

Restaging pN Classification in Early Gastric Cancer with Inadequate Lymph Node Retrieval: Multi-Institutional Development and Prognostic Validation of a Revised Staging System

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Objective: This study aimed to propose and validate a new and practical lymph node (LN) staging strategy to mitigate staging migration due to examined LN (ELN) retrieval and improve the accuracy of prognostic evaluation for early gastric cancer (EGC) patients.

Background: EGC patients often face staging inaccuracies due to inadequate ELNs, as there is no clear standard for ELN retrieval requirements.

Methods: From an initial cohort of 7001 EGC patients across fifteen large institutions in China, 6566 eligible patients were included as the training and validation cohort after applying predefined exclusion criteria. We analyzed these data to determine the optimal cutoff value for the number of ELNs, construct a prediction model, and propose a new LN staging method distinct from that of the latest AJCC guidelines. Subsequently, 2094 patients (from 2326 with survival data available in the multicenter dataset) and 1944 patients (from 5262 initially retrieved from the SEER database after exclusions) were included as independent test cohorts to evaluate model performance, including the correlation between ELNs and metastatic LNs (MLNs) and survival differences.

Results: This study found that ≤ 20 ELNs were inadequate for accurate LN evaluation in EGC patients. In the test cohort, MLNs was positively associated with ELNs. A model was constructed, and accurate MLNs could be displayed after correction for patients with

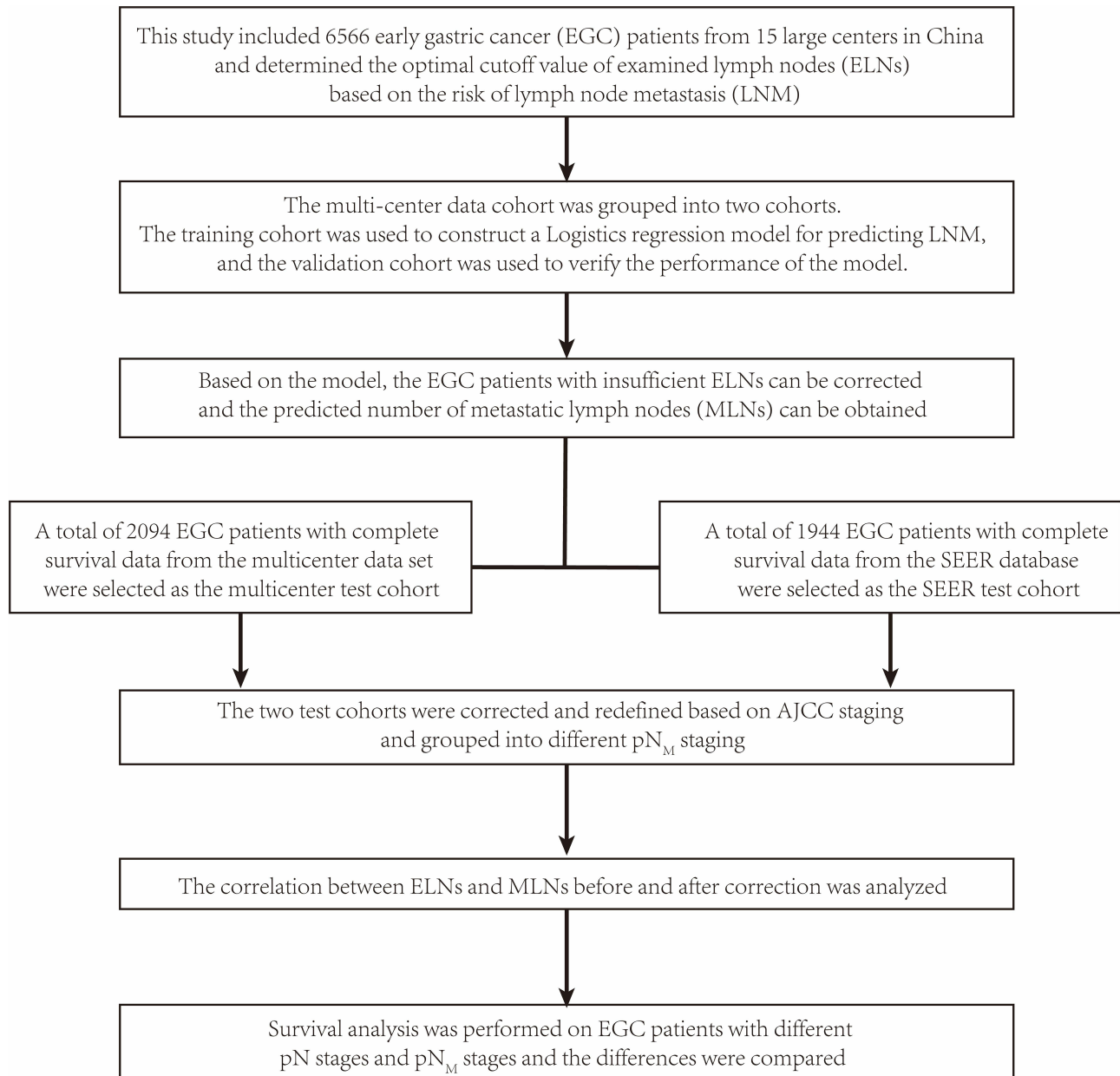


inadequate ELNs. Survival analysis revealed significant differences between patients with different pN_M (pN_{modified}) stages in both the multicenter test cohort and the SEER test cohort.

Conclusion: Model-corrected pN_M staging may improve staging migration and survival prediction than the AJCC staging, showing great clinical applicability for EGC patients with ELN ≤ 20.

Keywords: stomach, neoplasm, lymph node, metastasis, prognosis

Graphical Abstract



Introduction

Gastric cancer (GC) is a prevalent malignant tumor worldwide. According to the latest global reports, there are nearly one million new cases of GC, making it the fifth most common cancer worldwide. Tragically, approximately 650,000 individuals succumb to GC, ranking it as the fifth leading cause of cancer-related deaths, following lung cancer, colorectal cancer, liver cancer and breast cancer.¹ Compared with those in Western countries, the number of GC cases and deaths in China remains high, accounting for approximately half of the number of GC cases and deaths in the world.² Due to the use of relatively rigorous screening programs, the proportion of patients identified as having early gastric cancer (EGC) is increasing among patients with GC. According to the definition provided by the Japanese Society of Gastrointestinal Endoscopy in 1962, EGC is a lesion confined to the mucosa and submucosa regardless of the status of lymph node metastasis (LNM).³ Some patients with EGC can be treated via endoscopic resection. The current clear criterion for endoscopic resection is a differentiated mucosal tumor less than 2 cm in diameter without ulceration. However, in most cases, surgical treatment is still necessary and will bring the best prognosis to EGC patients.⁴

Research findings on the survival outcomes of EGC patients have not yielded consistent results. Most Eastern studies have reported that the 5-year overall survival (OS) rate of EGC patients is more than 90%. In contrast, Western studies have shown a broader range of 5-year OS rates, varying from 68% to 92%.^{5,6} The prognosis of EGC patients is influenced by two major factors: LNM and depth of wall invasion. However, only LNM has been demonstrated to be an independent prognostic factor.⁷ Previous statistical analyses have indicated an LNM rate of approximately 20% among EGC patients, highlighting the importance of adequate examination of examined lymph nodes (ELNs) to thoroughly assess metastatic lymph nodes (MLNs).^{8–10} While ELNs count positively correlates with MLNs detection, quantitative ELN thresholds remain controversial.^{11,12} The American Joint Committee on Cancer (AJCC)¹³ and the Chinese Society of Clinical Oncology (CSCO)¹⁴ recommend >16 ELNs for accurate pN staging, while recent large-scale studies have suggested that >30 is optimal in GC.¹⁵ We previously demonstrated that <16 ELNs caused pN underestimation and significantly reduced overall survival.¹⁶ Similarly, <10-15 ELNs increased.¹⁷ However, these thresholds are mainly derived from advanced GC. In EGC, the prevalence of LNM is lower and the number of MLNs is fewer, which paradoxically necessitates a higher number of ELNs to reliably detect all metastatic nodes. Currently, no clear ELNs requirement exists specifically for EGC. Given the critical role of accurate LNM evaluation in determining postoperative pTNM staging per AJCC guidelines and its strong prognostic implications, inadequate ELNs retrieval may lead to pN misclassification and subsequent bias in survival assessment, ie., stage migration. Therefore, we aim to define the optimal ELNs cutoff value for EGC, construct and validate an accurate prediction model for MLNs, and more importantly, apply this model to mathematically correct the pN category in patients with inadequate ELNs retrieval, achieving a more precise assessment of patient prognosis.

Materials and Methods

Patients and Eligibility Criteria

This research is a multicenter retrospective study. The clinicopathological data of 7001 patients of EGC from fifteen large medical centers of China included Tianjin Medical University Cancer Institute and Hospital, The General Hospital of the People's Liberation Army, Xijing Hospital of Air Force Medical University, Sun Yat-sen University Cancer Hospital, Jiangsu Cancer Hospital, Anyang Cancer Hospital of Henan Province, Sixth Affiliated Hospital of Sun Yat-sen University, Fujian Cancer Hospital, The Cancer Institute and Hospital of Chinese Academy of Medical Sciences, Liaoning Cancer Hospital, Fujian Provincial Hospital, Affiliated Hospital of North Sichuan Medical College, Affiliated Cancer Hospital of Harbin Medical University, West China Hospital of Sichuan University, and Guangdong Provincial People's Hospital were collected between 2005 to 2015.

Patients satisfying the following criteria were included: underwent radical gastrectomy for GC, pathologically confirmed EGC adenocarcinoma, and none accepted neoadjuvant therapy. The patients would be excluded if the following conditions occurred: accompanied by relevant missing data, accompanied by other synchronous malignancy, presence of residual GC, and no performing endoscopic submucosal dissection or resection biopsy. Missing data for key variables were below 5%, and complete case analysis was applied. Ultimately, a total of 6566 patients for data analysis

was included, and they were divided into training and validation cohorts according to a certain proportion. Additionally, a total of 2326 patients with survival data from Tianjin Medical University Cancer Institute and Hospital, Sun Yat-sen University Cancer Hospital, Sixth Affiliated Hospital of Sun Yat-sen University, Fujian Cancer Hospital, and Anyang Cancer Hospital of Henan Province were collected. After screening and excluding missing data and lost follow-up data, a total of 2094 EGC patients from multicenter with complete data were used to survival analysis as the internal test cohort. The flow diagram of the selection process was presented in [Additional file 1: Figure S1A–B](#). All patients provided informed consent for the use of their data for scientific purposes prior to surgery. The study protocol adhered to the regulations of the Declaration of Helsinki (as revised in Edinburgh 2000) and ethical approval was obtained from the Tianjin Medical University cancer institute and hospital institutional review board (bc2022220).

Retrieval of Patients from the SEER Database

We conducted an analysis of the SEER database to identify GC cases that met similar inclusion criteria to those mentioned above, spanning from January 2000 to December 2019. Initially, 5262 cases of EGC were retrieved. Cases with incomplete information regarding age, tumor location, tumor size, differentiation type, depth of tumor invasion, MLNs, ELNs were excluded. This refined dataset, eventually comprising 1944 cases, was designated as the SEER test cohort. The flow diagram of the selection process was presented in [Additional file 1: Figure S1C](#).

Construction and Verification of the Prediction Model

A total of 6566 patients were randomly divided into training cohort (70%) and validation cohort (30%). The random split was performed using SPSS with a fixed random seed and stratification by center. According to the results of post-operative pathological examination, EGC patients in different groups were divided into positive lymph node metastasis (PLNM) group and negative lymph node metastasis (NLNM) group. In this study, the optimal cut-off value (corresponding to the maximum value of the Yoden's index) of ELN corresponding to the prediction of LNM in this data is used to define whether the ELN count is sufficient. The number of adequate ELNs defined and selected in this study was 20, and the results of the Yoden's index for different ELN counts are presented in [Table S1](#).

The independent risk factors of LNM were determined by multivariate analysis. Variables with $P < 0.05$ in univariate analysis were entered into multivariate binary logistic regression using forward stepwise selection. Based on the β coefficient of independent risk variables, a logistic prediction model was established to predict the probability of LNM. The performance of the model was verified by drawing nomogram, ROC and calibration graphs. In addition, the artificial neural network (ANN) model was used to include logistics variables for verification. Internal validation was performed using the held-out validation cohort (30% of data), and no cross-validation was applied. The ANN architecture consisted of an input layer with 10 predictors, two hidden layers (5 nodes each), and an output layer with 2 nodes (PLNM and NLNM). The softmax transfer function and scaled conjugate gradient training algorithm were applied. The training group was used to train the neural network, while 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 model was calculated to compare and evaluate diagnostic accuracy using the chi-square test. The superiority of the fitting prediction model was evaluated by plotting the calibration curve, and the net benefit rate was evaluated by the DCA curve.

Construction of Modified pN Stage and Survival Analysis

The multicenter test cohort and the SEER test cohort were included, and the patients with survival data were substituted into the model for survival test. Among them, OS was the study endpoint which defined as the time interval from the date of surgery to the last date of follow-up or death. The correction procedure was performed as follows: (a) Obtain the predicted probability of LNM (P) from the logistic model; (b) For patients with ELNs ≤ 20 , calculate the expected number of MLNs in unexamined lymph nodes: $(20 - \text{actuals ELN}) \times P$; (c) Calculate predicted total MLNs = actual MLNs + $(20 - \text{actual ELN}) \times P$; (d) Assign pN_M stage according to AJCC 8th edition pN categories (N0: 0, N1: 1-2, N2: 3-6, N3a: 7-15, N3b: ≥ 16) based on corrected MLNs. ([Figure S2A](#)) It should be noted that the corrected MLN count and pN_M stage

are model-derived estimates rather than directly observed pathological data. The correlation between ELNs and MLNs and the difference in survival will be further analyzed before and after correction.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (version 26.0; IBM Corp, New York, NY). χ^2 test or Fisher exact test was used for univariate analysis to evaluate the correlation between clinicopathological characteristics and LN involvement of patients with EGC. The factors with 2-tailed $P < 0.05$ were included in the multivariate analysis. Multivariate binary logistic regression analysis was used to further screen independent risk factors for LNM in patients with EGC. R statistical software (version 4.3.1, the R Foundation for Statistical Computing) was used to draw nomogram, ROC, and calibration graphs. Comparisons of the predictive value of each model were performed using the likelihood-ratio test, Akaike Information Criterion, and Bayesian Information Criterion by R statistical software. A model with low AIC, low BIC, and high likelihood-ratio score had a better predictive value. The accepted level of significance was P less than 0.05. The correlation between ELNs and MLNs was calculated by fitting linear model using Origin 2024 (Origin, Northampton, MA, USA). The Kaplan–Meier method was used for graphical representation of the OS curves and the Log rank test was used to assess the differences between the survival curves, and the relative graphs were generated using GraphPad Prism 9 (GraphPad, San Diego, CA). For all Cox regression models, the proportional hazards assumption was tested using Schoenfeld residuals (all $P > 0.05$). The ANN model and further statistical analyses were performed using IBM SPSS Statistics software.

Results

Clinical and Pathological Characteristics in the Multicenter Dataset

The following is a summary of the clinicopathological characteristics of the 6566 EGC patients included in this study. Overall, 70.61% of the patients were male, while 29.39% were female. Patients were separated into groups of individuals who were less than 65 years old (71.29%) and those who were more than 65 years old (28.71%) based on their ages at the time of operation. The tumors were mainly located in the lower 1/3 (56.88%), followed by the upper 1/3 (21.06%), middle 1/3 (15.93%), and more than 1/3 of the stomach (6.12%). Tumors with a maximum diameter less than 2 cm accounted for 55.92%, and those with a maximum diameter greater than 2 cm accounted for 44.08%. According to the degree of differentiation, the tumors were divided into moderate or good type (39.95%) and undifferentiated or poor type (60.05%). According to the Lauren classification, the patients were divided into intestinal type (44.36%), diffuse type (31.69%) and mixed type (23.94%). There were 2846 patients with pT1a stage EGC (43.34%) and 3720 patients with pT1b stage EGC (56.66%). According to the pN stage, the patients were divided into 5 groups that were consistent with the TNM stage: pN0 (84.01%), pN1 (9.05%), pN2 (4.84%), pN3a (1.71%) and pN3b (0.40%). There were 367 patients with perineural invasion (5.59%) and 612 patients with lymphovascular invasion (9.32%). After grouping by the number of ELNs, 3743 patients had > 20 ELNs, accounting for 57.01% of the total ([Table S2](#)). The data were randomly divided into a training cohort (4597) and a validation cohort (1969) at a ratio of approximately 7:3, and a comparison of clinicopathological factors between the cohorts is shown in [Table S3](#). The results showed that there were no statistically significant differences in the variables between the two cohorts.

Construction and Validation of a Predictive Model for LNM

Univariate analysis was performed on the risk of LNM in the training cohort of EGC patients. Sex, tumor location, tumor size, differentiation type, Lauren type, pT stage, ELN count (bounded by 20), perineural invasion and lymphovascular invasion were significantly associated with LN involvement in patients with EGC and were thus included in multivariate analysis. Multivariate analysis using a multiple logistic regression model confirmed that sex ($P=0.003$), tumor location ($P=0.001$), tumor size ($P<0.001$), differentiation type ($P<0.001$), pT stage ($P<0.001$), ELN count (bounded by 20, $P<0.001$), and lymphovascular invasion ($P<0.001$) were found to be independent predictors of LNM ([Table 1](#) and [Figure 1A](#)).

A logistic prediction model was established to predict the probability of LNM based on the β coefficients of the aforementioned seven independent risk variables that were identified via multivariate analysis. The ROC curve was

Table 1 Univariate and Multivariate Analysis of LNM Risk in Training Cohort

Clinicopathological Characteristics	Univariate Analysis			Multivariate Analysis		
	NLNM n=3874 (%)	PLNM n=723 (%)	P value	OR	95% CI	P value
Sex			<0.001			0.003
Male	2792 (72.07)	449 (62.10)		Ref.		
Female	1082 (27.93)	274 (37.90)		1.33	1.10–1.60	
Age at surgery (years)			0.065			
<65	2730 (70.47)	534 (73.86)				
≥65	1144 (29.53)	189 (26.14)				
Tumor location			<0.001			0.001
Lower 1/3	2119 (54.70)	471 (65.15)		Ref.		
Middle 1/3	599 (15.46)	142 (19.64)		0.98	0.78–1.24	
Upper 1/3	902 (23.28)	72 (9.96)		0.58	0.44–0.78	
More than 1/3 stomach	254 (6.56)	38 (5.26)		0.69	0.47–1.03	
Tumor size			<0.001			<0.001
≤2cm	2298 (59.32)	288 (39.83)		Ref.		
>2cm	1576 (40.68)	435 (60.17)		1.95	1.63–2.33	
Differentiation type			<0.001			<0.001
Moderately or well	1695 (43.75)	167 (23.10)		Ref.		
Undifferentiated or poorly	2179 (56.25)	556 (76.90)		2.05	1.68–2.52	
Lauren type			<0.001			
Intestinal	1845 (47.63)	219 (30.29)				
Diffuse	1163 (30.02)	286 (39.56)				
Mixed	866 (22.35)	218 (30.15)				
pT stage			<0.001			<0.001
pT1a	1831 (47.26)	155 (21.44)		Ref.		
pT1b	2043 (52.74)	568 (78.56)		2.78	2.27–3.41	
Examined lymph node count			<0.001			<0.001
≤20	1840 (47.50)	168 (23.24)		Ref.		
>20	2034 (52.50)	555 (76.76)		2.49	2.03–3.04	
Perineural invasion			<0.001			
No	3691 (95.28)	645 (89.21)				
Yes	183 (4.72)	78 (10.79)				
Lymphovascular invasion			<0.001			<0.001
No	3671 (94.76)	502 (69.43)		Ref.		
Yes	203 (5.24)	221 (30.57)		5.56	4.41–7.01	

Abbreviations: NLNM, negative lymph node metastasis; PLNM, positive lymph node metastasis; OR, odds ratio, 95% CI, 95% confidence interval.

plotted using the training cohort, and the AUC, which was 0.789 (95% CI, 0.771–0.807), was used to evaluate the discriminant ability of the model. The accuracy of the prediction model was confirmed using the validation cohort, and the AUC was 0.775 (95% CI, 0.748–0.802). The calibration curve and DCA curve were generated at the same time, confirming the model's superiority (Figure 1B–E). We also established an ANN model and assessed its ability to predict LNM in EGC patients. The structure of the established ANN model was presented and affected by nine important predictors, of which the number of ELNs (bound by 20) was a relatively high factor. The predictive model demonstrated the AUC was 0.781 (95% CI, 0.767–0.797) (Figure 1F and G).

Survival Analysis and LN Correlation of EGC Patients After Model Correction

The multicenter dataset with survival data and the SEER validation dataset were used as the test cohorts to test the predictive efficacy of the model, and the specific clinicopathological characteristics are shown in Tables S4–S5. First, we

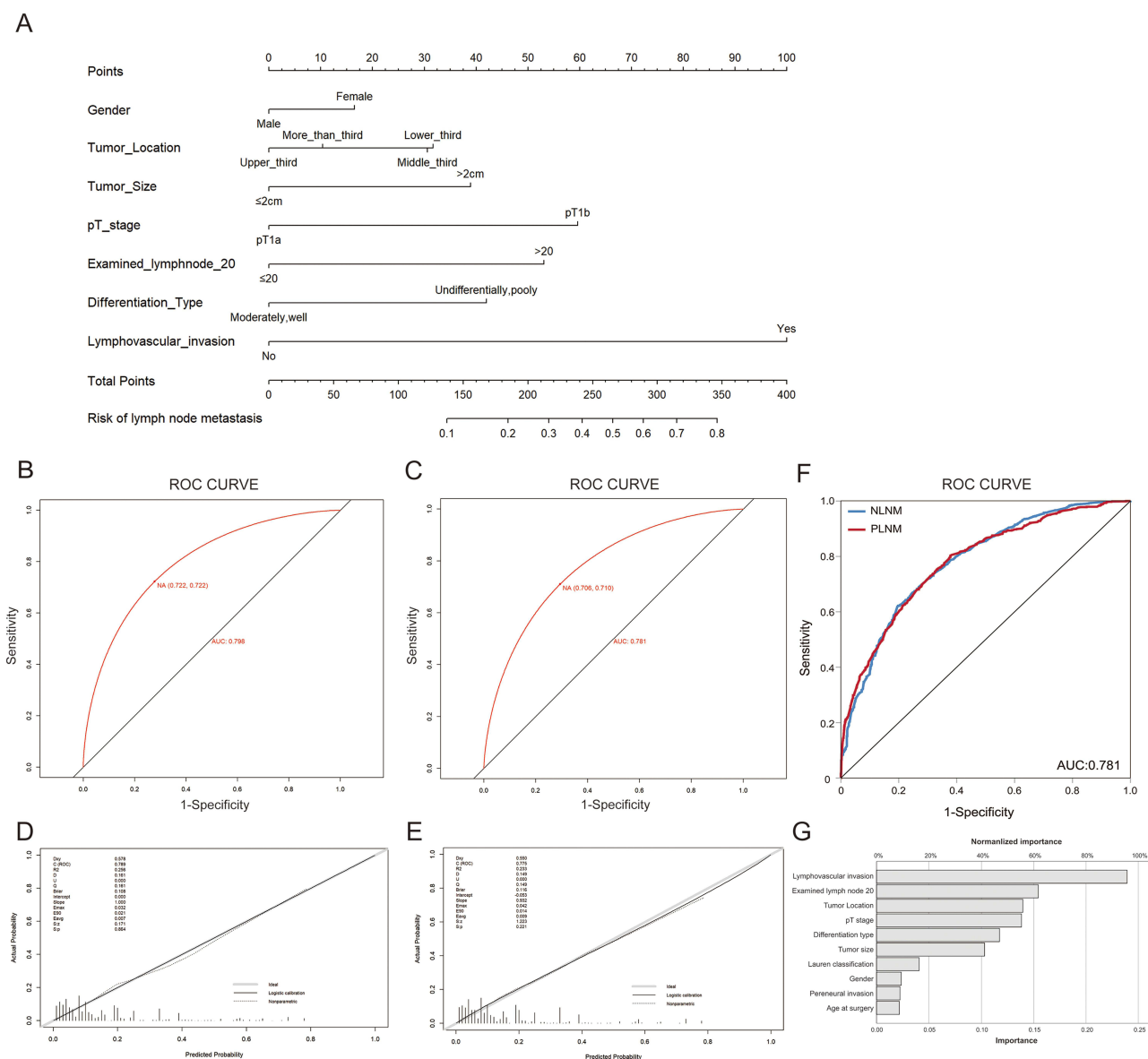


Figure 1 Construction and verification of LNM prediction model: **(A)** Nomogram graph of risk factors for LNM from multivariate logistic regression analysis in training cohort; **(B)** Receiver operating characteristic curve of prediction model for LNM of training cohort; **(C)** Receiver operating characteristic curve of prediction model for LNM of validation cohort; **(D)** The calibration curve of LNM prediction model in the training cohort; **(E)** The calibration curve of LNM prediction model in the validation cohort; **(F)** Receiver operating characteristic curve based on artificial neural network (ANN) model; **(G)** ANN model for predicting LNM in EGC.

found that patients with > 20 ELNs had better survival in the survival analysis of the two datasets (all $P < 0.0001$). Moreover, according to the β coefficient of the independent variables of the logistic regression model, the probability of LNM (P) was calculated (Figure S2B). After further correction for EGC patients with insufficient ELNs, the predicted MLN number and pN_M stage were obtained by using the formula. In the multicenter test cohort, survival analysis of patients with different stages showed that the 5-year OS rates of patients with pN_0 , pN_1 , and $pN_2 + pN_3$ disease were 97.96%, 96.26%, and 89.84%, respectively. However, the difference between the independent stages was not statistically significant. The corrected 5-year OS rates of pN_{0M} , pN_{1M} and $pN_{2M} + pN_{3M}$ patients were 98.22%, 97.12% and 89.78%, respectively, and there were significant differences between different stages (pN_{0M} vs. pN_{1M} , $P = 0.0012$; pN_{0M} vs. $pN_{2M} + pN_{3M}$, $P = 0.0044$; pN_{1M} vs. $pN_{2M} + pN_{3M}$, $P < 0.0001$). This trend was also consistent in the SEER test cohort, and the difference between different pN_M intervals after correction was highly significant (all $P < 0.0001$) (Figure 2).

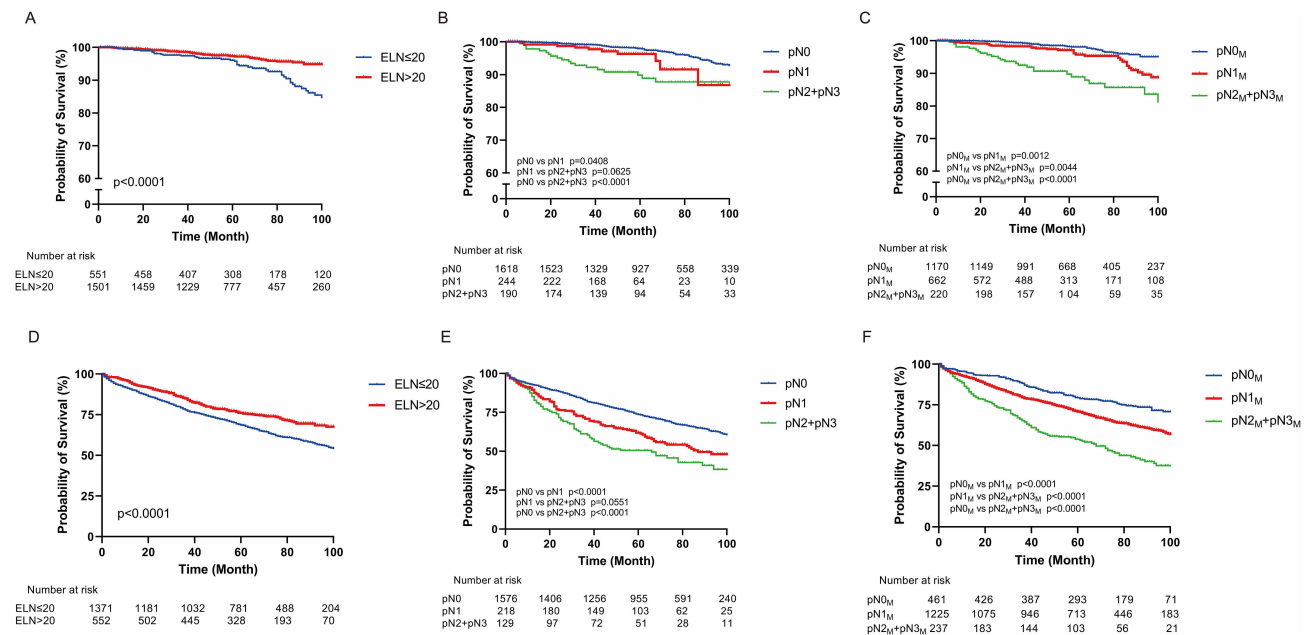


Figure 2 The survival analysis in multicenter test cohort and SEER test cohort: (A) Kaplan-Meier curves of EGC patients with ELN ≤ 20 and ELN > 20 in multicenter test cohort; (B) Kaplan-Meier curves of EGC patients with different pN stages in multicenter test cohort; (C) Kaplan-Meier curves of EGC patients with different pN_M stages after correction in multicenter test cohort; (D) Kaplan-Meier curves of EGC patients with ELN ≤ 20 and ELN > 20 in SEER test cohort; (E) Kaplan-Meier curves of EGC patients with different pN stages in SEER test cohort; (F) Kaplan-Meier curves of EGC patients with different pN_M stages after correction in SEER test cohort.

In this study, the number of ELNs and the number of MLNs in EGC patients were linearly fitted, and the correlation trend between the two was judged by the coefficient ($Y=aX+b$) of the linear equation. The number of ELNs was positively associated with the number of MLNs in EGC patients in both the multicenter test cohort ($a=0.020$) and the SEER test cohort ($a=0.044$). After model correction, the number of MLNs was nearly unrelated to the number of ELNs in the two datasets (multicenter cohort: $a=-0.003$, SEER cohort: $a=-0.004$). When the condition was limited to patients with insufficient ELNs, the number of MLNs approached a fixed value after correction (multicenter cohort: $b=1.588$, SEER cohort: $b=1.695$), and the linear slope of the correlation analysis was lower than that before (multicenter cohort: $a=-0.005$ vs. $a=0.038$, SEER cohort: $a=-0.015$ vs. $a=0.036$). Finally, in LNM patients with ≤ 20 ELNs, the above trend was more significant after model correction (multicenter cohort: $a=0.057$, $b=3.495$ vs. $a=0.149$, $b=0.839$; SEER cohort: $a=-0.005$, $b=3.567$ vs. $a=0.077$, $b=1.312$) (Figure 3).

Evaluation and Validation of the Model

Based on the different pN stages, we calculated the TNM and modified TNM stages of the patients, and the survival curves are shown in Figure 4A–D. There were some differences in the number of patients with different TNM stages before and after correction in the multicenter dataset (IA vs. IA_M: 1655 vs. 1172, IB vs. IB_M: 249 vs. 700, IIA vs. IIA_M: 141 vs. 164, IIB vs. IIB_M: 40 vs. 48, IIIB vs. IIIB_M: 9 vs. 10) of the SEER dataset (IA vs. IA_M: 1592 vs. 462, IB vs. IB_M: 222 vs. 1244, IIA vs. IIA_M: 98 vs. 197, IIB vs. IIB_M: 26 vs. 35, IIIB vs. IIIB_M: 6 vs. 6). Moreover, the survival rates of patients with different TNM stages also exhibited different degrees of change before and after correction. In the multicenter test cohort, the 5-year OS rates of patients with stage IA, IB, IIA, IIB and IIIB disease were 97.96%, 96.26%, 92.71%, 83.17%, and 74.07%, respectively. After correction, the 5-year OS rates of patients with IA_M, IB_M, IIA_M, IIB_M and IIIB_M were 98.22%, 97.12%, 93.64%, 78.04% and 74.07%, respectively. In the SEER test cohort, the 5-year OS rates of patients with stage IA, IB, IIA, IIB and IIIB disease were 73.62%, 61.90%, 50.33%, 60.00%, and 16.67%, respectively, and those of patients with stage IA_M, IB_M, IIA_M, IIB_M and IIIB_M disease were 79.38%, 70.79%, 55.57%, 49.67% and 16.67%, respectively (Figure 4E and F). The results showed varying increases in the 5-year OS rates for patients with stage IA, IB, and IIA after model adjustment, whereas stages IIB and IIIB show varying decreases in 5-year OS.

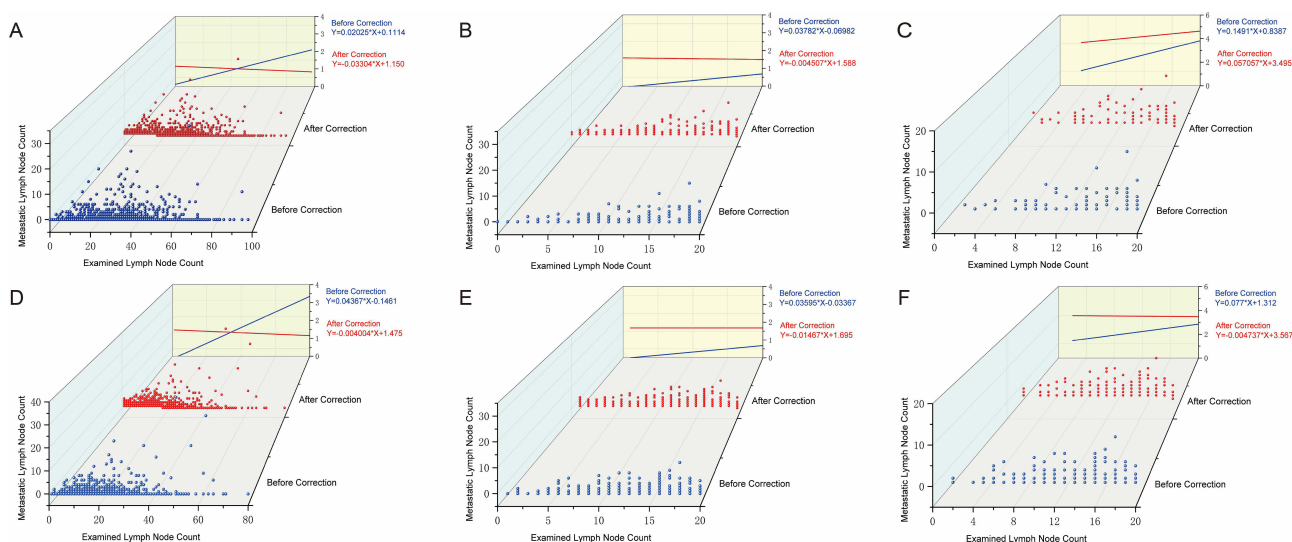


Figure 3 The correlation between the counts of ELNs and MLNs of EGC patients: **(A)** shows total EGC patients in multicenter test cohort; **(B)** shows EGC patients with LNM in multicenter test cohort; **(C)** shows EGC patients with LNM and ELN ≤ 20 in multicenter test cohort; **(D)** shows total EGC patients in SEER test cohort; **(E)** shows EGC patients with LNM in SEER test cohort; **(F)** shows EGC patients with LNM and ELN ≤ 20 in SEER test cohort.

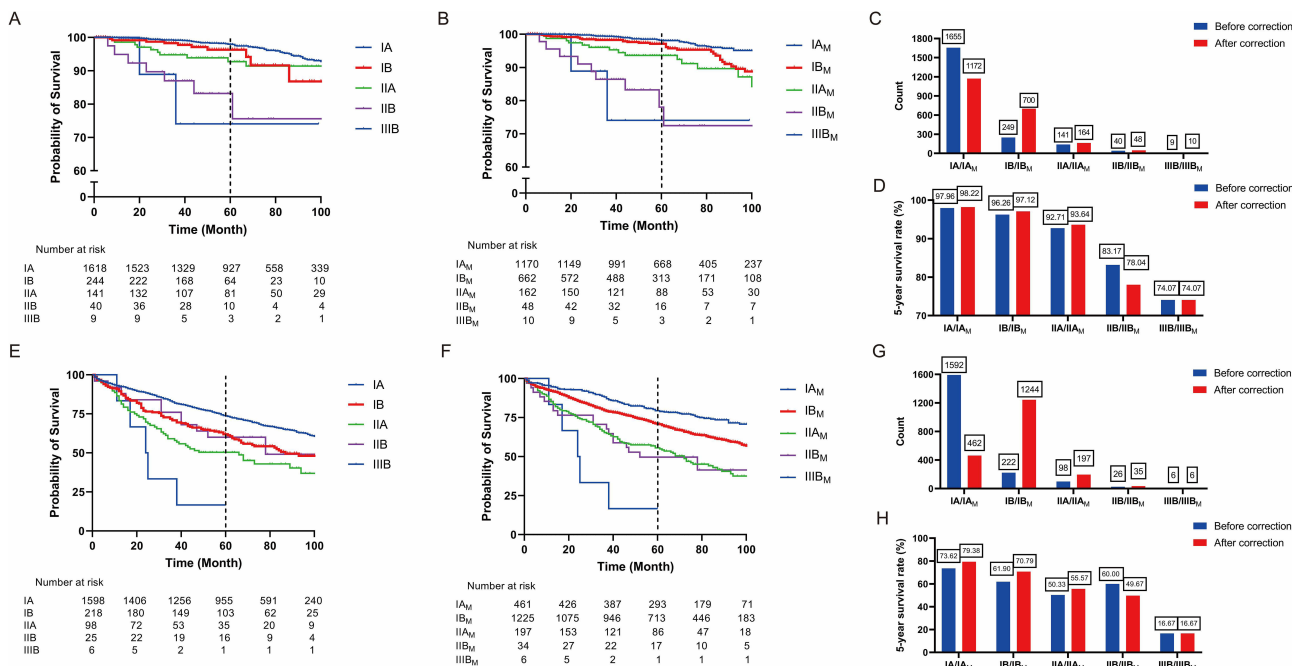


Figure 4 Survival analysis in test cohorts: **(A)** Kaplan-Meier curves of EGC patients with different 8th AJCC staging groups in multicenter test cohort; **(B)** Kaplan-Meier curves of EGC patients with different modified staging groups in multicenter test cohort; **(C)** Bar chart of the number of EGC patients in different stages before and after correction in multicenter test cohort; **(D)** The bar chart of 5-year survival rate of EGC patients with different stages before and after correction in multicenter test cohort; **(E)** Kaplan-Meier curves of EGC patients with different 8th AJCC staging groups in SEER test cohort; **(F)** Kaplan-Meier curves of EGC patients with different modified staging groups in SEER test cohort; **(G)** Bar chart of the number of EGC patients in different stages before and after correction in SEER test cohort; **(H)** The bar chart of 5-year survival rate of EGC patients with different stages before and after correction in SEER test cohort.

Finally, we performed Cox regression analysis of the different grouping methods, including grouping by pN stage according to the AJCC guidelines and pN_M stage, to identify the best grouping method for predicting survival efficacy. Cox regression analysis of the AIC, BIC, and $-2\log$ -likelihood values revealed that the pN_M stage had lower AIC, BIC, and $-2\log$ -likelihood values than did the pN stage in both the multicenter cohort (AIC, pN stage vs. pN_M stage = 486.13 vs. 484.04; BIC, pN stage vs. pN_M stage = 487.93 vs. 485.84; $-2\log$ -likelihood value, pN stage vs. pN_M stage = 484.12

Table 2 Prognostic Performance of Different LN Staging System in Test Cohorts

Characteristics	Multicenter Test Cohort				SEER Test Cohort			
	AIC	BIC	-2log-Likelihood value	Likelihood-Ratio χ^2 (P value)	AIC	BIC	-2log-Likelihood value	Likelihood-Ratio χ^2 (P value)
pN stage	486.13	487.93	484.12	66.54 (P<0.001)	10,257.93	10,262.50	10,255.93	55.76 (P<0.001)
pN _M stage	484.04	485.84	482.04	27.30 (P<0.001)	10,229.10	10,233.67	10,227.10	70.75 (P<0.001)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

vs. 482.04; all $P<0.0001$) and the SEER cohort (AIC, pN stage vs. pN_M stage = 10,257.93 vs. 10,229.10; BIC, pN stage vs. pN_M stage = 10,262.50 vs. 10,233.67; -2log-likelihood value, pN stage vs. pN_M stage = 10,255.93 vs. 10,227.10; all $P<0.0001$) (Table 2). Therefore, we considered that the pN_M stage had better discrimination ability than the pN stage given the evident improvement in the accuracy of the prognostic prediction of patients with EGC.

Discussion

LNM can strongly affect the prognosis of patients with GC. Currently, this has become an important topic in the field of GC that cannot be ignored, especially when EGC is considered by most people to be a curable malignant disease.^{18,19} Studies have shown that in patients with EGC, the 5-year and 10-year survival rates of patients who undergo gastrectomy and extended (D2) LN dissection are 2–3% greater than those of patients who undergo localized (D1) LN dissection.²⁰ Hence, ensuring an adequate number of ELNs in EGC patients, determining the presence of LNM, and accurately assessing the number of MLNs are crucial for evaluating postoperative pTNM stage and prognosis. Based on the analysis of a large-scale multicenter cohort of EGC patients in China, we developed a LNM prediction model and validated it across Eastern and Western populations, showing its potential cross-ethnic applicability. We further propose a novel LN staging system based on the 8th edition AJCC guidelines, which may offer improved staging accuracy and prognostic stratification capacity compared with the current AJCC pN system, thereby potentially enhancing precision management for EGC.

Previous studies have shown that insufficient ELNs may lead to evaluation bias in pN staging,^{15,16} but there is no standard definition of sufficient ELNs in EGC. Based on large-scale data analysis, this study determined that 20 ELNs serves as the optimal cut-off value for assessing LNM risk in EGC which was greater than the 16 in patients with GC.¹⁶ Considering that patients with EGC had fewer MLNs than did those with GC, more ELNs were needed to ensure the detection of MLNs, which was also in line with this trend. Then, we analyzed the clinicopathological data of 6566 EGC patients from fifteen medical centers in South and North China, which represented the basic disease information and general therapeutic level of EGC in China. We found that sex, tumor location, tumor size, differentiation type, pT stage, and lymphovascular invasion were important risk factors for LNM in patients with EGC. These results were also consistent with those of other small-scale studies.^{21–23} Additionally, this study suggests for the first time that insufficient ELNs represent a critical independent risk factor for LNM. This result has also been confirmed in ANN analysis. Given the better performance of the logistic algorithm in our comparative assessment, we finally chose to build the prediction model using logistic regression.

Based on the independent risk factors included in the above analysis, we recognized that patients with an adequate number of ELNs were more likely to develop LNM, which also meant that patients with insufficient ELNs had more undetected potential MLNs. An incorrect metastatic LN count will lead to pN and even pTNM stage migration directly, ultimately leading to incorrect survival expectations.^{16,24,25} This view has been proposed as early as in previous studies, but there is no complete data to support this phenomenon in patients with EGC. Therefore, we constructed an LNM prediction model and observed its good predictive performance through a highly representative high-capacity data cohort. Based on the logistic regression model, we calculated the expected LNM probability, identified the MLNs in the potential unexamined LNs, and finally obtained the pN_M staging. To test the performance of the model and pN_M staging, we fitted a multicenter validation database with survival data from China and the SEER database, which cover the EGC patients in Eastern and Western countries to a great extent, respectively. In different validation cohorts, it was shown that EGC

patients with < 20 ELNs had worse survival, which also showed that insufficient ELNs could be used as an important prognostic factor. Comparatively, the corrected pN_M classification proposed in this study had considerable resemblance to the pN classification proposed by the 8th edition of the AJCC guidelines, with the exception that patients with < 20 ELNs were promoted to one higher nodal class. In fact, this change had a great impact on the evaluation of the patients' prognosis. The use of pN_M staging method appeared to better reflect the survival differences of patients with different stages than pN classification, which was reflected in both the multicenter test cohort and the SEER test cohort. This suggests that even if there are differences in patient characteristics and survival outcomes between the Chinese and SEER datasets, the proposed classification method may be applicable to EGC patients in different populations, although further validation is needed.

Moreover, we found that the number of MLNs in patients with EGC was positively associated with the number of ELNs, and this trend was not obvious after model correction. This difference was more significant in the subgroup. When the condition was limited to patients with insufficient ELNs and those with PLN_M, the number of MLNs increased after model correction than before and does not change significantly or even tends to be stable with the change of ELN. This suggests that the calibration model might help identify more MLNs and obtain more accurate pN_M staging. Compared with that of patients in the normal pN category, the OS distribution of EGC patients in each subgroup (N_{0M} , N_{1M} , and $N_{2M}+N_{3M}$) in the pN_M category was more distinct, and the overall number of MLNs was more stable, which indicated that the pN_M category had improved discrimination and homogeneity in this dataset. Finally, we used multiple indices, including the likelihood ratio test, AIC, and BIC, to evaluate and compare the prognostic value of different LN staging systems. After comparison, this staging method showed better model fit than the 8th edition of AJCC classification guidelines in both populations, suggesting potential clinical utility. Therefore, this model could be more effective and widely used in the clinic, such as in areas where high-quality gastrectomy cannot be effectively performed ($ELNs \leq 20$) or where resources are limited, as it may provide more accurate individualized staging and OS prediction. However, given its model-derived nature, prospective validation in independent cohorts is required before routine clinical adoption.

Although this study has potential clinical value, several limitations should be acknowledged. First, the prediction model was developed based on a Chinese multicenter dataset, which may have resulted in incomplete inclusion of relevant variables. Second, given the relatively small number of EGC patients and the long study period required to accrue sufficient cases, temporal heterogeneity in surgical techniques and perioperative management may have influenced the results. Third, it is difficult to achieve full consistency between the variables in the multicenter validation cohort and those in the SEER database. Although the trends of the results are similar, independent external validation is still necessary. Next, we plan to collaborate with more medical centers worldwide to further refine the model and confirm the robustness of our findings using large, diverse populations with adequate variable information. The ultimate goal is to provide additional reference for future updates of the AJCC staging guidelines and potentially inform amendments to the pN staging criteria.

Conclusion

In conclusion, this study suggests that insufficient ELNs are an important contributor to LNM in patients with EGC. Through the development of a prediction model and reclassification of EGC patients with fewer than 20 ELNs, a new pN_M category is proposed as a model-derived correction, which may reduce staging migration and could improve survival outcome accuracy. Our findings were generally validated in large datasets from both Eastern and Western populations, but given the estimated nature of the correction, further external validation is needed before confirming broad clinical applicability.

Data Sharing Statement

Due to ethical restrictions, the raw data cannot be made publicly available. However, de-identified data may be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The experiments related to human specimens were performed according to the Institutional Research Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) (Ethics Approval License: bc2022220).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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