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A prognostic model based on gamma-glutamyl transpeptidase-derived neutrophil-platelet for predicting intrahepatic recurrence in hepatocellular carcinoma

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Abstract

Aims This study aims to investigate the prognostic significance of the combined GNR and GPR in patients with early-stage hepatitis B virus-associated hepatocellular carcinoma (HBV-HCC).

Methods Retrospective analysis was performed on clinical data of 145 HBV-infected patients with early-stage HCC (ESHCC) who underwent radiofrequency ablation (RFA) and/or surgical resection. Patients were randomly allocated to training (n = 103) and validation (n = 42) cohorts for further survival analysis and model verification. The area under the receiver operating characteristic curves (ROC) was used for evaluating the diagnostic performance of ERM-model. And at the optimal cutoff, a survival analysis on all patients was conducted. Simultaneously, all patients were divided into different subgroups to evaluating ERM-Model.

Results Multivariate Cox analysis identified GNR and GPR as independent risk factors for postoperative intrahepatic recurrence (IHR). The combined biomarkers panel demonstrated superior diagnostic accuracy (AUC = 0.812) compared to AFP (AUC = 0.773). Survival analysis showed a significantly higher 2-year cumulative non-IHR rate in the low-risk group (logit(P) < 0.398) verus the high-risk group (logit(P) ≥ 0.398, $p < 0.001$). Subgroup analysis of all patients that ERM-model showed differencesin HCC stage stratification, with higher diagnostic accuracy for BCLC stage A cases compared to BCLC stage 0 cases.

Conclusions GNR and GPR are valuable predictors of IHR in ESHCC. Clinicians can leverage this dual-marker model to assess risk and tailor personalized follow-up strategies.

Keywords Gamma-glutamyl transpeptidase-to-neutrophil Ratio, Gamma-glutamyl transpeptidase to-platelet Ratio, Model, Intrahepatic Recurrence, Hepatocellular carcinoma, Prognosis

1 Introduction

Hepatocellular carcinoma (HCC), comprising 75%-85% of primary liver malignancies [1], is strongly associated with HBV infection, accounting for approximately 50% of global cases [2]. By conducting regular screening of high-risk populations, such as patients with chronic hepatitis virus infection and liver cirrhosis, the detection rate of ESHCC can be increase [3]. Currently, surgical resection, liver transplantation, and local ablation therapies (such as radiofrequency ablation) are the main radical treatment methods for ESHCc [4, 5]. Due to the relatively high recurrence and metastasis rates of HCC, the prognosis of ESHCC after treatment remains unsatisfactory.

The Tumor-Node-Metastasis (TNM) staging system and the Barcelona Clinic Liver Cancer (BCLC) staging system are widely used to evaluate the prognosis and select treatment methods of HCC. However, the TNM staging system primarily relies on pathological factors, which limits its predictive ability and the BCLC staging system is initially developed based on hepatitis C virus (HCV) infection and alcoholic liver disease as the primary causes of HCC [1, 6]. HBV infection is the predominant cause of HCC in China, this etiological difference may reduce the predictive power of the BCLC staging system. The development of HCC is closely associated with chronic inflammation, which can alter the counts of peripheral blood cell and expression of liver inflammation markers [7]. These changes have significant prognostic implications. In light of this, numerous studies have established prognostic models based on blood cell counts and biochemical parameters. Post-operative recurrence management and prognostic assessment remain critical components for this patient population with ESHCC. Currently, Alpha-fetoprotein (AFP) levels may reflect tumour burden, including tumour size and growth rate. [8]. Elevated AFP is often associated with greater tumour mass, more increased invasiveness and potentially poorer prognosis [9]. Gamma-Glutamyl transpeptidase (GGT) plays a crucial role in glutathione metabolism and demonstrates relatively high activity in the epithelial cells of intrahepatic bile ducts and the microsomes of hepatocytes. This enzyme plays a key role in diagnosing liver function and disorders [10]. Elevated preoperative GGT levels have been associated with a poor prognosis in HCC patients [11]. Neutrophils, a key component of the inflammatory response, have been closely correlated with the invasive behavior of HCC [12]. A low platelet counts independently predict worse overall survival (OS) in HCC, with a hazard ratio of 1.25 (per 50×10^9/L decrease). In addition, platelet count is positively associated with BCLC stage and tumour size [13]. Converging evidence indicates that the gamma-glutamyl transpeptidase-to-neutrophil ratio (GNR) and gamma-glutamyl transpeptidase-to- platelet ratio (GPR) serve as a prognostic tool for HCC patients after radical resection, thus providing solutions for early detection and precision medicine [14, 15]. A single indicator may produce false positives or false negatives due to testing errors and individual variations, potentially obscuring true disease status. In clinical practice, combining different indicators is common to assess disease status from multiple angles. This approach enhances disease differentiation and reduces misjudgment, making combined indicator testing generally superior. At present, research on GNR and GPR is still in its initial stage, and their application remains limited to the stage of scientific research exploration. Although GNR and GPR have shown potential in liver diseases, there are differences in the thresholds of gamma-glutamyl transpeptidase-derived neutrophil-platelet among different studies, and the applicability of the individualized diagnostic efficacy of GNR and GPR

still needs further improvement [16]. Notably, to date, there has been no reports on the prognostic impact of GNR combined with GPR in HBV-induced ESHCC. This study investigates the combination of GNR and GPR in BCLC 0/A stage HBV-HCC and aims to evaluate the prognostic implications in HCC population who have undergone radiofrequency ablation (RFA) and/or resection.

2 Methods

2.1 Patients cohort

145 HBV-HCC patients (BCLC 0/A) who underwent RFA and/or resection at Tianjin Second People's Hospital (2013–2024) were included. These patients were randomized into two groups at a 7:3 ratio. The study protocol was approved by the Medical Ethics Committee of Tianjin Second People's Hospital (No. 2023–43).

Diagnosis of HCC in these patients was made in accordance with the standardized criteria: the American Association for the Study of Liver Diseases (AASLD) [17] and the Guideline for the Diagnosis and Treatment of Primary Liver Cancer (GLDT-PLC) [18]. The ESHCC was defined based on the Barcelona Clinic Liver Cancer (BCLC) staging system.

The inclusion and exclusion criteria for patients in this study are as follows: (1) All patients are diagnosed HBV-HCC; (2) Patients have undergone at least one session of radiofrequency ablation and/or surgical resection; patients who have undergone liver transplantation, immunotherapy, or molecular targeted therapy are excluded; (3) Patients are classified as BCLC stage 0 or A; patients with BCLC stage B or higher are excluded; (4) Patients with extrahepatic metastasis or other malignancies are excluded; (5) Patients with preoperative gastrointestinal bleeding or those who received antibiotic treatment are excluded; (6) Patients lacking blood test results within 30 days before surgery are excluded; (7) Patients with incomplete follow-up data are excluded.

2.2 Data collection and follow-up

Demographic, clinicopathological, and laboratory parameters were collected, including quantitative Hepatitis B surface antigen (qHBsAg), alpha-fetoprotein (AFP), prothrombin time (PT), international normalized ratio (INR), albumin (ALB), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), absolute neutrophil count, absolute lymphocyte count, and platelet count. We considered several inflammatory indices associated with HCC, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) [19], GGT-to-neutrophil ratio (GNR) [14], GGT-to- lymphocyte ratio (GLR) [20] and GGT-to-platelet ratio (GPR) [21]. We also collected liver fibrosis-related indices, including the aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis-4 index (Fib-4). The APRI was computed as: APRI index = (AST / upper limit of normal AST) × 100 / PLT (× 10^9/L). The Fib-4 index was determined by the formula: Fib-4 index = (Age (years) × AST (U/L)) / (PLT (× 10^9/L) × √(ALT (U/L)).

Intrahepatic Recurrence (IHR) was radiologically defined as newly developed enhancing lesions demonstrating characteristic imaging features on contrast-enhanced cross-sectional imaging (CT or MRI). Postoperative surveillance comprised quarterly to biannual outpatient visits incorporating: (1) hepatic function panels, (2) complete blood

counts, and (3) multiphase contrast-enhanced imaging. This standardized protocol aimed to ensure precise detection of IHR events. The final follow-up cutoff date for outcome assessment was December 31, 2024.

2.3 Statistical analysis

Patient characteristics were summarized as continuous or categorical variables. Normally distributed continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies (percentages). Univariate and multivariate Cox proportional hazards regression analyses were performed to assess prognostic factors, and reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The diagnostic value of clinical parameters was evaluated by receiver operating characteristic (ROC) curve analysis, with optimal cut-off values determined by maximizing the Youden index. Survival outcomes were analyzed using Kaplan–Meier methodology, with between-group comparisons assessed by log-rank testing. Missing data were handled via complete-case analysis under the missing completely at random (MCAR) assumption to preserve analytical validity. A two-sided p-value < 0.05 was considered statistically significant. SPSS 26.0 (IBM Corp., Armonk, NY), R 4.4.2 (R Foundation for Statistical Computing), and GraphPad Prism 9.5.0 (GraphPad Software) were used to analyse data in this study.

3 Results

3.1 Cohort characteristics

Figure 1 shows a comprehensive flowchart in this study. Between 2021 and 2024, 471 patients with liver cancer were initially identified at Tianjin Second People's Hospital. According to the inclusion and exclusion criteria, 145 participants were included in the final analysis. Using the caret package in R, the cohort was randomly stratified into a training subset (n = 103) and a validation subset (n = 42) to ensure a robust framework for subsequent predictive modeling and evaluation.

Table 1 summarizes the baseline characteristics of all enrolled patients. The cases had a mean age of 58.4 years (23–76). Among these patients, 72.41% (105/145) were male and 27.59% (40/145) were female. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, 45 patients (31.03%) were classified as stage 0 and 100 patients (68.97%) were classified as stage A. In addition, 66.9% (97/145) of the patients had a total tumor size of less than 2 cm. A single tumor lesion was present in 72.41% (105/145) of the patients prior to surgery. We used the caret package in R language to divide the cohort into a training cohort (n = 103) and a validation cohort (n = 42). Except for prothrombin time (PT), there were no statistically significant differences in clinical parameters between the two groups (as shown in Table 1).

3.2 Independent risk factors for IHR

Univariate and multivariate regression analyses were systematically employed to identify significant risk determinants for IHR (as shown in Table 2). Univariate Cox analysis showed that qHBsAg (HR = 1.616; 95% CI: 1.010–2.585; p = 0.045), the presence of multiple tumours (HR = 2.059; 95% CI: 1.177–3.601; p = 0.011), Albumin (HR = 0.939; 95% CI: 0.90–0.980; p = 0.004), ALT levels (HR = 1.008; 95% CI: 1.004–1.011; p < 0.001), increased AST levels (HR = 1.012; 95% CI: 1.007–1.017; p < 0.001), increased GGT levels

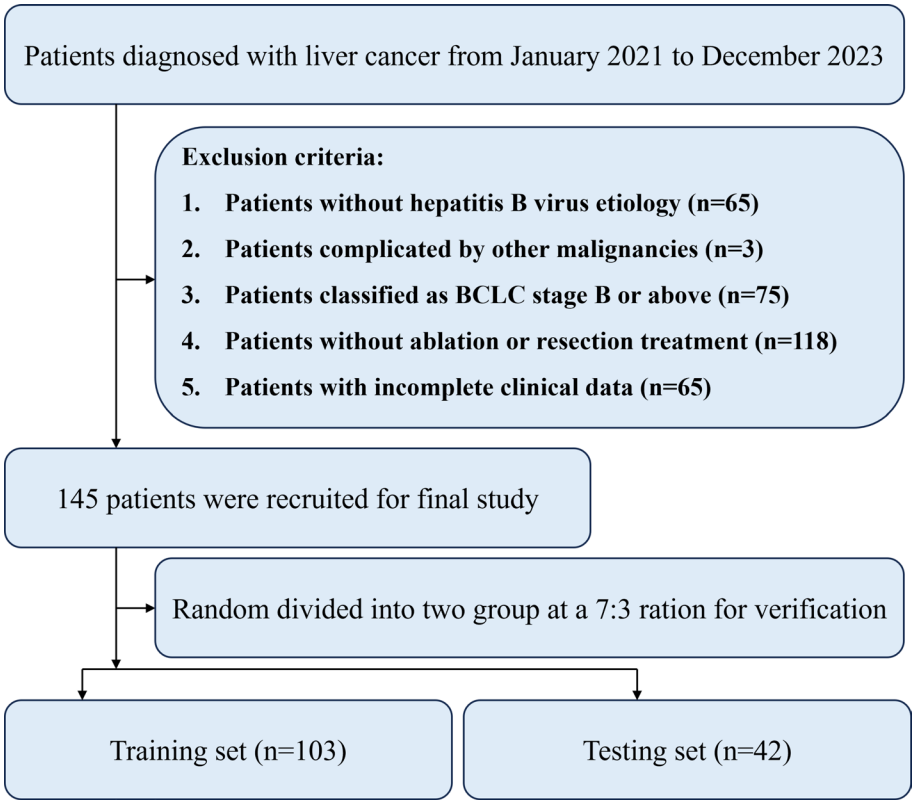

Fig. 1 Flowchart for the selection of study cohorts

(HR = 1.006; 95% CI: 1.004–1.008; p < 0.001), increased GNR (HR = 1.007; 95% CI: 1.004–1.010; p < 0.001), increased GLR (HR = 1.004; 95% CI: 1.002–1.005; p < 0.001), high GMR (HR = 1.002; 95% CI: 1.002–1.003, p < 0.001), high GPR (HR = 1.442; 95% CI: 1.262–1.649; p < 0.001), an elevated APRI (HR = 1.579; 95% CI: 1.028–1.948; p < 0.001) and an elevated Fib-4 Index (HR = 1.109; 95% CI: 1.048–1.174; p < 0.001) were all considered risk factors for IHR. Conversely, normal absolute Neutrophil count (HR = 0.711; 95% CI: 0.547–0.923, p = 0.011), Platelet (HR = 0.991; 95% CI: 0.986–0.996, p = 0.001), PLR (HR = 0.993; 95% CI:0.986–0.999, p = 0.031) were identified as protective factors against IHR.

Subsequently, clinical parameters with a P value of less than 0.1 were selected for multivariate Cox analysis. As is shown in Table 2, elevated GNR (HR = 1.013; 95% CI: 1.006–1.021; p = 0.001) and GPR levels (HR = 1.605; 95% CI: 1.189–2.166; p = 0.002) were significantly associated with an increasing risk of IHR.

Restricted cubic spline (RCS) indicates positive correlations between GNR, GPR, and predictive model with IHR (p < 0.001 for all) (Fig. 2). These indicators showed statistically significant predictive value in assessing the risk of IHR. We developed the model formula by integrating GNR and GPR based on the regression equation (formula: Logit(P) = 0.08*GNR + 0.431*GPR-2.235) to predict early IHR after radical surgery in patients with ESHCC. In this study, we designated the GGT-derived Neutrophil-Platelet Ratio Model as the Er Ren Min Model (ERM-Model).

3.3 Diagnostic efficacy of the ERM-model in the training and test cohorts

We performed ROC curve, predictive value and accuracy analysis to evaluate the discriminative ability of AFP and the ERM-Model for IHR in ESHCC (Table 3; Fig. 3).

Table 1 Basline characteristics of the cohort

Characteristics	Total (n = 145)	Training chort (n = 103)	Testing chort (n = 42)	P value
Age, years	58.40 (23–76)	57.85 (23.0–76.0)	59.76 (33.0–75.0)	0.238
Male,n/total(%)	105/145 (72.41)	75/103 (72.82)	30/42 (71.43)	0.865
Tumor number				
Single, n/total(%)	105/145 (72.41)	78/103 (75.73)	27/42 (64.28)	0.162
Multiple, n/total(%)	40/145 (27.59)	25/103 (24.27)	15/42 (35.72)	
Tumor size (cm)				
< 2 cm, n/total(%)	97/145 (66.90)	67/103 (65.0)	30/42 (71.40)	0.459
≥ 2 cm, n/total(%)	48/145 (33.10)	36/103 (35.0)	12/42 (28.60)	
BCLC staging				
0, n/total(%)	45/145 (31.03)	29/103 (28.16)	16/42 (38.10)	0.241
A, n/total(%)	100/145 (68.97)	74/103 (71.84)	26/42 (61.90)	
qHBsAg (log_{10}IU/mL)	2.84 (– 2.00 to 4.19)	2.90 (– 2.00 to 4.15)	2.57 (0–4.19)	0.084
AFP (ng/ml)	42.85 (1.11–926.72)	51.35 (1.11–926.72)	22.20 (1.33–260.96)	0.184
PT(s)	12.22 (2.10–20.0)	12.10 (10.10–15.70)	11.74 (2.10–14.40)	0.041
INR	1.05 (0.9–2.0)	1.07 (0.9–2.0)	1.03 (0.90–1.30)	0.203
Albumin(g/L)	44.17 (27.20–53.10)	40.84 (27.20–53.10)	42.81 (30.70–52.60)	0.066
Total bilirubin (μmol/L)	21.21 (6.6–59.6)	21.54 (6.60–59.60)	20.42 (8.70–54.50)	0.575
ALT(U/L)	32.18 (6.0–388.0)	29.55 (6.0–154.30)	38.62 (6.8–388.0)	0.203
AST(U/L)	32.57 (11.0–271.0)	31.88 (11.0–199.90)	34.26 (11.40–271.0)	0.653
GGT(U/L)	53.0 (7.0–494.20)	52.22 (7.0–494.20)	54.92 (11.0–336.0)	0.822
LYM (10^9/L)	1.34 (0.27–3.54)	1.31 (0.27–3.54)	1.42 (0.41–3.26)	0.333
Neutrophil (10^9/L)	2.91 (0.66–8.30)	3.04 (0.66–8.30)	3.30 (1.34–8.29)	0.664
PLT (10^9/L)	128.41 (13–290.0)	123.97 (13.0–265.0)	139.28 (34.0–290.0)	0.127
MONO(10^9/L)	0.39 (0.11–1.06)	0.39 (0.11–1.03)	0.40 (0.19–1.06)	0.699
NLR	2.72 (0.38–17.65)	2.68 (0.38–17.65)	2.84 (1.03–12.56)	0.682
PLR	107.14 (26.53–326.92)	105.71 (26.53–326.92)	110.66 (43.59–253.03)	0.611
LMR	3.51 (0.96–7.09)	3.44 (0.96–7.03)	3.70 (1.14–7.09)	0.275
GNR	22.95 (2.85–371.58)	23.89 (2.85–371.58)	20.65 (3.23–150.0)	0.662
GLR	50.83 (4.38–726.76)	52.95 (4.38–726.76)	45.63 (5.24–184.62)	0.611
GMR	150.77(14.89–1270.37)	158.32(15.09–1270.37)	132.24(14.89–441.96)	0.934
GPR	0.60 (0.05–7.60)	0.61 (0.05–7.60)	0.54 (0.08–2.68)	0.655
APRI	0.82 (0.04–5.15)	0.89 (0.15–5.15)	0.65 (0.04–2.92)	0.130
Fib-4	3.61 (0.66–23.14)	3.81 (0.71–23.14)	3.12 (0.66–13.67)	0.254

The findings indicate that, in the training cohort, the area under the receiver operating characteristic curve (AUC) of the ERM-Model was 0.803, with a sensitivity of 0.686 and a specificity of 0.852, reflecting a reasonable level of accuracy in identifying negative samples. Its validity was further confirmed in an independent validation cohort of 42 patients, achieving an AUC of 0.812. Compared with the AFP marker, the model demonstrated higher negative predictive value (NPV: 96.29% vs. 50.0%) and overall accuracy (83.33% vs. 73.68%), further highlighting its advantages in reliable negative prediction and comprehensive diagnostic performance.

3.4 Survival analysis underscored the clinical relevance of ERM-Model

Figure 4 showed comparing cumulative IHR rates between different risk stratification groups based on the ERM-Model through the Kaplan–Meier survival analysis. In both the training cohort, the test cohort and the overall patient population, the low-risk group (the best cutoff value: 0.378) showed significantly increased 2-year cumulative non-IHR rates compared to the high-risk group, with statistically significant differences observed in all comparisons ($p < 0.001$ for all).

Table 2 Univariate and multivariate cox analysis of clinical parameters of IHR

Variables	Univariable association		Multivariable association	
	HR(95%CI)	P value	HR(95%CI)	P value
Age, years	0.983 (0.956–1.011)	0.239		
Male vs. Female	1.255 (0.703–2.240)	0.443		
qHBsAg (log_{10}IU/mL)	1.616 (1.010–2.585)	**0.045**		
Tumor number Multiple vs. Single	2.059 (1.177–3.601)	**0.011**		
Tumor size ≥ 2 vs. < 2 cm	1.629 (0.936–2.836)	0.084		
BCLC A vs.0 stage	1.930 (0.992–3.757)	**0.053**		
AFP (ng/ml)	1.0 (0.997–1.002)	0.821		
PT(s)	1.075 (0.935–1.236)	0.308		
INR	1.440 (0.369–5.625)	0.600		
Albumin(g/L)	0.939 (0.900–0.980)	**0.004**		
Total bilirubin(μmol/L)	1.019 (0.997–1.041)	0.084		
ALT(U/L)	1.008 (1.004–1.011)	**< 0.001**		
AST(U/L)	1.012 (1.007–1.017)	**< 0.001**		
GGT(U/L)	1.006 (1.004–1.008)	**< 0.001**		
Lymphocyte (10^9/L)	0.874 (0.563–1.357)	0.549		
Neutrophil(10^9/L)	0.711 (0.547–0.923)	**0.011**		
Platelet (10^9/L)	0.991 (0.986–0.996)	**0.001**		
Monocyte (10^9/L)	0.794 (0.138–4.561)	0.795		
NLR	0.898 (0.754–1.070)	0.229		
PLR	0.993 (0.986–0.999)	**0.031**		
LMR	0.960 (0.777–1.185)	0.701		
GNR	1.007 (1.004–1.010)	**< 0.001**	1.013 (1.006–1.021)	**0.001**
GLR	1.004 (1.002–1.005)	**< 0.001**		
GMR	1.002 (1.002–1.003)	**< 0.001**		
GPR	1.442 (1.262–1.649)	**< 0.001**	1.605 (1.189–2.166)	**0.002**
APRI	1.579 (1.028–1.948)	**< 0.001**		
Fib-4	1.109 (1.048–1.174)	**< 0.001**		

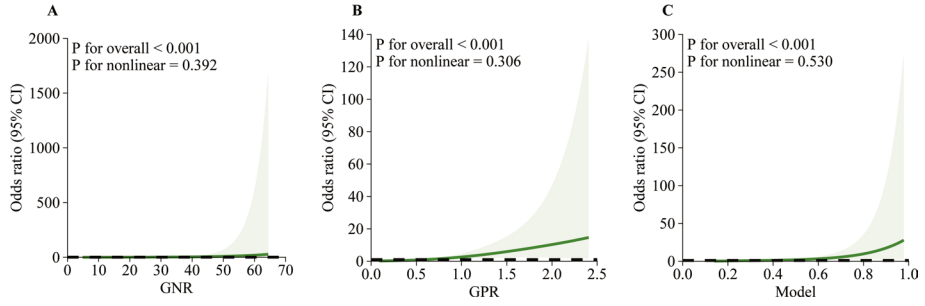

Fig. 2 Restricted cubic splines illustrating the associations between GNR (**A**), GPR (**B**) and model predicted values (**C**) with odds ratios.

3.5 The performance of the ERM-Model in different subgroups

To further investigate the diagnostic performance between non-IHR and IHR subgroups about BCLC stages, statistical analysis revealed no significant differences between subgroups in BCLC 0 stage. However, a highly statistically significant discrepancy between non-IHR and IHR subgroups was observed in the BCLC A stage group ($p < 0.001$), suggesting a substantial differentiation between non-IHR and IHR subgroups at this stage. These findings have direct relevance for clinical practice in BCLC-A stage HCC management. To assess the discriminative power of the model across HCC stages, ROC curves

Table 3 Comparison of diagnostic performance: Serum AFP versus Predictive Model in Training and Test Cohorts

	Auc	Sensitivity	Specificity	PPV(%)	NPV(%)	Coincidence rate (%)
Training set						
AFP	0.650	0.829	0.537	82.86	53.70	65.17
Model	0.803	0.686	0.852	64.86	90.62	77.67
Testing set						
AFP	0.773	0.800	0.727	80.0	50.0	73.68
Model	0.812	0.600	0.955	60.0	96.29	83.33

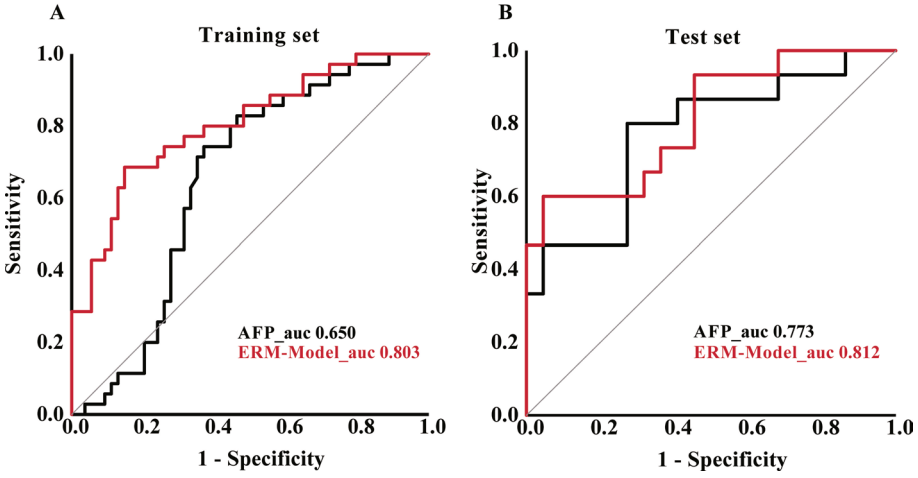

Fig. 3 Receiver Operating Characteristic (ROC) curves of the AFP level and the constructed model in the training set (**A**) and the test set (**B**)

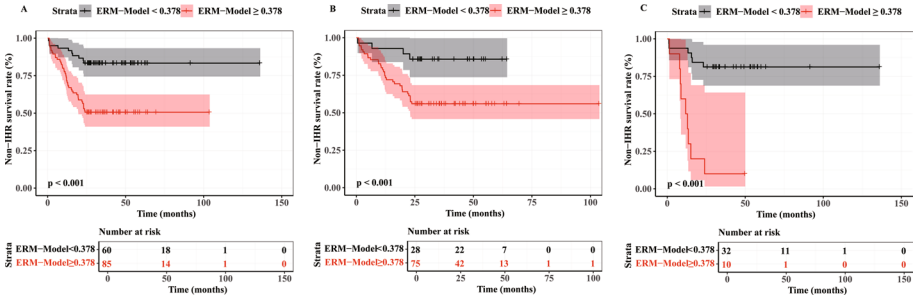

Fig. 4 Kaplan–Meier Survival Curves Comparing Model Performance Across Cohorts. **A** Total Cohort: Kaplan–Meier survival analysis of all patients (n = 145) stratified by model-predicted risk levels. **B** Training Cohort: Survival analysis in the training cohort (n = 103). **C** Test Cohort: External validation in the independent test cohort (n = 42).

were constructed for both BCLC 0 and A stages. The model achieved AUCs of 0.689 (BCLC-0) and 0.832 (BCLC-A), indicating stage-dependent diagnostic accuracy (Fig. 5). In BCLC-A HCC cases, the model's performance remained robust regardless of tumor multiplicity (AUC 0.799 for ≤ 1 tumors vs. 0.876 for > 1 tumors), supporting its clinical applicability (Sup-Figure). These results provide valuable insights for the application of the model in the differential diagnosis of different HCC status, particularly highlighting its improved utility in the assessment of the multiple-tumor of BCLC A stage population.

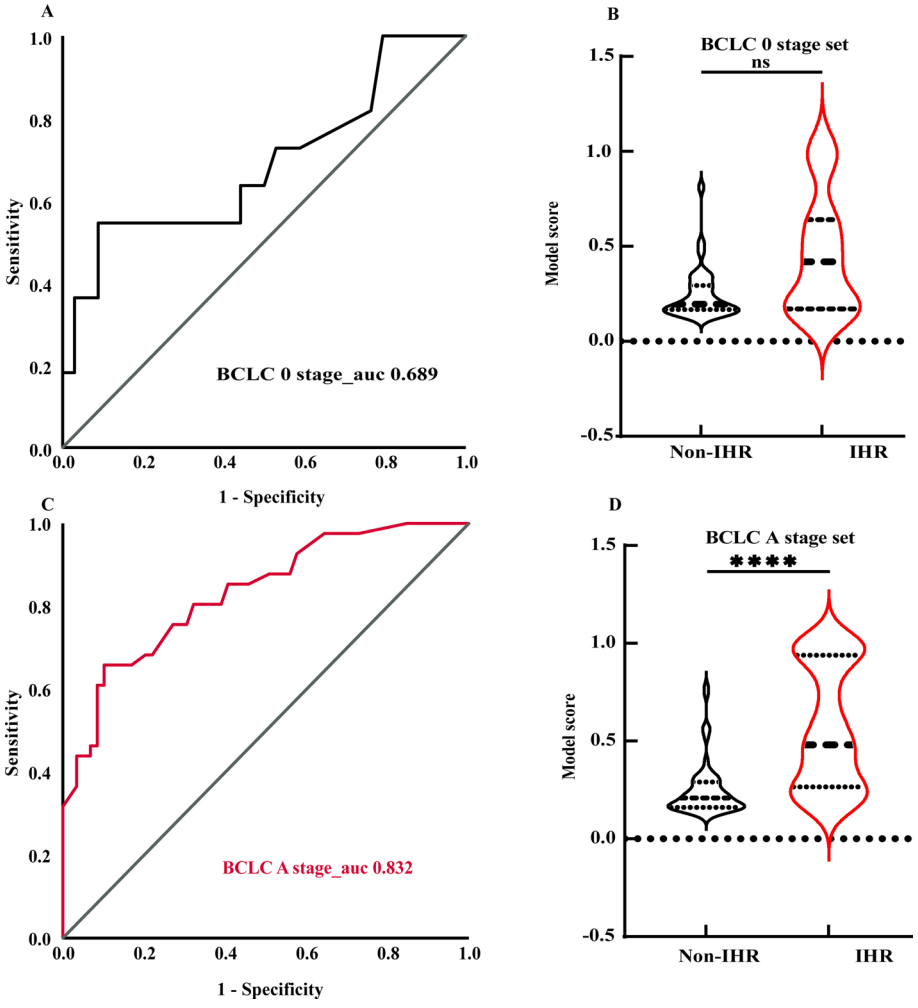

Fig. 5 Comparative model performance in differentiating BCLC stage 0 and stage A datasets. **A**, **B** Model performance evaluation results on the BCLC stage 0 cohort. **C**, **D** Model performance evaluation results on the BCLC stage A cohort

4 Discussion

Both surgical resection and radiofrequency ablation (RFA) represent primary therapeutic modalities for ESHCC with curative intent. However, emerging evidence indicates a substantial risk of postoperative recurrence [22]. Clinically, the 2-year threshold distinguishes prognostically distinct HCC recurrence subtypes—early recurrences (≤ 24 months) correlate with aggressive tumor biology (e.g., microvascular invasion), while late recurrences (> 24 months) often mirror the initial tumor's indolent characteristics [23, 24]. ESHCC patients following curative treatment has a significant recurrence rate of approximately 50% [25], with intrahepatic recurrence (IHR) being the predominant pattern. Therefore, a reliable biomarker for regular detection of potential risks, will allow early intervention and facilitate proactive selection of patient-tailored therapeutic strategies. This comprehensive approach may significantly improve long-term survival and quality of life for patients.

Emerging evidence suggests that inflammatory biomarkers, particularly gamma-glutamyl transferase (GGT), platelet count (PLT) and neutrophil-related parameters, exert significant regulatory effects throughout the continuum of HCC pathogenesis—from

initial hepatocarcinogenesis to disease progression and metastasis [26–28]. Recent evidence has identified novel prognostic biomarkers based on inflammatory status in HCC. For example, systemic immune inflammation indices (e.g., neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), GGT-derived Neutrophil-Platelet-Monocyte-Lymphocyte Ratio and serum N-glycomics) have been validated as independent predictors of postoperative recurrence and survival outcomes [14, 15, 29–31]. This study demonstrates that peripheral blood GNR and GPR are both important indicators for predicting IHR within 2 years in patients with ESHCC. It is a similar conclusion of Shen's research, they have found that GNR is independently associated with postoperative overall survival (OS) and recurrence-free survival (RFS) in patients with HCC, and helps identify patients at high risk of poor prognosis [14]. The noninvasive model developed in this study is based on GNR and GPR, that can more assess the risk of IHR in HCC. The optimal cut-off value of ERM-Model was determined to be 0.378 through statistical analysis. Compared with the diagnostic performance of AFP, the ERM-Model demonstrated lower sensitivity (60.0% vs. 80.0%) but significantly higher specificity (95.5% vs. 72.7%), indicating its enhanced ability to identify true negative cases. Furthermore, the ERM-Model achieved superior diagnostic accuracy with an overall coincidence rate of 83.33% versus 73.68% for AFP alone. Empirically, elevated AFP levels show a strong positive correlation with adverse clinical outcomes in HCC patients, but, its sensitivity is relatively low (about 60%) [32]. Notably, AFP testing has limited specificity in clinical practice and is therefore often combined with other detection methods to enhance the accuracy and reliability of diagnosis [33]. Our cohort analysis identified 5.36 ng/mL as the optimal cutoff (Youden index-derived), achieving enhanced sensitivity (0.80) with preserved specificity (0.73), suggesting improved early detection potential in screening contexts. Comparative analysis between IHR and non IHR subgroups exhibited no statistically difference in AFP levels. This observation may be attributable to the substantial proportion of subthreshold AFP cases (71/126, 56.3%) in our cohort, potentially obscuring biomarker discriminative capacity.

This study evaluated inflammation-based biomarkers for predicting metachronous IHR following radical therapy in patients with very early/early-stage HCC (BCLC stage 0/A), providing data to inform post-treatment disease prediction. Survival analysis demonstrated ERM-Model diagnose HCC progression sates in clinical, with particularly robust performance in stratifying multifocal tumors within the BCLC-A cohort ($p < 0.001$). In our multivariate analysis, inflammatory indices including NLR, PLR, LMR, GMR and GLR failed to demonstrate independent associations with intrahepatic tumor recurrence. This discrepancy may stem from population heterogeneity, particularly variations in clinical stages and treatment modalities across cohorts. Notably, prior studies similarly observed limited prognostic generalizability of inflammatory biomarkers. These findings underscore the context-dependent specificity of inflammation-based prognostication, necessitating population-tailored biomarker selection.

This study highlights GNR and GPR as predictors of early IHR in HBV-HCC, outperforming traditional markers like AFP. The ERM-Model has favourable clinical applicability due to its simplicity and compatibility with routine diagnostic workflows. Specifically, this model used only preoperative imaging and serological indicators to predict intrahepatic recurrence of ESHCC. Yet, our findings represent only preliminary insights, underscoring the need for further research to elucidate the impact of GNR and GPR

on IHR in individuals with liver cancer. Several limitations of this study warrant consideration. Firstly, as a single-center investigation, it may limit the generalizability of the findings due to potential inherent biases in patient selection and institutional-specific clinical practices. Secondly, the relatively small sample size might compromise the statistical power of the analyses and affect the robustness of the conclusions drawn. Meanwhile, the validation set where it is reduced to just n = 42, has the potential to influence the stability of the results achieved. This constraint in size may exacerbate the degree of variation and introduce greater uncertainty in the outcomes. Additionally, baseline characteristics of enrolled patients, including body mass index, were not assessed; these factors may be associated with intrahepatic recurrence and thus might have impacted the interpretation of results. Finally, the diagnosis of intrahepatic recurrence relied on imaging modalities including CT and/or MRI. Although these are widely employed in clinical practice, their inherent limitations in sensitivity and specificity for identifying early or subtle recurrent lesions may have affected the accuracy of recurrence assessment. Moving forward, collaborations with multiple centers will be essential to broaden the scope of our investigations and validate our conclusions through increased sample sizes. Simultaneously, additional foundational experiments, such as cell culture studies and the development of animal models, will be essential in order to corroborate our discoveries across diverse dimensions. In recent years, there have been numerous studies focusing on the poor prognosis of HCC. For example, Li Jin et al. demonstrated that higher lymphatic vessel density (LVD) serves as a reliable prognostic biomarker for poor overall survival and recurrence-free survival in patients with hepatobiliary malignancies (including HCC, cholangiocarcinoma, and gallbladder cancer) following radical resection. This finding provides novel insights into the prognostic assessment of HCC [34]. Therefore, further large-scale, multi-center and multi-stage integrated analytical models are needed to enhance clinical staging accuracy and therapeutic decision-making.

5 Conclusion

Patients after definitive therapy with ESHCC need to find more suitable prognostic monitoring indicators.The combined GNR-GPR model offers a novel, clinically applicable tool for predicting IHR in ESHCC, enabling risk-adapted management, improving patient outcomes, and surveillance protocols in this population.

6 Summary

We evaluated different inflammation markers for predicting early intrahepatic recurrence in Hepatocellular carcinoma

A gamma-glutamyl transpeptidase-derived neutrophil-platelet ratio model was found to be an accurate predictive indicator.

The model has simplicity and compatibility, and is also favourable clinical applicability in routine diagnostic workflows.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-03997-9.

Sub-Figure. Comparative performance metrics of the model in solitary vs. multifocal HCC stratification within BCLC-A stage. (A, B) Model performance evaluation results on single-tumor cohort. (C, D) Model performance evaluation results on multiple-tumor cohort.

Acknowledgements
We are grateful to Hong Cui from the Department of Medical Records at Tianjin Second People's Hospital for assisting with data retrieval using the Electronic Medical Record Analytical Database (TSPH-EHRD).

Author contributions
The research was conceived by ZH, LY, and RS. Literature search was conducted by ZH. Data collection and analysis were carried out by ZH, LY, WK and QD. Data visualization was completed by ZH, LY, KQ, JX and BJ. The manuscript was drafted by ZH and LY while WL, KY, YC, LX and RS reviewed it. All authors contributed to the article and approved the submitted version.

Funding
This study was supported by grants from Tianjin Public Health Science and Technology Major Project (24ZXGZSY00110), Natural Science Foundation of Tianjin (23JCYBJC00950) and Tianjin Health Science and Technology Project Key Discipline Special (TJWJ2022XK034).

Data availability
The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Tianjin Second Peple's Hospital. 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. This study was approved by the Medical Ethics Committee of Tianjin Second People's Hospital (No. 2023-43). Informed consent was obtained from all individual participants included in the study. In the case of participants under the age of 16, informed consent was obtained from a parent or legal guardian.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 July 2025 / Accepted: 30 October 2025
Published online: 15 December 2025

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