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Original Article

Application of a nomogram in detection of lymph node metastases in T1 colorectal cancer

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Abstract: Objective: The aim of this study was to establish a simple nomogram as a reference measure to predict lymph node metastases (LNM) in stage T1 colorectal cancer patients, ultimately aiding in the development of treatment strategies. Materials and methods: This study retrospectively analyzed 19,238 patients with pathological stage $T_1N_{any}M_0$ colorectal cancer who underwent surgical resection from 1998 to 2011 according to the Surveillance Epidemiology and End Results (SEER) database. Clinicopathological risk factors of LNM were identified by univariate and multivariate logistic regression analyses. A nomogram to predict the probability of LNM for T1 colorectal cancer was developed from the multivariate logistic regression model. Results: In total, 14.4% of the T1 colorectal cancer patients had pathological LNM. The multivariate analysis indicated that independent risk factors for LNM included the patient's age (P<0.001), race (P<0.001), tumor site (P<0.001), grade (P<0.001), histological differentiation and tumor size (P<0.001). A nomogram consisting of these six factors was developed and predicted the LNM status with a concordance index (c-index) of 0.66. The nomogram showed a good calibration with a 200 bootstrapping corrected c-index of 0.66. Conclusion: A nomogram based on patient's age, race, tumor site, grade, and tumor size is a useful tool to predict the LNM status of T1 colorectal cancer patients.

Keywords: Colorectal cancer, lymph node metastasis, risk factors, nomogram

Introduction

Accurate assessment of loco-regional nodal status is crucial when planning different therapeutic strategies for early stage colorectal cancer. T1-stage colorectal cancers without lymph node disease can be safely removed by local excision. Local excision has reduced postoperative morbidity and mortality rates and better preserves the anal sphincter, bladder, bowel and sexual function compared with traditional abdominal resection [1, 2]. However, one of the drawbacks associated with local excision for colorectal cancer is the poor oncological outcome. The local recurrence or metastatic rate after T1 colon and rectal cancer local excision is approximately 2.3% [3]. One possibility accounting for the high local failure and poor survival rate is regional lymph node metastasis [LNM], which cannot be detected by imaging or be removed surgically. Therefore, accurate preoperative staging plays a crucial role in selecting patients who are candidates for local excision. Unfortunately, current radiological techniques only have accuracy rates ranging from 53% to 85% in N staging [4-7]. The aims of this study were to investigate the potential risk factors for LNM, to construct a nomogram model to predict the probability of LNM in T1 colorectal cancer patients and to help to determine individually tailored regimens for each early stage colorectal cancer patient.

Patients and methods

T1-stage colorectal cancer patients with a confirmed pathological diagnosis who underwent surgical resection (tumors were confined to the submucosa) from 1998 to 2011 were identified using the Surveillance Epidemiology and End Results (SEER) database and included in this study. The following inclusion criteria were

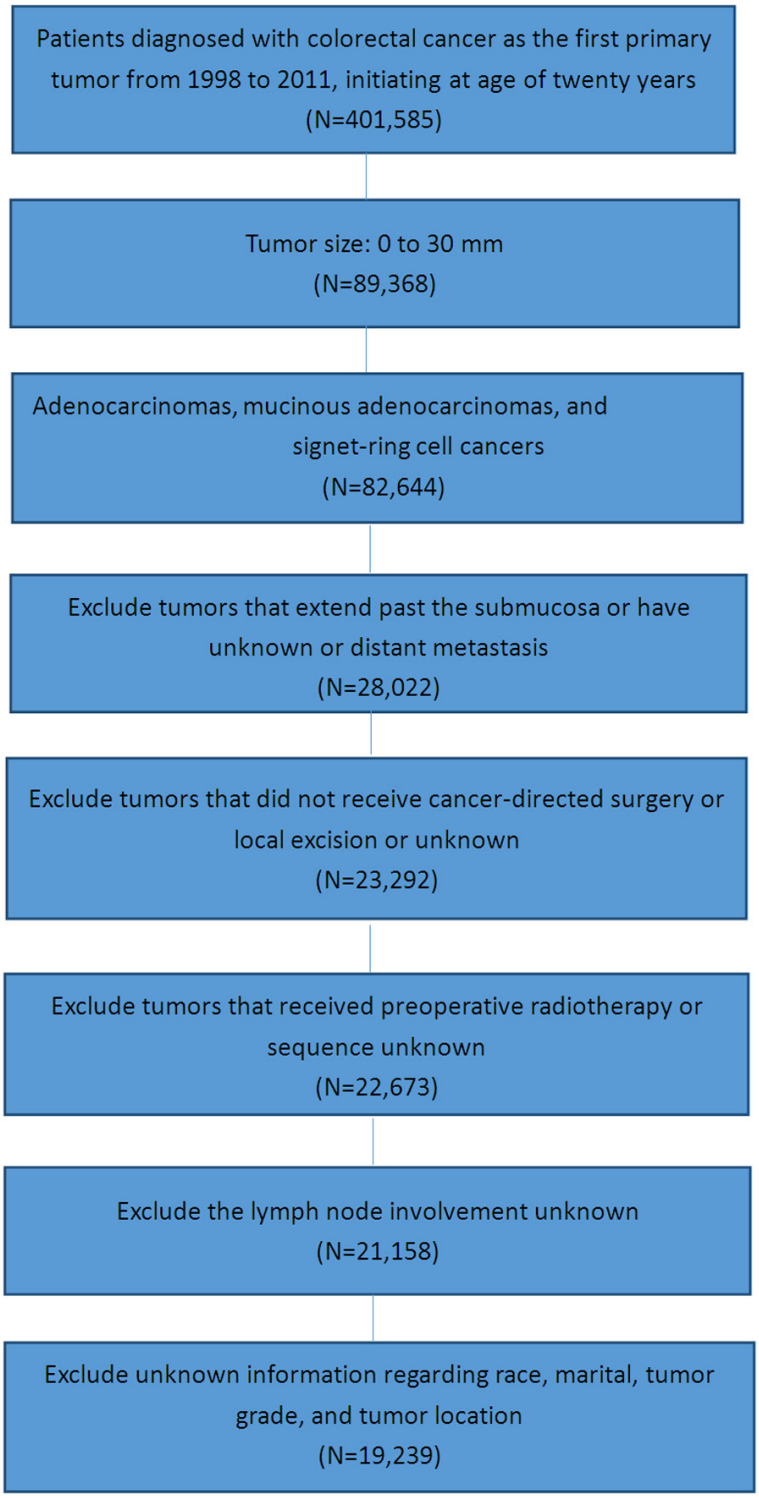

Figure 1. Selection chart for data creation from the SEER database.

employed (**Figure 1**): (1) tumors removed by surgical resection; (2) tumors diagnosed as adenocarcinoma, mucinous adenocarcinoma or signet-ring cell adenocarcinoma by postoperative pathology with corresponding ICD-10 codes [adenocarcinoma (8010, 8020-8022, 8140-8141, 8144-8145, 8210-8211, 8220-8221, 8230-8231, 8260-8263), mucinous adenocarcinoma (8470, 8472-8473, 8480-8481), signet ring cell carcinoma (8490)]; and (3) complete medical data including the patient's age and race, gender, marital status, tumor site, tumor size, differentiation, the status of lymph node involvement, and follow-up period data. The exclusion criteria included the following: (1) preoperative radiotherapy; (2) no cancer-directed surgery and local excision only; or (3) presence of non-first-tumors and synchronous distant metastases. This study was approved by the institutional ethics review board of Shanghai Electric Power Hospital, Shanghai, China. In total, 19,238 colorectal cancer patients were eligible for analysis.

Statistical analysis

All included patients were randomly divided into two cohorts (**Table 1**), a training set (two thirds, n = 12,825 [67%]) and an external validation set (one-thirds, n = 6,413 [33%]). Clinicopathological variables included the patient's age, gender, race, and marital status, tumor site, tumor size, histology and differentiation. These covariates were analyzed for correlations with LNM by univariate analysis of Chi-square method, and a multivariate logistic regression model was applied to multivariate analysis. Only statistically significant ($P<0.05$) factors were used to construct the final nomogram model, which was used to calculate the individual probability of having

Table 1. General clinicopathological description of included patients

Characteristics	Training set	External validation set
	N = 12,825 (100%)	N = 6,413 (100%)
Age (yr)		
20-34	74 (1)	31 (0%)
35-49	834 (7)	(421, 7%)
50-74	7760 (61)	(3895, 61%)
≥75	(4157, 32%)	(2066, 32%)
Mean (SD)		
Gender		
Male	(6574, 51%)	(3293, 51%)
Female	(6251, 49%)	(3120, 49%)
Race		
White	(10584, 83%)	(5226, 81%)
Black	(1146, 9%)	(591, 9%)
Other*	(1095, 9%)	(596, 9%)
Marital		
Single	(1281, 10%)	(619, 10%)
Separated/divorced	(1053, 8%)	(513, 8%)
Widowed	(2317, 18%)	(1158, 18%)
Married	(8174, 64%)	(4123, 64%)
Primary site		
Proximal colon	(5334, 42%)	(2617, 41%)
Distal colon	(4297, 34%)	(2167, 34%)
Rectum	(3194, 25%)	(1629, 25%)
Tumor size (mm)		
0-9	(2378, 19%)	(1160, 18%)
10-20	(5855, 46%)	(2945, 46%)
21-30	(4592, 36%)	(2308, 36%)
Histologital type		
AC	(12197, 95%)	(6097, 95%)
MAC	(582, 5%)	(300, 5%)
SRC	(46, 0%)	(16, 0%)
Grade		
I	(2328, 18%)	(1105, 17%)
II	(9249, 72%)	(4659, 73%)
III	(1189, 9%)	(620, 10%)
IV	(59, 0%)	(29, 0%)
No. of LNs dissected		
<12	(7290, 57%)	(3706, 58%)
≥12	(5535, 43%)	(2707, 42%)
LN+		
Positive	(1864, 15%)	(898, 14%)
Negative	(10,961, 85%)	(5,515, 86%)

Abbreviations: AC = regular adenocarcinomas; MAC = mucinous adenocarcinomas; SRC = signet-ring cell carcinomas. *American Indian/AK Native, Asian/Pacific Island.

lymph node metastasis by assigning a corresponding point total to each patient.

Nomogram validation was constructed using two components, discrimination and calibration. The implication of discrimination was assessed by determining the c-index, which is similar to the area under the ROC curve (AUC). A good prediction model is always accompanied by a c-index>0.5, and a c-index ≤0.5 indicates no predictive or anti-prediction ability. We used 200 bootstrapping to obtain a corrected c-index to detect whether the model overfit the data and generated 95% confidence interval (CI) of c-index. Calibration was assessed by calculating the Hosmer-Lemeshow goodness of fit test (H-L test) and visualizing the agreement between true probabilities and predicted frequencies (validation graphs). External validation was also evaluated by a separated data set. Finally, we divided the training cohort into five risk groups according to quartiles of total score assigned per patient: group 1 (<68.5); group 2 (68.51-98.25); group 3 (98.26-115.00); group 4 (115.01-154.25); and group 5 (>154.25). All analyses were performed using R statistical software version 3.1.3 (http://www.R-project.org) with rms and other libraries.

Results

Univariate analysis and multivariate analysis of LNM risk factors

As indicated in **Table 2**, age (P<0.001), race (P<0.001), marital status (P<0.001), histology differentiation (P<0.001), grade (P<0.001), tumor site (P<0.001), and tumor size (P<0.001) were significantly related to LNM in the univariate analysis. No association was observed between LNM and gender (P = 0.7977). Multivariate analysis based on a training set revealed that the patient's age (P<0.001), race (P<0.001), grade (P<0.001), histology differentiation (P<0.001), tumor site (P<0.001) and tumor size (P<0.001) were independent LNM risk factors (**Table 2**).

Table 2. Univariate and multivariate analysis of clinical variables correlated with LNM in the training set

	Univariate*		Multivariate†	
	LNM%	*p*-value	OR (95% CI)	*p*-value
Age (yr)		<0.001		<0.001
20-34	18		1.41 (0.76, 2.62)	0.276
35-49	24		2.13 (1.75, 2.58)	<0.001
50-74	15		1.38 (1.23, 1.56)	<0.001
≥75	11		Ref.	-
Gender		0.7977	-	-
Male	15		-	-
Female	14		-	-
Race		<0.001	-	<0.001
White	14		0.74 (0.63, 0.88)	0.937
Black	17		Ref.	-
Other#	19		0.99 (0.79, 1.24)	0.937
Marital		<0.001		
Single	14		-	-
Separated/divorced	15		-	-
Widowed	12		-	-
Married	15		-	-
Primary site		<0.001		<0.001
Proximal colon	10		0.62 (0.55, 0.7)	<0.001
Distal colon	16		Ref.	
Rectum	20		1.15 (1.02, 1.3)	0.025
Tumor size (mm)		<0.001		<0.001
0-9	1		Ref.	
10-20	14		1.64 (1.4, 1.92)	
21-30	17		1.32 (1.13, 1.54)	
Histologital type		<0.001		
AC	14		Ref.	-
MAC	18		1.54 (1.23, 1.93)	<0.001
SRC	40		2.68 (1.45, 4.96)	0.002
Grade		<0.001		<0.001
I	6.7		Ref.	-
II	15		2.2 (1.85, 2.62)	<0.001
III	29		5.04 (4.08, 6.24)	<0.001
IV	27		4.91 (2.69, 8.95)	<0.001

*Pearson's chi-square method; †logistic regression analysis. #American Indian/AK Native, Asian/Pacific Island.

A nomogram to predict LNM probability

A nomogram was developed based on the multivariate logistic regression model (**Figure 2**). Nomogram performance was evaluated by discrimination and calibration analyses. Harrell's concordance index (c-index) was used to assess the nomogram discrimination. Bootstrap corrected c-index of the model were 0.66 with 95% CI (0.65-0.68) in the training dataset, 0.67 with 95% CI (0.68-0.69) in the external validation dataset, indicating potentially promising predictive nomogram power. The calibration graph (**Figure 3**) presents the actual and predicted rates of having LNM (calibration). The nomogram exhibited good performance because the calibration curve was very close to the 45-degree line, which represents an ideal agreement that the model would perfectly predict the real event. The Hosmer-Lemeshow test also demonstrated that the model has a satisfied goodness of fit with a 9.1 chi-square value (*p*-value = 0.34). We further divided patients into five risk groups according to the four thresholds, which were determined by quartiles of total risk score of LNM (**Table 3**): group 1 (<68.50), group 2 (68.51-98.25), group 3 (98.26-115.00), group 4 (115.01-154.25) and group 5 (>154.25). These results show a significantly increased possibility of LNM (training set: 7.3%, 12%, 16%, 21%, and 34%, respectively; validation set:7.4%, 14%, 14%, 21%, and 31%, respectively) and significantly increased adverse 5-year survival rate (training set: 94.2%, 92.4%, 93.9%, 93.0%, and 90.5%, respectively; validation set: 93.9%, 91.2%, 94.4%, 92.3%, and 87.1%, respectively) (**Figures 2** and **4**).

Discussion

Local excision has advantages, such as a lower rate of postoperative complications, quicker recovery period, preservation of anal function and a better quality of life; therefore, this method is recommended for several colorectal cancer patients during early stages. However, LNM occurs in approximately 6.5% to 18% of T1 and 17% to 38% of T2 colorectal cancer cases [8-11]. Therefore, determining the status of regional lymph nodes for colorectal cancer patients is necessary because colorectal can-

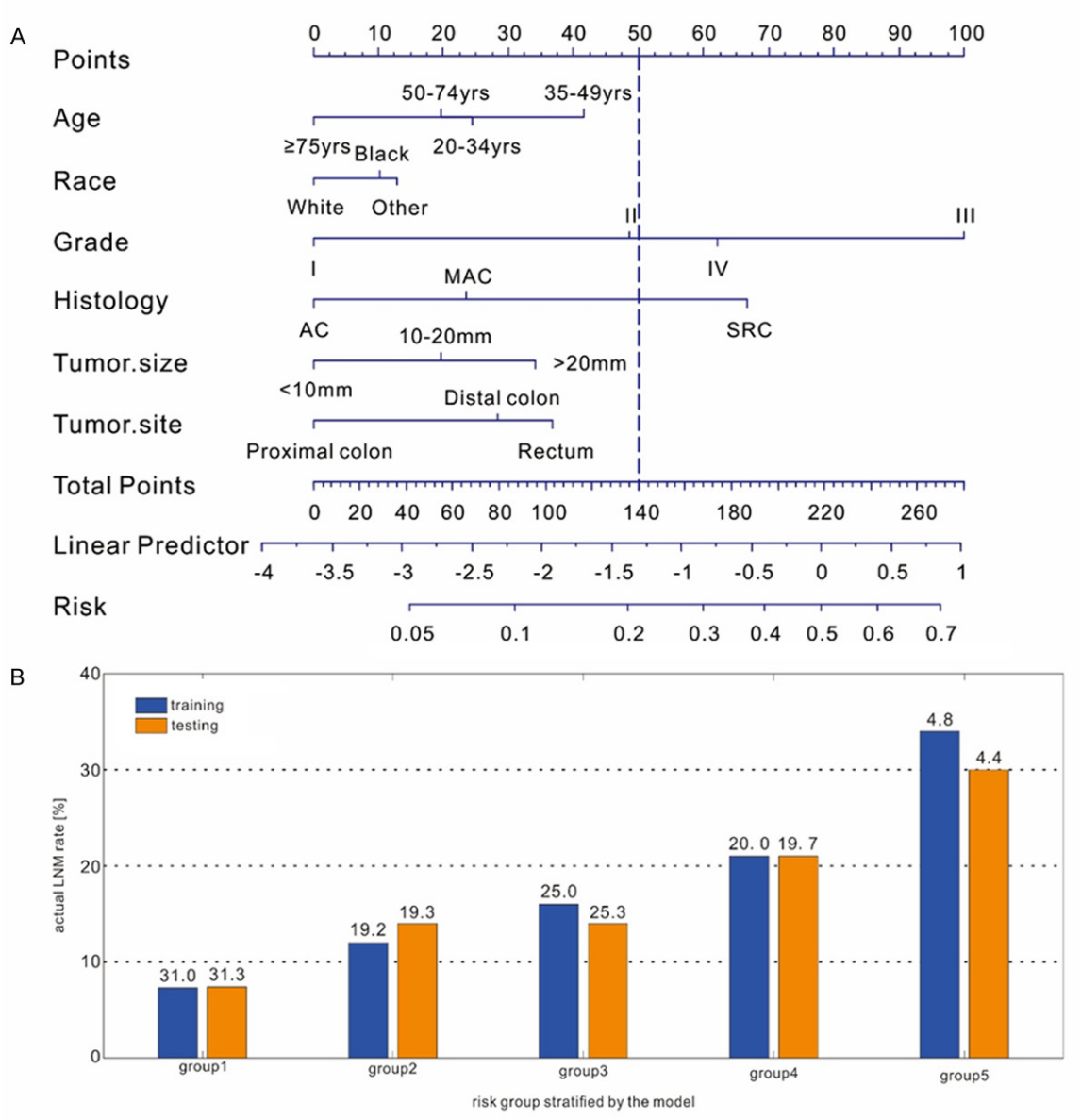

Figure 2. A. Nomogram predicting the LNM based on multivariate logistic regression. B. Actual LNM rates in training and validation in five risk groups predicted from the model: group 1 (<68.50), group 2 (68.51-98.25), group 3 (98.26-115.00), group 4 (115.01-154.25) and group 5 (>154.25). The corresponding number of patients (%) per group is also indicated above the bars.

cer local excision does not remove the regional lymph nodes. In addition, the residual metastatic lymph nodes may have a postoperative recurrence. In recent years, radiological modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and endorectal ultrasound (ERUS), perform a crucial role in preoperative staging of colorectal cancer. CT scans are the major imaging technique utilized for the local staging of colorectal cancer; however, this method has limitations due to low sensitivity and specificity. Transrectal ultrasound (TRUS) and MRI are the principal staging tools used for the assessment of preoperative staging. According to most published studies, preoperative MRI demonstrates 65% to 91% agreement with histopathological findings in the prediction of correct T stages [12]. However, MRI performance is relatively poor in determining N stage with an accuracy of 43% to 85% because this technique is incapable of detecting tumorous involvement in lymph

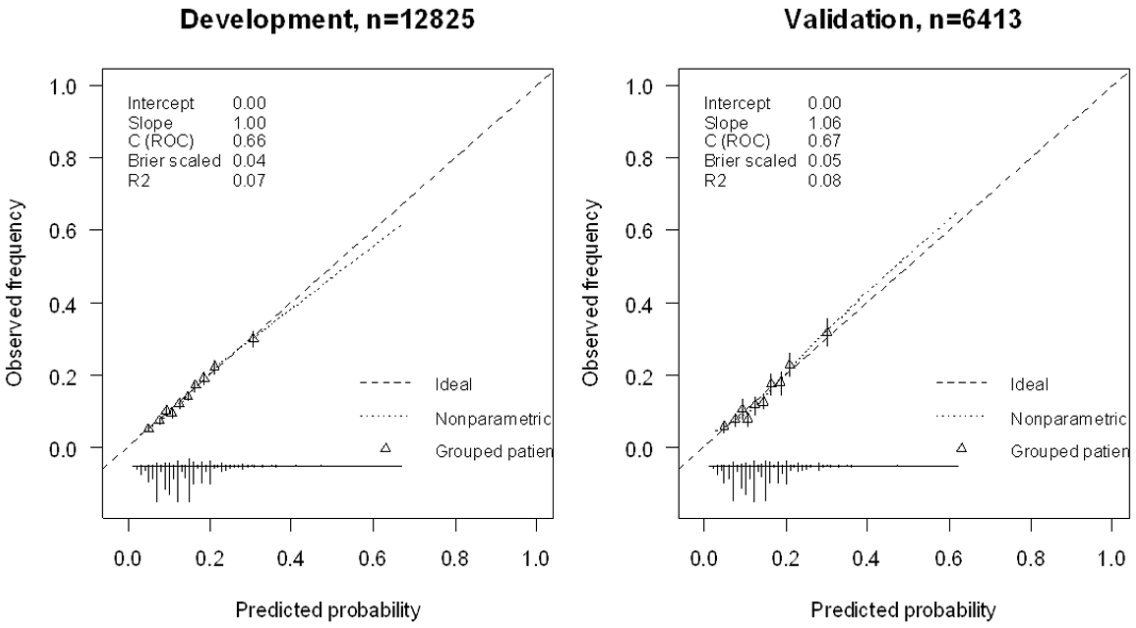

Figure 3. Validation graphs of the prediction model.

nodes less than 3 mm. Many lymph nodes (~20%) measuring<3 mm in size are affected by the tumor [13, 14]. Although TRUS has better accuracy in N staging (62% to 87%) compared with MRI [14, 15], this technique also has multiple drawbacks. TRUS can neither provide a sufficient wide field of view for assessing the involvement of lymph nodes nor pass through a stenotic intestinal cavity caused by the tumor. Current imaging modalities are inadequate to define metastatic lymph nodes. A local excision can be introduced to patients without preoperative imaging-based evidence of regional LNM or strong recurrence risk factors. The purpose of our study was to establish a simple and complementary tool based on clinicopathological parameters to predict the status of regional lymph nodes for T1 colorectal cancer patients.

Nomograms have been widely used for predicting the risk and prognosis in colorectal, breast and urinary tumors [16, 17]. Our nomogram based on 6 clinicopathological parameters (age, race, grade, histology, tumor site, and tumor size) displays accepted discrimination (c-index = 0.66) and calibration values (**Figure 2**). Physicians can calculate a total score according to the parameters of this nomogram, which can then be used to value the probability of LNM for individual patients corresponding to the scale at the bottom of **Figure 2**.

The present study demonstrated that the grade was a significant independent predictor for LNM in T1 colorectal cancer, which is in accordance with previous reports [11]. Of the above 6 risk factors, grade was the strongest predictor correlated with LNM, with an odds ratio (OR) of 2.20 to 5.04 (P<0.001). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) and the National Comprehensive Cancer Network (NCCN) identify the well/moderately differentiated or papillary histologic grade as one criterion predicting positive outcomes of endoscopic resection of T1 colorectal carcinoma [18, 19].

The patient's age is also associated with LNM, and younger patients are more likely to have an incidence of lymph node positivity [20, 21]. Sitzler and colleagues reported that in patients less than 45 years old, the percentage of lymph node involvement was 33.3% and 30% compared with 3.1% and 8.4% in patients aged 45 years or above for pT1 and pT2 tumors, respectively [22]. Our research also demonstrated that patients younger than 50 exhibit a significantly increased risk of LNM compared with patients older than 50 (P<0.001).

Signet-ring cell cancers (SRC) and mucinous adenocarcinomas (MAC) are two rare entities that differ from conventional adenocarcinomas and account for approximately 0.1% to 25.4%

Table 3. Score assignment and LNM risk score

	Score	Estimated risk of LNM%
Age (yr)		
20-34	43.75	
35-49	44	
50-74	21	
≥75	0	
Race		
White	0	
Black	13.75	
Other#	15	
Primary site		
Proximal colon	0	
Distal colon	35	
Rectum	35	
Tumor size (mm)		
0-9	0	
10-20	16	
21-30	32.5	
Histologital type		
AC	0	
MAC	18.25	
SRC	62.5	
Grade		
I	0	
II	47.5	
III	100	
IV	62.5	
Total LNM score		
<68.50		7.3
68.51-98.25		12
98.26-115.00		16
115.01-154.25		21
>154.25		34

of primary colorectal cancers [23, 24]. Histology is a well-known factor for predicting the postoperative prognosis of colorectal cancer; however, in contrast to TNM staging and grade differentiation, histology is not incorporated into the present grading system. JSCCR recommends considering histology and grade differentiation together and proposes that T1 colorectal cancers with poorly differentiated, SRC or MAC should not be treated endoscopically. In our study, histology was the second strongest independent predictive LNM factor.

Six studies have analyzed tumor location using as a LNM predictive factor, and they found rectum tumors to have a higher LNM rate compared with the colon [25-30]. Our study also observed that the incidence of LNM increased as the tumor location becomes distal (proximal: 10%; distal colon 16%; rectum 20%). The data were also consistent with previous genetic studies, which attributed this phenomenon to intrinsic tumor biology variation, increased MSI (microsatellite instability) in proximal colon lesions and the diploid status of these tumors. In contrast, tumors in the rectum are typically accompanied by a high rate of MSS (microsatellite stability), aneuploidy and chromosomal deletions and p53 mutations [11, 31, 32].

Several studies have been conducted to evaluate predictive LNM factors; however, few studies have explored the total risk using known risk factors. Our nomogram can estimate the probability of LNM after integrating a variety of risk factors. When stratifying patients into five risk groups of LNM, the actual risk of LNM increases, and the 5-year survival rate decreases. The nomogram model is very important to the assessment of risk of recurrence for patients before and after local treatment. We suggest that radical resection is essential for those assessment results with a high risk of recurrence.

To our knowledge, our research, which is based on a population cohort, is the only and largest study combining multiple clinicopathological variables to predict regional lymph node metastasis. Our methods provide 65% to 68% accuracy at detecting LNM incidence, offer helpful supplemental information for assisting individual management and reduce the number of patients undergoing overtreatment of surgical resection, especially for elderly patients with concurrent comorbidity.

This study includes several limitations and strengths. First, interestingly, when stratifying the T1 into sm1 (upper 1/3), sm2 (middle 1/3) and sm3 (lower 1/3), similar results were observed. Nascimbeni et al. analyzed 353 patients and found that the probabilities of LNM in sm1, sm2, and sm3 were 2%, 9% and 35%, respectively [33]. The subclassification of depth needs further in-depth research. However, the application of three levels of submucosa is difficult because local excision specimens do not include muscularis propria, and we do not currently have sm1/2/3 data. Second, the lymphovascular invasion (LVI) and perineural invasion (PNI) status of the tumor are not easily detected preoperatively in biop-

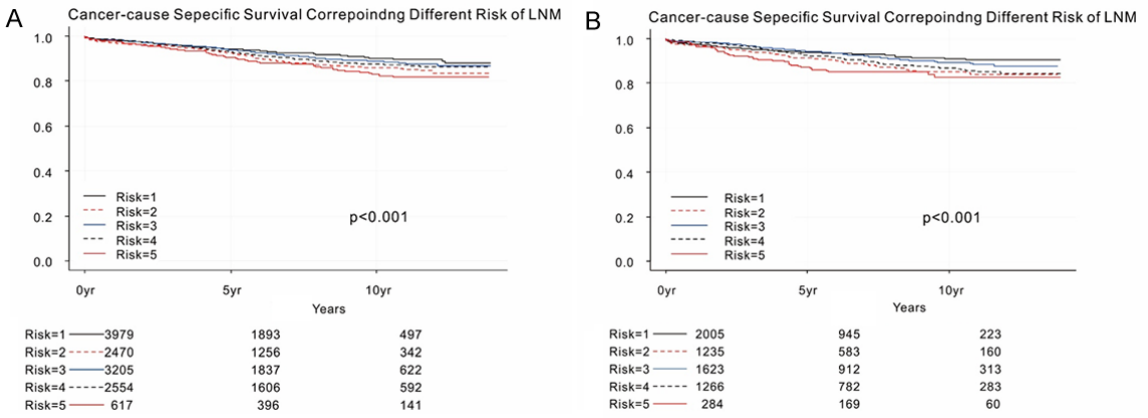

Figure 4. K-P curve of training set (A) and testing set (B) corresponding to group 1 (<68.50), group 2 (68.51-98.25), group 3 (98.26-115.00), group 4 (115.01-154.25) and group 5 (>154.25).

sies; therefore, those parameters were not included in our study. Third, the SEER database was constructed using U.S. patients; therefore, the model can be adjusted after integrating other races.

In summary, the patient's age, race, tumor grade, histology, tumor site and tumor size are independent LNM risk factors. Our data suggest that the probability of LNM in T1 colorectal cancer patients can be evaluated using a nomogram consisting of these simple clinicopathological parameters with acceptable discrimination and calibration.

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Disclosure of conflict of interest

None.

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