ORIGINAL RESEARCH

# Combining Pre- and Postoperative Lymphocyte–C-Reactive Protein Ratios Can Better Predict Hepatocellular Carcinoma Prognosis After Partial Hepatectomy

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**Background:** Various preoperative inflammatory indicators have been identified as potential predictors of poor prognosis in patients with hepatocellular carcinoma (HCC), but the role of postoperative inflammatory indicators remains unclear. This study aimed to explore the prognostic value of the postoperative lymphocyte–C-reactive protein ratio (PostLCR) on its own and combined with preoperative LCR (PreLCR).

**Methods:** A total of 290 patients with primary HCC were retrospectively enrolled in the study. Univariate analysis was used to identify factors significantly associated with poor disease-free survival (DFS) and overall survival (OS), then multivariate analysis was performed to identify independent prognostic indicators of poor survival. Prognostic models based on preoperative, postoperative, and both types of indicators were then constructed, and their predictive performance were evaluated using time-dependent receiver operating characteristic curves and the concordance index (C-index).

**Results:** PreLCR and PostLCR levels correlated with DFS and OS more strongly than other pre- and postoperative inflammatory indicators, respectively. Decreased PreLCR and PostLCR were independent prognostic factors for both DFS and OS, while HCC patients with decreased PreLCR and PostLCR had worse prognosis than patients with increased PreLCR and PostLCR. Patients into three groups based on their cut-off values of PreLCR and PostLCR, Kaplan–Meier survival analysis indicated that HCC patients with low PreLCR and PostLCR had the worst DFS and OS. The combined model showed better predictive performance at 1 and 3 years post-surgery than individual pre- and postoperative models, the American Joint Committee on Cancer/Tumor-Node-Metastasis (8th edition) staging system and the Barcelona Clinic Liver Cancer system. The combine model demonstrated a markedly superior C-index compared with the other models in DFS and OS.

**Conclusion:** Our study showed PreLCR and PostLCR are independent predictors of DFS and OS in HCC patients after partial hepatectomy. Models that include both PreLCR and PostLCR can predict prognosis better than well-established clinical staging systems.

**Keywords:** hepatocellular carcinoma, lymphocyte-to-C-reactive protein ratio, partial hepatectomy, disease-free survival, postoperative

## Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Although partial hepatectomy is the most common treatment for HCC, the 5-year disease-free survival (DFS) rate after partial hepatect-omy is only 30–40%[2,3] and tumor recurrence remains the major cause of poor prognosis. To improve postoperative

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survival rates in HCC patients, robust biomarkers are needed to predict disease recurrence, identify high-risk patients, facilitate close patient follow-up, and decide on appropriate postoperative treatments. The 8th edition of the American Joint Committee on Cancer (AJCC)/Tumor-Node-Metastasis (TNM) staging system and the Barcelona Clinic Liver Cancer (BCLC) classification are commonly used for HCC risk stratification and identification of potential anticancer therapies, but their application is limited as they can incorporate only a few clinicopathological indicators.[4] Other many factors also affect tumor occurrence and progression, such as inflammation, viral infection, and the tumor macro-and microenvironment.

Unlike most other malignancies, more than 90% of HCC cases develop due to chronic inflammation.[5] The host inflammatory response has also been related to cancer progression and patient survival,[6,7] while systemic inflammation due to host–tumor interactions is currently considered a cancer hallmark.[8] Therefore, the prognostic value of various preoperative inflammatory indicators has been extensively studied, including preoperative platelet–lymphocyte ratio (PrePLR), preoperative lymphocyte–monocyte ratio (PreLMR), systemic immune inflammation index (PreSII), preoperative derived NLR (PredNLR), and preoperative neutrophil–lymphocyte ratio (PreNLR).[9–13] The preoperative lymphocyte–C-reactive protein ratio (PreLCR) has also recently been identified as a powerful prognostic marker in HCC.[14,15]

However, the balance between immune and inflammatory responses may change after the surgical removal of HCC lesions.[16] Indeed, postoperative inflammatory indicators, such as postoperative platelet–lymphocyte ratio (PostPLR) and postoperative neutrophil–lymphocyte ratio (PostNLR), can greatly affect HCC prognosis.[17–19] Various postoperative inflammatory indicators have been linked to the long-term prognosis of patients with different solid tumors.[20,21] For instance, PostNLR has been identified as an independent prognostic factor of survival in patients with small HCC undergoing radiofrequency ablation.[22] Whether postoperative LCR (PostLCR) has prognostic value in HCC, analogous to PreLCR, has not yet been investigated.

In this study, we explored the prognostic value of PostLCR and compared its performance to that of models based only on PreLCR or the combination of PreLCR and PostLCR. We also compared these models against existing clinical staging systems.

## Materials and Methods

### Study Population

In this study, we retrospectively investigated the medical records of 290 HCC patients treated with R0 resection at the Affiliated Cancer Hospital of Guangxi Medical University in Nanning, China, between August 2014 and January 2017. Patients were enrolled if they met all the following criteria: (1) definitive HCC diagnosis based on World Health Organization criteria; (2) Child-Pugh A stage and Performance Status Test score of 0–1; (3) no prior anticancer treatment, such as transarterial chemoembolization or radiation; (4) complete clinical pathological data; and (5) underwent R0 resection, defined as complete macroscopic tumor removal, negative resection margins, and no detectable intra- or extrahepatic metastatic lesions. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Cancer Hospital of Guangxi Medical University. The requirement for written informed consent was waived because all patients, on admission, consented for their anonymized medical data to be analyzed and published for research purposes.

### Clinicopathological Indicators

Preoperative blood samples were collected and assayed within one week before surgery. Postoperative blood samples were collected and assayed within 25–40 days after surgery (the first reexamination after surgery discharge). Laboratory measurements included alpha fetoprotein (AFP), hepatitis B virus DNA (HBV-DNA), C-reactive protein, total peripheral white blood cell count (W), total peripheral lymphocyte count (L), total peripheral platelet count (P), total peripheral monocyte count (M), and total peripheral neutrophil count (N). Inflammation biomarkers were defined as follows: NLR = N/L, PLR = P/L, LMR = L/M, SII = (P×N)/L, and dNLR = (W−N)/L. LCR was defined as the ratio of lymphocyte count (number/mL) to the level of serum C-reactive protein (mg/dL).

## Patient Follow-Up

After initial treatment, laboratory examinations (serum AFP, liver function, blood tests), abdominal ultrasonography, and contrast-enhanced CT were performed every three months for the first two years and every six months thereafter. The first date of follow-up was the date of the initial diagnosis of HCC, and the last day was the date of the most recent follow-up visit (June 2021) or the date of the patient's death. DFS was measured from the date of hepatectomy until tumor recurrence. Overall survival (OS) was measured between the date of hepatectomy and the date of death or the date of the last follow-up visit. Recurrence was defined as a significant increase in postoperative AFP levels or tumor lesions.

## Statistical Analysis

Statistical analysis was performed with SPSS 26.0 (IBM, Chicago, IL, USA), MedCalc version 20.015 (Broekstraat 52, 9030; Mariakerke, Belgium), and R version 4.1.2 (http://www.r-project.org/). Patient characteristics were analyzed using descriptive statistics. Significant intergroup differences were determined using the chi-squared test. Kaplan–Meier survival curves were compared using the Log rank test. Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the ROC curve (AUC), together with 95% confidence intervals (95% CIs). Correlation between patient characteristics and survival rates was investigated using univariate and multivariate Cox proportional hazard regression models. The optimal LCR cut-off values for DFS were determined using the X-Tile statistical package (version 3.6.1, Yale University, New Haven, CT, USA) and the highest $\chi^2$ value obtained from Kaplan–Meier survival analysis and the Log rank test.[23] C-indexes were calculated using the "Hmisc" package in R, and time-dependent ROC (timeROC) analysis was performed with the "timeROC" package in R.

The ability of the models to predict DFS and OS was evaluated by 1000 bootstrapping replications, and their performance at 1 and 3 years post-surgery was assessed using calibration plots. The risk score of each patient was determined with the "nomogramFormula" package, and timeROC analysis was used to compare the predictive performance of the models at different time points. All $P$ values were two-sided, and differences associated with $P < 0.05$ were considered statistically significant.

# Results

## Patient Characteristics and Clinical Outcomes

The study included 239 males (82.4%) and 51 females (17.6%) with a mean age of 49.7 years (range, 20–79). None of the patients received chemotherapy or radiotherapy prior to surgery, and no perioperative mortality was observed. Of the 290 patients, 135 (46.6%) showed MVI and 134 (46.2%) liver cirrhosis. In addition, 143 patients had positive AFP levels before surgery (Table 1).

## Predictive Performance of PreLCR and PostLCR

To identify inflammation biomarkers with the highest prognostic value for DFS and OS, we calculated the AUC values of preoperative and postoperative NLR, LCR, LMR, PLR, SII, and dNLR. PreLCR and PostLCR showed the highest AUCs (Figure 1–2 and Figures S1 and S2) and were therefore further assessed for their clinical impact and potential as biomarkers in HCC using respective optimal cut-off values of 4600 and 4300. Kaplan–Meier survival analysis indicated that HCC patients with higher PreLCR and PostLCR had significantly better DFS and OS than those with lower PreLCR and PostLCR (Figures 3 and S3).

## Predictive Performance of Combined PreLCR and PostLCR

We divided the total of 290 patients into three groups based on their cut-off values of PreLCR and PostLCR. Patients with low PreLCR and PostLCR were categorized into Cohort A (n=53); Patients with high PreLCR and PostLCR were categorized into Cohort C (n=133); And patients with either high PreLCR or high PostLCR were categorized into Cohort B (n=104). Kaplan–Meier survival analysis indicated that HCC patients with low PreLCR and PostLCR (Cohort A) had the worst DFS and OS, whereas patients with high PreLCR and PostLCR (Cohort C) presented the best DFS and OS (Figure 4).

**Table 1** Demographic and Clinical Characteristics of the Hepatocellular Carcinoma Patients Enrolled in the Study

| Variable | n | % |
|---|---|---|
| Sex | | |
|     Male | 239 | 82.4 |
|     Female | 51 | 17.6 |
| Age (years) | | |
|     <50 | 148 | 51.0 |
|     ≥50 | 142 | 49.0 |
| HBsAg | | |
|     Negative | 26 | 9.0 |
|     Positive | 264 | 91.0 |
| Liver cirrhosis | | |
|     Negative | 156 | 53.8 |
|     Positive | 134 | 46.2 |
| HBV-DNA (IU/mL) | | |
|     $<5\times10^2$ | 90 | 31.0 |
|     $≥5\times10^2$ | 200 | 69.0 |
| AFP (ng/mL) | | |
|     <400 | 147 | 50.7 |
|     ≥400 | 143 | 49.3 |
| Tumor size (cm) | | |
|     <5 | 124 | 42.8 |
|     ≥5 | 166 | 57.2 |
| Tumor number | | |
|     1 | 211 | 72.8 |
|     >1 | 79 | 27.2 |
| BCLC stage | | |
|     0-A | 162 | 55.9 |
|     B-C | 128 | 44.1 |
| Tumor capsule | | |
|     Complete | 217 | 74.8 |
|     Incomplete | 73 | 25.2 |
| MVI | | |
|     Negative | 155 | 53.4 |
|     Positive | 135 | 46.6 |

**Abbreviations**: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus DNA; MVI, microvascular invasion.

## Prognostic Model Based on Preoperative Indicators

Univariate analysis showed that AFP, tumor size, tumor number, MVI, PreLCR, and PostLCR were significantly associated with poor DFS in patients with primary HCC after partial hepatectomy (Table 2). Multivariate analysis of PreLCR and preoperative clinicopathological indicators also showed that AFP, tumor size, tumor number, MVI, and PreLCR were independent prognostic factors of poor DFS (Table 3). These indicators were further used to construct a preoperative prognostic model for DFS (Figure 5A).

Similarly, AFP, tumor size, HBV-DNA, MVI, PreLCR, and PostLCR were found to be significantly associated with poor OS after partial hepatectomy in primary HCC patients (Table 2), while multivariate analysis indicated that AFP, tumor size, MVI, and PreLCR were independent prognostic factors of poor OS (Table 3). These indicators were then included in a preoperative prognostic model for OS (Figure S4A).
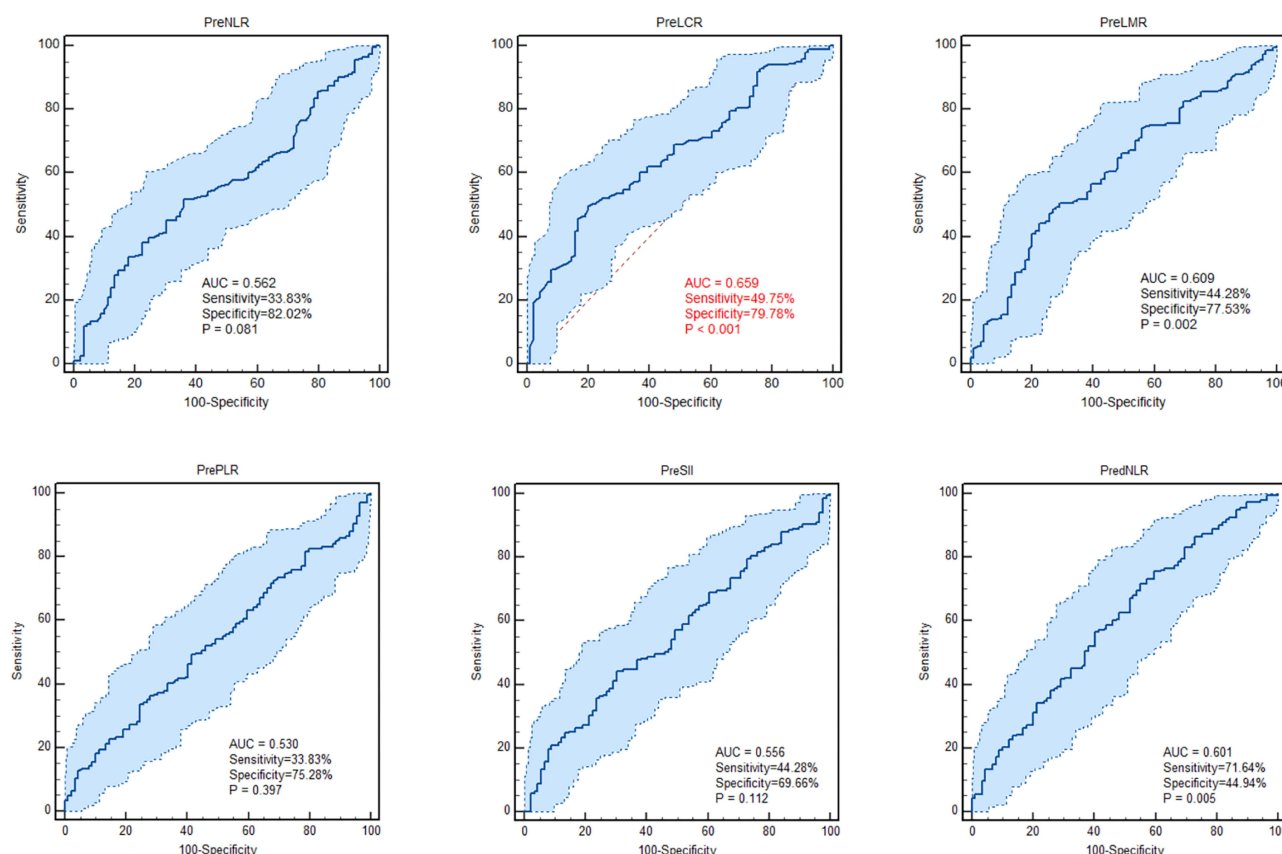
**Figure 1** Receiver operating characteristic curves of preoperative markers for disease-free survival in patients with hepatocellular carcinoma. The red font means the largest AUC among all 6 inflammation biomarkers.
**Abbreviations**: AUC, area under the curve; PredNLR, preoperative derived neutrophil–lymphocyte ratio; PreLCR, preoperative lymphocyte–C-reactive protein ratio; PreLMR, preoperative lymphocyte–monocyte ratio; PreNLR, preoperative neutrophil–lymphocyte ratio; PrePLR, preoperative platelet–lymphocyte ratio; PreSII, preoperative systemic immune inflammation index.

The high consistency between predicted results and actual observations was confirmed by the calibration curves for 1- and 3-year DFS (Figure 5B–C) and OS (Figure S4B and C).

## Prognostic Model Based on Postoperative Indicators

Multivariate analysis of PostLCR and postoperative clinicopathological indicators showed that AFP, tumor size, tumor number, MVI, and PostLCR were independent prognostic factors of poor DFS (Table 3). These indicators were used to construct a postoperative prognostic model for DFS (Figure 6A). Similarly, AFP, tumor size, MVI, and PostLCR were identified as independent prognostic factors of poor OS (Table 3) and were included in a postoperative prognostic model for OS (Figure S5A).

The high consistency between predicted results and actual observations was confirmed by the calibration curves for 1- and 3-year DFS (Figure 6B–C) and OS (Figure S5B and C).

## Prognostic Model Based on Pre- and Postoperative Indicators

Multivariate analysis of PreLCR, PostLCR, and clinicopathological indicators suggested that AFP, tumor size, tumor number, MVI, PreLCR, and PostLCR were independent prognostic factors of poor DFS and OS (Table 3). These indicators were then used to construct combined prognostic models for DFS (Figure 7A) and OS (Figure S6A).

In addition, the calibration curves for 1- and 3-year DFS (Figure 7B–C) and OS (Figure S6B and C) confirmed that the predictions of the combined model were consistent with observations.
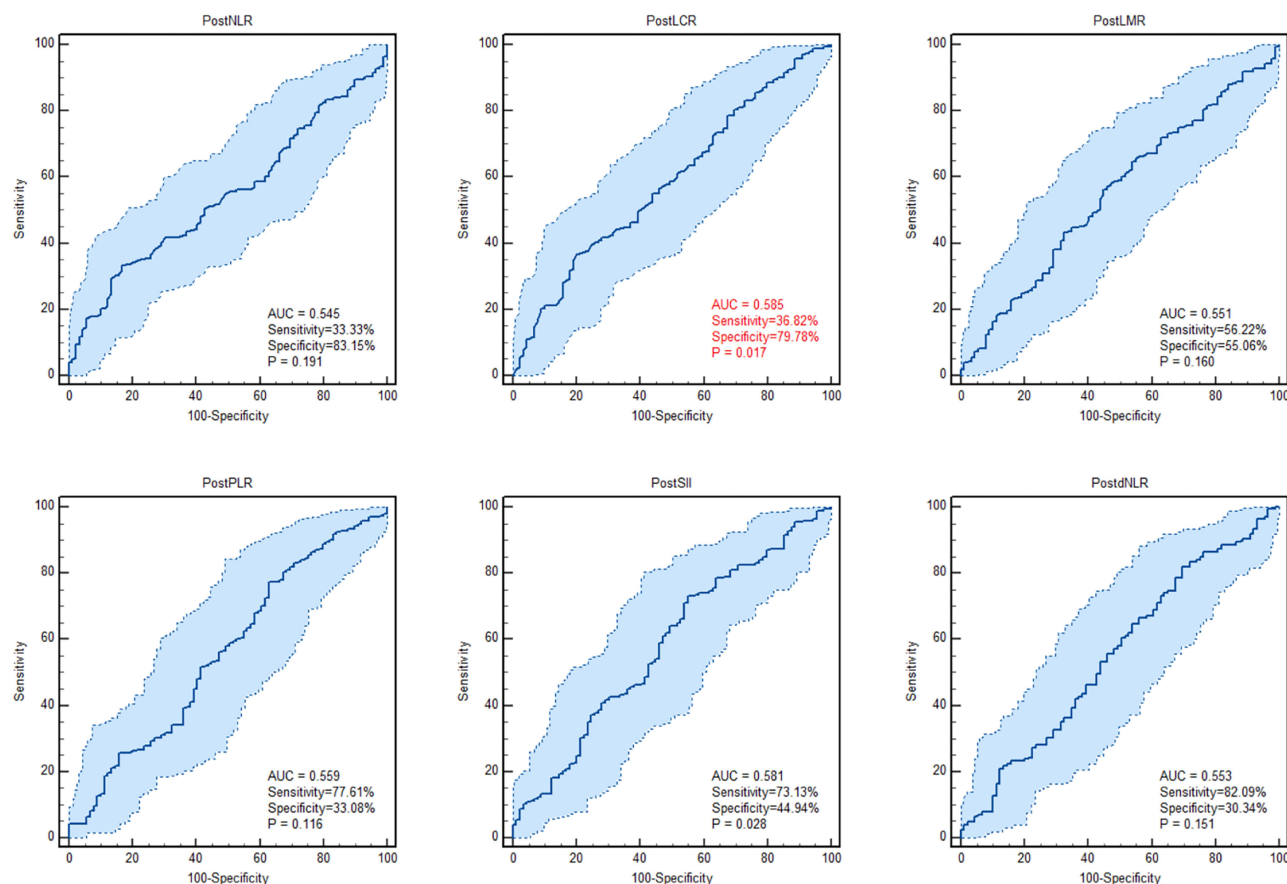
**Figure 2** Receiver operating characteristic curves of postoperative markers for disease-free survival in patients with hepatocellular carcinoma. The red font means the largest AUC among all 6 inflammation biomarkers.
**Abbreviations**: AUC, area under the curve; PostdNLR, postoperative derived neutrophil–lymphocyte ratio; PostLCR, postoperative lymphocyte–C-reactive protein ratio; PostLMR, postoperative lymphocyte–monocyte ratio; PostNLR, postoperative neutrophil–lymphocyte ratio; PostPLR, postoperative platelet–lymphocyte ratio; PostSII, postoperative systemic immune inflammation index.
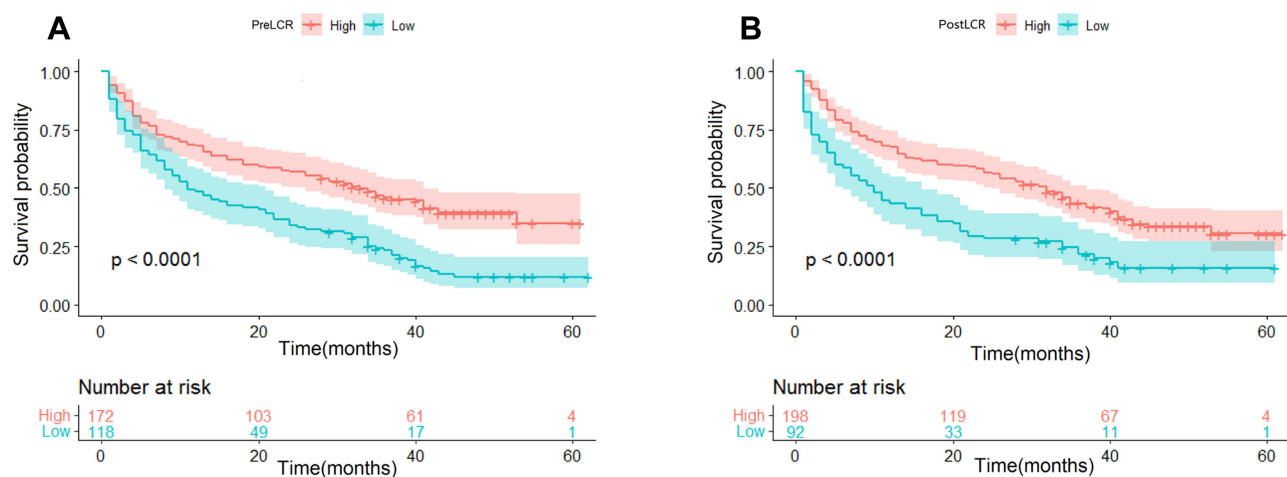


**Figure 3** Kaplan–Meier survival curves of disease-free survival in hepatocellular carcinoma patients based on (**A**) preoperative lymphocyte–C-reactive protein ratio (PreLCR) and (**B**) postoperative lymphocyte–C-reactive protein ratio (PostLCR).
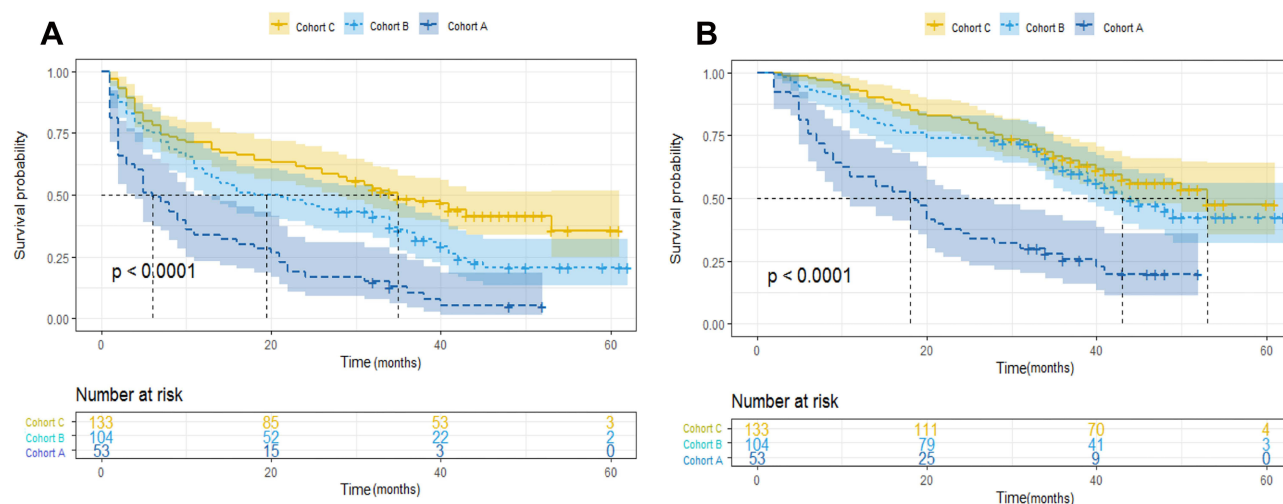
**Figure 4** Kaplan–Meier survival curves of disease-free survival (**A**) and overall survival (**B**) in hepatocellular carcinoma patients based on PreLCR and PostLCR.

## Comparison of Prognostic Models with Traditional Clinical Staging Systems

The predictive performance of the various prognostic models in the present study was compared with that of traditional clinical staging systems. The combined model had higher C-index values (0.670) than other models (0.596–0.669) in DFS of HCC, and the prognostic performance of combined model was superior to that of the preoperative model (0.670 vs 0.656, P=0.015), AJCC TNM (8th) (0.670 vs 0.596, P <0.001) and BCLC (0.670 vs 0.604, P <0.001). Similarly, the combined model had higher C-index values (0.686) than other models (0.592–0.681) in OS of HCC, and the prognostic performance of combined model was superior to that of the preoperative model (0.686 vs 0.676, P=0.019), AJCC TNM (8th) (0.686 vs 0.592, P <0.001) and BCLC (0.686 vs 0.600, P <0.001) (Table 4).

Further comparison of their prognostic efficacy at different time points by timeROC analysis revealed that the predictive performance of the combined model at 1 year (AUC = 0.690) and 3 years (AUC = 0.747) after surgery was better than that of the preoperative model, the postoperative model, the AJCC TNM (8th) system, and the BCLC system in DFS (Figure 8), similarly, the combined model had the best predictive performance in OS (Figure S7).

**Table 2** Univariate Analysis to Identify Clinicodemographic Factors Associated with Disease-Free Survival and Overall Survival

| Variable | Disease-Free Survival | | | Overall Survival | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Sex (M/F) | 0.790 | 0.538–1.159 | 0.228 | 0.661 | 0.412–1.059 | 0.085 |
| Age (≥50) | 0.946 | 0.717–1.247 | 0.692 | 0.740 | 0.534–1.025 | 0.070 |
| HBsAg (positive) | 1.026 | 0.632–1.666 | 0.916 | 1.155 | 0.640–2.084 | 0.633 |
| Liver cirrhosis (positive) | 0.956 | 0.724–1.262 | 0.749 | 0.832 | 0.601–1.152 | 0.267 |
| HBV-DNA (≥5×10$^2$ IU/mL) | 1.300 | 0.953–1.774 | 0.097 | 1.486 | 1.024–2.156 | 0.037 |
| AFP (≥400 ng/mL) | 1.606 | 1.215–2.123 | 0.001 | 1.737 | 1.253–2.408 | 0.001 |
| Tumor size (≥5 cm) | 2.077 | 1.546–2.791 | <0.001 | 2.472 | 1.731–3.529 | <0.001 |
| Tumor number (>1) | 1.876 | 1.394–2.524 | <0.001 | 1.354 | 0.956–1.920 | 0.088 |
| Tumor capsule (incomplete) | 1.047 | 0.789–1.390 | 0.751 | 1.047 | 0.751–1.461 | 0.785 |
| MVI (positive) | 1.545 | 1.170–2.040 | 0.002 | 1.766 | 1.276–2.444 | 0.001 |
| PreLCR (<4600) | 1.953 | 1.478–2.581 | <0.001 | 2.133 | 1.544–2.948 | <0.001 |
| PostLCR (<4300) | 1.880 | 1.407–2.512 | <0.001 | 1.725 | 1.232–2.451 | 0.001 |

**Abbreviations**: AFP, alpha-fetoprotein; 95% CI, 95% confidence interval; DFS, disease-free survival; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus DNA; HR, hazard ratio; MVI, microvascular invasion; PostLCR, postoperative lymphocyte–C-reactive protein ratio; PreLCR, preoperative lymphocyte–C-reactive protein ratio.

**Table 3** Multivariate Analysis of the Preoperative, Postoperative, and Combined Models for Disease-Free Survival and Overall Survival

| Variable | Preoperative Model | | | Postoperative Model | | | Combined Model | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P | HR | 95% CI | P |
| **Model for Disease-free Survival** | | | | | | | | | |
| AFP (≥400 ng/mL) | 1.541 | 1.161–2.046 | 0.003 | 1.430 | 1.075–1.903 | 0.014 | 1.444 | 1.085–1.922 | 0.012 |
| Tumor size (≥5 cm) | 1.533 | 1.101–2.133 | 0.011 | 1.793 | 1.328–2.422 | <0.001 | 1.530 | 1.104–2.121 | 0.011 |
| Tumor number (>1) | 1.867 | 1.384–2.519 | <0.001 | 1.957 | 1.446–2.647 | <0.001 | 1.968 | 1.455–2.661 | <0.001 |
| MVI (positive) | 1.360 | 1.027–1.800 | 0.032 | 1.358 | 1.026–1.798 | 0.033 | 1.367 | 1.033–1.810 | 0.029 |
| PreLCR (<4600) | 1.569 | 1.154–2.135 | 0.004 | | | | 1.482 | 1.090–2.014 | 0.012 |
| PostLCR (<4300) | | | | 1.792 | 1.332–2.411 | <0.001 | 1.723 | 1.278–2.322 | <0.001 |
| **Model for Overall Survival** | | | | | | | | | |
| AFP (≥400 ng/mL) | 1.534 | 1.101–2.138 | 0.011 | 1.440 | 1.032–2.010 | 0.032 | 1.467 | 1.050–2.049 | 0.025 |
| Tumor size (≥5 cm) | 1.768 | 1.185–2.638 | 0.005 | 2.125 | 1.477–3.057 | <0.001 | 1.765 | 1.188–2.622 | 0.005 |
| MVI (positive) | 1.543 | 1.110–2.143 | 0.010 | 1.570 | 1.129–2.183 | 0.007 | 1.576 | 1.134–2.190 | 0.007 |
| PreLCR (<4600) | 1.596 | 1.117–2.281 | 0.010 | | | | 1.547 | 1.084–2.207 | 0.016 |
| PostLCR (<4300) | | | | 1.559 | 1.110–2.191 | 0.010 | 1.514 | 1.076–2.131 | 0.017 |

**Abbreviations**: AFP, alpha-fetoprotein; 95% CI, 95% confidence interval; HR, hazard ratio; MVI, microvascular invasion; PostLCR, postoperative lymphocyte–C-reactive protein ratio; PreLCR, preoperative lymphocyte–C-reactive protein ratio.

# Discussion

To date, several preoperative inflammatory indicators have been identified as potential prognostic markers for patients with HCC. However, the prognostic value of postoperative indicators has not been adequately explored. In the present
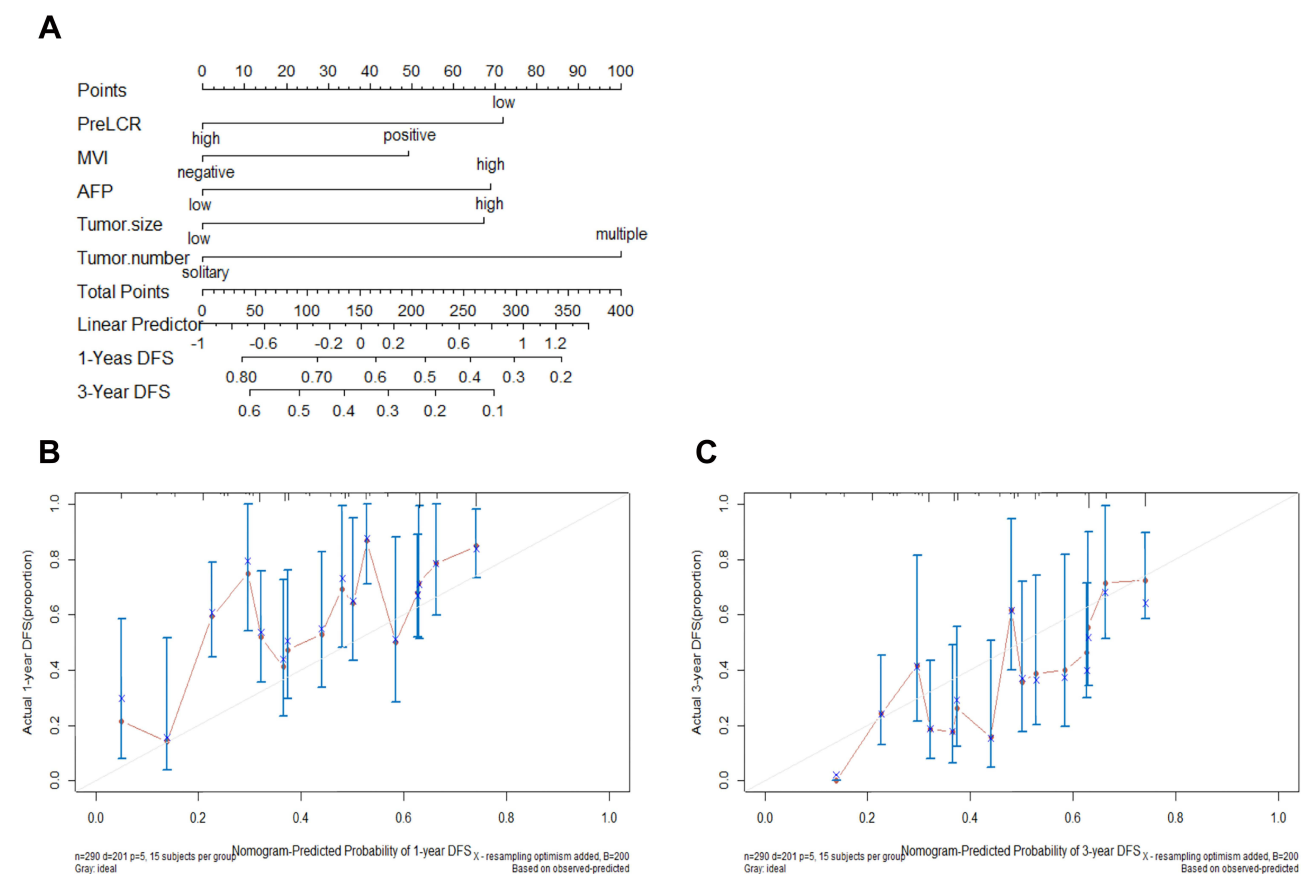
**Figure 5** Nomogram of the preoperative model for disease-free survival (DFS) in patients with hepatocellular carcinoma (**A**). Calibration curves of the preoperative model for (**B**) 1-year and (**C**) 3-year DFS.
**Abbreviations**: AFP, alpha-fetoprotein; MVI, microvascular invasion; PreLCR, preoperative lymphocyte–C-reactive protein ratio.
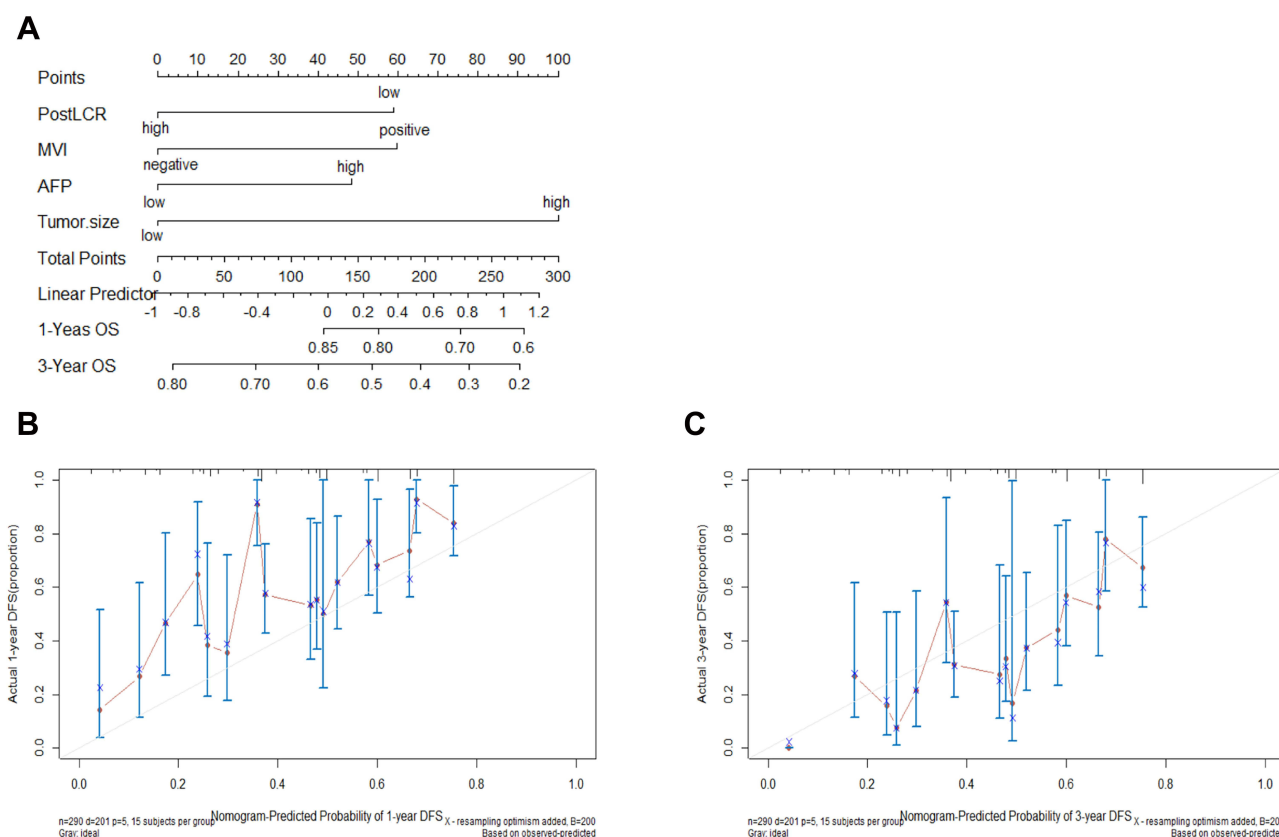
**Figure 6** Nomogram of the postoperative model for disease-free survival (DFS) in patients with hepatocellular carcinoma (**A**). Calibration curves of the postoperative model for (**B**) 1-year and (**C**) 3-year DFS.
**Abbreviations**: AFP, alpha-fetoprotein; MVI, microvascular invasion; PostLCR, postoperative lymphocyte–C-reactive protein ratio.

study, we investigated PostLCR as a potential predictor of poor DFS and OS and assessed the performance of a combined model incorporating both PreLCR and PostLCR, comparing it to separate preoperative and postoperative models as well as to existing clinical staging systems. Our results indicate that LCR is a significantly better predictor of DFS and OS than other inflammation-based prognostic scores and that decreased PreLCR and PostLCR are independent predictors of DFS and OS in HCC patients after partial hepatectomy. In addition, we found that HCC patients with lower PreLCR and PostLCR values have worse prognosis than those with higher PreLCR and PostLCR.

Systemic inflammation due to host–tumor interactions is known to promote tumor growth and metastasis in patients with various types of malignancies.[7,24] High levels of serum C-reactive protein have been associated with poor systemic inflammatory response, early HCC recurrence, and worse survival after hepatic resection.[25,26] Lymphopenia, defined as a reduced number of anti-cancer lymphocytes,[27,28] has also been identified as a marker of poor immune response and a prognostic factor in patients with malignant disease.[29,30] For this reason, low PreLCR has been associated with poor immunological response, malnutrition, and/or enhancement of systemic inflammatory response in cancer patients, and it is a convenient prognostic marker for patients with HCC.[14,15,31]

LCR may not only directly impact a patient's outcome but also rather reflect an systemic inflammatory state. A low LCR indicates low immunity or high inflammatory state, and thus in our results, low PreLCR and low PostLCR (cohort A) has worst DFS and OS in these patients. Patients with depressed postLCR have a relative lymphocytopenia and increased CRP, which indicated that the balance is tipped in favor of inflammatory or Immunosuppression response after surgery, and is associated with poor oncologic outcome. The survival of patients with lower or higher preLCR can be distinguished more accurate by postLCR change, which can also reflect the efficacy of treatment.

To the best of our knowledge, this study is the first to compare the prognostic efficacy of traditional clinical staging systems and a prognostic model combining PreLCR and PostLCR. Our results showed that the combined model had
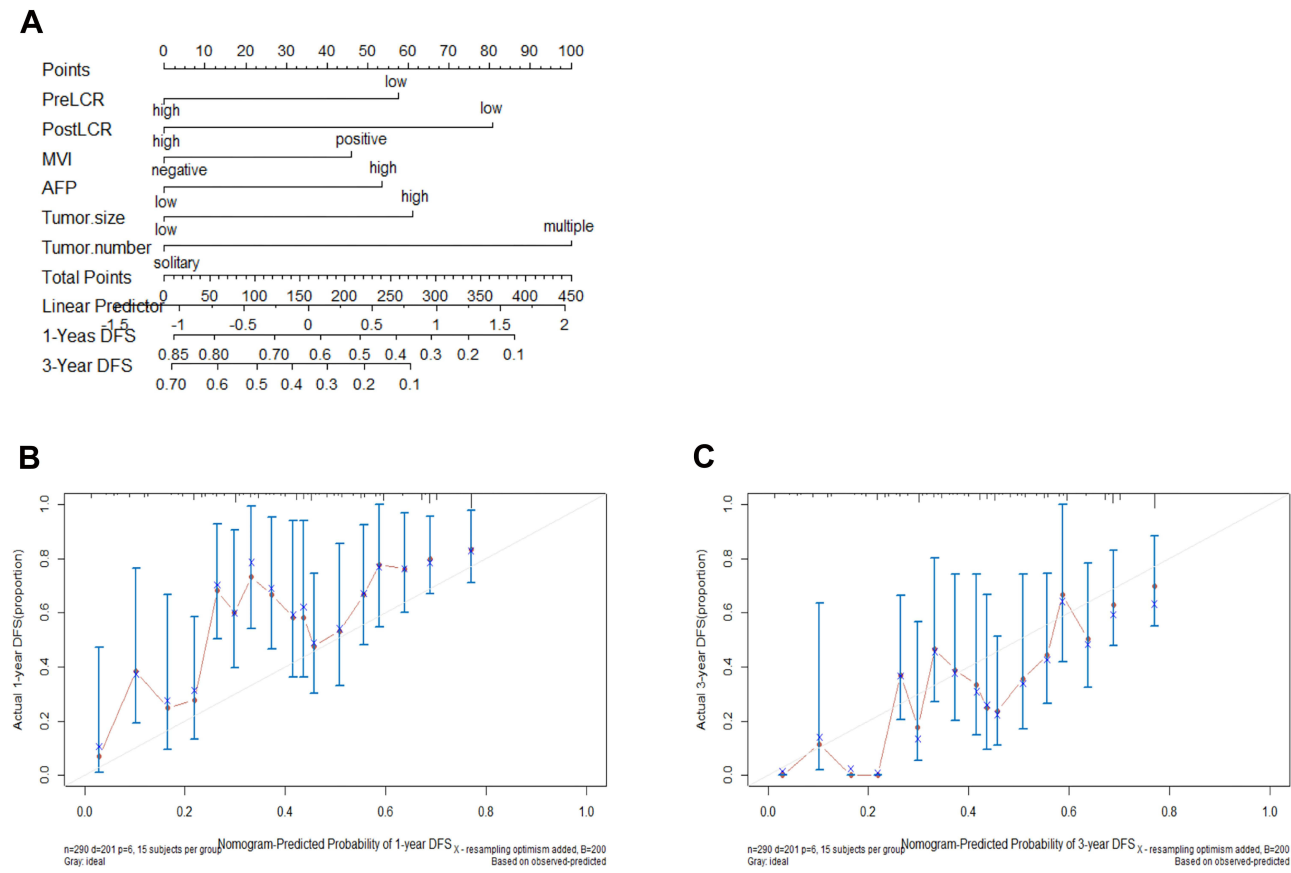
**Figure 7** Nomogram of the combined prognostic model for disease-free survival (DFS) in patients with hepatocellular carcinoma (**A**). Calibration curves of the combined prognostic model for (**B**) 1-year and (**C**) 3-year DFS.
**Abbreviations**: AFP, alpha-fetoprotein; MVI, microvascular invasion; PostLCR, postoperative lymphocyte–C-reactive protein ratio; PreLCR, preoperative lymphocyte–C-reactive protein ratio.

a better prognostic performance for 1- and 3-year DFS and OS than individual models and traditional clinical staging systems. This superior performance may reflect that the combined model considers both pre- and postsurgical phases of cancer treatment. It may also be attributable to severe postoperative inflammation that activates micrometastasis and affects the microenvironment of residual liver cancer tissue, thus promoting HCC recurrence even after complete removal or ablation of the tumor tissue.[32]

A recent study of postoperative inflammatory biomarkers revealed that their prognostic value stabilized at three days after liver transplantation.[33] It has also been shown that the optimal period for measuring postoperative inflammatory markers is at 21–56 days after surgery, when surgery-induced inflammation is minimal.[34] Our blood samples were

**Table 4** Concordance Index for the Comparison of Different Model of Disease-Free Survival and Overall Survival

| Model | Disease-Free Survival | | Overall Survival | |
|---|---|---|---|---|
| | C-Index | P | C-index | P |
| Combined model | 0.670 | | 0.686 | |
| Preoperative model | 0.656 | 0.015 | 0.676 | 0.019 |
| Postoperative model | 0.669 | 0.981 | 0.681 | 0.572 |
| AJCC TNM (8th) | 0.596 | <0.001 | 0.592 | <0.001 |
| BCLC | 0.604 | <0.001 | 0.600 | <0.001 |

**Abbreviations**: AJCC TNM (8th), American Joint Committee on Cancer/Tumor-Node-Metastasis; BCLC, Barcelona Clinic Liver Cancer.
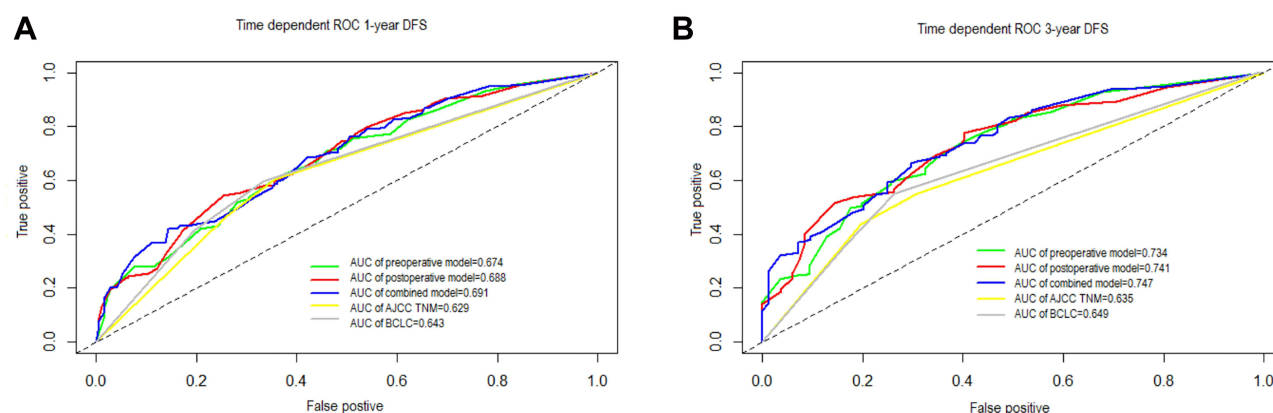
**Figure 8** Comparison of prognostic models and traditional clinical staging systems for predicting disease-free survival (DFS) at (**A**) 1 year and (**B**) 3 years after surgery.
**Abbreviations**: AJCC TNM, American Joint Committee on Cancer/Tumor-Node-Metastasis; AUC, area under the time-dependent receiver operating characteristic curve; BCLC, Barcelona Clinic Liver Cancer.

collected at 25–40 days postoperatively. Thus, we speculate that PreLCR and PostLCR can be used to decide whether a patient with HCC who underwent surgical resection can forego postoperative chemotherapy, although further studies are needed to confirm our hypothesis.

Our study has certain limitations. First, it was a retrospective study and included patients from a single institution, although the study population was relatively large and homogeneous in terms of cancer stage. Moreover, the timing of blood sampling varied over a nearly two-fold range, which might have affected the data on inflammatory status. Therefore, our findings should be confirmed by large-scale prospective studies in which blood is sampled during a narrow window.

## Conclusion

Our study showed that PreLCR and PostLCR are valuable prognostic markers of survival in patients with HCC after partial hepatectomy. Moreover, we found that the combined prognostic model performed much better than pre- or postoperative models or the well-established TNM and BCLC staging systems. Further studies of postoperative inflammatory indicators are needed in order to exploit their full prognostic potential.

## Funding

## Disclosure

The authors report no conflicts of interest in this work.

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