Nomogram for Predicting Occurrence of Synchronous Liver Metastasis in Colorectal Cancer: A Single-center Retrospective Study Based on Pathological Factors

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Abstract

Purpose

The purpose of this study was to explore the risk factors for liver metastasis (LM) of colorectal cancer (CRC) and to construct a nomogram for predicting the occurrence of synchronous LM based on baseline and pathological information.

Methods

The baseline and pathological information of 3190 CRC patients from the Department of Colorectal Surgery, the Second Affiliated Hospital of Harbin Medical University between 2012 and 2020 were included. All patients were divided into development and validation cohorts with the 1:1 ratio. Univariate and multivariate logistic regression models were utilized to identify the potential predictors of LM in CRC patients. Using the R tool to create a predictive nomogram. In addition, receiver operating characteristic (ROC) curves was calculated to describe the discriminability of the nomogram. A calibration curve was plotted to compare the predicted and observed results of the nomogram. Decision-making curve analysis (DCA) was used to evaluate the clinical effect of nomogram.

Results

The nomogram consisted of six features including tumor site, vascular invasion (VI), T stage, N stage, preoperative CEA and CA-199 level. ROC curves for the LM nomogram indicated good discrimination in the development cohort (AUC = 0.885, 95% CI 0.854-0.916) and the validation cohort (AUC = 0.857, 95% CI 0.821-0.893). The calibration curve showed that the prediction results of the nomogram was in good agreement with the actual observation results. Moreover, the DCA curves determined the clinical application value of predictive nomogram.

Conclusions

The pathologic-based nomogram could help clinicians to predict the occurrence of synchronous LM in postoperative CRC patients and provide a reference to perform appropriate metastatic screening plans and rational therapeutic options for the special population.

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the world, with high incidence and mortality globally. Metastases are one of the most common contributors for death in CRC, of which liver metastasis (LM) is the most fatal[1]. At present, research on LM in CRC patients is continuing [2–4]. It is important to note that LM are found in more than 25% of patients with CRC at the time of their first diagnosis and occur in up to 25% of patients following removal of the primary tumor. Over the course of the disease, a total of 50% of patients with CRC are likely to develop LM [5, 6]. The 5-year survival rate for

patients with CRC is about 56%, but it can be significantly shortened when metastases are diagnosed [7, 8].

LM of CRC can be divided into synchronous and metachronous LM. Synchronous LM was defined as LM detected at the time of diagnosis of the primary tumor or within 6 months after diagnosis. *Jennie et al* found that up to 18.3% of patients developed LM after radical CRC surgery [9]. Therefore, early detection of high-risk postoperative populations for synchronous LM can help physicians to improve survival by targeting screening and individualizing treatment. With the deepening of research in recent years, more and more risk factors affecting LM of CRC have been discovered such as T stage, N stage, tumor site, preoperative CEA level and so on[10, 11]. However, most studies did not include vascular invasion (VI) as a pathological factor. Both the Association of Directors of Anatomic and Surgical Pathology[12] and the College of American Pathologists[13] emphasis is placed on documenting VI during routine pathological examination of cancer specimens. These institutions emphasized that VI was an independent predictor of poor prognosis and increased risk of LM because VI necessarily increased the risk of tumor cell entry into the bloodstream. Many studies back this up [14, 15]. In addition, VI is an indication for adjuvant chemotherapy in stage II patients. Therefore, there are sufficient and necessary reasons to consider VI as a risk indicator for LM. Nomogram is a kind of graphical prediction model with friendly interface, which has strong clinical application value. By assigning points, we can not only observe the influence of certain parameters but also predict the probability of a particular event from the total score. To our knowledge, this is the first nomogram including VI to predict LM of CRC.

Methods

Patients

CRC cases were collected from the department of colorectal surgery, the Second Affiliated Hospital of Harbin Medical University between 2012 and 2020.

Inclusion criteria included: 1) Patients diagnosed with colorectal cancer and underwent surgery; 2) Aged ≥ 18 years old; 3) Patients with complete pathological information; 4) CRC was the only primary malignancy. Exclusion criteria included: 1) Patients received preoperative neoadjuvant chemoradiotherapy; 2) The baseline and pathological information of the patient was incomplete and 3) distant metastases other than LM.

Variables

According to our study, age was regrouped into < 60, 60-74 and ≥ 75 years old; sex was classified as male and female; BMI was recorded as < 25 and ≥ 25; tumor size was divided into three groups; ≤ 5cm and > 5 cm. The tumor site was grouped into right-sided colon (cecum, ascending colon, hepatic flexure and transverse colon) and left-sided colon (splenic flexure, descending colon and sigmoid colon). The histology variable was classified as “adenocarcinoma”, “mucinous adenocarcinoma” or “others”; the

grade variable was classified as I/II and III/IV stage and the tumor type variable was classified as “ulcer type”, “uplift type” and “infiltrating type”. Similarly, T stages, N stages and lymph nodes examined (LNE) are grouped. The most prominent variable that VI, nerve invasion and lymphatic invasion were classified as “yes” or “no”. The preoperative CEA and CA-199 level variable was classified as “positive” and “negative”.

Statistical analysis

All statistical analyses were performed by R software and SPSS 22.0. In this study, all patients were randomly (1:1 ratio) divided into development and validation cohorts and summarized by number and percentage. Univariate and multivariate logistic regression analyses were performed to determine risk factors for LM in colorectal patients. Nomogram was established based on the results of multivariate regression model, and its performance was further evaluated by calibration and AUC curves. The DCA curve was used to evaluate the clinical decision ability of the model. In addition, all variables were assigned and the best cutoff value was calculated based on the total score by Youden’s index. The difference was considered statistically significant for a two-sided $P < 0.05$.

Results

Patients characteristics

A total of 3190 patients were divided evenly into the development and validation cohorts. There were 104(6.5%) LM patients in development cohort and 107(6.7%) LM patients in validation cohort. In all patients, the majority of patients were men, aged 60-74 and had a BMI of less than 25. Overall, the main proportions of the patients were associated with rectum, tumor size ≤5 cm, ulcer type, grade I/II, adenocarcinoma, preoperative CEA and CA-199 level negative, T4 stage, N0 stage and LNE≥12. In the encroachment around, VI accounted for 28.8% and 30.5% in the development and validation cohorts. The detailed data was summarized in Table 1.

Table 1
Baseline characteristics of CRC patients in our study

Characteristics	Development cohort (n, %)	Validation cohort (n, %)	P-value
Age(years)			**0.923**
60	645(40.4)	644(40.4)	
60-74	737(46.2)	745(46.7)	
≥75	213(13.4)	206(12.9)	
BMI			**0.273**
25	1123(70.4)	1151(72.2)	
≥25	472(29.6)	444(27.8)	
Sex			**0.054**
Male	1011(63.4)	958(60.1)	
Female	584(36.6)	637(39.9)	
Tumor site			**0.663**
Right-sited colon	353(22.1)	373(23.4)	
Left-sited colon	376(23.6)	373(23.4)	
Rectum	866(54.3)	849(53.2)	
Tumor size(cm)			**0.187**
≤5	915(57.4)	878(55.0)	
5	680(42.6)	717(45.5)	
Tumor type			**0.671**
Ulcer type	1152(72.2)	1170(73.4)	
Uplift type	430(27.0)	415(26.0)	
Infiltrating type	13(0.8)	10(0.6)	
Grade			**0.678**
I/II	1376(86.3)	1384(86.8)	
III/IV	219(13.7)	211(13.2)	
Histology			
Adenocarcinoma	1288(80.8)	1270(79.6)	**0.726**
Mncinous	290(18.2)	307(19.2)	

Characteristics	Development cohort (n, %)	Validation cohort (n, %)	P-value
Other	17(1.1)	18(1.1)	
T			**0.128**
T1/T2	172(10.8)	166(10.4)	
T3	703(44.1)	653(40.9)	
T4	720(45.1)	776(48.7)	
N			**0.839**
N0	1009(63.3)	1014(63.6)	
N1	372(23.3)	378(23.7)	
N2	214(13.4)	203(12.7)	
LNE			
12	262(16.4)	274(17.2)	
≥12	1333(83.6)	1321(82.8)	
Vascular invasion			**0.295**
no	1135(71.2)	1108(69.5)	
yes	460(28.8)	487(30.5)	
Nerve invasion			**0.667**
no	682(42.8)	670(42.0)	
yes	913(57.2)	925(58.0)	
Lymphatic invasion			**0.499**
no	1071(67.1)	1053(66.0)	
yes	524(32.9)	542(34.0)	
CEA			**0.472**
Positive	504(31.6)	523(32.8)	
Negative	1091(68.4)	1072(67.2)	
CA199			**0.516**
Positive	241(15.1)	228(14.3)	
Negative	1354(84.9)	1367(85.7)	
liver metastasis			**0.831**

Characteristics	Development cohort (n, %)	Validation cohort (n, %)	P-value
Yes	104(6.5)	107(6.7)	
No	1491(93.5)	1488(93.3)	

Construction and validation of nomogram to predict LM probability

Univariate and multivariate logistic regression analyses were performed to determine the independent risk factors for DM step by step. In univariate analysis, the candidate predictors for the model were age, BMI, sex, tumor size, tumor site, tumor type, grade, histology, T stage, N stage, LNE, VI, nerve invasion, lymphatic invasion, preoperative CEA and CA-199. All the predictors except for age, BMI, sex, tumor type, histology and LNE were of statistical significance in the development cohorts, which were then further analyzed by multivariate logistic regression model. And the results indicated that tumor site (OR = 2.228, 95%CI =1.272-3.901 for right-sited colon, P = 0.005; OR =1.635, 95%CI = 0.889-3.007 for left-sited colon, P = 0.114; using rectum as the reference), VI (OR = 1.965, 95%CI = 1.182-3.266 for yes, P = 0.009; using no as the reference), T stage (OR = 0.130, 95%CI = 0.017-1.014 for T1/T2, P = 0.052; OR = 0.417, 95%CI = 0.245-0.710 for T3, P = 0.001; using T4 as the reference), N stage (OR = 1.252, 95%CI = 0.665-2.359 for N1, P = 0.487; OR = 4.071, 95%CI = 2.117-7.830 for N2, P 0.001; using N0 as the reference), CEA level (OR = 3.043, 95%CI =1.836-5.043 for CEA Positive, P < 0.001, using CEA negative as the reference), CA-199 level (OR = 6.006, 95%CI = 3.697-9.756 for CA-199 positive, P < 0.001, using CA-199 negative as the reference) were independent risk factors in predicting LM (Table 2).

Table 2
Logistic regression analysis of the risk factors for LM in CRC patients

	Univariate analysis		Multivariate analysis	
Characteristics	**OR [95% CI]**	**P-value**	**OR [95% CI]**	**P-value**
Age(years)				
<60	0.966[0.526-1.774]	0.912		
60-74	0.858[0.469-1.572]	0.621		
≥75	Ref			
BMI				
<25	1.151[0.538-1.151]	0.538		
≥25	Ref			
Sex				
Male	1.004[0.664-1.516]	0.987		
Female	Ref			
Tumor site				
Right-sited colon	2.787[1.764-4.402]	**<0.001**	2.228[1.272-3.901]	**0.005**
Left-sited colon	1.446[0.857-2.441]	0.168	1.635[0.889-3.007]	0.114
Rectum	Ref		Ref	
Tumor size(cm)				
≤5	0.670[0.450-0.998]	**0.049**	1.033[0.638-1.671]	0.896
>5	Ref		Ref	
Tumor type				
Ulcer type	0.438[0.096-2.009]	0.288		
Uplift type	0.226[0.047-1.102]	0.066		
Infiltrating type	Ref			
Grade				
I/II	Ref		Ref	
III/IV	2.793[1.779-4.384]	**<0.001**	0.982[0.555-1.737]	0.949
Histology				

	Univariate analysis		Multivariate analysis	
Adenocarcinoma	0.297[0.083-1.055]	0.060		
Mncinous	0.421[0.113-1.568]	0.197		
Others	Ref			
T				
T1/T2	**0.049[0.007-0.354]**	**0.003**	0.130[0.017-1.014]	0.052
T3	0.321[0.203-0.507]	**<0.001**	0.417[0.245-0.710]	**0.001**
T4	Ref		Ref	
N				
N0	0.123[0.077-0.199]	**<0.001**	0.246[0.128-0.472]	**<0.001**
N1	0.263[0.156-0.443]	**<0.001**	0.308[0.165-0.573]	**<0.001**
N2	Ref		Ref	
LNE				
<12	0.920[0.531-1.595]	0.767		
≥12	Ref			
Vascular invasion				
no	0.258[0.171-0.387]	**<0.001**	0.509[0.306-0.846]	**0.009**
yes	Ref		Ref	
Nerve invasion				
no	0.402[0.253-0.637]	**<0.001**	1.050[0.594-1.856]	0.866
yes	Ref		Ref	
Lymphatic invasion				
no	0.547[0.367-0.817]	**0.003**	1.383[0.810-2.363]	0.235
yes	Ref		Ref	
CEA				
Positive	0.148[0.095-0.232]	**<0.001**	0.329[0.198-0.545]	**<0.001**
Negative	Ref		Ref	
CA199				
Positive	0.080[0.052-0.123]	**<0.001**	0.167[0.103-0.270]	**<0.001**

	Univariate analysis	Multivariate analysis
Negative	Ref	Ref

Subsequently, we built a nomogram to predict LM for postoperative patients based on independent risk factors (tumor site, VI, T stage, N stage, preoperative CEA and CA-199 level) (Figure 1). The AUCs for development cohort and validation cohort were 0.885 (95%CI = 0.854-0.916) and 0.857 (95%CI =0.821-0.893), respectively (Figure 2). The calibration curves (development cohort: p = 0.772; validation cohort: p = 0.198) showed the relatively satisfactory prediction accuracy of the nomogram (Figure 3). In addition, the DCA curve also indicated good clinical practicability in both cohorts (Figure 4).

Using the nomogram derived scores, all LM patients were classified into two subgroup low-risk (risk score ≤ 193) and high-risk groups (risk score > 193) (Figure 5). And we found there were significant differences in the occurrence of LM between the high and low risk groups in development cohort (P < 0.001) and validation cohort (P < 0.001) (Figure 6).

Discussion

CRC is one of the major causes of cancer morbidity and mortality both in the worldwide. Distant metastasis disease is the main cause of unfavorable prognosis in patients with CRC and the liver is the most common organ for metastasis. Over the course of the disease, a total of 50% of patients with CRC are likely to develop LM. And the death rate remains high[16]. This also explains the necessity of this study. Nowadays, many studies [17, 18] have identified many independent factors for LM in patients with CRC but few studies developed predictive nomogram and the factors included are incomplete, this also has led to questions about the accuracy of those nomograms. Our study included not only the baseline information of the patients, but also the postoperative pathological information of the patients such as the VI. This greatly increases the sensitivity and specificity of this model. This nomogram can help identify high-risk groups for synchronous LM after surgery and help clinicians conduct targeted screening and individualized treatment.

According to previous studies, the prevalence of CRC LM is more common than other metastases, such as the brain or bone [19, 20] and the prevalence of LM was more than 20% [21, 22]. However, the prevalence in this study was less than 20% which was consistent with one study conducted by Manfredi and his colleagues in France [23]. In this study, the incidence was only 13.2% in older patients, which was significantly lower than in younger patients. Because in the past few years, as colonoscopy screening has become more widespread, more and more early signs of cancer have been detected, leading to higher rates of disease in younger people and reducing the prevalence of LM. Tumor size has been shown to be an important factor in the development of LM from CRC [11], while little effect of tumor size was found in this study which might be partly attributed to sample size. Therefore, the various factors contributing to the development of LM in CRC should be identified and a screening method developed to determine whether CRC patients will develop LM.

This study showed that tumor site, T stage, N stage, VI, preoperative CEA level and CA-199 level, were significantly associated with LM development, which were seldom reported before. In our nomogram, colon cancer is found to be more likely to metastasize than rectal cancer. The most common mechanism is that the metastatic pattern is different. In colon cancer(CC), most mesenteric drainage enters the hepatic portal vein system and the rectal venous-collected blood flows into the systemic circulation[24]. And right-sited CC is found to be more likely to metastasize than left-sited CC, which is consistent with previous articles [11, 22, 23], it was reported that the discrepancy was caused by molecular biological differences [25, 26]. In addition, it is well known that high T stage, N stage and tumor marker levels represent the malignancy of the tumor, indicating a high likelihood of LM. To some extent, it may explain the difference in prognosis, but this complex issue needs further research.

Since VI is closely related to progression and recurrence of the disease, both the Association of Directors of Anatomic and Surgical Pathology and the College of American Pathologists emphasis is placed on documenting VI during routine pathological examination of cancer specimens. It is reported that the pathologic detection rate of VI was 23% [27]. The proliferation of tumor cells requires energy and nutrition, tumor and other cells secrete VEGF, angiopoietin like protein and corresponding inflammatory cells to promote the formation of new blood vessels, thus providing an important channel for these functions [28]. Invasion of blood vessels by tumor cells is a key step in LM. *Fujii T* and *Xie W* et al found that VI is closely related to the depth of tumor invasion and degree of differentiation [29, 30]. A previous study has shown that VI is significantly associated with metastasis and high recurrence rates [31]. Furthermore, VI has been shown to be associated with reduced overall survival and disease-free survival, serving as a strong prognostic indicator [32], which was significantly associated with distant metastasis. These studies indicate that VI is an essential factor in LM of CRC. The inclusion of this factor improves the accuracy and persuasiveness of our model.

In addition, our research has certain research significance and advantages. Our model mainly predicts high-risk patients who are prone to synchronous LM after surgery by pathological factors. In high-risk groups, where there may be micrometastases that were not detected before surgery, the cost of enhanced computed tomography and monitoring should be justified after surgery.In addition, for high-risk patients, invasive procedures such as needle biopsy are also recommended for definite diagnosis if there is an undefined low-density liver lesion. Of course, this study only provides a reference rather than a guide, and specific decisions should be made based on clinical practice.

The study has several limitations. First of all, since this study is a retrospective study, involving 3190 patients from 2012 to 2020, there may be a possibility of inaccuracy due to the small amount of data, and inevitably there is observer and confusion bias. The current results require further validation in prospective clinical studies. Second, although our model has internal validation, there is a lack of external validation to further determine the model's accuracy. Third, some underlying factors such as BRAF and RAS mutation status are unknown. The inclusion of these important factors can further improve the effectiveness of the nomogram.

In conclusion, this study performed prediction of synchronous LM in patients undergoing CRC surgery. Therefore, if patients with preoperative diagnosis of colorectal cancer, no LM and underwent surgery are identified as a high-risk patient by nomogram, we should enhance post-operative imaging of the liver, such as enhanced computed tomography, MRI and positron emission tomography computed tomography (PET-CT). It can help clinicians timely detect the disease progression of patients and take effective interventions to improve the quality of life of patients. This is crucial.

Declarations

Acknowledgments

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Data availability

The study data of validation cohort used and/or analyzed during the current study are available from the Second Affiliated Hospital of Harbin Medical University, China

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None

Competing Interests

The authors have no conflicts of interest to declare.

Consent to publication: No applicable.

Ethical statements

This study was approved by the Second Affiliated Hospital of Harbin Medical University and Zhejiang Cancer Hospital. The study used de-identified data and adhered to World Medical Association's Declaration of Helsinki for Ethical Human Research. The informed consent was not required according to personal identifying information was not included.

Author Contributions

Study concept and design: YXL and YLMW. Acquisition of data: YXL, YLMW, MYZ and CLW. Analysis and interpretation of data: YXL, YLMW, HZ, MYZ, YW and CLW. Drafting of the manuscript: YXL and YLMW. Critical revision of the manuscript for important intellectual content: YXL, YLMW, ZQH, HX, HQH, QCT and GYW. Corresponding author: GYW.

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Figures

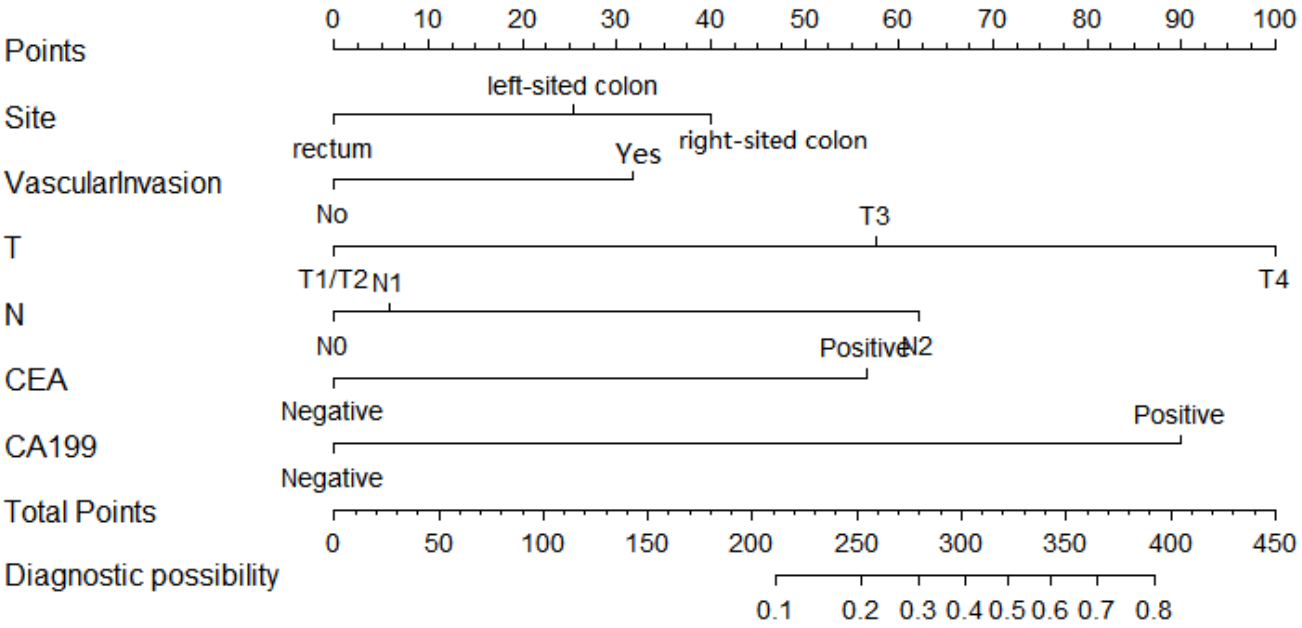

Figure 1

Nomogram for predicting the probability of LM

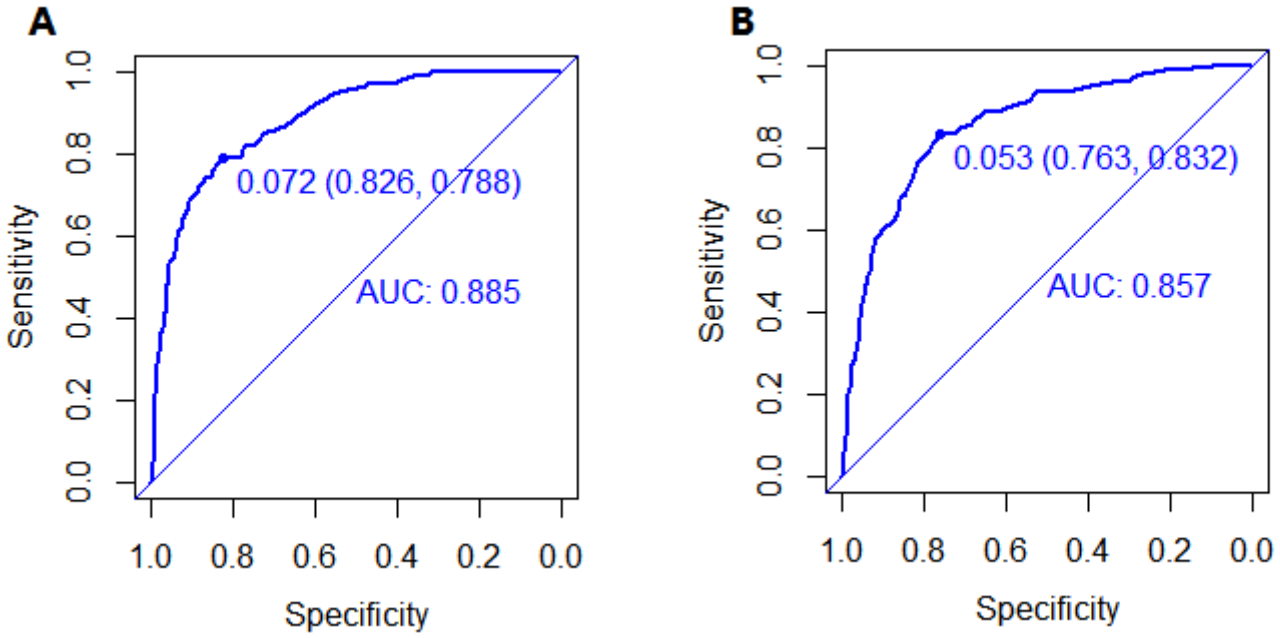

Figure 2

The ROC curves of nomogram for predicting LM in the development cohort (A) and validation cohort (B)

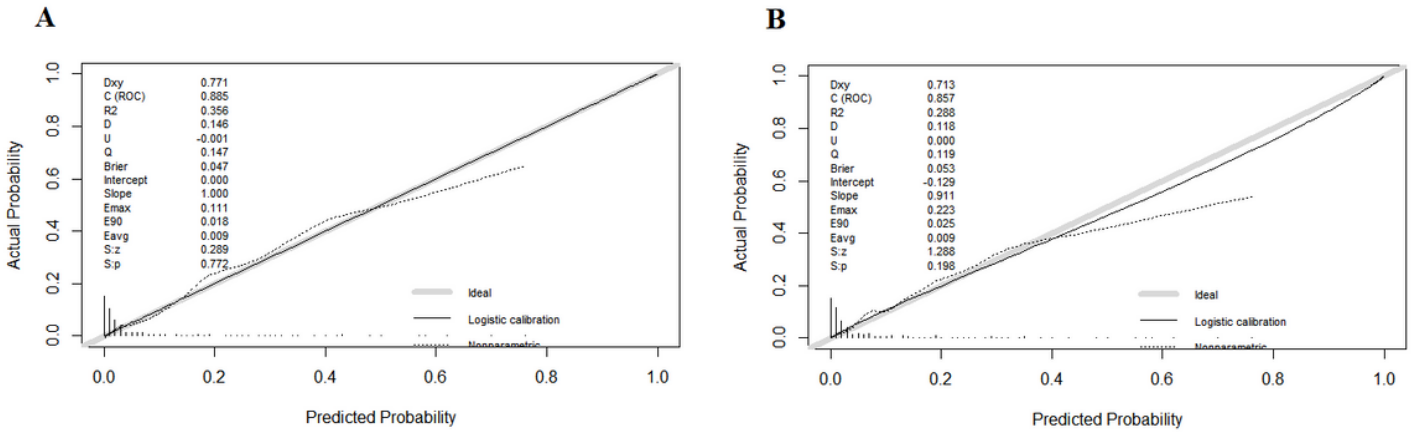

Figure 3

The calibration curves of the nomogram for predicting LM in the development cohort (A) and validation cohort (B)

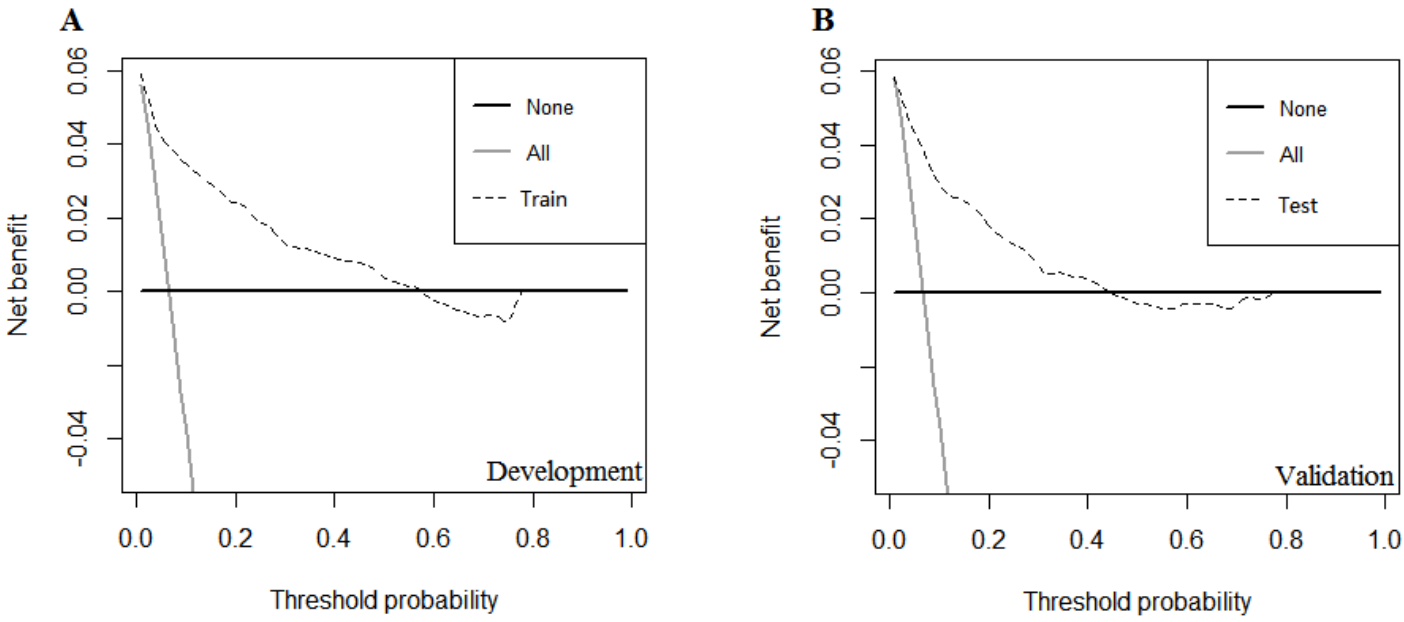

Figure 4

The DCA curves of the nomogram for predicting the occurrence of LM in the development cohort (A) and validation cohort (B)

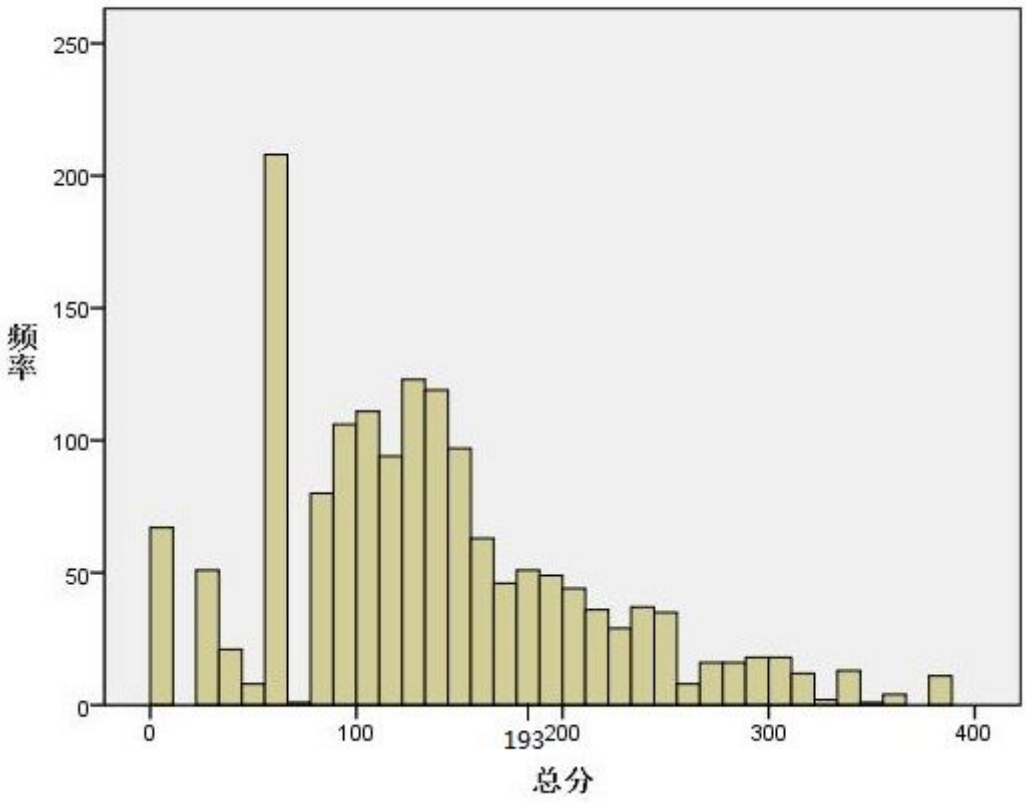

Figure 5

Calculate the cutoff value in LM patients

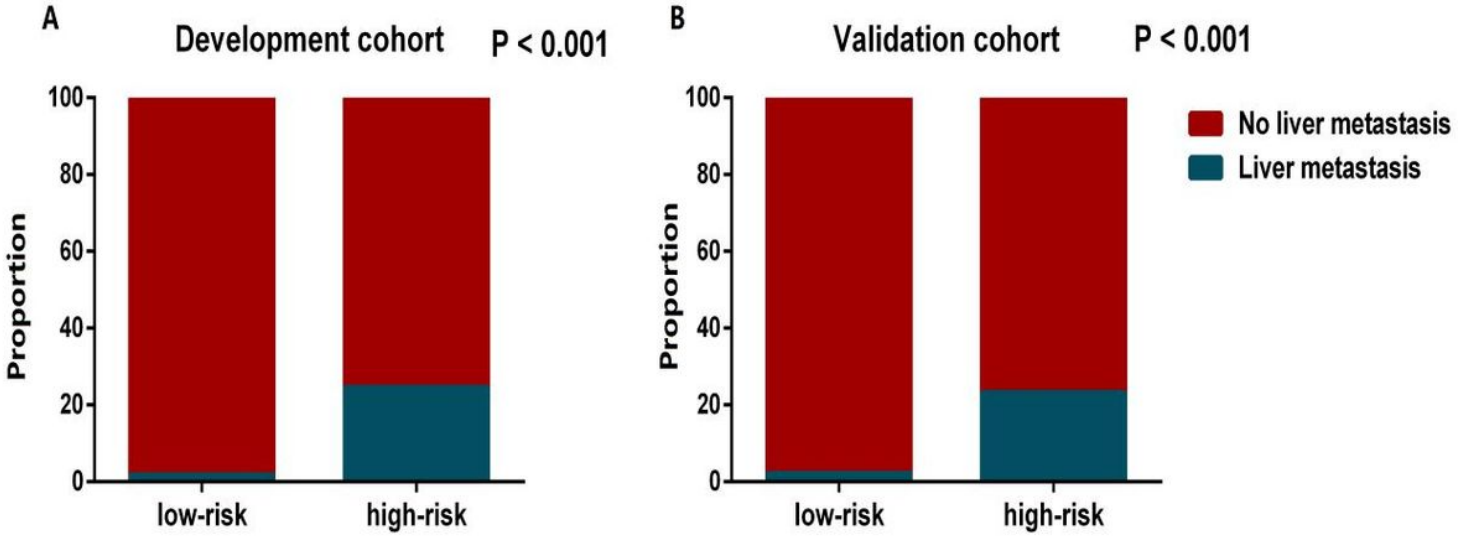

Figure 6

The proportion for LM patients in the low- and high-risk groups in the development cohort (A) and validation cohort(B)