Development and external validation of prognostic nomograms for liver disease-free and overall survival in locally advanced rectal cancer with neoadjuvant therapy: a post cohort study based on the FOWARC trial

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Background: There is still a lack of nomograms that can accurately predict liver metastasis and poor prognosis after neoadjuvant therapy for locally advanced rectal cancer (LARC). Effective nomograms may help clinicians better identify LARC patients with potential high-risk risks, so as to carry out more targeted monitoring, treatment and follow-up.

Methods: The nomograms were based on the FOWARC trial (NCT01211210), which included 302 LARC patients who underwent neoadjuvant treatment before surgery at the Sixth Affiliated Hospital of Sun Yat-sen University from 2011 to 2014. The predictive accuracy and discriminative ability of the nomograms were determined by the concordance index (C-index) and calibration curve. The results were validated using bootstrap resampling and a prospective study on 100 patients in 2017.

Results: The 3-year liver disease-free survival (LDFS) rate after neoadjuvant treatment for LARC was 91.65% (training cohort 92.22%, validation cohort 90.01%). Factors associated with LDFS were hepatitis B virus (HBV) infection, anemia, lymph node number, postoperative T stage and tumor nodule, which were all included in the nomogram for LDFS. The C-indies of the nomogram for LDFS were 0.828 and 0.845 in the training and validation cohorts. The 3-year overall survival (OS) rate was 94.14% (training cohort 94.13%, validation cohort 94.05%). Factors in the nomogram for OS were mesorectal fascia involvement (MRF), postoperative N stage, pathological differentiation, tumor nodule and neural invasion. The C-indies of the nomogram for predicting OS were 0.73 and 0.774 in the training and validation cohorts. The calibration curve for the survival probability showed good agreement between the nomogram predictions and the actual observations.

Conclusions: The nomograms established in this study can effectively predict LDFS and has good clinical application potential for OS in LARC patients treated with neoadjuvant therapy.

Keywords: Locally advanced rectal cancer (LARC); liver metastasis; nomogram; HBV infection; neoadjuvant therapy

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Introduction

The incidence rate of malignant tumors of colorectal cancer (CRC) ranks the third in the world, the fourth among men and the third among women (1). There are nearly 80,000 new cases in China every year, and the statistical incidence rate is 27.47/100,000 (2). Neoadjuvant therapy can improve the stage of locally advanced rectal cancer (LARC) and reduce the difficulty of surgery and local recurrence rate, improving the long-term prognosis. However, 50% of patients still have distant metastases within two years after surgery, most of which are concentrated in the liver (3).

The liver is the most common metastatic organ of rectal cancer. Malignant nodules of the liver due to metastasis from rectal cancer are called liver metastases (LM). At the first diagnosis, 15–25% of patients had synchronous liver metastasis, while the proportion of metachronous liver metastasis (MET-LM) within five years after the first diagnosis was close to 18–25% (4). At present, no studies have clearly reported the incidence of LM and the liver disease-free survival (LDFS) rate after neoadjuvant treatment for LARC, and there is a lack of prediction nomograms for LM.

Age, serum tumor marker level, pathological TN stage, circumferential resection margin (CRM) involvement, lymph node metastasis, gene mutation and so on were considered to be related factors for the prognosis of LARC. Some scholars have developed nomograms for the prognosis of LARC receiving neoadjuvant therapy, but they were based on the data of retrospective cohort, and did not predict the occurrence of liver metastasis (5-7). Therefore, on the basis of prospective cohort, the establishment of nomograms that can predict the prognosis of LARC, especially the risk of liver metastasis, is of great significance for identifying potential high-risk patients and adjusting treatment, monitoring and follow-up.

In this study, we used patients from a randomized clinical trial of neoadjuvant therapy for LARC (FOWARC) as a training cohort to establish prediction nomograms for LM and overall survival (OS). A validation cohort of 100 consecutive patients in the same center was established to test the accuracy of the prediction nomograms. We present the following article in accordance with the TRIPOD reporting checklist (available at available at https://atm.amegroups.com/article/view/10.21037/atm-22-2790/rc).

Methods

Patients and study design

Patients from the FOWARC trial were used as a training cohort in this study. FOWARC is an open-label, multicenter, randomized, phase 3 clinical trial registered on the clinicaltrials.gov website, with the identifying number NCT01211210 (8). From 2011 to 2014, 321 patients were enrolled and were randomized to receive one of the following schemes at a ratio of 1:1:1: Neoadjuvant radiation with 5-fluorouracil (5-FU) infusion (arm 1), neoadjuvant radiation with FOLFOX chemotherapy (arm 2), or neoadjuvant FOLFOX chemotherapy alone (arm 3).

The eligible patients were aged from 18 to 75 years old. They were diagnosed as rectal adenocarcinoma by pathology and considered it suitable for curative resection. At the first diagnosis, we confirmed that the tumor was stage II (T3-4N0) or stage III (T1-4N1-2) by magnetic resonance imaging (MRI) or computed tomography (CT) plus endorectal ultrasound. The positive lymph nodes were defined as ≥1.0 cm in diameter at the time of imaging, and the distal boundary was <12 cm from the anal verge. Patients were adequate liver, renal and hematologic function and required to have an Eastern Cooperative Oncology Group performance status ≤1. The key exclusion criteria were metastatic disease, previous radiotherapy or chemotherapy, or history of other cancers, clinically significant heart disease and known peripheral neuropathy. In addition to the above criteria, we excluded 19 patients who lacked the results of hepatitis B virus serological markers (HBVM) or died within 30 days after operation according to the purpose of this study. A total of 302 patients were included in the training cohort.

Using the same criteria as the training cohort, we conducted a prospective study on consecutive patients receiving LARC neoadjuvant therapy in the Sixth Affiliated Hospital of Sun Yat-sen University from January to September 2017, and formed a validation cohort. The study was censored on Jan 1, 2021.

Diagnosis and treatment

After completing a detailed medical history and complete physical examination, we recorded the results of hemoglobin, serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and hepatitis B serum markers in the first blood test. At the same time, we recorded the results of the first electronic colonoscopy, pathological biopsy, chest, abdominal and pelvic contrast-enhanced CT and rectal MRI. After confirmation of LARC according to the imaging and pathological results, patients in the training cohort received neoadjuvant therapy according to the random results, while patients in the validation cohort received neoadjuvant therapy after discussion with the multidisciplinary team (MDT). After completing neoadjuvant therapy, all patients underwent radical surgery for rectal cancer, and postoperative pathological data, including T stage, N stage, neural invasion, vascular invasion, and tumor nodule were collected. Patients continued adjuvant chemotherapy according to National Comprehensive Cancer Network (NCCN) guidelines after the operation, then entered the follow-up period.

LDFS, OS, and follow-up

LDFS was defined as the time between the first diagnosis and the first examination of LM, and OS was defined as the time between the first diagnosis and death. During the follow-up period, CT or B-ultrasound examination was performed every 3–6 months after operation. If abnormal nodules were found in the liver, CRLM will be further diagnosed by contrast-enhanced ultrasound or MRI. When necessary, biopsy will be performed for pathological diagnosis. All patients were followed up by the follow-up office of the Sixth Affiliated Hospital of Sun Yat-sen University.

Judgment of LM

All patients in this study were excluded with synchronous LM at the first diagnosis. For intrahepatic nodules after the first diagnosis, we performed liver imaging examination, detected the level of serum tumor markers, and performed ultrasound-guided biopsy and pathological diagnosis if necessary. After excluding primary liver cancer, hemangioma and hepatic cyst, we diagnosed these abnormal hepatic tumor nodules as MET-LM. All results were determined by two radiologists with more than five years of specific diagnostic experience.

Determination of HBV infection

HBVM was detected in all patients at the first diagnosis to determine whether they were infected with HBV. According to the results and combinations of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe) and hepatitis B core antibody (anti-HBc), the patients were divided into three HBV infection statuses. Chronic hepatitis B virus infection (CHB) was defined as HBsAg positive HBV infected patients. Occult hepatitis B virus infection (OHB) was defined as HBV infected patients who were HBsAg negative but positive with anti-HBe or anti HBc. No HBV infection (NHB) was defined as patients who were all HBVM negative or only anti-HBs positive.

Statistical methods

We used SPSS 21 software (IBM company) for statistical analysis, and GraphPad Prism 8 for survival analysis and mapping. For measurement data in the consistency test, the median was converted to two-class count data, and the chi-square test or Fisher's test was used to analyze the correlations with LM and poor prognosis. Factors with P values less than 0.1 in univariate analysis were included in multivariate analysis. We compared patients' LDFS and OS using Kaplan-Meier survival analysis. A two-tailed P value <0.05 was interpreted as statistically significant.

Nomograms were formulated based on the results of multivariate analyses and by using the rms package in R version 2.14.1 (http://www.r-project.org/). The final models adopted Akaike information criterion and were selected through the backward step-by-step selection process. We used the consistency index (C-index) to measure the performance of nomograms, and compared the probability predicted by nomograms with the observed Kaplan-Meier survival data for evaluation. Bootstraps for these activities were used with 1,000 resamples. Comparisons between nomograms were evaluated using the C-index. The larger the C-index was, the more accurate the prognosis was. During the external validation of the nomogram, the total score of each patient in the validation queue is calculated according to the established nomogram. Cox regression was then performed in this cohort using the total points as a factor, and finally, the C-index and calibration curve

were derived based on the regression analysis. P<0.05 was considered statistically significant.

Ethical approval

The design of this study was in accordance with the Declaration of Helsinki (as revised in 2013). The relevant plans and conclusions were approved by the ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No. 2010017). All included participants signed an informed consent form.

Results

Clinicopathologic characteristics of patients

The training cohort consisted of 302 patients and the validation cohort of 100 consecutive patients. The clinicopathologic characteristics of patients in both cohorts are listed in *Table 1*, which shows LM was found in 23 patients in the training cohort (7.06%), and nine in the validation cohort (9%).

Independent prognostic factors of LM and poor prognosis in training cohort

The results of the univariate and multivariate analyses were listed in Tables S1,S2. The analysis demonstrated HBV infection, number of lymph nodes in pathological specimens, and tumor nodule were independent risk factors for LM. On the other hand, pathological differentiation, tumor nodules, and neural invasion were independent risk factors for poor prognosis, as shown in *Table 2*.

Prognostic nomograms for LDFS and OS

The prognostic nomogram integrating all factors for LDFS in the training cohort is shown in *Figure 1*. The C-index for LDFS prediction was 0.828 (95% CI: 0.746 to 0.910), and the calibration plot for the probability of LDFS at 1 to 3 years after surgery showed an optimal agreement between the prediction by the nomogram and the actual observation, as shown in Figure S1.

The prognostic nomogram that integrated all factors for OS in the training cohort is shown in *Figure 2*. The C-index for LDFS prediction was 0.730 (95% CI: 0.595 to 0.865), and the calibration plot for the probability of OS at 3 and 5 years after surgery showed an optimal agreement between the prediction by the nomogram and the actual observation, as shown in Figure S2.

Comparison of the predictive accuracy between nomograms with and without HBV infection and tumor nodules for LDFS

As shown in *Figure 1*, the hazard ratios of HBV infection and tumor nodules for LDFS were higher than the hazard ratios for the other factors. The predictive power for LDFS between the nomograms with and without HBV infection was compared, and the C-index for LDFS prediction without HBV infection was 0.768 (0.681–0.855), which was significantly lower than that considered with HBV infection (P=0.004).

Similarly, we also compared the C-index of nomograms with and without tumor nodules. The C-index for LDFS prediction without tumor nodules was 0.784 (0.704–0.864), which was significantly lower than that with tumor nodules (P=0.009).

Validation of the predictive accuracy of nomograms for LDFS and OS

In the validation cohort, the median follow-up was 39 months (range, 4–42 months), and the median LDFS time was 18 months (range, 7–30 months) in patients who experienced LM. The LDFS rates were 97% for 1 year, 93.5% for 2 years, and 90% for 3 years, while the OS rates were 100% for 1 year, 97.7% for 2 years, and 94% for 3 years.

The C-index of the nomogram for predicting LDFS was 0.845 (95% CI: 0.733 to 0.957), and a calibration curve showed good agreement between the predicted and observed probabilities of 1- to 3-year LDFS (Figure S3). The C-index of the nomogram for predicting OS was 0.774 (95% CI: 0.528 to 0.999), and a calibration curve also showed good agreement between the predicted and observed probabilities of 3-year OS (Figure S4).

Taking the total point value of 25 in the nomogram for LDFS as the cutoff, we divided patients into two groups and verified the LDFS differences between them. The results showed that in the two cohorts, the LDFS of patients with a total score ≥25 was significantly worse than those with a total score <25 (P<0.001, *Figure 3*). Similarly, we used a total point value of 10 in the nomogram for OS as the cutoff for verification. The results showed that in the two cohorts, the OS of patients with a total score ≥10 was significantly worse than those with a total score <10 (P<0.001, *Figure 4*).

Table 1 Clinicopathologic characteristics of patients

Characteristics	Training cohort, N=302	Validation cohort, N=100	P value
Gender			0.835
Male	205	69	
Female	97	31	
Age, years			0.204
≥56	150	57	
<56	152	43	
Anemia			0.378
Yes	60	24	
No	242	76	
HBV infection			0.357
Chronic HBV infection	27	12	
Occult HBV infection	59	24	
No HBV infection	216	64	
ALT >40 U/L			0.902
Yes	20	7	
No	281	93	
AST >40 U/L			0.169
Yes	9	6	
No	292	94	
ALB >35 g/L			0.003
Yes	301	97	
No	0	3	
CA19-9 >37 U/mL			0.303
Yes	44	19	
no	256	81	
CEA >5 ng/mL			0.003
Yes	98	49	
No	202	51	
Pathological differentiation			0.101
High and median	267	82	
Poor or mucinous	35	18	
Pretreatment T stage			0.846
2 or 3	245	82	
4	57	18	
Pretreatment N stage			0.058
0	59	18	
1	143	36	
2	100	46	
Pretreatment stage 3			0.735
Yes	243	82	
No	59	18	
Tumor bottom to anal >5 cm			0.526
Yes	180	56	
No	122	44	
Mesorectal fascia involvement			0.525
Yes	96	34	
No	206	66	
Tumor length			0.941
≥4 cm	189	63	
<4 cm	113	37	
Preoperation radiation			0.022
Yes	193	51	
No	109	49	
Lymph node number <12			0.658
Yes	195	67	
No	107	33	
Postoperative T stage			0.914
0 to 2	174	57	
3 or 4	128	43	
Postoperative N stage			0.504
1 or 2	56	16	
0	239	84	
ypTNM stage			0.356
2 or 3	155	46	
0 or 1	147	54	

Table 1 (*continued*)

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Training cohort, N=302	Validation cohort, N=100	P value
Tumor nodule			0.229
Yes	41	9	
No	261	91	
Vascular invasion			0.718
Yes	8	2	
No	294	98	
Perineural invasion			0.741
Yes	21	6	
No	281	94	
Efficacy of neoadjuvant therapy			0.661
0 or 1	133	47	
2 or 3	166	53	
HER-2			0.007
Positive	52	15	
Negative	124	85	
MSS			0.976
Yes	233	92	
No	20	8	
Metachronous liver metastasis			0.658
Yes	23	9	
No	279	91	
Death during follow-up			0.826
Yes	20	6	
No	282	94	

HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, serum albumin; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; MSS, microsatellite stability.

Discussion

Neoadjuvant therapy has been recognized as the standard regimen for the treatment of LARC. According to existing report, the 5-year OS and disease-free survival (DFS) of LARC patients treated with neoadjuvant therapy were 74.4% and 65.4%, respectively, the local recurrence rate was 3.5%, and the distant metastasis rate was 20.6% (3). With the wide application of standardized treatment, many nomograms for rectal cancer after neoadjuvant treatment have been developed (5-7). However, these nomograms have some limitations, such as a lack of a summary of DFS, failure to clarify the metastasis site, and failure to analyze LM. Although there are several nomograms for LM of rectal cancer (9-13), none can predict its emergence after neoadjuvant treatment.

According to the recommendations of guidelines for the neoadjuvant treatment of rectal cancer, the observation and follow-up period was performed after 4–6 months of adjuvant chemotherapy (14). However, the median time of LM occurrence in this study was 18 months (range, 7–30), indicating the treatment was not enough to eliminate micrometastasis in the liver, and when adjuvant chemotherapy was stopped, the undetected metastatic tumor cells in the liver proliferated again. Therefore, early screening of high-risk patients with LM, appropriately prolonging the duration of chemotherapy, and adjusting the frequency of monitoring and follow-up are of great significance to reduce the incidence of LM and improve OS.

FOWARC is a rigorous and objective randomized controlled trial. Zhang *et al.* established a nomogram for predicting pathological complete response and tumor downstaging with the data of this study, which showed good predictive ability (15). The training cohort of this study also came from the FOWARC study, and with the observation and follow-up of up to 5 years, nomograms were constructed in the same cohort to predict LDFS and OS. In this study, prospective continuous cohort data were used as the validation cohort, and the follow-up observation period was more than 3 years. Therefore, the source of the data and the predicted results are effective and reliable.

LM is the most common metastatic mode of rectal cancer, and its incidence is higher than that of local recurrence and lung and peritoneal metastases (16). This study showed for the first time that the 3-year LM rate of rectal cancer after neoadjuvant treatment was 7.96%, which is significantly lower than the MET-LM rate reported in previous literature (4). A previous study reported the incidences of LM in stage 1, stage 2, and stage 3 disease were 1.2%, 13.6%, and 27.8%, respectively (17,18). According to the results from the training cohort in this study, the LM rates for stage 0, stage 1, stage 2, and stage 3 disease were 1.96% (1/51), 6.25% (6/96), 7.32% (6/82) and 13.70% (10/73), respectively, and the time of LM occurrence was 7–30 months after the operation. We did not observe LM more than 36 months after surgery, which

Table 2 Prognostic factors of liver metastasis and poor prognosis in the training cohort

Factors	Liver metastasis			Poor prognosis		
	Univariate, P value	Multivariate, P value	HR (95% CI)	Univariate, P value	Multivariate, P value	HR (95% CI)
HBV infection	0.079	0.037	3.885 (1.084–13.92)	0.605		
Anemia	0.057	0.059	0.144 (0.019–1.079)	0.953		
MRF	0.885			0.004	0.191	1.866 (0.733–4.748)
Postoperative T stage	0.0788	0.464	1.756 (0.389–7.929)	0.434		
Postoperative N stage	0.165			0.011	0.741	0.828 (0.272–2.527)
Lymph node harvest <12	0.04	0.014	0.349 (0.150–0.809)	0.354		
Pathological differentiation	0.8226			0.031	0.044	0.335 (0.116–0.969)
Tumor nodule	0.023	0.005	4.208 (1.530–11.56)	0.021	0.024	3.45 (1.182–10.07)
Vascular invasion	0.117			0.429		
Neural invasion	0.207			0.001	0.003	5.008 (1.745–14.37)
ypTNM stage	0.069	0.777	0.782 (0.142–4.301)	0.331		

HBV, hepatitis B virus; MRF, mesorectal fascia involvement.

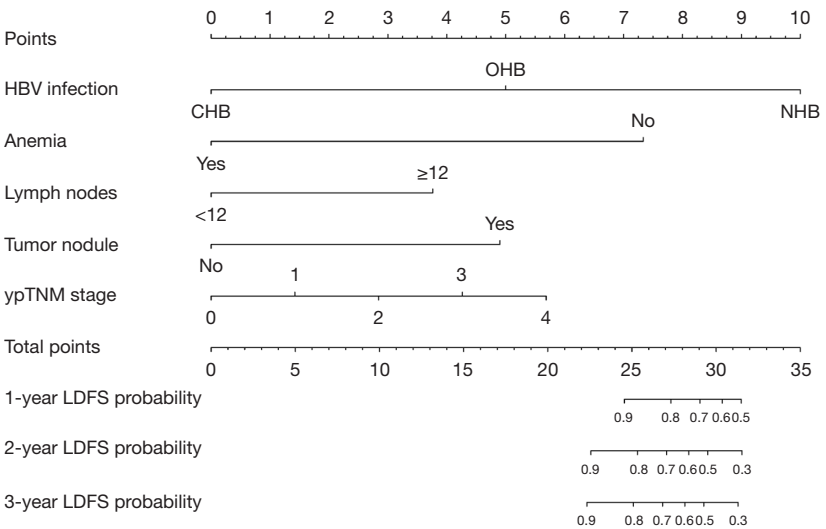

Figure 1 Liver disease-free survival nomogram. HBV, hepatitis B virus; LDFS, liver disease-free survival.

was better than the previously reported data and shows neoadjuvant therapy plays a positive role in reducing LM.

Previous studies suggested the application of radiotherapy and oxaliplatin can increase the local descending phase of the primary tumor (19), and data suggests primary tumors may indeed respond more strongly to neoadjuvant therapy than metastatic tumors (20). However, in this study, the analysis showed that occurrence of LM was not associated with the application of oxaliplatin or radiotherapy. While existing nomograms are based on primary tumor-related indicators to predict the occurrence of LM, its occurrence cannot be predicted only by the index of the primary tumor. Our nomograms are the first to consider the impact of HBV infection on LM, and in the prediction model, in addition to primary tumor-related indicators, the weight of HBV infection status was very large. A significant difference was

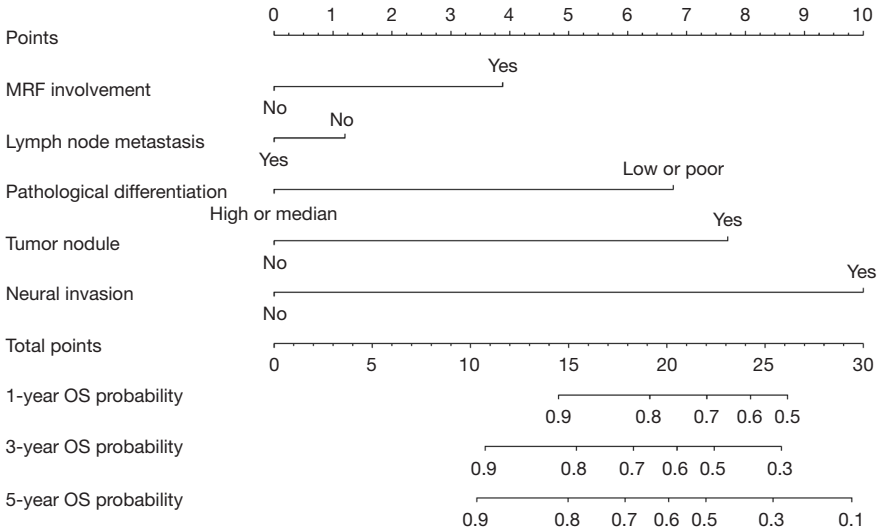

Figure 2 Overall survival nomogram. MRF, mesorectal fascia involvement; OS, overall survival.

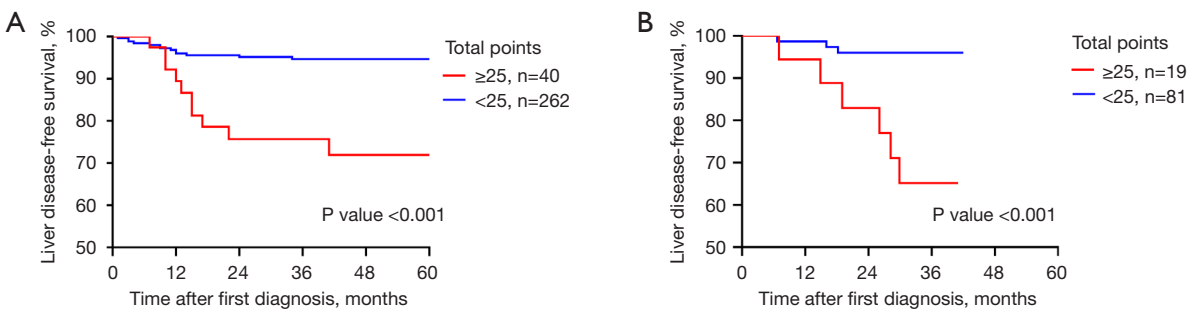

Figure 3 Liver disease-free survival of local advanced rectal cancer in training cohort (A) and validation cohort (B).

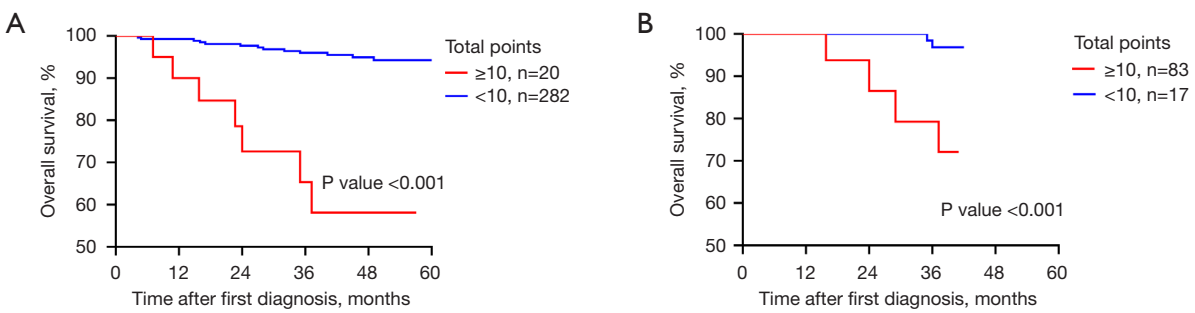

Figure 4 Overall survival of local advanced rectal cancer in training cohort (A) and validation cohort (B).

observed between the nomograms with and without HBV infection (C-index 0.845 *vs.* 0.768, P=0.004), which shows the importance of the liver microenvironment for LM.

Hepatitis B is the most common liver related infectious disease in China and even in the world. China is also the country with the largest number of HBV infections (21). According to statistics, there are about 70 million cases of HBV infection in China, of which about 30 million are

HBsAg positive chronic hepatitis B infections (22). Previous reports have suggested HBV reduces the incidence of LM (23-27), and our study found a similar phenomenon. In the training cohort, there were two patients with LM among 86 patients with HBV infection (CHB and NHB) and 21 patients with LM among 216 patients without HBV infection (2.33% *vs.* 9.72%, P=0.03). Multivariate analysis showed NHB was an independent risk factor for LM (P=0.037, HR =3.885, 95% CI: 1.084–13.929). The active replication of HBV is usually accompanied by an increase in liver enzymes, but our analysis showed no differences in ALT and AST between patients with and without LM. This suggests the reason for the reduced risk of LM may be changes in liver immune status and microenvironment caused by HBV infection rather than HBV itself.

Song *et al.* developed a nomogram for the OS of LARC patients treated with neoadjuvant therapy (C-index =0.724). However, the training cohort was based on retrospective data, the nomogram lacked external verification, and they did not take into account factors such as tumor nodules and neural invasion (5). In this study, the C-index of the nomogram for the OS of LARC patients was 0.73, and that of the validation cohort reached 0.774. Studies have shown the ypTNM stage is a good prognostic factor for predicting local recurrence and distant metastasis, and is even more accurate than preoperative clinical stage or descending degree (28,29). However, while TN stage can be effectively improved after neoadjuvant therapy with the improvement of the scheme, it cannot effectively reflect the prognosis. Our nomogram includes pathological differentiation, tumor nodules and neural invasion, which can better indicate poor prognosis. Therefore, we believe the effect of the nomograms developed in this study will be greater than that of previous nomograms.

In conclusion, the nomograms developed in this study based on several clinical indicators can effectively predict the LDFS and OS of LARC patients after neoadjuvant therapy. The nomograms can effectively identify patients at high risk of developing LM and poor prognosis, allowing clinicians to individually adjust treatment and follow-up strategies.

The nomograms in this study have some limitations. First, due to the sample size, they can only predict the risk of LM and LDFS and cannot verify liver progression-free survival (LPFS) after treatment. Second, we only collected indicators of liver infection and function commonly used in the clinic, such as HBV, ALT, and AST, which cannot reflect the immune state of the liver in detail. Some predictors, such as RAS mutation and HBV-DNA titer, were not available for all patients, so they were not evaluated in this study. Third, all data were from a single center, and all patients were Chinese.

Conclusions

The nomograms established in this study can effectively predict LDFS and has good clinical application potential for OS in LARC patients treated with neoadjuvant therapy.

HBV infection, pathological lymph nodes, and tumor nodules were independent risk factors for LM. Anemia, primary N stage, pathological differentiation, tumor nodules, and neural invasion were related to poor prognosis.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2790/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2790/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2790/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The design of this study was in accordance with the Declaration of Helsinki (as revised in 2013), and relevant plans and conclusions were approved by the ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No. 2010017). All included participants signed an informed consent form.

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Supplementary

Table S1 Prognostic factors of liver metastasis and poor prognosis in the training cohort in details

Factors	Group	Liver metastasis					Poor prognosis				
		Yes	No	Univariate P value	Multivariate P value	HR (95% CI)	Yes	No	Univariate P value	Multivariate P value	HR (95% CI)
Gender				0.818					0.849		
	Male	15	190				3	59			
	Female	8	89				3	35			
Age, years				0.325					0.946		
	≥56	8	141				4	53			
	<56	15	137				2	41			
FOWARC group				0.649					0.591		
	Radiation + 5 FU	9	85				2	22			
	Radiation + FOLFOX	6	93				1	35			
	FOLFOX	8	101				3	37			
HBV infection				0.079	0.037	3.885(1.084-13.929)			0.605		
	Chronic HBV infection	0	27				0	12			
	Occult HBV infection	2	57				2	22			
	No HBV infection	21	195				4	60			
Anemia				0.057	0.059	0.144(0.019-1.079)			0.953		
	Yes	1	59				2	22			
	No	22	220				4	72			
ALT >40 U/L				0.188					0.895		
	Yes	3	17				1	6			
	No	20	261				5	88			
AST >40 U/L				0.516					0.253		
	Yes	1	8				0	2			
	No	22	270				6	92			
ALB >35 g/L				-					null		
	Yes	23	278				6	94			
	No	0					0	0			
CA19-9 >37				0.758					0.637		
	Yes	4	40				1	14			
	No	19	237				5	80			
CEA >5				1					0.89		
	Yes	7	91				2	37			
	No	16	186				4	57			
Pretreatment T stage				0.721					>0.99		
	2 or 3	18	226				4	71			
	4	5	52				2	23			
Pretreatment N stage				0.9604					0.686		
	0	4	55				1	18			
	1	11	132				2	45			
	2	8	92				3	31			
Clinical stage 3				0.7872					0.699		
	Yes	19	224				5	76			
	No	4	55				1	18			
Tumor length				0.7859					0.239		
	≥4 cm	15	174				2	62			
	<4 cm	8	105				4	32			
Mesorectal fascia involvement				0.885					0.004	0.191	1.866(0.733-4.748)
	Positive	7	89				3	6			
	negative	16	190				3	88			
Postoperative T stage				0.0788	0.464	1.756(0.389-7.929)			0.434		
	0 to 2	9	165				2	55			
	3 or 4	14	114				4	39			
Postoperative N stage				0.165					0.011	0.741	0.828(0.272-2.527)
	1 or 2	7	49				4	15			
	0	16	223				2	79			
Lymph node number				0.04	0.014	0.349(0.150-0.809)			0.354		
	<12	10	185				0	24			
	≥12	13	94				6	70			
Pathological differentiation				0.8226					0.031	0.044	0.335(0.116-0.969)
	Poor or mucinous	2	31				3	10			
	High or median	19	248				3	84			
Tumor nodule				0.023	0.005	4.208(1.530-11.569)			0.021	0.024	3.45(1.182-10.071)
	Yes	7	34				3	9			
	No	16	245				3	85			
Vascular invasion				0.117					0.429		
	Yes	2	6				1	2			
	No	21	273				5	92			
Neural invasion				0.207					0.001	0.003	5.008(1.745-14.374)
	Yes	3	18				3	3			
	No	20	261				3	91			
Efficacy of neoadjuvant therapy				0.158					0.287		
	0 or 1	7	126				1	45			
	2 or 3	16	150				5	49			
HER-2				0.585					0.839		
	Positive	6	46				2	40			
	Negative	11	113				4	46			
Microsatellite stable				0.577					0.699		
	Yes	20	213				6	89			
	No	1	19				0	5			
Tumor to anal verge				0.146					0.866		
	≥5	17	163				3	42			
	<5	6	116				3	52			
ypTNM stage				0.069	0.777	0.782(0.142-4.301)			0.331		
	2 or 3	16	139				6	69			
	0 or 1	7	140				0	25			

ALT, alanine transaminase; AST, aspartate transaminase; ALB, serum albumin; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

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Table S2 Relationship between with and without radiation or oxaliplatin in liver metastasis and poor prognosis

	Group	Liver metastasis			Poor prognosis		
		Yes	No	P value	Yes	No	P value
Radiation				0.891			0.931
	Yes	15	178		3	57	
	No	8	101		3	37	
Oxaliplatin				0.328			0.952
	Yes	14	204		4	72	
	No	9	85		2	22	

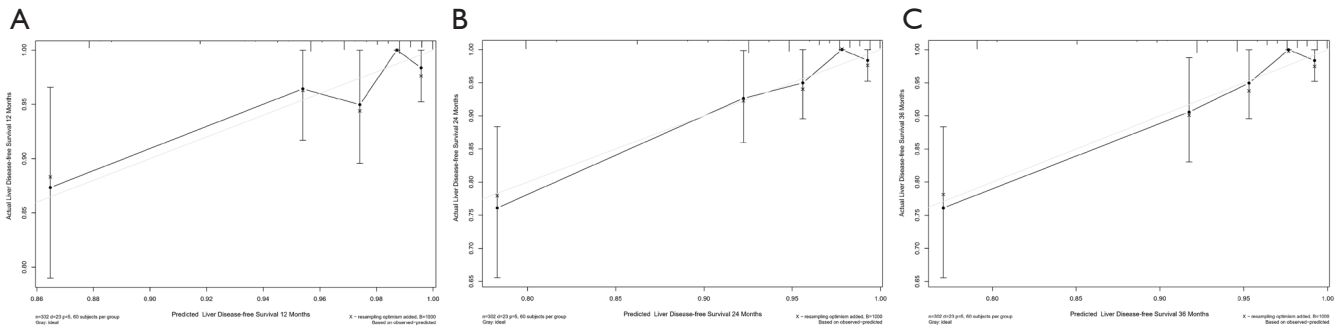

Figure S1 Calibration curve for predicting patients liver disease-free survival at 1-year (A), 2-year (B), and 3-year (C) in training cohort.

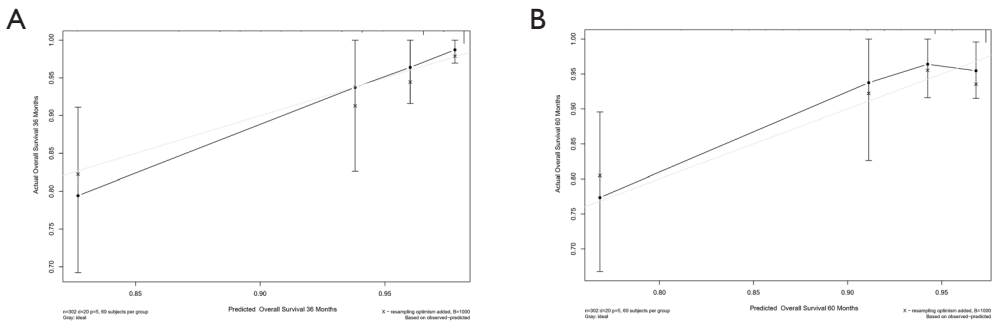

Figure S2 Calibration curve for predicting patients overall survival at 3-year (A) and 5-year (B) in training cohort.

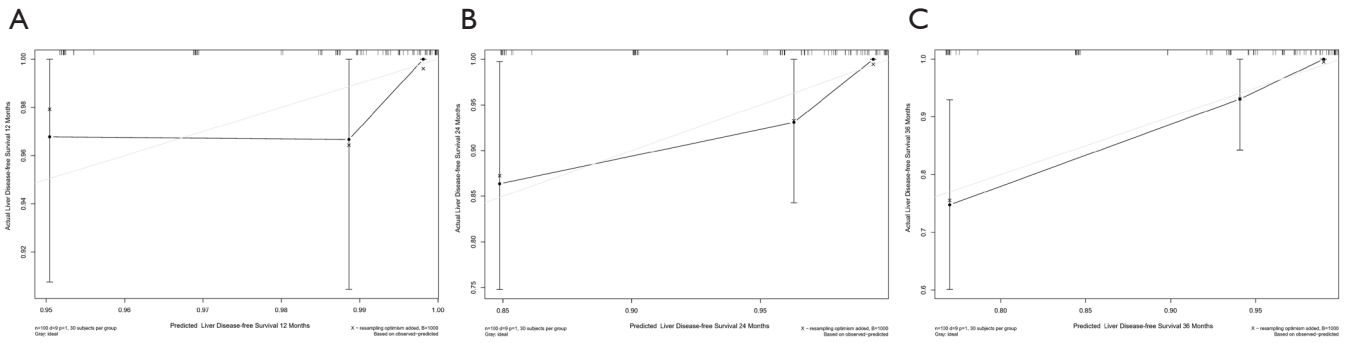

Figure S3 Calibration curve for predicting patients liver disease-free survival at 1-year (A), 2-year (B), and 3-year (C) in validation cohort.

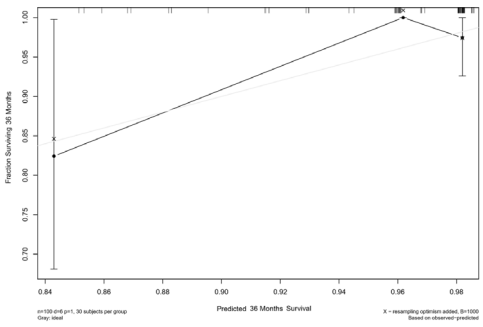

Figure S4 Calibration curve for predicting patients overall survival at 3-year in validation cohort.

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