A nomogram to predict vascular invasion before resection of colorectal cancer

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Abstract. Vascular invasion (VI) is an important feature for systemic recurrence and an indicator for the application of adjuvant therapy in colorectal cancer (CRC). Preoperative knowledge of VI is important in determining whether adjuvant therapy is necessary, as well as the adequacy of surgical resection. In the present study, a predictive nomogram for VI in patients with CRC was constructed. The prediction model consisted of 664 eligible patients with CRC, who were divided into a training set (n=468) and a validation set (n=196). Data were collected between August 2013 and April 2018. The feature selection model was established using the least absolute shrinkage and selection operator regression model. Multivariable logistic regression analysis was used to construct the predictive nomogram. The performance of the nomogram was evaluated by calibration, discrimination and clinical usefulness. Differentiation, computed tomography (CT)-based on N stage (CT N stage), hemameba and tumor distance from the anus (cm) were integrated into the nomogram. The nomogram exhibited good discrimination, with an area under the curve (AUC) of 0.731 and good calibration. Application of the nomogram in the validation cohort showed acceptable discrimination, with an AUC of 0.710 and good calibration. Decision curve analysis revealed that the nomogram was clinically useful. These findings suggests, to the best of our knowledge, that this may be the first nomogram for individual

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preoperative prediction of VI in patients with CRC, which may promote preoperative optimization strategies for this selected group of patients.

Introduction

According to the 2018 global cancer statistics, colorectal cancer (CRC) has the third highest incidence rate of all types of cancers worldwide; it also has the second highest mortality rate (1). In USA, it has been estimated that there will be >140,000 new CRC cases and 23,380 deaths 2019, accounting for ~1 in 7 cancer cases and deaths (2).

Adjuvant therapy is typically selected by pathological and clinical staging as two of the prognostic predictors (3). Vascular invasion (VI) is prevalent in CRC; it has been reported that ~23% of CRC and VI cases are combined in postoperative pathology (4). Therefore, accurate identification of VI involvement in patients with CRC is crucial for prognosis and treatment strategy decisions.

VI is a strong prognostic indicator in CRC (3). A previous study has shown that there is a significant association between VI and metastasis and a high rate of recurrence in univariate analysis and multivariable analysis (5). In the Union for International Cancer Control, stage I rectal cancer (T1, T2 N0), VI is a high-risk factor for disease progression and recurrence (6). In addition, VI is associated with poor loco-regional outcomes, which are potentially valuable predictors of local recurrence in rectal cancers (7). A previous study demonstrated that VI is also associated with reduced overall survival rate and disease-free survival rates, therefore serving as a strong prognostic marker (8). In the clinical practice guidelines published by the National Comprehensive Cancer Network (NCCN) (3), VI is regarded as a high-risk factor for systemic recurrence and stage III or high-risk stage II.

It is recommended that patients with CRC with VI receive adjuvant therapy (9). VI is a strong prognostic indicator, and a predictor of CRC metastasis and recurrence (5). A better understanding of VI supports the decision of whether adjuvant therapy is required, determining the adequacy of surgical resection, and selecting the optimal treatment (8). Vascular endothelial growth factor (VEGF) and its expressed

products Fms related tyrosine kinase-1 and kinase insert domain receptor, regulate endothelial cell proliferation, migration, invasion, survival and branching morphogenesis, which are reported to be associated with VI (10,11). However, the practicality of these biomarkers is limited (10,11).

Since the first reported clinical application of a nomogram in 1928 (12), nomograms have attracted increased attention. A nomogram is a user-friendly graphical prediction model with strong clinical application (13-15). Users can build the nomogram to obtain points assigned to each predicted factor at the top of the scale (13-15). Through this, the total points can be transformed to predict the possible risk of a specific event for patients in the lowest scale. To date, nomograms have been widely used in the diagnosis and prognostic prediction of a variety of malignancies, such as Ewing sarcoma and thymoma prognosis (14,15). The use of some notional diagrams has even been considered to assess the efficacy of chemotherapy in prognostic prediction (13). However, to the best of our knowledge, no nomogram is available for the preoperative prediction of VI in CRC.

In the present study, a nomogram with clinical features for the individualized preoperative prediction of VI in patients with CRC was developed and validated. The goodness of fit, differentiation and clinical application value of the nomogram were evaluated. To the best of our knowledge, this is the first nomogram to predict preoperative VI in patients with CRC, which can provide preoperative optimization strategies for selected patients.

Patients and methods

Study population. The present retrospective analysis was approved by the Ethics and Human Subject Committee of Affiliated Tumor Hospital of Guangxi Medical University. According to the specific inclusion and exclusion criteria, the present study recruited 989 patients with CRC between August 2013 and April 2018 in the Affiliated Tumor Hospital of Guangxi Medical University. The inclusion criteria consisted of the following: i) Pathological confirmation of CRC in patients; ii) primary tumor resection had been performed; and iii) the status of VI was obtainable in the postoperative pathological report. The exclusion criteria included the following: i) Preoperative therapy involving radiotherapy, chemotherapy or chemoradiotherapy; ii) patients currently suffering from other cancer diseases; and iii) the presence of hereditary non-polyposis colon cancer or familial adenomatous polyposis. The corresponding demographic and preoperative clinical parameters, such as age, sex, body mass index (BMI), first-degree relatives' tumor history, blood routine examination, serum immunoglobulin level, tumor primary site, computed tomography (CT)-based on T stage (CT T stage) or N stage (CT N stage), preoperative histologic grade and tumor gross type, were collected. Weight change was obtained by self-reporting within the last three months prior to diagnosis and measured every week after hospitalization.

In total, 664 patients, including 389 male and 275 female patients, with complete information were enrolled. All 664 patients were randomly divided into two independent datasets at a ratio of 7:3 based on a computer-generated random number (training datasets: 468 cases; and validation datasets:

196 cases). T and N stages were determined on the basis of the 7th edition of The American Joint Committee on Cancer, Cancer Staging Manual (16).

Feature selection. Least absolute shrinkage and selection operator (LASSO) is a penalized 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 (17). Regression coefficients estimated by LASSO are sparse, and many components are exactly 0. Therefore, LASSO automatically deletes unnecessary covariates. The LASSO logistic regression algorithm is used for determining the regression of high-dimensional data, which is applied in many fields, including in genome-wide association studies, when it is difficult to find significant genetic factors with expected statistical significance in a large amount of data. The LASSO method can be used to screen out significant genetic factors with expected statistical significance, to produce a number of algorithms (18). The present study employed the LASSO logistic regression algorithm in the training dataset to select the most diagnostically predictive features. All of the categorical variables were transformed into dummy variables. The status of VI served as the dependent variable. The suitable tuning parameter (λ) for LASSO logistic regression was determined using cross-validation. LASSO logistic regression was performed by package 'glmnet' function of 'glmnet' package. A minimum λ was used for features selection. Features with non-zero coefficients at the optimal were selected by the LASSO logistic regression algorithm. Finally, the multiple logistic regression was performed using the diagnostic features selected by LASSO in the training dataset to construct the prediction model. The evaluation of the prediction model was performed in the validation dataset.

Nomogram construction and performance assessment. The prediction model was constructed in the training dataset, which used features selected by the LASSO algorithm, using a multivariate logistic regression model. All of the selected features entered the multivariate logistic regression model and the coefficient of each feature was calculated. The predicted index of each patient was calculated by the 'predict' function, based on the model constructed in the training dataset. A nomogram was formulated according to the resultants of the multivariable analyses, which incorporated the selected features. The goodness of fit between the observed value and the predicted value was examined by the calibration curve and tested using the Hosmer-Lemeshow test, which is a statistical test for goodness of fit for logistic regression models and used frequently in risk prediction models (19). An ideal calibration curve perfectly fits the 45-degree reference line. The predictive discrimination of the nomogram was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). In the logistic regression model, the value of the AUC was the same as the concordance index (c-index). An AUC of 1.0 was determined, indicating perfect discrimination of the nomogram.

Validation of the nomogram. To assess the performance of the nomogram, the constructed nomogram was validated in the validation dataset. The predicted value of each patient in this

dataset was calculated based on the formula constructed in the training dataset. The ROC and AUC were used to evaluate the predictive discrimination of the nomogram in the validation dataset. The calibration curve and Hosmer-Lemeshow test were used to assess the goodness of fit of the nomogram in the aforementioned dataset.

Decision curve analysis (DCA). The DCA method was employed to evaluate the clinical usefulness of the nomogram through quantitative training and verification, and compared with treat-all-patients scheme or the treat-none scheme to predict the net benefit under the dataset's different threshold probabilities (20). The treat-none scheme assumed no patient had a disease and the treat-all-patients scheme assumed all patients had a disease.

Statistical analysis. Statistical analysis was performed using R version 3.4.0 and RStudio (Version 1.1.447) (21,22). LASSO logistic regression analysis was carried out with the 'glmnet' software package (version 2.0-16; https://cran.r-project.org/web/packages/glmnet/index.html). In addition, the multivariate logistic regression analysis, nomogram building and calibration plots were conducted using the 'rms' package (version 5.1-3.1; https://cran.r-project.org/web/packages/rms/). The DCA and Hosmer-Lemeshow test were performed with the functions, 'dca.R' and 'HLtest.R,' respectively. P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics. A total of 664 patients were included in the analysis; >200 clinical parameters were collected in the present study. Patient demographics and pathologic parameters are listed in Table I. The average age of the included patients was 59.2 years (range, 17-87 years). In total, 314 patients had were diagnosed with rectal cancer, and 350 patients were diagnosed with colon cancer at the Affiliated Tumor Hospital of Guangxi Medical University. Of the 664 total patients, 139 had a history of first-degree relatives with tumors, while 525 patients did not. The average weight loss over the last 3 months was 1.73 kgk (range, -3-16 kgk). In addition, these patients were identified as VI-positive (203 cases) in the postoperative pathology report.

Feature selection. The LASSO logistic regression method was employed to select the most significant prediction features in the prediction model. The present study performed feature selection based on the training dataset. Overall, 154 features were used in the LASSO logistic regression. In addition, 4 features with non-zero coefficients were selected by the LASSO logistic regression algorithm with an optimal λ of 0.048 (Fig. 1A and B). The 4 features included differentiation, CT-based N stage (CT N stage), hemameba and tumor distance from the anus (cm).

Nomogram construction and performance assessment. The 4 features selected by LASSO logistic regression were included in the multivariate logistic regression modeling. As shown in Table II, multivariate logistic regression identified poor differentiation (P=4.66x10^{-3}), CT-based N1/N2 stage

(P=4.48x10^{-6}) and hemameba (P=0.02) as independent impact factors of VI. The present study constructed a nomogram based on the features (Fig. 2). A nomogramn can indicate the points assigned to each variable by the top of the scale. The summation of each point (the total points) can be transformed to predict the possible risk of VI for patients at the lowest scale.

The calibration plot of the nomogram for the probability of VI demonstrated a good agreement between prediction and observation in the training data set (Fig. 3A). The P-value for the Hosmer-Lemeshow test was 0.60 (Fig. 3A), which indicated that there was no departure from a perfect fit. The AUC for the prediction nomogram was 0.731 in the training dataset (Fig. 3B).

These 4 features were used in the construction of the nomogram (Fig. 2). Each feature corresponds to a specific point by drawing a straight line up to the point axis. After the summation of the points has been plotted on the master axis, which represents the probability of VI, it is drawn directly down to the diagnostic axis. For example, 1 patient with CRC was recorded to have poor differentiation (100 points), a CT N stage of N1 (32 points), a tumor distance from the anus <5 cm (10 points), and the hemameba count was 10x10^9 (51 points). In this example, the total points equated to equals 193, and the VI probability is ~60%. According to the 50% threshold for this patient, they are high-risk and neoadjuvant chemotherapy should be considered.

Validation of the nomogram. The present study observed good identification (Fig. 4B) and good calibration (Fig. 4A) in the validation dataset. The nomogram exhibited an AUC of 0.710 (Fig. 4B). Validation of the calibration curve exhibited good concordance between the predicted probability and actual probability. The Hosmer-Lemeshow test yielded a non-significant statistic (P=0.281; Fig. 4A).

Clinical usefulness of the nomogram. Predicted probability of VI could be obtained from the nomogram. With the DCA based on 664 patients, the present study performed decision-making based on the evaluation for improvement of the nomogram. As shown in Fig. 5, the DCA curve indicated that if the probability of producing VI by the nomogram is >20 and <70%, it is more beneficial to predict VI with the treat-all-patients scheme or the treat-none scheme. For example, with a 60% probability of VI, the nomogram increases the net benefit by 4.4% of the treat-all-patients scheme or the treat-none scheme. This suggests the nomogram is clinically useful.

Discussion

In the present study, the single preoperative clinical features of a nomogram for the prediction of VI in patients with CRC, combined with clinical features was constructed and validated. Nomograms have high prediction accuracy and reliability. To the best of our knowledge, this is the first preoperative predictive tool for patients with CRC, who are at a high-risk of VI, in addition to facilitating the preoperative optimization strategy for this group. Although magnetic resonance imaging (MRI) and CT are the main diagnostic methods recommended by the NCCN guidelines for preoperative clinical staging, they are also the main diagnostic basis for the differential diagnosis of VI.

Table I. Patient characteristics.

Factor	n	%
Age, years		
17-30	14	2.1
31-45	69	10.4
46-60	259	39.0
>60	322	48.5
Sex		
Male	389	58.6
Female	275	41.4
Body mass index, kg/m^2		
≤18.4	73	11.0
18.5-23.9	431	64.9
24-27.9	136	20.5
≥28	24	3.6
Primary site		
Rectum	314	47.3
Colon	350	52.7
Weight loss, kg		
<3	474	71.4
3-6	132	19.9
>6	56	8.4
First-degree relatives' tumor history		
No	525	79.1
Yes	139	20.9
CT T Stage		
T1	10	1.5
T2	70	10.5
T3	200	30.1
T4	384	57.8
CT N Stage		
N0	371	55.9
N1	190	28.6
N2	103	15.5
Differentiation		
Well	25	3.8
Moderately	537	80.9
Poorly	102	15.4
Tumor gross type		
Ulceration	337	50.8
Infiltrative	43	6.5
Ulceration and Infiltrative	40	6.0
Protruded	239	36.0
Other	5	0.8
Tumor distance from anus, cm		
<5	65	9.8
5-10	165	24.8
11-15	73	11.0
>15	361	54.4
Perineural invasion		
No	329	49.5
Yes	335	50.5

Table I. Continued.

Factor	n	%
Vascular invasion		
No	461	69.4
Yes	203	30.6
Lymphovascular invasion		
No	429	64.6
Yes	235	35.4

CT, computed tomography.

Table II. Multivariable logistic regression analysis of the selected clinical features in the training set.

Variable	Odds ratio (95% CI)	P-value
Differentiation		
Well	1	
Moderately	5.92 (1.17-108.09)	0.09
Poorly	20.52 (3.77-384.19)	4.66×10^{-3}
CT N Stage		
N0	1	
N1/N2	2.73 (1.78-4.22)	4.48×10^{-6}
Tumor distance from anus, cm		
<5	1	
5-10	0.76 (0.34-1.73)	0.50
11-15	1.95 (0.81-4.81)	0.14
>15	0.88 (0.42-1.89)	0.74
Hemameba	0.88 (0.79-0.97)	0.02

CT N Stage, computed tomography-based N stage; CI, confidence interval.

However, due to the limitations of these imaging techniques, CT and MRI need to accurately identify VI, especially small vessel invasion; however, technical problems remain, affecting the staging and prognosis (23,24). A previous reported that the accuracy of CT recognition of VI is 30.9%, and the accuracy of MRI recognition of VI is 54% (23,24). However, the accuracy of CT and MRI in the identification of VI is associated with the clinical experience of doctors, therefore this accuracy rate may be even lower (23,24). However, the present nomogram revealed that the AUC value of VI is 0.731, which is of high sensitivity and specificity. Both have their own advantages, however the combination of the two can better identify VI (23,24). VI is a fundamental determinant of solid tumor progression, which is a strong prognostic indicator in CRC (25). A number of studies have demonstrated that VI is a negative prognostic index for the survival of patients undergoing radical resection of CRC (3,9,16).

The tumor microenvironment (TME) is a complex system composed of cells, cytokines and extracellular matrix (26). VI
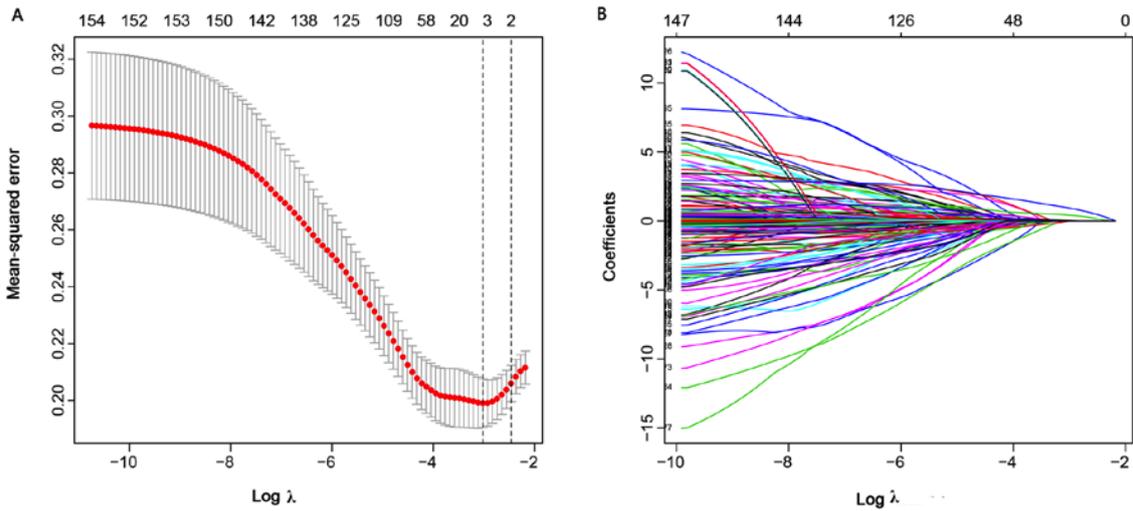
Figure 1. Texture feature selection using the LASSO binary logistic regression model. (A) By selecting a 10-fold cross-validation in the LASSO model with minimum standards. The binomial deviance was plotted versus log (λ). Dotted vertical lines were drawn at the optimal λ values based on the minimum criteria and 1 standard error of the minimum standards and the optimal λ was 0.048.(B) The LASSO logistic regression algorithm was used to screen out 4 features with non-zero coefficients out of 154 features. LASSO, least absolute shrinkage and selection operator.
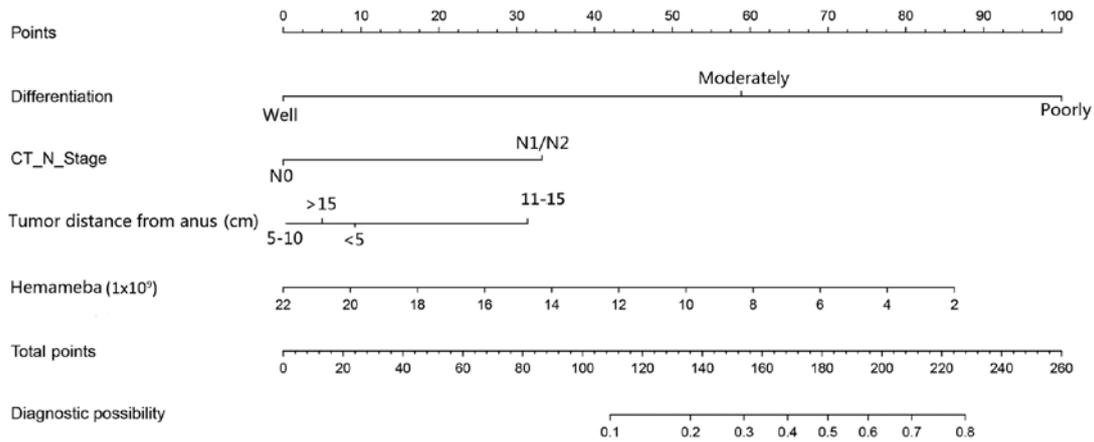
Figure 2. Developed clinical features nomogram, with the features: Differentiation, CT N Stage, tumor distance from anus (cm) and hemameba. CT N Stage, computed tomography-based N stage.
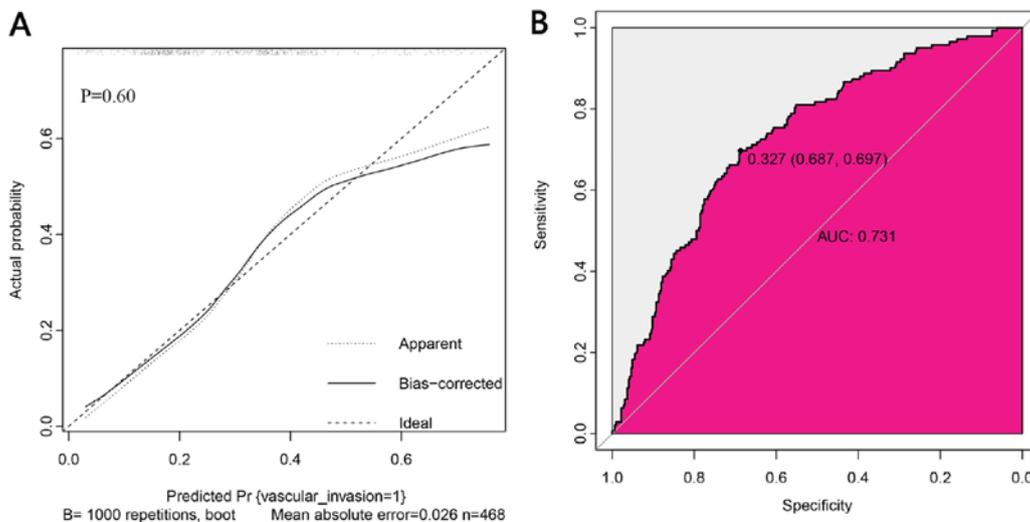
Figure 3. The performance of the nomogram in the training set. The LASSO algorithm and the Hosmer-Lemeswell test was used in the training set. (A) Calibration curve of the nomogram in the training dataset. (B) AUC curve of the nomogram in the training dataset. AUC, area under the curve; LASSO, least absolute shrinkage and selection operator.
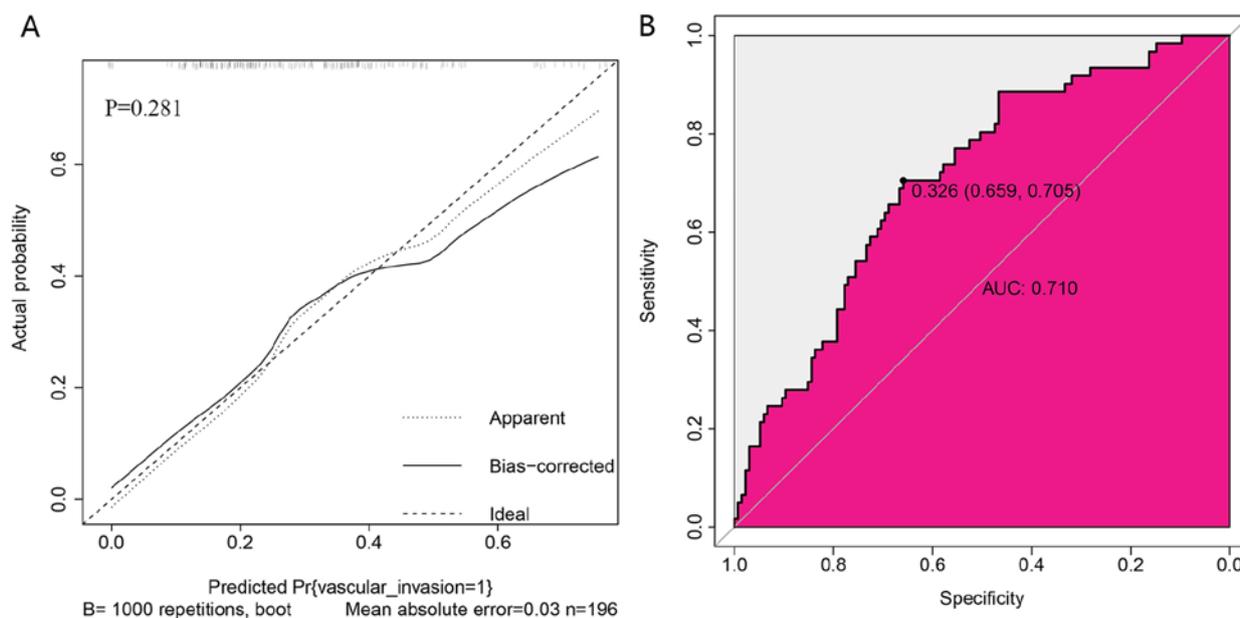
Figure 4. The performance of the nomogram in the validation set. The LASSO algorithm and the Hosmer-Lemeswell test was used in the validation set. (A) Calibration curve of the nomogram in the validation set. (B) AUC curve of the nomogram in the validation set. AUC, area under the curve; LASSO, least absolute shrinkage and selection operator.
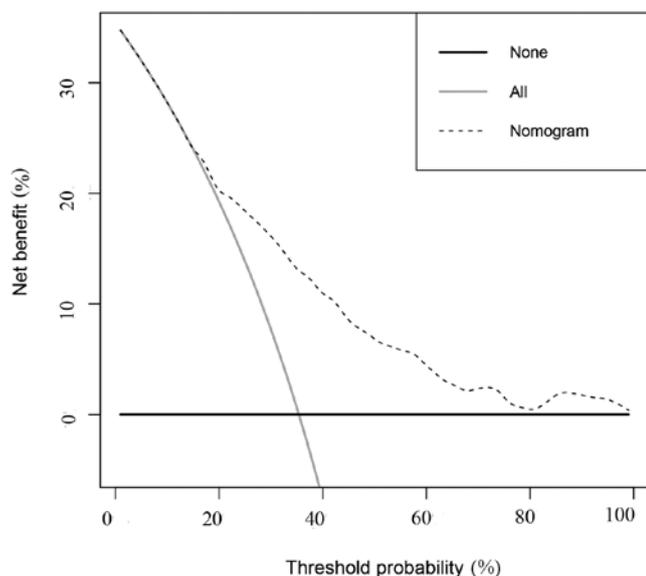
Figure 5. DCA for the VI production nomogram and the model. The y-axis shows the net benefit. The dotted line represents the VI production nomogram. The grey line represents the assumption that all patients have VI. The thin black line represents the assumption that no patients have VI. When the nomogram is >20 and <70%, the dotted line indicates that patients benefit from the nomogram. DCA, decision curve analysis; VI, vascular invasion.

is associated with the influence of TME (26,27). Tumor cell proliferation requires nutrients and energy, and vessels are important channels for providing the above (27). The secretion of VEGF, fibroblast growth factor, angiopoietin-like proteins and the corresponding inflammatory cells by tumor cells and other cells in the TME environment can promote the formation of new vessels (28,29). This can lead to the recurrence and metastasis of the tumor (27-29). Therefore, VI-positive can mean the progression or recurrence of the disease (30).

To construct a nomogram for the preoperative prediction of VI in patients with CRC, the present study first screened out the most significant predictive features using a LASSO logistic regression. This method has been widely used in the feature selection of high-dimensional data (18). It is more suitable than the linear regression method to analyze the data of the selection study with dichotomous fitness results, and it is regarded as an analytical tool for the empirical study of multivariate selection (31).

The nomogram had favorable discrimination and calibration, with a P-value for the Hosmer-Lemeshow test of 0.60 and an AUC of 0.731 in the training dataset. The results of the nomogram were evaluated in the validation dataset, which indicated that the nomogram had reasonable discrimination and good calibration, with an AUC of 0.710 and a P-value 0.281 via the Hosmer-Lemeshow test. The DCA curve showed that if the probability of VI generated by the nomogram was >20 and <70%, the prediction of VI will be more effective than either the treat-all scheme or the treat-none scheme. Therefore, the preoperative nomogram could be used as a clinical predictor of VI in patients with CRC.

A total of 4 factors were finally identified by the present nomogram: Differentiation, CT N stage, hemameba and tumor distance from the anus. Previous reports have demonstrated that these factors have an unusual impact on the prognosis of CRC (32-34), however, to the best of our knowledge, this is the first time they have been incorporated for modeling. A previous study reported the association between VI and distant metastasis and depth of invasion (32). As the differentiation level is associated with the malignant degree of the tumor, this study suggests that the degree of differentiation may be a reasonable predictor of VI (3,32). Preoperative MRI examination is an effective and convenient method for evaluating tumor staging, depth of invasion and local metastasis (35).

Inflammatory markers include inflammatory cells, various immune cells, cytokines, chemokines and pro-inflammatory mediators, of which hemameba is the most significant indicator (28,36). This is because hemameba is associated with the pathogenesis of various inflammatory processes, including allergies, parasitic diseases, bacterial and viral infections, and tumor immune tissue damage (29,33,37). Chronic inflammation can be caused by tumor proliferation (34). Hemameba accumulate in inflammatory sites through blood circulation (28). Hemameba and their secreted products promote the development and metastasis of tumors through the immune response. For example, CCL 20/CCR 6 mediate organ selective liver metastasis of colorectal cancer (29,36-39).

A previous tudy reported that ~20% of cancer-related mortality is associated with inflammatory cells leading to cell transformation and the enhancement of tumor cell invasion. White blood cells are an important component of inflammatory cells (27). Hemameba also play an important role at different stages of tumor development, including initiation, promotion, malignant conversion, invasion and metastasis (34), which is the index of tumor therapy. It can also be used to predict postoperative infection in patients (40). A previous study also reported that it is an independent risk factor for surgical site infection (40).

The present study presented with several limitations. First of all, due to the single center utilized for retrospective research, potential selection bias is inevitable. Secondly, although a genome classifier is a promising predictor, no application of genome features has been considered. In addition, the sample size of the validation set is small, which may affect the credibility of the evaluation results to some extent. Finally, the validation of the results using the same cohort of patients is another potential limitation of the study, and a larger external validation with multi-center and larger samples may the optimal choice. Therefore, further efforts are required to collect additional data and incorporate more impartial predictors to improve the performance of the model.

In conclusion, this model has good discrimination and calibration capability. It may be used in patients with CRC prior to surgery as it predicted VI for the majority of patients and it may help to provide accurate treatment options.

Acknowledgements

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Authors' contributions

WT, LG, WX, XH and JL conceived and designed the experiments. XH, JL, GW, FJ, SC, CZ, WX, WT, LG, WY, CL and ZL performed the experiments. XH, JL and GW analyzed the data. XH, JL, GW, FJ, SC, CZ, WX, WT, WY, CL and ZL contributed to the reagents, materials and analysis tools used in the present study. XH, JL, WT and WX wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics and Human Subject Committee of Affiliated Tumor Hospital of Guangxi Medical University (approval no. LW2019020, Nanning, China). Due to the retrospective design of the current study and patient anonymization, the review board determined that informed consent was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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