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Nomogram based on clinical characteristics for preoperative prediction of perineural invasion in gastric cancer

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Abstract

Purpose: Gastric cancer (GC) has a poor prognosis and high rate of recurrence. Perineural invasion (PNI) is a prognostic factor in GC that is associated with a high risk of systemic recurrence. Preoperative identification of PNI may facilitate patient stratification and optimal preoperative treatment. We therefore developed and validated a nomogram for the preoperative prediction of PNI.

Methods: We retrospectively collected clinical data from 261 GC patients, who were randomly assigned to training (n = 185) and validation (n = 76) sets. The least absolute shrinkage and selection operator regression model was used to identify potentially relevant clinical parameters, and multivariable logistic regression analysis was used to develop the nomogram.

Results: The nomogram consisted of body mass index, immunoglobulin A level, and computed tomography-based T- and N-stages. Good calibration was observed for both the training and validation sets, with areas under the curve of 0.77 and 0.79, respectively. Decision curve analysis revealed that the nomogram was clinically relevant.

Conclusion: We developed and validated a nomogram for the preoperative prediction of PNI in patients with GC. Our nomogram may facilitate the identification of high-risk patients and optimization of preoperative decision-making.

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Introduction

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the third most common cause of cancer-related deaths worldwide.[1] The incidence of GC varies geographically, with half of all cases occurring in East Asia.[2] Surgery remains the main treatment for GC. However, the rate of local or distant recurrence after radical surgery is 20% to 60%,[3] and locoregional tumor dissemination and distant micrometastases of cancer cells are the main causes of postoperative recurrence.[4,5] Furthermore, increased growth factor levels and immunosuppression induced by surgery can contribute to postoperative recurrence.[6] In recent years, neoadjuvant treatment has received increasing attention for its advantages in controlling locoregional tumor dissemination, eliminating distant micrometastases, and ultimately reducing the risk of recurrence.[7] In this context, it is crucial to identify patients with GC at high risk of recurrence to improve pre-treatment decision-making and determine the adequacy of surgical resection. Although several biomarkers and pathological parameters have been reported to show an association with recurrence, most have limitations related to clinical usability or can only be assessed through postoperative pathological examination.

Perineural invasion (PNI), defined as the infiltration of the perineurium or neural fascicles around a tumor by cancer cells, is one of the earliest steps of locoregional tumor dissemination.[8] PNI is a crucial route for local tumor spreading, and is associated with a high risk of systemic recurrence in GC.[9] A series of studies reported the association between PNI and poor prognosis in GC using univariable and multivariable analyses,[8,10] and PNI was found to be associated with poor prognosis, recurrence, and advanced disease.[8,11] Given the significant prognostic value of PNI in GC, an increasing number of researchers recommend the incorporation of PNI status into the TNM staging system for optimal patient stratification.[9,12] Although PNI is of significant prognostic value in GC, it can only be assessed postoperatively.

Nomograms, statistics-based tools that can predict the probability of a specific event, were first applied clinically in 1928 and have recently attracted increased attention for their substantial clinical utility.[13] Nomograms combine several predicting factors and allow the score for each factor to be calculated using a scale, so that the total score can be used to predict the risk of a specific event. In recent years, nomograms have significantly benefited in diagnosis and prognostication of various malignancies. Of note, some nomograms have shown a better predictive value in GC than the TNM staging system.[14] Considering the value of PNI in determining the risk of recurrence, we aimed to develop and validate a nomogram for predicting the presence of PNI using preoperative clinical characteristics in patients with GC. Moreover, we evaluated the predictive value of the nomogram based on goodness of fit, discrimination ability, and clinical utility using separate training and validation cohorts.

Methods

Study population

We retrospectively analyzed data from patients who underwent surgery for GC at the Guangxi Medical University Cancer Hospital between October 2013 and May 2018. The inclusion criteria were as follows: (i) pathologically confirmed primary GC; (ii) treatment with primary tumor resection; (iii) availability of postoperative pathological reports containing information on PNI status; and (iv) availability of complete symptoms, signs, previous history, and results of auxiliary examinations such as computed tomography (CT), electronic gastroscopy, and blood biochemical examination. Patients who underwent any preoperative therapy (including radiotherapy, chemotherapy, or chemoradiotherapy) or had another tumor during the same period were excluded. The study protocol was approved by the Ethics and Human Subject Committee of Guangxi Medical University Cancer Hospital, and all experiments and methods met the standards of the relevant guidelines and regulations.[15,16]

We collected information on clinical parameters including age, sex, body mass index (BMI), past and present medical history, family history, routine blood test results, tumor markers, serum immunoglobulin level, computed tomography (CT)-based T and N status, preoperative histological grade, postoperative pathology, and TNM stage. Patients were restaged according to the eighth edition of the American Joint Committee on Cancer staging system. Eligible patients were randomly assigned to the training and validation datasets at a ratio of 7:3.[17–19]

Feature selection

We performed a univariate analysis to identify clinical characteristics for nomogram construction. Characteristics were compared between the PNI-positive and -negative groups using t-tests for continuous variables and chi-square tests for categorical variables, and those with a P-value <0.1 were selected. As univariate analysis was a preliminary screening method, a relatively lenient threshold value ($P < 0.1$) was used. The selected variables were subjected to least absolute shrinkage and selection operator (LASSO) logistic regression[20] — a penalizing regression method that estimates the regression coefficients by maximizing the log-likelihood function while restraining the sum of the absolute values of the regression coefficients and thus has an advantage in handling high-dimensional data[21] — using the "glmnet" package of R software (version 3.4.0; www.r-project.org).[13,22,] A minimum λ was used for the selection of characteristics. We performed LASSO logistic regression in the training set. PNI served as the dependent variable, and the clinical characteristics showing significant differences in the univariate analysis served as the independent variables. Characteristics with non-zero coefficients at the minimum λ were selected using the LASSO logistic regression algorithm. Finally, multivariable logistic regression was performed using the characteristics selected by LASSO to construct the prediction model. The variance inflation factor (VIF) was used to evaluate collinearity among different characteristics in the logistic regression model, and the 95% confidence interval (CI) of the odds ratio was used to evaluate the accuracy of variables for predicting PNI.

Nomogram construction and assessment

The nomogram was generated using the "rms" package of R software.[23] A calibration plot was used to evaluate the goodness of fit between the observed values and the predicted values, and Spiegelhalter's Z-test

was used to test the degree of fitting. A receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to evaluate the discrimination ability of the nomogram.

Nomogram validation

The nomogram developed based on the training set was validated in the validation set. We calculated the individual probability of PNI in the validation set. We assessed the degree of fitting of the nomogram in the validation set using calibration plots and Spiegelhalter's Z-test. The ROC curve and AUC were used to evaluate the discrimination ability of the nomogram in the validation set. The treat-none scheme assumed that no patient had a disease and the treat-all-patients scheme assumed all patients had a disease.

Decision curve analysis

Decision curve analysis (DCA) is a recently proposed method for evaluating the clinical utility of nomograms[24] that shows the net benefit of each decision strategy at each threshold probability. In the present study, we performed DCA using the "dca.R" function of R software to evaluate the clinical utility of the nomogram in all patients.

Statistical analysis

All statistical analyses of were performed using R software. All tests were two-sided, and values of $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics

A total of 261 patients were included in our analysis, with 185 randomized to the training set and 76 to the validation set. The average patient age was 55.95 years, and there were 167 male and 94 female patients. Most patients had a normal BMI (n = 167, 63.98%). Preoperative CT examination showed that approximately half of the patients were at the T4 clinical stage (n = 131, 50.19%) and more than half did not have any evidence of lymph node metastasis (n = 143, 54.79%). Approximately two thirds of the patients had PNI confirmed by postoperative pathological examination (n = 163, 62.45%). A comparison of the basic demographic data, symptoms, and results of blood tests and imaging examinations between the PNI-positive and -negative groups is summarized in the supplementary material. PNI-negative patients had a significantly higher BMI and hemoglobin level compared with PNI-positive patients. Moreover, the proportion of patients in CT T1–2 and CT N0 stage was higher in the PNI-negative group (Table 1). In addition, lgA and CA199 levels were higher in PNI-positive patients, although the difference was not statistically significant. Although the proportion of patients with melena was higher in the PNI-negative group, the total number of patients with melena was small (4.21% of all patients), and the relationship between melena and PNI may have been coincidental. Thus, we excluded melena from the follow-up study.

Feature selection

Through univariate analysis, six characteristics (BMI, hemoglobin level, immunoglobulin A (IgA) level, CA199 level, CT T-stage, and CT N-stage) were selected and subjected to LASSO logistic regression. We selected an optimal lambda of 0.013 with the smallest binomial deviance. Under penalizing conditions, four clinical parameters with non-zero coefficients were selected (BMI, IgA level, CT T-stage, and CT N-stage) (Figure 1A and B) and used to

Table 1. Patient background characteristics.

Characteristic	PNI-positive (n = 163) [n (%)]	PNI-negative (n = 98) [n (%)]	P-value
Age (years)			0.85
[median (IQR)]	57 (46.65)	57 (47.65)	
Sex			0.38
Males	101 (60.5)	66 (39.5)	
Females	62 (66.0)	32 (34.0)	
BMI (kg/m^2)			7.2×10^{-3}
[median (IQR)]	20.90 (18.98,23.13)	21.87 (19.49,24.85)	
Hemoglobin (g/L)			0.013
[Mean ± SD]	115.6 ± 22.16	123.4 ± 25.80	
IgA (g/L)			0.057
[Mean ± SD]	2.41 ± 0.80	2.22 ± 0.73	
CA199 (U/L)			0.084
[Mean ± SD]	33.67 ± 104.35	18.02 ± 37.29	
CT T Stage			3.85×10^{-10}
T1	7 (22.6)	24 (77.4)	
T2	14 (36.8)	24 (63.2)	
T3	39 (63.9)	22 (36.1)	
T4	103 (78.6)	28 (21.4)	
CT N Stage			7.1×10^{-7}
N0	70 (49.0)	73 (51.0)	
N1–3	93 (78.8)	25 (21.2)	
Melena			0.005
No	161 (64.4)	89 (35.6)	
Yes	2 (18.2)	9 (81.8)	

Abbreviations: PNI, perineural invasion; IQR, interquartile range; BMI, body mass index; SD, standard deviation; IgA, immunoglobulin A; CA199, carbohydrate antigen 199; CT: computed tomography.

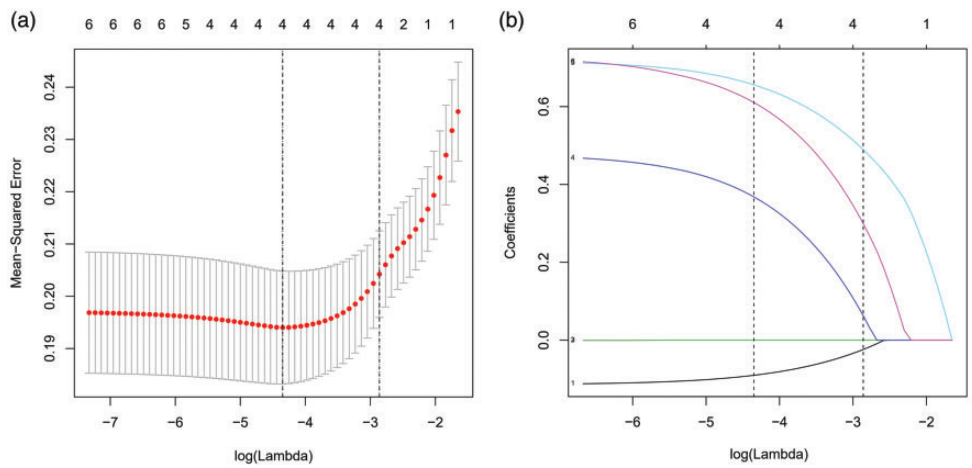

Figure 1. Feature selection using least absolute shrinkage and selection operator (LASSO) logistic regression. (a) Ten-time cross-validation for tuning parameter (λ) selection in the LASSO model. (b) LASSO coefficient profiles. A coefficient profile plot was produced versus the log (λ).

construct the multivariable logistic regressing model.

Nomogram performance

As shown in Table 2, BMI, IgA level, CT T-stage, and CT N-stage were found in the multivariable regression model to be independent predictors of PNI in GC. Low BMI and high IgA level were both associated with an increased risk of PNI. Furthermore, CT T-stage was found to be an important indicator of PNI, as the PNI-positive rate rose with increasing CT T-stage. The regression model was visualized using a nomogram (Figure 2), which included the four characteristics and a score for each feature assigned based on the top scale of the nomogram. The total score for the four characteristics was used to predict the risk of PNI.

Table 2. Multivariable logistic regression analysis of the selected clinical characteristics in the training set

Variable	Odds ratio (95%CI)	VIF	P
BMI	0.89 (0.80–0.99)	1.00	0.031
IgA	1.61 (1.03–2.61)	1.01	0.042
CT T stage	2.05 (1.47–2.94)	1.09	<0.001
CT N stage	2.06 (1.00–4.26)	1.11	0.048

Abbreviations: BMI, body mass index; IgA, immunoglobulin A; CT, computed tomography; CI, confidence interval; VIF, variance inflation factor.

We assessed the performance of the nomogram in the training set. The calibration plot for the nomogram showed good agreement between the predicted and observed rates (Figure 3A), and Spiegelhalter's Z-test also indicated good agreement, with a P-value of 0.95. The ROC and AUC for the prediction nomogram in the training set was 0.77, indicating favorable discrimination (Figure 3B).

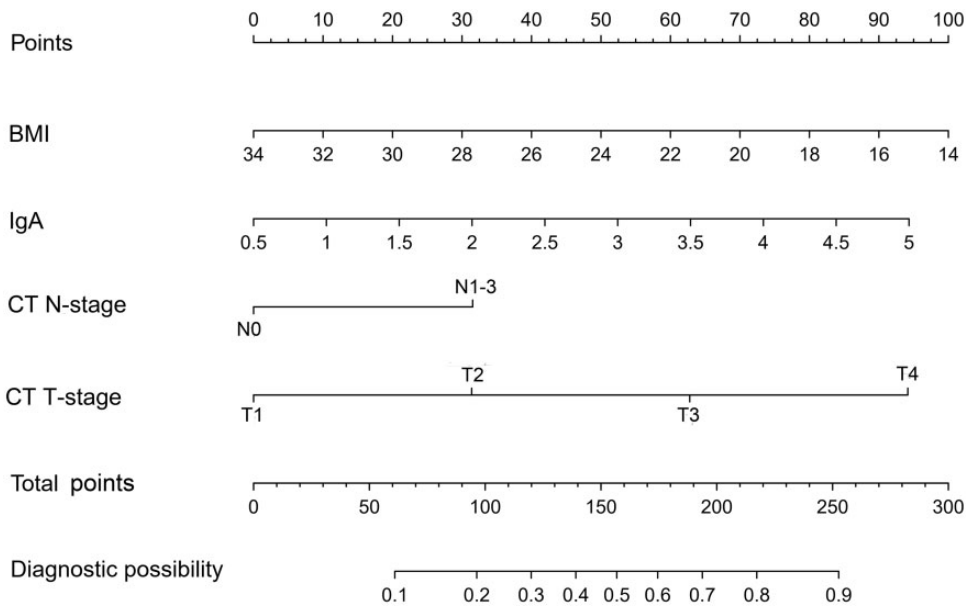

Figure 2. Nomogram for preoperative prediction of perineural invasion (PNI) in gastric cancer (GC). Points are assigned for BMI, IgA, CT T-stage and CT N-stage. The score for each value was assigned by drawing a line upward to the "Points" line, and the sum of the four scores was plotted on the "Total points" line (probability of PNI).

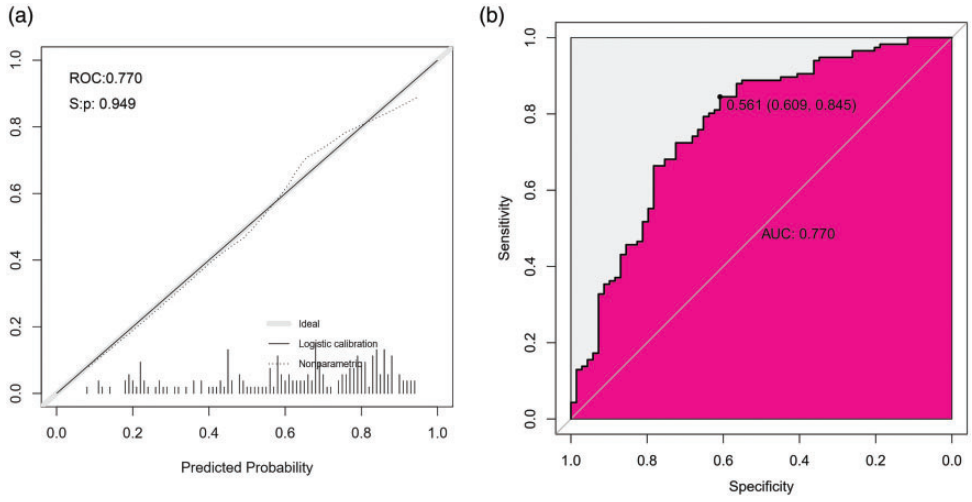

Figure 3. Assessment of the nomogram in the training set. (a) Calibration curve of the nomogram in the training set. The x-axis is the nomogram-predicted probability of perineural invasion (PNI) and the y-axis is the actual rate of PNI. (b) Receiver operating characteristic (ROC) curves of the nomogram in the training dataset. AUC, area under the curve.

Nomogram validation

Further validation of the nomogram was performed in the validation set. The multivariable logistic regression model constructed in the training set was applied to the validation set and the individual probability of PNI was calculated. The calibration curve revealed good correlation between the predicted and actual probabilities, and Spiegelhalter's Z-test yielded a non-significant result ($P = 0.54$), indicating that the nomogram had a good degree of fit in the validation set (Figure 4A). The nomogram showed an AUC of 0.79 in the validation set, indicating good discrimination (Figure 4B).

Clinical use

We used DCA to evaluate the clinical utility of the nomogram in all 261 GC patients. As shown in Figure 5, the nomogram provided greater benefits than the treat-all-patients and treat-none schemes when the nomogram-predicted probability of PNI was >30% and <80%. For instance, the nomogram provided a net benefit of 25% when the probability of PNI was 0.62. These results supported the clinical validity of the nomogram.

Discussion

In the present study, we constructed what, to our knowledge, is the first nomogram for the preoperative prediction of PNI in GC. Constructed based on routine examination results for GC diagnosis, the nomogram showed favorable discrimination and calibration values in both the training and the validation sets. Furthermore, the clinical utility of the nomogram was supported using DCA. We found that BMI, IgA level, CT T-stage, and CT N-stage were independent predictors of PNI. Thus, our nomogram may represent an easy-to-use preoperative predictor of PNI in patients with GC.

PNI, also referred to as perineural spread or neurotropic carcinomatous

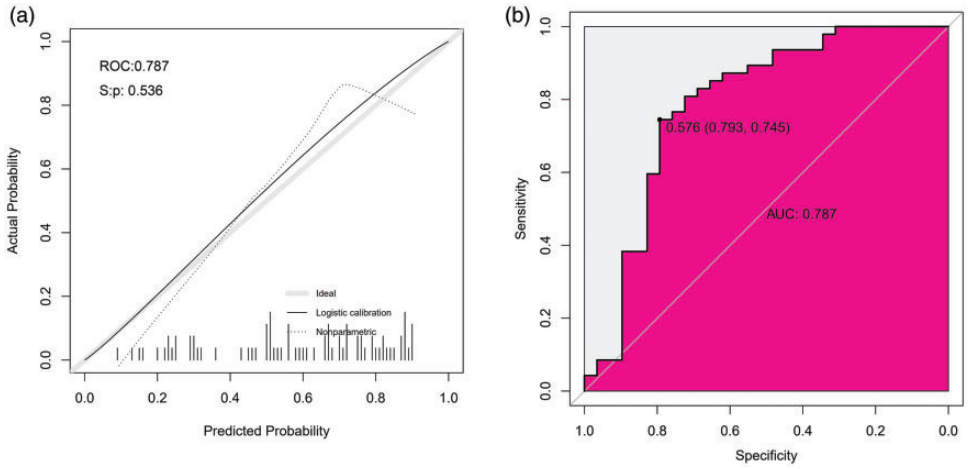

Figure 4. Assessment of the nomogram in the validation set. (a) Calibration curve of the nomogram in the validation set. The x-axis is the nomogram-predicted probability of perineural invasion (PNI) and the y-axis is the actual rate of PNI. (b) Receiver operating characteristic (ROC) curves of the nomogram in the validation set. AUC, area under the curve.

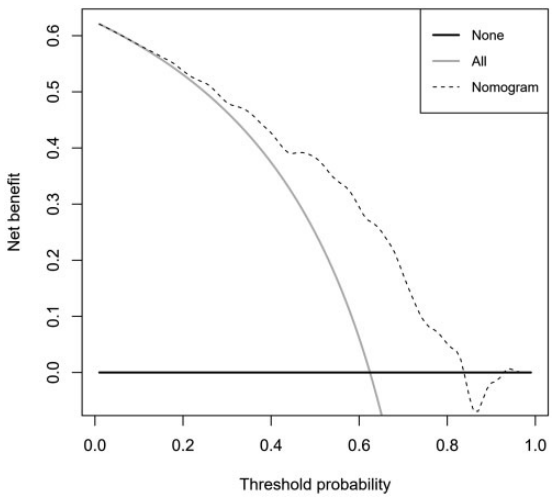

Figure 5. Decision curve analysis (DCA) for the nomogram. Net benefit was plotted versus the threshold probability. The dotted line represents the nomogram, the gray line represents the treat-all-patients scheme, and the black line represents the treat-none scheme.

spread, involves the neoplastic invasion of nerves. The rate of PNI in GC is approximately 59.6% to 75.6%.[8,10] The association between PNI and tumor size, tumor differentiation, recurrence, and poor prognosis in GC has been established.[25] According to statistical analysis, approximately 20% to 60% of patients who undergo radical surgical tumor dissection and receive adjuvant chemotherapy subsequently develop recurrence or new occurrence of GC.[26] Neoadjuvant treatment has the advantage

of reducing the risk of recurrence.[27] According to Chinese guidelines for the diagnosis and treatment of GC, neoadjuvant treatment is recommended for patients with locally advanced GC and no evidence of distant metastasis (T3/4, N+).[28] However, a previous study showed that even among node-negative GC patients who underwent curative gastrectomy, 17.1% had tumor recurrence.[29] According to the National Comprehensive Cancer Network (NCCN) Guideline for GC, neoadjuvant chemotherapy is recommended in patients at stage T2 or higher.[30] Hence, it is crucial to identify patients at high risk of recurrence and so that neoadjuvant chemotherapy can be considered during pre-treatment decision-making, and our nomogram may facilitate the identification of these patients.

The nomogram we developed contained four clinical characteristics: BMI, IgA level, CT T-stage, and CT N-stage. CT is a non-invasive diagnostic test widely used in GC diagnosis and in the assessment of the local extension of the tumor, nodal disease, and metastases.[31] With advancements in CT and increased resolution, the evaluation of tumor invasion in GC now has an accuracy of approximately 80% to 89%, while that of the evaluation of lymph node metastasis is 63%.[32,33] Thus, the use of CT-based T- and N-stage to predict PNI can be considered convenient and accurate. In 2010, Gumus and colleagues reported that PNI was associated with the depth of invasion (T stage) and lymph node metastasis (N stage) in GC.[10] At the pathological T1–2 stage of GC, the rate of PNI positivity on postoperative pathological assessment is approximately 28% but increases to approximately 80% at the pathological T3–4 stage. In patients with pathological N0 stage GC, the rate of PNI positivity is approximately 60%. However, in lymph node-positive GC, the rate is 78%.[34] Thus, PNI may be a precursor to the local spread of the tumor, and preoperative prediction of PNI may facilitate the identification of high-risk patients and subsequent optimization of the preoperative decision-making process. In the present study, CT T-stage and N-stage were selected by LASSO regression, with CT T-stage found to be an independent predictor of PNI. This finding indicated that PNI was closely related to tumor staging, consistent with previous research.[10] In addition, we found that low BMI was associated with an increased risk of PNI. BMI is a key index in preoperative nutrition status scoring systems. A previous study indicated that low BMI ($<18.5\,kg/m^2$) was an independent prognostic factor for GC.[35] We hypothesize that poor nutritional status may impair the patient's resistance to cancer, thus contributing to tumor progression, although future studies are required to explore the relationship between BMI and PNI in more detail.

There were some limitations to current study. First, the nomogram was constructed based on clinical data from a single institution. Thus, our results might be biased by institutional practice patterns, and external validation should be performed to assess the performance of the nomogram in other patient populations.[36] Second, the present study only included a limited number of patients. Further studies with larger samples are therefore needed to validate our results. Finally, our study was retrospective in nature. Thus, prospective studies to evaluate the predictive value of the nomogram should be performed.

Conclusions

We developed and validated a nomogram for the preoperative prediction of PNI in patients with GC, and the nomogram provided favorable discrimination and calibration values. To our knowledge, ours is the first nomogram that may facilitate the preoperative prediction of the risk of PNI in

patients with GC. Taken together, our results indicate that the nomogram may represent an easy-to-use preoperative predictor of PNI that may optimize preoperative decision-making in patients with GC.

Author Contributions

Conceived and designed the experiments: WT, XH, JL; performed the data collection: JL, XH, GW, FP, SC, CZ, LH, CT,WX, WT; analyzed the data: XH, JL, GW, WX, CS; contributed reagents/materials/analysis tools: JL, XH, GW, FP, SC, CZ, LH, CT,WX, WT; contributed to the writing of the manuscript: JL, XH, GW, FP, SC, CZ, LH, CT,WX, WT; all authors reviewed the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics and Human Subject Committee of Guangxi Medical University Cancer Hospital

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplementary material for this article is available online.

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