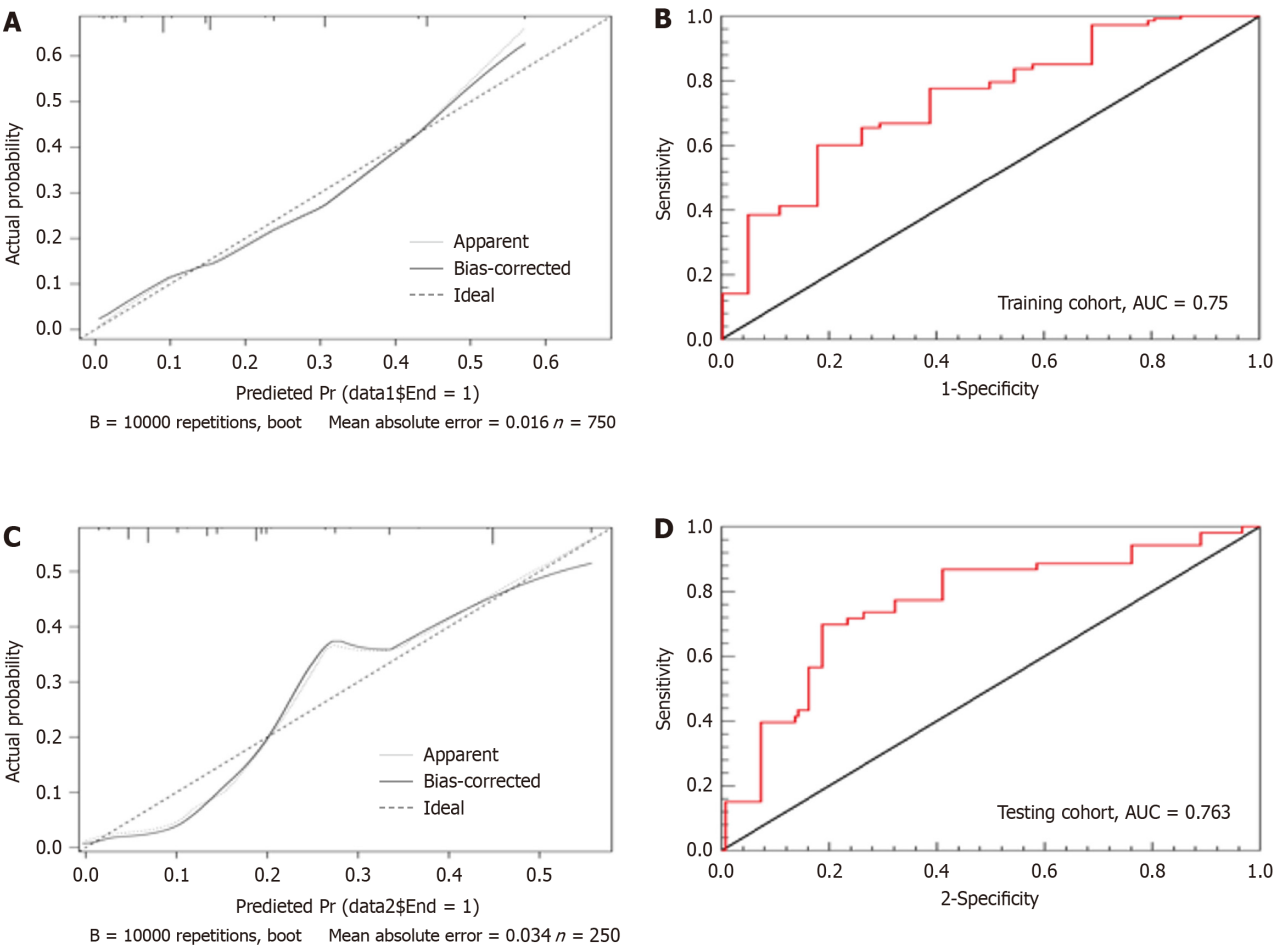

Figure 4 Discrimination and calibration of the model were evaluated. A: The calibration curve for predicting lymph node metastasis in early gastric cancer in the training cohort; B: In the training cohort, the area under the curve (AUC) of this prediction model is 0.75 [95% confidence interval (CI): 0.701-0.789] and the C index of predicting early recurrence is 0.75; C: The calibration curve for predicting lymph node metastasis in early gastric cancer in the testing cohort; D: The AUC of this prediction model is 0.763 (95%CI: 0.687-0.838) and the C index of predicting early recurrence is 0.763.

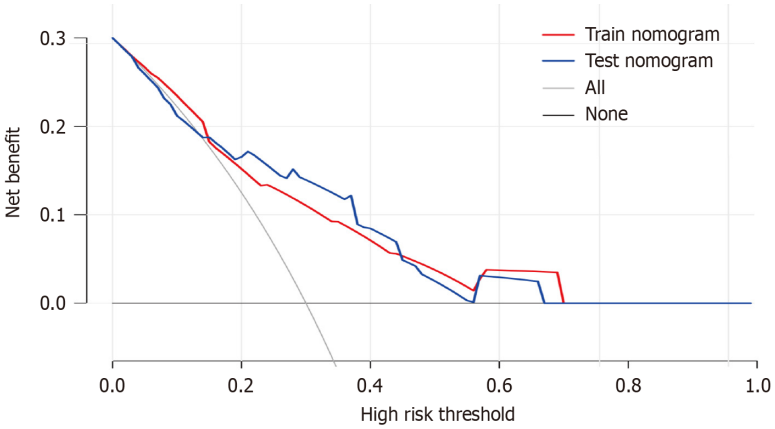

Figure 5 Decision curve analysis indicated strong clinical utility of the model. The decision curve analysis was used to evaluate the clinical value of the nomogram and other standard clinicopathological parameters.

developed to predict LNM risk in EGC patients using preoperative risk factors. We recommend that all EGC patients undergo preoperative endoscopy and pathological biopsy to aid in the selection of the most suitable treatment.

There are several limitations to this study: (1) This was a single-center retrospective study with potential selection bias; (2) The large time span of patient enrollment may introduce variability due to advancements in diagnostic and treatment modalities for gastric cancer, and factors such as the extent of resection, the scope of intraoperative lymph node dissection, the pathological detection method and the postoperative pathologist's experience can influence the detection of LNM in EGC and lead to false negatives; and (3) Due to the lack of preoperative clinical data such as imaging findings, specific tumor marker levels, and endoscopic ultrasound reports, these data were not included in the present analysis. Finally, with the establishment and improvement of a standardized gastric cancer database at our center, future research could incorporate data from multiple centers and additional indicators to improve the diagnostic efficiency of the prediction model. This could involve radiomic features and results from cutting-edge sequencing technologies to support the application of precision medicine.

CONCLUSION

In summary, through clinicopathological analysis of 1000 patients with EGC, we identified tumor size ≥ 2 cm, poor differentiation, middle and lower tumor locations, and signet ring cell carcinoma pathological type as independent risk factors for LNM in EGC. Among them, tumor pathological type and LNM were found to be independent prognostic factors for EGC patients. Moreover, the developed clinical prediction model for LNM in EGC demonstrated good discriminatory ability and accuracy and can thus guide the selection of clinical treatment strategies, such as surgery or endoscopic resection, providing certain value in clinical practice.

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FOOTNOTES

Author contributions: Xu ZY and Hu C designed the research study; Li EZ, Zhang YQ, and Zhang RL performed the primary literature search and data collection; He JY and Cao MX analyzed the data and wrote the manuscript; Cheng XD and Xu ZY revised the manuscript for important intellectual content; Xu ZY and Cheng XD contributed equally to this work and as such are co-corresponding authors of this manuscript; All authors read and approved the final version.

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