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Establishment and verification of a nomogram for predicting the risk of lymph node metastasis in early gastric cancer

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ABSTRACT

Background: endoscopic submucosal dissection (ESD) has been widely recognized by patients and doctors due to its advantages in early gastric cancer (EGC). The accurate prediction of the risk of lymph node metastasis (LNM) in EGC is important to select suitable treatments with this procedure for patients. Unfortunately, the accuracy of endoscopic ultrasound and computed tomography in the diagnosis of EGC lymph node status is extremely limited. The purpose of the present study was to establish an LNM nomogram risk model of early gastric cancer patients based on clinical data, to guide treatment for clinicians.

Methods: a retrospective examination of the records of EGC patients undergoing radical gastrectomy from August 2012 to August 2019 in the Gastrointestinal Center of Subei People's Hospital was performed. The clinicopathological data were classified into a training set and validation set according to the time. Univariate and

multivariate analyses were performed to identify risk factors related to LNM. A risk model for predicting the occurrence of LNM in EGC was established and validated.

Results: of the 503 EGC patients, 78 (15.5 %) had lymph node metastasis. Logistic stepwise regression analysis showed that the predictive factors included sex, tumor location, tumor diameter, differentiation, ulcer and lymphatic vascular invasion. The discrimination of the LNM prediction model was satisfactory with an AUC of 0.8033 (internal validation) and 0.7353 (external validation). The correction effect of the calibration was satisfactory and the DCA decision curve analysis showed a strong clinical practicability.

Conclusion: the nomogram risk prediction model of LNM has been established for EGC patients to assist in formulating personalized treatment plans.

Keywords: Early gastric cancer. Lymph node metastasis. Predictive model.

INTRODUCTION

Early gastric cancer is defined as a tumor limited to the gastric mucosa or submucosa, regardless of the lymph node metastasis. With the rapid development of endoscopic technology, the detection rate of early gastric cancer has reached 50 % in Asian countries such as Japan and South Korea (1). Meanwhile, endoscopic mucosal resection (ESD) has been generally used for the treatment of early gastric cancer in Asia. The fifth edition of the guidelines for the treatment of gastric cancer (2) highlighted that differentiated early gastric cancer with a diameter of less than 2 cm, no ulcer and a lymph node metastasis risk less than 1 % is the main indication for ESD treatment. Furthermore, the extended-indication includes an undifferentiated tumor less than 2 cm or differentiated tumor less than 3 cm. Although the enlarged indication still lacks long-term evidence of efficacy, the idea that patients with a high risk of lymph node metastasis should not accept ESD treatment has become the consensus of academia. Moreover, long-term follow-up of EGC patients showed that the three year overall survival rate of patients without lymph node metastasis (LNM) was better than that of patients with LNM (6). Given the fact that the incidence of lymph nodes in early gastric cancer (EGC) patients is

about 11-20 % (3-5) and LNM is an important prognostic risk factor for EGC, the involvement of lymph node metastasis should be given more attention when determining the surgical strategies for EGC patients.

Regretfully, current auxiliary examinations, both preoperative imaging and endoscopic examination, have a small impact on evaluating lymph node metastasis. Thus, affecting the choice of treatment strategy adversely. The accurate prediction of the risk of LNM in EGC becomes essential. Some studies have retrospectively analyzed the risk factors of lymph node metastasis in patients with EGC (7,8), such as age, tumor diameter, degree of differentiation, vascular invasion and so on. A few studies have established prediction models for LNM in EGC patients (9), but they tend to be unpersuasive as they are limited to single-centers and lack comprehensive internal and external validation. The conclusions drawn were different and controversial based on the data collected from a variety of regions. Thus, the purpose of our research was to determine the predictive factors of LNM and to construct a risk prediction model. It is expected that this model will be able to help surgeons choose the appropriate treatment based on the quantified estimation of LNM risk, rather than relying experience. Furthermore, the benefit of endoscopic treatment will be ensured, while minimizing the risk.

METHODS

Patients

The study included 2,512 patients who underwent radical resection of gastric cancer in the Northern Jiangsu People's Hospital. The inclusion criteria were as follows: a) gastric carcinoma confirmed by histopathology; b) gastrectomy with lymphadenectomy; and c) complete clinicopathological data. Patients with stage II, III and IV disease (n = 2,001) and patients who were pathologically confirmed as stump cancer (n = 1), metastasis (n = 3), as well as those who received neoadjuvant chemotherapy (n = 4), were excluded.

Patients were screened according to the scheme shown in figure 1 and the final study cohort was composed of 503 patients with EGC from 2012 to 2018, including 363 cases in the training set and 140 cases in the validation set. An additional 162

EGC patients who underwent a radical resection of gastric cancer from 2017 to 2018 were selected as an external validation set (Fig. 1).

The clinical baseline information was retrieved from medical records and pathological reports of each patient. Clinicopathological factors included age, sex, tumor location, histological type, ulcer, tumor size, degree of differentiation, depth of invasion and lymphovascular invasion. The clinical staging was determined by the American Joint Committee on Cancer (AJCC) 8th Edition (10) and the tumor location was classified into the upper, middle or lower third of the stomach. The ulcer was classified into an ulcerative type and non-ulcerative type by endoscopy and postoperative gross specimens. Histological types of tumors were defined by the Japanese gastric cancer and the World Health Organization gastric cancer classification (11). The differentiated type included well, moderately and poorly differentiated adenocarcinoma.

Statistical analysis

Statistics were analyzed using R version 3.5.6 (R Foundation for Statistics Computing), Stata 15.0 for Windows (StataCorp Texas, USA) and SPSS25.0. Continuous variables were transformed into categorical variables by SPSS visual box. Univariate logistic regression analysis was used to assess the relationship between clinicopathological factors and LNM. Independent risk factors of LNM were identified using multivariate logical regression analysis with a bilateral p-value < 0.2 (12). A nomogram that incorporated the significant factors related to LNM was developed to calculate the probability of LNM using R version 3.6.0 (RMS software package [13] in http://www.R-Project.org/). The likelihood ratio test was used in the forward step-by-step selection and the information criterion of Akaike was used as the stopping rule for final model selection. The discrimination was quantified by area under the curve (ROC) analysis. A larger AUC value implies a more accurate prognosis and an AUC of 1.0 indicates a good fit, whereas an AUC of 0.5 indicates no relationship. The calibration curve was evaluated by the U test, which uses the “rms” package. The decision curve analysis was performed to determine the clinical practicability of the nomogram diagram via quantification of the net income, under

different threshold probabilities in the validation data set. All statistical tests were two-sided and $p < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological characteristics

Among the 2,512 patients with gastric cancer included in the current study, the incidence of LNM was 20.02 %. In the training set of 363 EGC patients, 61 cases (15.5 %) of lymph node metastasis were confirmed by pathology. The distributions of N stage were as follow: 38 (62.3 %) patients were N1, 14 (23.0 %) patients were N2, eight (13.1 %) patients were N3a and one (1.6 %) patient was N3b. Among the 61 LNM-positive patients, 34 were males (55.7 %) and 27 were females (44.3 %), with 26 cases (42.6 %) over 63 years of age and 35 cases (57.4 %) under 63 years. The lesions were located in the lower part of the stomach in 37 (60.7 %) cases and 45 cases (73.8 %) showed ulcerative lesions. Undifferentiated EGC was present in more than half of the LNM positive patients. The distribution of tumor size were: 42.6 % (26 cases) less than 2 cm, 19.7 % (12 cases) were between 2.1 and 3.0 cm and 37.7 % (23 cases) were over 3 cm. In terms of depth of invasion, the number of patients with submucosal carcinoma, lymphatic vascular infiltration and nerve infiltration was 56 (91.8 %), 19 (31.1 %) and six (9.8 %), respectively.

According to the univariate analysis, sex, tumor size, depth of invasion, ulcer, differentiation, vascular invasion and nerve invasion were significantly correlated with LNM (all with $p < 0.05$), whereas age ($p = 0.40$), histomorphology ($p = 0.27$) and the number of lymph nodes in the biopsy ($p = 0.12$) were not related to LNM (Table 1).

Further multivariate logistic regression analysis with positive, backward and stepwise methods showed that gender, tumor location, tumor size, ulcer, differentiation and vascular invasion were independent risk factors for LNM. Simultaneously, the depth of tumor invasion, nerve invasion and lymph node biopsy were eliminated (Table 2). The above six predictors were chosen for the subsequent logistic regression model and the LNM risk prediction nomogram is

shown in figure 2.

Model validating and clinical practicability

To evaluate and verify the risk prediction model, data from 2017 to 2018 was designed for internal validation. The sensitivity and specificity were evaluated by the AUROC and calibration, and the clinical practicability was tested by DCA. The area under the characteristic curve of this model was 0.803 (95 % CI, 0.773-0.879). The U index in the calibration curve representing the bias between the predicted value and the measured value was -0.006, and the S p-value was 0.975, indicating a good concordance between the predicted and actual outcomes (Fig. 3).

DISCUSSION

With the advancement of diagnostic techniques, the diagnostic rate of early EGC has gradually increased. The rate of lymph node metastasis in EGC is reported to be approximately 11-20 %. Recently, less invasive treatments such as endoscopic mucosal resection have been performed for EGC in Asia (14). Compared with traditional surgery, ESD is appealing to both surgeons and patients due to less trauma, a faster recovery, better tolerance and rendering a good mental quality of postoperative life. However, the indications are strict. At present, the debate about the endoscopic treatment of EGC mainly revolves around the indication of ESD (15). Without lymph node metastasis: a) differentiated intramucosal carcinoma without an ulcer (cT1a); b) size ≤ 3 cm, differentiated intramucosal carcinoma with an ulcer (cT1a); c) high-grade intraepithelial neoplasia; and d) enlarged indication: undifferentiated intramucosal carcinoma with a lesion size ≤ 2 cm and no ulcer. In any case, the accurate evaluation of preoperative LNM is the key to treatment. However, the current laboratory and imaging examinations are extremely limited in the accuracy of LNM evaluation and clinicians look for ways to analyze and identify the risk factors of LNM in patients with EGC.

Previous studies have shown that (16) LNM is closely related to age, sex, tumor diameter and differentiation. Our study showed that there was no significant difference in age distribution in LNM, but Gu et al. reported that LNM was

correlated with age (17) and the most susceptible age range was between 50 and 60 years (35 %). Chen L et al. (18) performed a retrospective study of the risk factors of LNM in patients with early gastric cancer. The results also indicated that age ≥ 41 years old, tumor diameter ≥ 3 cm, poor differentiation and lymphatic vascular invasion (LVI) were more likely to be associated with LNM. On the contrary, some other studies have suggested that age was not a risk factor for LNM (19). Above all, it is generally considered that geographical distribution differences may have an effect. In terms of gender, we found that males had a higher LNM incidence rate than females. This is consistent with the findings of Fang (20) and others, showing there was a remarkable difference in LNM occurrence between males and females.

Most previous studies suggested that LVI was an independent risk factor for LNM. Along with the infiltration of the lymphatic network, the lymph node metastasis rate increased significantly. The results of this study also showed that LVI is a risk factor for LNM ($p < 0.001$) and it is included in the prediction model of LNM. The study by Hanada et al. of 176 cases of pT1 gastric cancer also showed that submucosal invasion and LVI were independent risk factors for lymph node metastasis. However, Pyo JH et al. (21) recently reported that patients with LVI who meet the criteria for endoscopic resection had not developed LNM. Specifically, there was no significant difference between these patients and LVI-negative EGC patients in terms of overall ($p > 0.05$) and disease-specific survival ($p > 0.05$), but the results needed to be supported by more clinical data.

At present, most studies divide tumor location into the upper, middle and lower third of the stomach. The univariate results of this study suggested that LNM may be more likely to occur in the lower part of the stomach, which may be related to the common occurrence of undifferentiated ulcer infiltrating carcinoma or submucosal carcinoma and vascular invasion in the antrum. It may also be related to the fact that some early cardiac cancers treated by endoscopic mucosal resection are not included in this study. It was supported by Li et al. (22), indicating that gastric antrum is one of the risk factors for LNM. Kang DH et al. (23) found that the upper stomach is one of the risk factors for LNM as there are more lymphatic capillaries in the submucous layer of the upper stomach. The above results

suggested that the value of tumor location in lymph node metastasis may be affected by the characteristics of patients collected by the research institutions, which needs further support from multicenter and large samples.

Whether ulcer is a risk factor for LNM is controversial. The results of this research indicated that an ulcer is a factor related with LNM in early gastric cancer. Lee YJ (24) found that 343 patients (71.7 %) had endoscopic EGC ulcers via a retrospective analysis of EGC patients. The study showed that the rate of LNM was significantly increased in ulcerative EGC compared with non-ulcerative EGC. According to the results of Xu C et al. (25), the presence and the size of ulcers may be a potential predictor of LNM in patients with gastric cancer.

However, these studies have exposed the shortcomings of the instability to predict LNM. In other words, it is very difficult for clinicians to assess the occurrence of individual LNM comprehensively and accurately and physicians rely more on personal experience to assess LNM. In this study, sex, tumor diameter, tumor location, differentiation, LVI and ulcers were important factors to predict the occurrence of LNM. Interestingly, the results of this study showed that the depth of tumor invasion is not a risk factor for LNM in EG. This is not completely consistent with the previous perception that the risk of lymph node metastasis increased with tumor invasion to the submucosa. The following reasons must be taken into account: a) a low number of cases included in this study may cause bias in the final results; and b) the detection of LNM in EGC is affected by intraoperative lymph node dissection, pathological detection methods and the pathologists' experience after surgery, which may lead to the occurrence of false-negative LNM and affect the results. However, it was also found in a recent retrospective study that 16 patients who underwent ESD were diagnosed as T1b (26). Eventually, just one case developed LNM, which may indicate the feasibility of tumor invasion to the submucosa as an extended indication for ESD. Obviously, we cannot draw this conclusion without more substantiating data.

Based on six risk factors, we established a risk model for predicting LNM and visualizing it by a nomogram. An internal and external validation of the data proved that the model has a good accuracy, stability and clinical practicability. Therefore,

this risk score model has certain value for predicting the LNM of patients with EGC. Thus, helping to more accurately and effectively evaluate the lymph node metastasis of EGC, standardize the indications of endoscopic treatment of EGC and improve the effect of individualized treatment.

At the same time, this study also had some limitations. First, this study is a retrospective study and the level of evidence needs further improvement. Second, although this study was validated internally and externally, a larger-scale prospective dataset is needed to improve the stability and applicability of the model.

CONCLUSION

This study identified the risk factors of LNM in EGC and established a risk prediction model of LNM. This model can potentially improve the prediction of LNM in patients with EGC so that a quantified estimation of risk can be made before surgery rather than relying solely on personal experience. More importantly, it can help standardize the endoscopic treatment of early gastric cancer and better guide the scientific and personalized clinical decision making for EGC patients.

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Table 1. Univariate analysis of clinicopathological factors

		Training set			*Validating set*		
		(n = 363, 2012-2016)				(n = 140, 2017-201	
Factor	Level	LNM (-)	LNM (+)	p-value	LNM (-)	LNM (+)	p-valu
N		302	61		123	17	
Sex							
	Male	226 (74.8 %)	34 (55.7 %)	0.005	97 (78.9 %)	10 (58.8 %)	0.12
	Female	76 (25.2 %)	27 (44.3 %)		26 (21.1 %)	7 (41.2 %)	
Age							
	≤ 63	155 (51.3 %)	35 (57.4 %)	0.40	48 (39.0 %)	10 (58.8 %)	0.19
	> 63	147 (48.7 %)	26 (42.6 %)		75 (61.0 %)	7 (41.2 %)	
Tumor location							
	Upper	104 (34.4 %)	10 (16.4 %)	< 0.001	57 (46.3 %)	3 (17.6 %)	0.071
	Middle	114 (37.7 %)	14 (23.0 %)		34 (27.6 %)	7 (41.2 %)	
	Lower	84 (27.8 %)	37 (60.7 %)		32 (26.0 %)	7 (41.2 %)	
pT							
	T1a	64 (21.2 %)	5 (8.2 %)	0.019	27 (22.0 %)	2 (11.8 %)	0.52
	T1b	238 (78.8 %)	56 (91.8 %)		96 (78.0 %)	15 (88.2 %)	
pN							
	N0	302 (100.0 %)	0 (0.0 %)	< 0.001	123 (100.0 %)	0 (0.0 %)	< 0.0

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			38			14	
	N1	0 (0.0 %)	(62.3 %)		0 (0.0 %)	(82.4 %)	
			14				
	N2	0 (0.0 %)	(23.0 %)		0 (0.0 %)	3 (17.6 %)	
			8				
	N3a	0 (0.0 %)	(13.1 %)		0 (0.0 %)	0 (0.0 %)	
	N3b	0 (0.0 %)	1 (1.6 %)		0 (0.0 %)	0 (0.0 %)	
Tumor size							
		182	26				
	≤ 2	(60.3 %)	(42.6 %)	0.033	52 (42.3 %)	8 (47.1 %)	1.00
			12				
	2~3	46 (15.2 %)	(19.7 %)		38 (30.9 %)	5 (29.4 %)	
			23				
	> 3	74 (24.5 %)	(37.7 %)		33 (26.8 %)	4 (23.5 %)	
Histologic morphology							
		250	46		109	16	
	Adenocarcinoma	(82.8 %)	(75.4 %)	0.27	(88.6 %)	(94.1 %)	1.00
	Signet-ring cell	21 (7.0 %)	6 (9.8 %)		4 (3.3 %)	0 (0.0 %)	
			8				
	Mixed	30 (9.9 %)	(13.1 %)		7 (5.7 %)	1 (5.9 %)	
	Others	1 (0.3 %)	1 (1.6 %)		3 (2.4 %)	0 (0.0 %)	
Differentiation							
	Well	43 (14.2 %)	1 (1.6 %)	< 0.001	20 (16.3 %)	0 (0.0 %)	< 0.00
		162	26				
	Moderate	(53.6 %)	(42.6 %)		77 (62.6 %)	5 (29.4 %)	
			34			12	
	Poor	97 (32.1 %)	(55.7 %)		26 (21.1 %)	(70.6 %)	
LVI							
	No	270	42	< 0.001	112	14	0.38

	(89.4 %)	(68.9 %)	(91.1 %)	(82.4 %)

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		270 (89.4 %)	42 (68.9 %)		112 (91.1 %)	14 (82.4 %)	
	Yes	32 (10.6 %)	19 (31.1 %)		11 (8.9 %)	3 (17.6 %)	
NI							
	No	291 (96.4 %)	55 (90.2 %)	0.048	122 (99.2 %)	16 (94.1 %)	0.23
	Yes	11 (3.6 %)	6 (9.8 %)		1 (0.8 %)	1 (5.9 %)	
NELN							
	≤ 13	126 (41.7 %)	17 (27.9 %)	0.12	62 (50.4 %)	2 (11.8 %)	0.006
	14~20	87 (28.8 %)	21 (34.4 %)		38 (30.9 %)	9 (52.9 %)	
	≥ 21	89 (29.5 %)	23 (37.7 %)		23 (18.7 %)	6 (35.3 %)	
Ulcer							
	No	35 (11.6 %)	16 (26.2 %)	0.005	37 (30.1 %)	5 (29.4 %)	1.00
	Yes	267 (88.4 %)	45 (73.8 %)		86 (69.9 %)	12 (70.6 %)	

LNM: lymph node metastasis; LVI: lymphovascular invasion; NI: neural invasion; NELN: number of examined lymph nodes.

Table 2. Multiple analysis of clinicopathological factors

LNM	Coef.	Std. Err	z	p > z	95 % CI	
Differentiation	0.634	0.264	2.400	0.017	0.116	1.152
LVI	1.141	0.373	3.060	0.002	0.410	1.872
Sex	0.790	0.324	2.440	0.015	0.155	1.426
Tumor location	0.862	0.219	3.940	0.000	0.433	1.291
Tumor size	0.287	0.173	1.660	0.097	-0.052	0.626
Ulcer	-1.378	0.406	-3.400	0.001	-2.173	-0.583
Cons	-5.669	0.962	-5.890	0.000	-7.553	-3.784

LNM: lymph node metastasis; LVI: lymphatic vascular invasion; Cons: constants; Coef: coefficient; CI: confidence interval; Std. Err: standard error.

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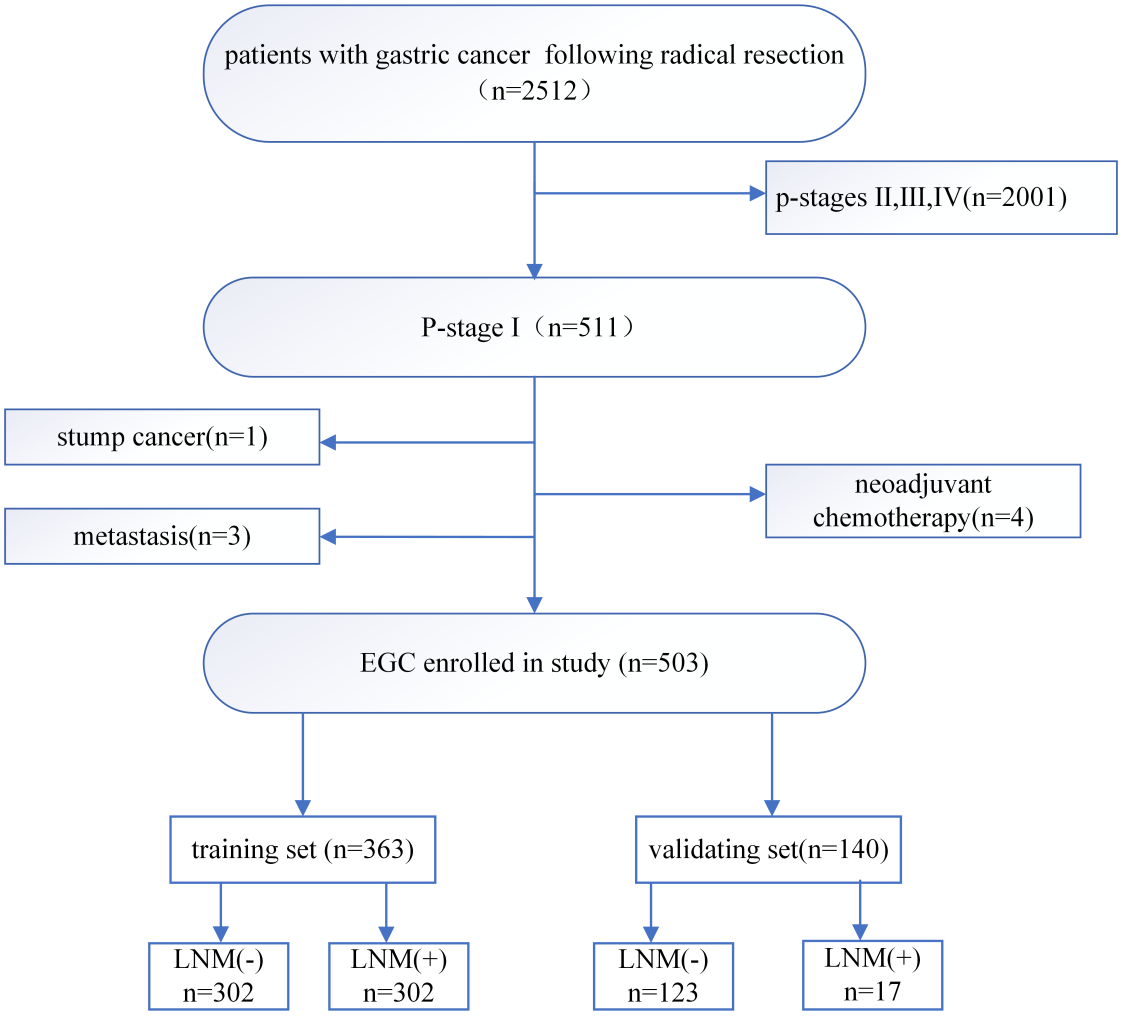

Fig. 1. Division of patient cohorts based on LNM.

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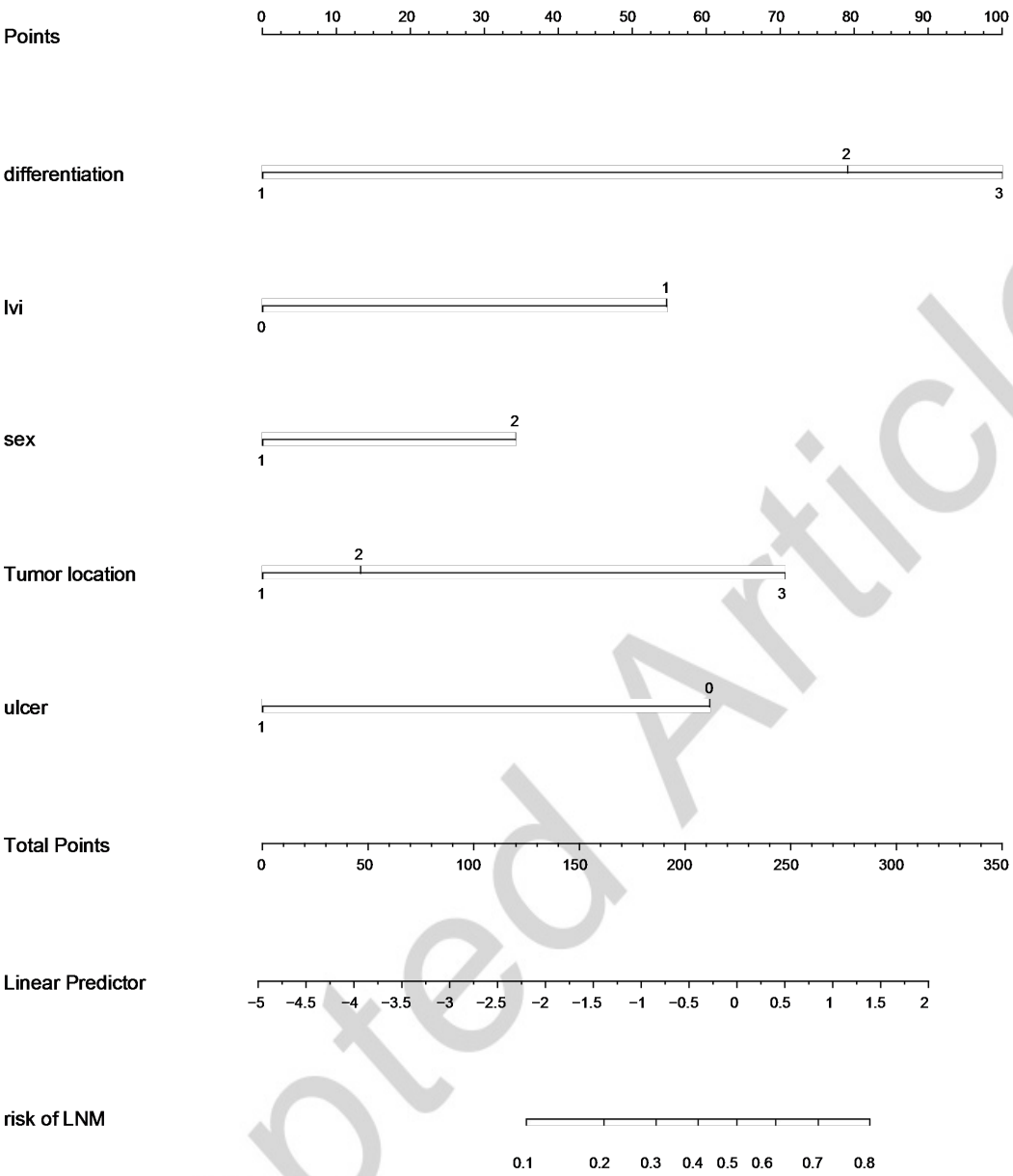

Fig. 2. Nomogram for forecasting the risk of lymph node metastasis in patients with EGC.

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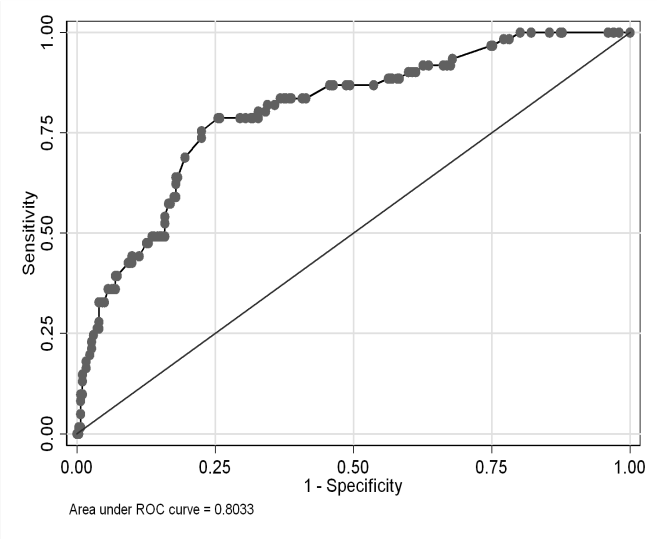
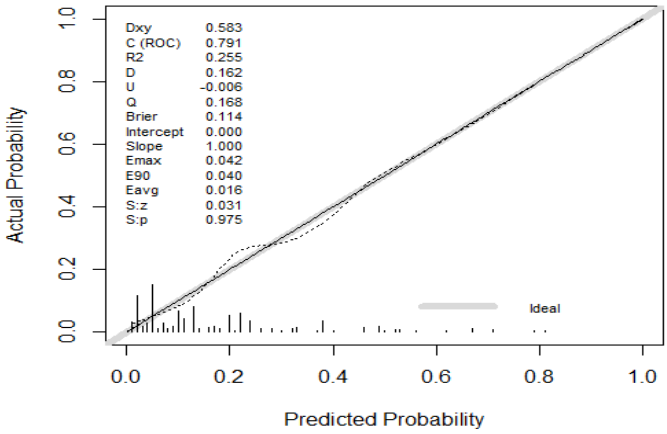
The Spanish Journal of Gastroenterology

A.



B.



C.

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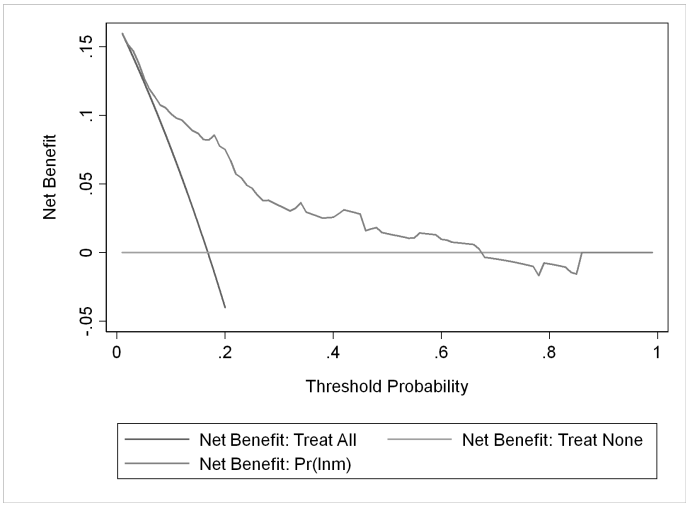

Fig. 3. Validation of the model. A. ROC plot: the ROC plot demonstrated that the area under the curve was 0.8033. B. Calibration plot: the solid line lay close to the dashed line (the ideal reference line), which demonstrated a well agreement between the predicted and actual results. C. DCA (decision curve analysis): the y-axis represents net benefits, calculated by subtracting the relative harms (false positives) from the benefits (true positives). The x-axis calculates the threshold probability.