Establishment of Lymph Node Metastasis Prediction Model For T1a Gastric Cancer

Zhi Zeng (miracle1116@126.com)
Qingdao University Medical College
ZHAN SHI
Zhejiang Chinese Medical University
YANG LIU
Qingdao University Medical College
JUNJUN ZHAO
Bengbu Medical College
QILIANG LU
Qingdao University Medical College
LINJUN HU
Qingdao University Medical College
YULING GAO
shao xing shi fu you bao jian yuan: Shaoxing Women and Children's Hospital
ZUNQIANG XIAO
Zhejiang Chinese Medical University
DONGSHENG HUANG
Zhejiang Provincial People's Hospital
QIURAN XU
Zhejiang Provincial People's Hospital

Research

Keywords: gastric cancer, lymph node metastasis, nomogram, endoscopic resection, bioinformatics

Posted Date: January 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-147565/v1

Abstract

Background and Aims: Endoscopic resection has been widely used in the treatment of early gastric cancer recent tears. For patients undergoing endoscopic resection, lymph node metastasis is an important prognostic factor. Thus, we built a model to predict the likelihood of lymph node metastasis in early gastric cancer.

Methods: Data of 789 gastric cancer patients were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. We picked several variables and chi-square analysis was used to come up with statistically significant factors. Then, we used these factors to build a nomogram predicting the lymph node metastasis risk in T1a gastric cancer. Finally, we evaluated this nomogram using C-index, ROC curve and DCA.

Results: We built a nomogram based on four factors. The C-index of this nomogram was 0.750. The AUC value of ROC curve for this nomogram was 0.750. DCA showed that it would be beneficial to use this nomogram if the threshold probability was between 0.01 and 0.41.

Conclusion: This study built a nomogram to predicted the lymph node metastasis risk in T1a gastric cancer based on four factors. Upon evaluation, this nomogram has a good ability of predicting the risk of lymph node metastasis.

Introduction

Gastric cancer is a malignant tumor originate from gastric epithelium. It is the sixth most common cancer and its mortality ranks second among all cancers globally (1). East Asia, including China, Japan and Korea, has a high incidence of gastric cancer (1).

Murakami firstly defined early gastric cancer (EGC) as the tumor limited to mucosa and submucosa of the stomach, regardless of tumor size or lymph node metastasis (2)(3). However, this definition has been controversial (4, 5). Saragoni suggested that gastric cancer with lesions that are confined to the mucosa or invade minimally the submucosa and without lymph node metastasis was defined as EGC (5). Such staging allows for more appropriate treatment, especially endoscopic resection in gastric cancer. Generally speaking, a standard gastrectomy, including the resection of more than two thirds of stomach and a D2 lymph node dissection, is the major treatment method for EGC and advanced gastric cancer (AGC) (2). However, gastrectomy is always related with long hospital stay and high complication rate (6). This can also lead to poor quality of life for patients (7). Compared with gastrectomy, endoscopic resection, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), had no significant difference in overall survival and fewer complications (8, 9). Among them, ESD has better efficacy, but it is difficult to operate (10–12). Endoscopic resection has been widely used in the treatment of EGC in many areas (13, 14). Japanese gastric cancer treatment guidelines suggested that, for those gastric cancers with a low possibility of lymph node metastasis, EMR or ESD would be a better choice (15). In this guideline, the absolute indication for EMR/ESD is “A differentiated-type

adenocarcinoma without ulcerative findings [UL (−)], of which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤ 2 cm". Besides, there are three expanded indications for ESD: Tumors clinically diagnosed as T1a and (1) Of differentiated-type, UL (−), but > 2 cm in diameter. (2) Of differentiated-type, UL (+), and ≤ 3 cm in diameter. (3) Of undifferentiated-type, UL (−), and ≤ 2 cm in diameter. So far, endoscopic resection has been widely performed on the patients with EGC worldwide.

For patients with EGC who undergo EMR/ESD, lymph node metastasis is an important prognostic factor (16–18). So, before performing EMR/ESD, we should make sure that the patient has a low possibility of lymph node metastasis. According to Japanese gastric cancer treatment guidelines, the object of our study was confined in patients with T1a gastric cancer. In this study, using the Surveillance, Epidemiology, and End Results (SEER) database, we screened several important factors (Sex, Race, Age, Primary site, Tumor size, Grade and Histologic type) and used these factors to build a model to predict the likelihood of lymph node metastasis in EGC.

Material And Methods

Data on gastric cancer patients were collected from SEER database (http://seer.cancer.gov/), including the information of sex, age, race, primary site, tumor size, grade, 7th Edition T stage of The American Joint Committee on Cancer (AJCC), histologic type and regional nodes positive. Selection criteria: 1) All data have detailed 7th Edition T stage classified by AJCC and are clinically diagnosed as T1a; 2) All data have detailed ICD-O-3 histologic type; 3) All data have lymph node information. Exclusion criteria 1): unknown age; 2) unknown sex; 3) unknown race; 4) unknown histologic type; 5) unknown tumor size; 6) unknown grade; 7) unknown detailed primary site; 8) no lymph node resection.

Variables classification

Sex was classified into 2 groups: male and female. Age was classified into 3 groups: ≤40, 40-64, ≥65. Race was classified into 3 groups: black, white and others. Primary site was classified into 4 groups: upper 1/3, middle 1/3, lower 1/3 and others; Tumor size was classified into 4 groups: ≤1, 1-2, 2-3 and ≥3; Grade was classified into 3 groups: Well differentiated, moderately differentiated and poorly differentiated. Histologic type was classified into 4 groups: adenocarcinoma, intestinal type adenocarcinoma, signet ring cell carcinoma and others.

Statistical analysis

All analyses above were performed using IBM SPSS 25.0 and R software 3.6.2(https://www.r-project.org/).

Chi-square test was used to evaluate the relationship between lymph node metastasis and the above variables (sex, race, age, primary site, tumor size, grade and histologic type) and P-value < 0.05 was viewed to have statistical significance. Multivariable logistic regression analysis was performed to construct a lymph node metastasis prediction model including the variables with a P-value < 0.05. Then,

a nomogram based on the result of logistic regression analysis was constructed. After that, Harrell's concordance index (C-index), Calibration curve and Receiver Operating Characteristic (ROC) curve was used to evaluate the accuracy of the nomogram for lymph node metastasis prediction. Finally, Decision Curve Analysis (DCA) was performed to assess the clinical utility of this nomogram.

Besides, aimed at the expanded indications mentioned in the Japanese gastric cancer treatment guidelines, chi-square analysis was performed to explore whether diameter affects the rate of lymph node metastasis in differentiated gastric cancers and whether differentiation affects the rate of lymph node metastasis in gastric cancers no more than 2 in diameter. [Figure 1]

Results

Patients Characteristics

A total of 164269 cases of gastric cancer were obtained from SEER database. After screening according to the selection criteria and removing the non-conforming cases according to the exclusion criteria, 789 cases were remained [Table 1]. There were 80 positive cases of lymph node metastasis and 709 negative cases of lymph node metastasis.

Establishment of lymph node metastasis prediction model

The result of chi-square analysis showed race, tumor size, grade and histologic type were significantly related to the risk of lymph node metastasis [Table 1]. These four factors were selected to perform multivariable logistic regression analysis [Table 2] and draw Nomogram [Figure 2].

Accuracy test of Nomogram

The calibration curve of lymph node metastasis rate demonstrated a good agreement between our nomogram and the actual situation [Figure 3]. The C-index of our nomogram was 0.750(95CI, 0.695 to 0.805). The ROC curve of nomogram was showed in Figure 4 and the Area Under Curve (AUC) values was 0.750. The result of DCA was showed in Figure 5, showing that it would be beneficial to use this nomogram if the threshold probability was between 0.01 and 0.41.

Evaluation of expanded indications

for differentiated intramucosal gastric cancer, the difference in lymph node metastasis rate between diameter□2cm group and diameter≤2cm group had statistical significance. For intramucosal gastric cancer with diameters no more than 2cm, the difference in lymph node metastasis rate between differentiation group and undifferentiation group didn’t have statistical significance [Table 3].

Disscusion

In the past, a standard gastrectomy, including the resection of more than two thirds of stomach and a D2 lymph node dissection, is the major treatment method for EGC and AGC. But, with the development of endoscopic technique, endoscopic resection, including EMR and ESD, has been widely used in the patients of EGC. Recently, researches have showed that in EGC, there was no significant difference in overall survival between the patients underwent radical gastrectomy and endoscopic resection, although the latter had a higher recurrence rate (8)(9). And the complication rate of endoscopic resection is lower than that of radical gastrectomy (8).

For those EGC patients who underwent endoscopic resection, lymph node metastasis has a significant adverse effect on the prognosis. So, endoscopic resection was suggested to be used in the EGC with a low possibility of lymph node metastasis. In our screened data, the lymph node metastasis rate of T1a gastric cancer is 10.1%, while in all T1a gastric cancer patients in SEER database, this rate is 9.7%. Choi (19) reported that the lymph node metastasis rate of T1a gastric cancer in western population is 7.8%, which is relatively close to our data. But Gotoda (20) suggested the lymph node metastasis rate of intramucosal cancers in the Japanese people is 2.2%. This could be because of ethnic differences, but it could also be because of other factors and all residents over 40 years old in Japan will be screened for gastric cancer (21). Therefore, they can always detect gastric cancer at a very early stage, which may be one of the reasons for its low lymph node metastasis rate. However, even after careful examination, it is still possible to misjudge whether there is lymph node metastasis. A method to predict the rate of lymph node metastasis is needed clinically.

Previous studies have shown that for EGC, age, tumor size, tumor location, ulceration, histological type, grade, macroscopic appearance (Such as ulcer, border, color) and depth of invasion are risk factors of lymph node metastasis (22-25). Especially the depth of invasion is the most critical risk factors. Only patients with T1a gastric cancer, whose depth of invasion is limited to the mucosa are suitable for ESD/EMR treatment in Japanese gastric cancer treatment guidelines. Thus, the object of our study were the patients with T1a gastric cancer. In this study, we selected seven factors (Sex, Race, Age, Primary site, Tumor size, Grade and Histologic type) to study their relationship with lymph node metastasis in EGC. After chi-square analysis, we found that for EGC, four factors (Race, Tumor size, Grade and Histologic type) were significantly related to the risk of lymph node metastasis. By logistic regression analysis, Race, Tumor size and Grade were considered to be the independent factors of lymph node metastasis. EGC with diameter≥3cm or poor differentiation is prone to lymph node metastasis. In addition, blacks and whites are more likely than others to develop lymph node metastasis. Many studies had focused on the lymph node metastasis rate in EGC and its influencing factors, but there is a lack of a suitable method to predict lymph node metastasis of EGC clinically.

Nomogram has been widely used in the prediction of various clinical events. This is the first time a nomogram was used to predict lymph node metastasis in EGC. In this study, we construct a nomogram to directly predict the possibility of lymph node metastasis of EGC in T1a stage based on these four variables (Race, Tumor size, Grade and Histologic type) and the results of C-index, Calibration curve and ROC curve had revealed its great ability of prediction on lymph node metastasis. With this nomogram, we

can calculate the score based on the level of the four variables, and then get the corresponding lymphatic metastasis rate according to the score in clinical practice. For patients with a low risk of lymph node metastasis, endoscopic resection might be a better treatment. In contrast, the patients with a high risk of lymph node metastasis are better candidates for standard gastrectomy or endoscopic resection with laparoscopic lymph node dissection (26).

Conclusion

Through the screening of SEER database, we obtained a large sample of patients with T1a gastric cancer. After analyzing the data, we found that 10% of T1a gastric cancer patients had lymph node metastasis. If ESD/EMR was performed on these patients, the prognosis might may not be ideal. We designed a nomogram to predict the probability of lymph node metastasis to help patients choose surgical methods and decide whether to expand the operation after surgery. We believe that patients with high probability of lymph node metastasis still need standard gastrectomy or endoscopic resection with laparoscopic lymph node dissection.

Besides, we verified two of the expanded indications mentioned in the Japanese guidelines for gastric cancer treatment using the data obtained from SEER database. Through chi-square analysis, we found that for differentiated intramucosal gastric cancer, there is significant difference in lymph node metastasis rate between diameter>2cm group and diameter≤2cm group. But for intramucosal gastric cancer with diameters no more than 2cm, differentiation did not significantly affect the rate of lymphatic metastasis.

There are some limitations in our study. Due to the limited clinical information contained in the SEER database, some risk factors were not included in our study. However, the results of accuracy test show that nomogram based on the existing 4 factors has a good accuracy.

In conclusion, this study constructs a nomogram to help clinicians predict lymph node metastasis rates in EGC patients. Based on the calculated risk of lymph node metastasis, the clinician can choose the appropriate treatment.

Abbreviations

EGC: Early gastric cancer; AGC: Advanced gastric cancer; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; SEER: The Surveillance, Epidemiology, and End Results; AJCC: The American Joint Committee on Cancer; C-index: Harrell's concordance index; ROC: Receiver Operating Characteristic; AUC: Area Under Curve; DCA: Decision Curve Analysis

Declarations

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

All data supporting the findings in our research are available in SEER database (http://seer.cancer.gov/).

Competing interests

All authors declare no competing interests.

Funding

This study was supported by grants from the National Natural Science Foundation of China (81874049, 81672474); the Co-construction of Provincial and Department Project (WKJ-ZJ-1919); the Zhejiang Provincial Natural Science Foundation of China (LY19H160036); Key R&D project of Zhejiang Science and Technology Department(2020C03008)

Authors Contributions: (I) Conception and design: Zhi Zeng and Zhan Shi; (II) Administrative support: Qiuran Xu and Dongsheng Huang; (III) Provision of study materials or patients: Linjun Hu, Qiliang Lu and Yuling Gao; (IV) Collection and assembly of data: Junjun Zhao, Yang Liu and Zunqiang Xiao; (V) Data analysis and interpretation: Zhi Zeng and Zhan Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Acknowledgements

Thank for open access of SEER database.

Authors' information

1. The Medical College of Qingdao University, Qingdao, Shandong 266071, China.

Zhi Zeng; Yang Liu; Qiliang Lu; Linjun Hu

2. Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang 310014, China

Zhi Zeng

3. The Second Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310014, China

Zhan Shi; Zunqiang Xiao

4. Graduate Department, Bengbu Medical College, Bengbu, Anhui 233030, China

Junjun Zhao

5. Department of Genetic laboratory, Shaoxing Women and Children Hospital, Shaoxing, Zhejiang 312030, China

Yuling Gao

6. The Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang 310014, China

Dongsheng Huang; Qiuran Xu

[#]: These authors contributed equally to this work as co-first authors.

Corresponding authors: Qiuran Xu, MD, PHD, Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang 310014, China. Email: windway626@sina.com
Dongsheng Huang, MD, PhD, Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang 310014, China. Email: dshuang@zju.edu.cn

References

1. Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA oncology. 2018;4:1553–68. DOI:10.1001/jamaoncol.2018.2706.
2. Saragoni L, Morgagni P, Gardini A, Marfisi C, Vittimberga G, Garcea D, et al. Early gastric cancer: diagnosis, staging, and clinical impact. Evaluation of 530 patients. New elements for an updated definition and classification. Gastric cancer: official journal of the International Gastric Cancer Association the Japanese Gastric Cancer Association. 2013;16:549–54. DOI:10.1007/s10120-013-0233-2.
3. Murakami T. (1979) Early cancer of the stomach. World journal of surgery;3:685 – 92. DOI: 10.1007/bf01654788.
4. Abe S, Yoshimura H, Nagaoka S, Monden N, Kinugasa S, Nagasue N, et al. Long-term results of operation for carcinoma of the stomach in T1/T2 stages: critical evaluation of the concept of early carcinoma of the stomach. J Am Coll Surg. 1995;181:389–96.

5. Saragoni L. (2015) Upgrading the definition of early gastric cancer: better staging means more appropriate treatment. Cancer biology & medicine;12:355 – 61. DOI: 10.7497/j.issn.2095-3941.2015.0054.
6. Meng FS, Zhang ZH, Wang YM, Lu L, Zhu JZ, Ji F. Comparison of endoscopic resection and gastrectomy for the treatment of early gastric cancer: a meta-analysis. Surgical endoscopy. 2016;30:3673–83. DOI:10.1007/s00464-015-4681-0.
7. McCall MD, Graham PJ, Bathe OF. Quality of life: A critical outcome for all surgical treatments of gastric cancer. World journal of gastroenterology. 2016;22:1101–13. DOI:10.3748/wjg.v22.i3.1101.
8. Ning FL, Zhang CD, Wang P, Shao S, Dai DQ. Endoscopic resection versus radical gastrectomy for early gastric cancer in Asia: A meta-analysis. International journal of surgery (London England). 2017;48:45–52. DOI:10.1016/j.ijsu.2017.09.068.
9. Sun K, Chen S, Ye J, Wu H, Peng J, He Y, et al. Endoscopic resection versus surgery for early gastric cancer: a systematic review and meta-analysis. Digestive endoscopy: official journal of the Japan Gastroenterological Endoscopy Society. 2016;28:513–25. DOI:10.1111/den.12596.
10. Chung IK, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc. 2009;69:1228–35. DOI:10.1016/j.gie.2008.09.027.
11. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009;58:331–6. DOI:10.1136/gut.2008.165381.
12. Fujishiro M, Yoshida S, Matsuda R, Narita A, Yamashita H, Seto Y. Updated evidence on endoscopic resection of early gastric cancer from Japan. Gastric cancer: official journal of the International Gastric Cancer Association the Japanese Gastric Cancer Association. 2017;20:39–44. DOI:10.1007/s10120-016-0647-8.
13. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. (2015) Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy;47:829 – 54. DOI: 10.1055/s-0034-1392882.
14. Ono H, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Digestive endoscopy: official journal of the Japan Gastroenterological Endoscopy Society. 2016;28:3–15. DOI:10.1111/den.12518.
15. Japanese Gastric Cancer Association. (2017) Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association;20:1–19. DOI: 10.1007/s10120-016-0622-4.
16. Chu YN, Yu YN, Jing X, Mao T, Chen YQ, Zhou XB, et al. Feasibility of endoscopic treatment and predictors of lymph node metastasis in early gastric cancer. World journal of gastroenterology. 2019;25:5344–55. DOI:10.3748/wjg.v25.i35.5344.

17. Ahmad R, Setia N, Schmidt BH, Hong TS, Wo JY, Kwak EL, et al. Predictors of Lymph Node Metastasis in Western Early Gastric Cancer. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract. 2016;20:531–8. DOI:10.1007/s11605-015-2945-6.
18. Gotoda T. (2006) Endoscopic resection of early gastric cancer: the Japanese perspective. Current opinion in gastroenterology;22:561-9. DOI: 10.1097/01.mog.0000239873.06243.00.
19. Choi AH, Nelson RA, Merchant SJ, Kim JY, Chao J, Kim J. Rates of lymph node metastasis and survival in T1a gastric adenocarcinoma in Western populations. Gastrointest Endosc. 2016;83(e1):1184–92. DOI:10.1016/j.gie.2015.10.039.
20. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. (2016) Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association 2000;3:219 – 25. DOI: 10.1007/pl00011720.
21. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. (2008) The Japanese guidelines for gastric cancer screening. Japanese journal of clinical oncology;38:259 – 67. DOI: 10.1093/jjco/hyn017.
22. Shin N, Jeon TY, Kim GH, Park DY. Unveiling lymph node metastasis in early gastric cancer. World journal of gastroenterology. 2014;20:5389–95. DOI:10.3748/wjg.v20.i18.5389.
23. Kwee RM, Kwee TC. Predicting lymph node status in early gastric cancer. Gastric cancer: official journal of the International Gastric Cancer Association the Japanese Gastric Cancer Association. 2008;11:134–48. DOI:10.1007/s10120-008-0476-5.
24. An JY, Baik YH, Choi MG, Noh JH, Sohn TS, Kim S. (2007) Predictive factors for lymph node metastasis in early gastric cancer with submucosal invasion: analysis of a single institutional experience. Annals of surgery;246:749 – 53. DOI: 10.1097/SLA.0b013e31811f3fb7.
25. Kang HJ, Kim DH, Jeon TY, Lee SH, Shin N, Chae SH, et al. (2010) Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. Gastrointestinal endoscopy;72:508 – 15. DOI: 10.1016/j.gie.2010.03.1077.
26. Degiuli M, De Manzoni G, Di Leo A, D'Ugo D, Galasso E, Marrelli D, et al. Gastric cancer: Current status of lymph node dissection. World journal of gastroenterology. 2016;22:2875–93. DOI:10.3748/wjg.v22.i10.2875.
27. Yamao T, Shirao K, Ono H, Kondo H, Saito D, Yamaguchi H, et al. (1996) Risk factors for lymph node metastasis from intramucosal gastric carcinoma. Cancer;77:602–6. DOI: 10.1002/(sici)1097-0142(19960215)77:4<602::Aid-cncr3>3.0.Co;2-i

Tables

Table 1 chi-square analysis on the association between factors and lymph node metastasis in intramucosal gastric cancer

Variable	Level	n (%)	lymphatic metastasis, n (%)		P value	χ^2
			Positive	Negative		
Sex	Female	326(41.3)	33(10.1)	293(89.9)	0.990	<0.001
	Male	463(58.7)	47(10.2)	416(89.8)		
Age	≤40	20(2.5)	1(5.0)	19(95.0)	0.749	1.184
	40-64	283(35.9)	33(11.7)	250(88.3)		
	65-84	443(56.2)	42(9.5)	401(90.5)		
	≥85	43(5.5)	4(9.3)	39(90.7)		
Primary site	Cardia	200(25.4)	25(12.5)	175(87.5)	0.439	6.737
	Fundus	14(1.8)	2(14.3)	12(85.7)		
	Body	83(10.5)	9(10.8)	74(89.2)		
	Gastric antrum	297(37.6)	23(7.7)	274(92.3)		
	Pylorus	30(3.8)	2(6.7)	28(93.3)		
	Lesser curvature of stomach NOS	109(13.8)	15(13.8)	94(86.2)		
	Greater curvature of stomach NOS	28(3.5)	1(3.6)	27(96.4)		
	Overlapping lesion of stomach	28(3.5)	3(10.7)	25(89.3)		
Tumor size(cm)	0-1	321(40.7)	17(5.3)	304(94.7)	<0.001	39.837
	1-2	220(27.9)	19(8.6)	201(91.4)		
	2-3	120(15.2)	12(10.0)	108(90.0)		
	≥3	128(16.2)	32(25.0)	96(75.0)		
Grade	Well differentiated	166(21.0)	7(4.2)	159(95.8)	0.002	11.662
	Moderately well differentiated	261(33.1)	21(8.0)	240(92.0)		
	Poorly differentiated	398(50.4)	52(13.1)	346(86.9)		
Histologic type	Adenoma	349(44.2)	42(12.0)	307(88.0)	0.003	14.071
	Adenocarcinoma, intestinal type	166(21.0)	8(4.8)	158(95.2)		

	Signet ring cell carcinoma	182(23.1)	20(11.0)	162(89.0)		
	Others	42(5.3)	10(23.8)	32(76.2)		
Race	Black	93(11.8)	15(16.1)	78(83.9)	0.023	7.526
	White	473(59.9)	51(10.8)	422(89.2)		
	Others	223(28.3)	14(6.3)	209(93.7)		

Table2 multivariable logistic regression analysis on the association between four factors and lymph node metastasis in intramucosal gastric cancer

Variable	Level	β^{1}	Odds ratio (95%CI)	P value
Tumor size(cm)	0-1	1 (Referent)	1 (Referent)	
	1-2	0.416	1.516(0.755-3.064)	0.241
	2-3	0.581	1.788(0.795-3.909)	0.148
	≥3	1.667	5.296(2.785-10.376)	$5.88e^{-07}$*
Grade	Well differentiated	1 (Referent)	1 (Referent)	
	Moderately well differentiated	0.659	1.933(0.813-5.140)	0.156
	Poorly differentiated	1.409	4.090(1.764-10.745)	0.002*
Histologic type	Adenoma	1 (Referent)	1 (Referent)	
	Intestinal type adenocarcinoma	-0.777	0.460(0.191-0.989)	0.061
	Signet ring cell carcinoma	-0.520	0.594(0.305-1.141)	0.121
	Others	-0.569	0.566(0.245-1.206)	0.158
Race	Black	1 (Referent)	1 (Referent)	
	White	-0.471	0.625(0.327-1.246)	0.166
	Others	-0.941	0.390(0.172-0.883)	0.023*

[1]:β is the regression coefficient

Table 3 chi-square analysis on the association between differentiation, diameter and lymph node metastasis in intramucosal gastric cancer

Variable		lymphatic metastasis		P value	χ^2
		Positive	Negative		
Differentiated gastric cancers					
diameter	≤2	36	496	0.001	23.173
	>2	44	199		
diameter≤2					
Grade	Differentiated	36	496	1.000	
	Undifferentiated	0	10		

Figures

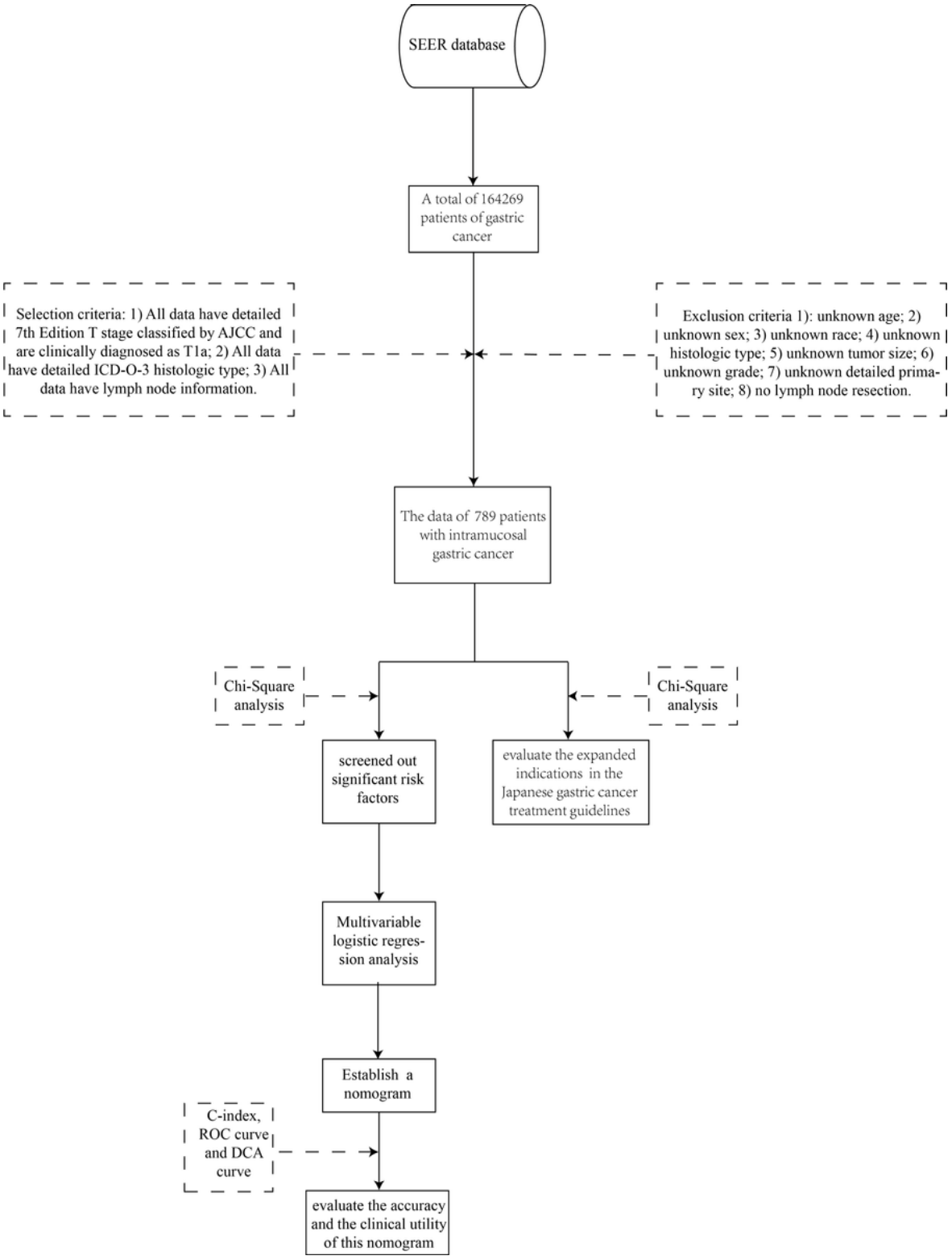

Figure 1

Flow chart

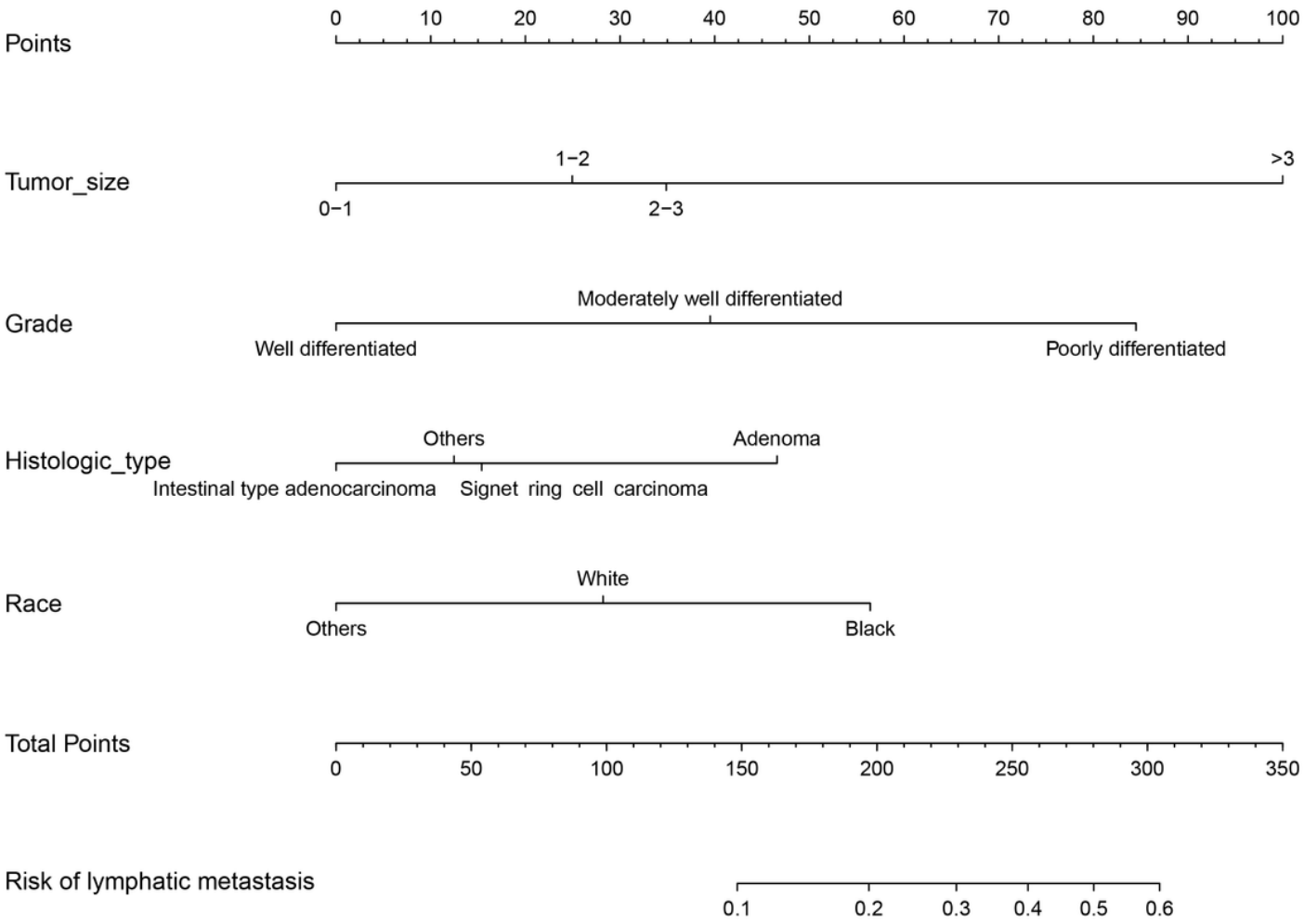

Figure 2

Nomogram of lymph node metastasis risk.

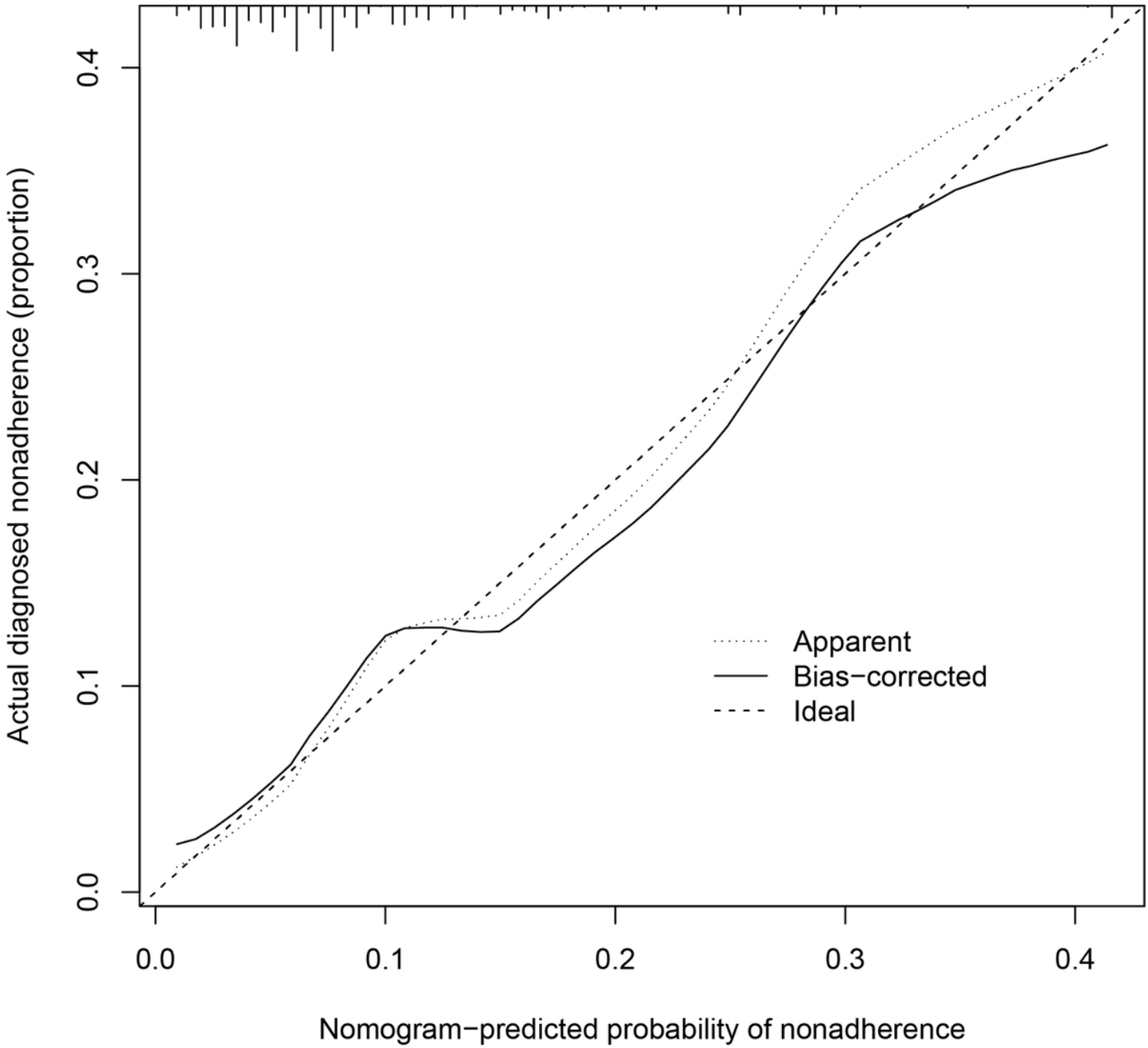

Figure 3

calibration curves for predicting lymph node metastasis

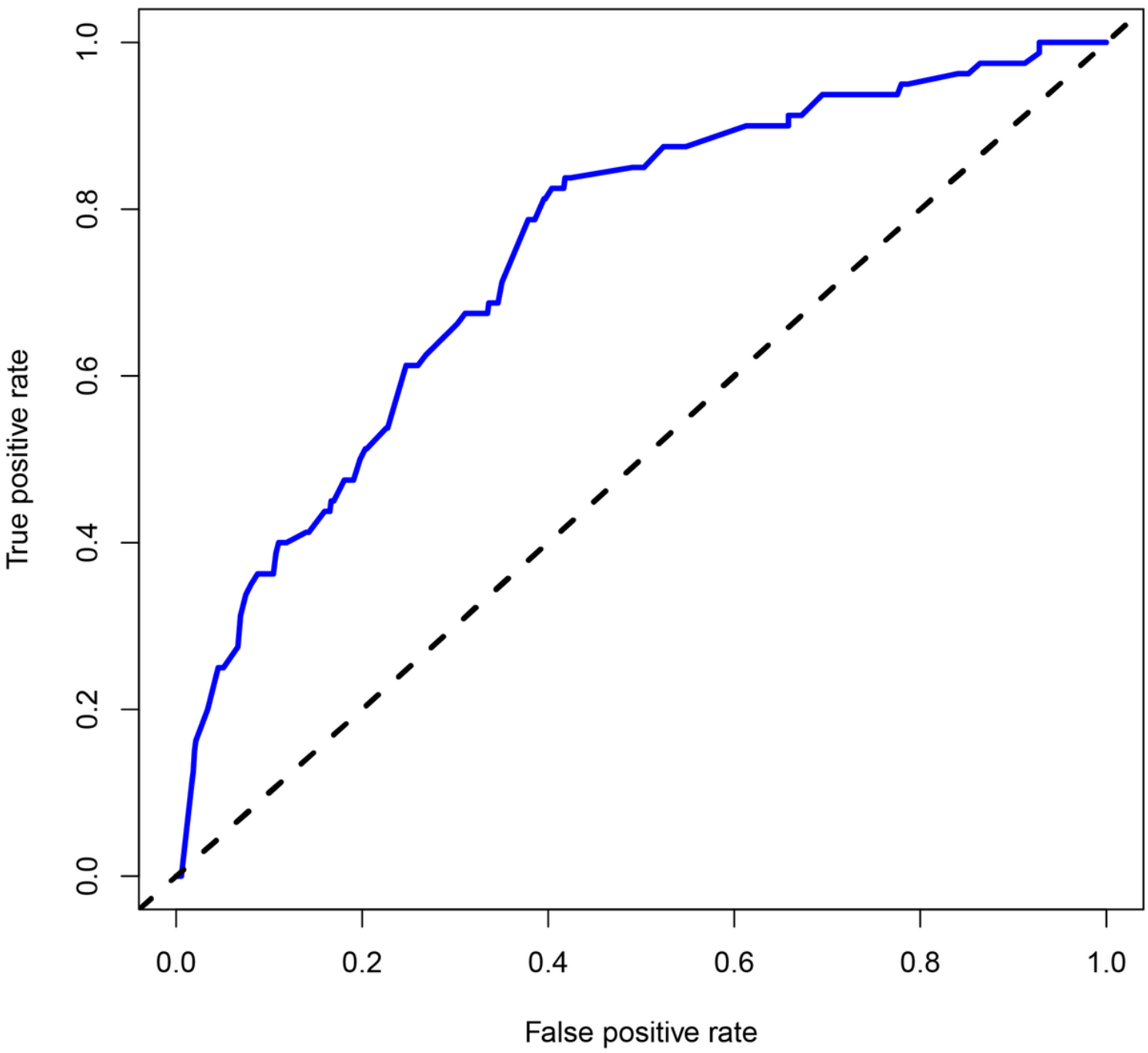

Figure 4

ROC curve and AUC value of nomogram of lymph node metastasis risk

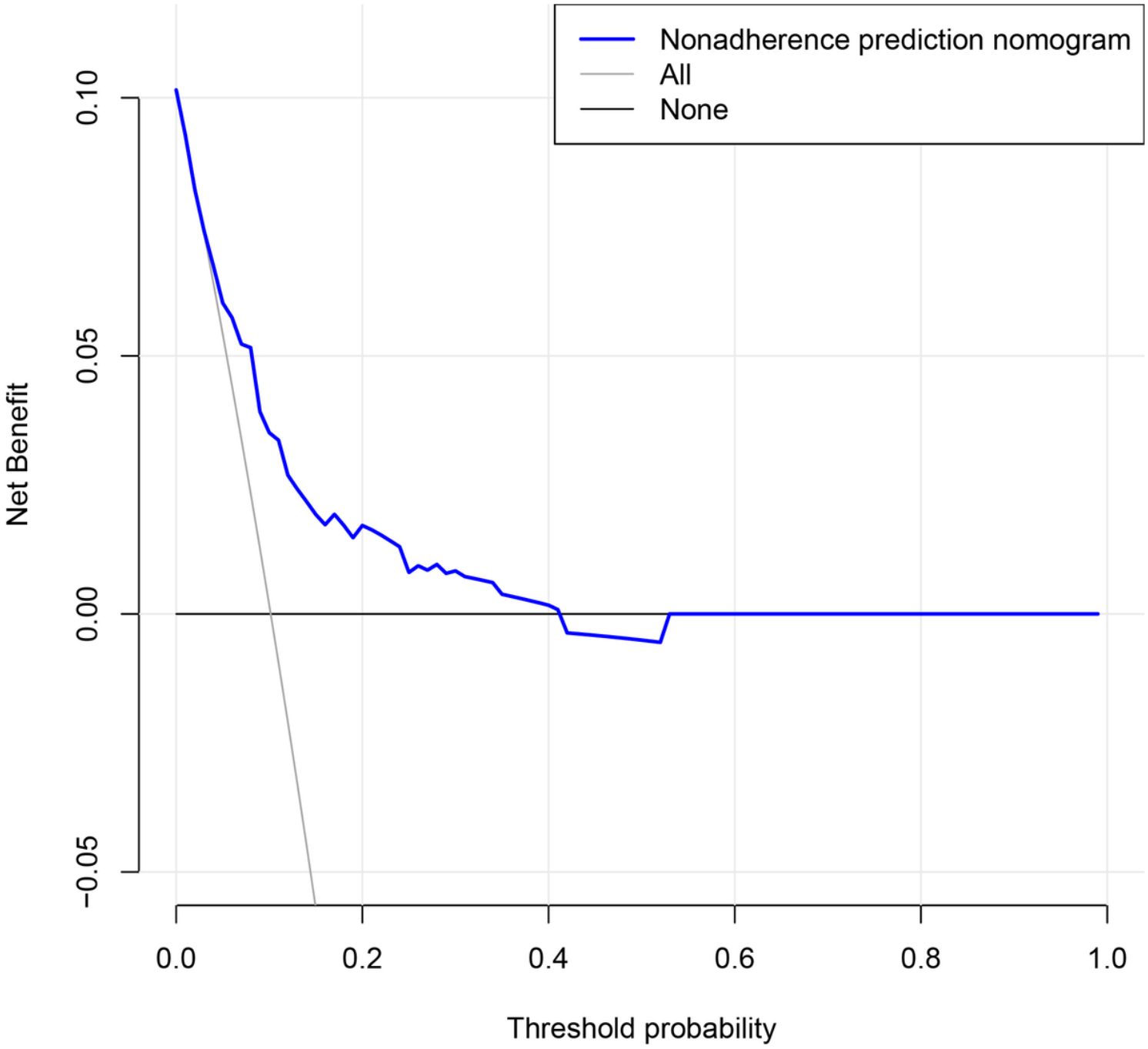

Figure 5

Decision curve analysis on nomogram of lymph node metastasis risk