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ORIGINAL ARTICLE

Unlocking Prognostic Potential: Serum Uric Acid and Prothrombin Time as Predictors of HCC Recurrence

Yanping Xiao [1], Qing lin [1], Kunrong Yang [1], Guangjian Su [1]

Laboratory of Biochemistry and Molecular Biology Research, Department of Clinical Laboratory, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, NHC Key Laboratory of Cancer Metabolism, Fuzhou, Fujian, China

ABSTRACT

Background: **This study aims to explore the prognostic value of pre-treatment serum uric acid (UA) and prothrombin time (PT) levels on the risk of tumor recurrence in patients with hepatocellular carcinoma (HCC) after receiving comprehensive therapy.**

Methods: **A total of 199 HCC patients who underwent combination therapy (including surgical resection, local ablation, interventional therapy, and systemic therapy) at Fujian Cancer Hospital from January 2020 to December 2022 were consecutively enrolled. Baseline clinical data and pre-treatment laboratory indicators were collected. The primary endpoint was recurrence-free survival (RFS), with a median follow-up time of 19 months. The optimal cutoff values for UA and PT of predicting recurrence were determined using receiver operating characteristic (ROC) curves. Independent risk factors affecting RFS were analyzed using the Cox proportional hazards regression model. The Kaplan-Meier method was used to plot survival curves to compare differences between groups and to construct nomograms. Spearman's correlation analysis was also conducted.**

Results: **A total of 116 patients (58.3%) experienced recurrence. Multivariate Cox regression analysis showed that UA (HR = 1.486, 95% CI: 1.009 - 2.189, p = 0.045) and PT (HR = 1.510, 95% CI: 1.011 - 2.261, p = 0.046) were independent risk factors for HCC recurrence. Furthermore, based on optimal cutoff values determined by ROC curve analysis, Kaplan-Meier survival analysis confirmed that recurrence-free survival (RFS) was significantly lower in the low-UA group and short-PT group (p < 0.05). Correlation analysis indicated that UA and PT had no significant correlation with alpha-fetoprotein (AFP), a traditional tumor marker for HCC, with p > 0.05, suggesting that their prognostic information is independent of traditional tumor markers.**

Conclusions: **Elevated pre-treatment serum uric acid (UA) levels and prolonged prothrombin time (PT) are independent predictive factors for recurrence after combined therapy in HCC patients. These two indicators, as routine and easily accessible clinical tests, are cost-effective and have significant potential for application in improving postoperative risk stratification, identifying high-risk patient groups, and guiding individualized follow-up strategies for HCC patients.**

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Correspondence:
Guangjian Su
Laboratory of Biochemistry and
Molecular Biology Research
Department of Clinical Laboratory
Clinical Oncology School of
Fujian Medical University, Fujian Cancer Hospital
No. 420, Fuma Road
Jin'an District, Fuzhou City 350014
China
Email: suguangjian@fjmu.edu.cn

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KEYWORDS

hepatocellular carcinoma, serum uric acid, prothrombin time, recurrence, disease-free survival, prognostic factors

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It has high incidence and mortality rates, posing a heavy burden on public health systems both globally and in our country [1]. For HCC

patients, main treatments include surgical resection, local ablation, transarterial chemoembolization (TACE), targeted therapy, and immunotherapy, which may provide a chance of cure. However, despite these treatment options, the high recurrence rate after therapy remains a major challenge that affects patients' long-term survival and greatly limits improvements in treatment outcomes [2]. Currently, prognosis assessment of HCC largely relies on clinical staging systems like BCLC Barcelona Clinic Liver Cancer (BCLC) and Tumor Node Metastasis (TNM), as well as traditional serological biomarkers such as AFP, but these tools still have limitations in sensitivity and specificity for predicting recurrence [3]. Therefore, identifying effective supplementary biomarkers to complement existing staging systems is a key focus in HCC clinical research. These biomarkers should be easy to measure and reliable for identifying patients at high risk of recurrence, as well as for guiding individualized follow-up and intervention.

In recent years, increasing attention has been paid to the role of the tumor microenvironment in hepatocellular carcinoma (HCC) initiation and progression. Serum uric acid (UA), the end product of purine metabolism, may strongly influence oxidative stress and inflammation, the latter being a key part of the pro-tumor microenvironment [4]. Multiple studies have shown that UA promotes tumor progression, and elevated levels correlate with poorer prognosis [5,6]. However, existing studies provide inconsistent evidence regarding UA's value in predicting HCC recurrence risk, warranting further investigation [7]. Prothrombin time (PT), a routine and vital test, directly reflects the liver's synthetic capacity and functional reserve in patients [8]. Hepatic insufficiency is the basis for the occurrence and recurrence of HCC, and PT may more sensitively reflect subtle changes in liver function compared to some indicators in the Child-Pugh classification (such as albumin and bilirubin), thus having the potential to predict recurrence [9,10]. The latest research by Hayakawa et al. also confirmed that incorporating PT into risk scoring models can effectively predict mortality after liver resection [11].

Based on the above background, this study aims to explore the predictive value of pre-treatment serum UA and PT levels on the risk of recurrence in patients with hepatocellular carcinoma. These indicators are easily obtainable from routine clinical tests. Through a retrospective cohort study, we systematically analyze the relationship between UA and PT with disease-free survival, and evaluate whether they can serve as independent prognostic factors, ultimately providing evidence support for the clinical construction of a simple and effective postoperative recurrence risk stratification tool.

MATERIALS AND METHODS

Subjects

This study is a single-center retrospective cohort study. It continuously included 199 patients with hepatocellular carcinoma (HCC) treated at Fujian Cancer Hospital from January 2020 to December 2022. The treatments included surgical resection, local ablation, interventional therapy, targeted therapy, immunotherapy, and combined chemotherapy. Inclusion criteria include: 1) Diagnostic criteria, including patients diagnosed with HCC by pathological histology or cytology, or those meeting the clinical diagnostic criteria in the "Guidelines for Diagnosis and Treatment of Primary Liver Cancer"; 2) Treatment method, defined as patients receiving "comprehensive treatment" as the initial or primary plan. Comprehensive treatment includes one or more of the following: a. Surgical resection; b. Local ablation therapy (e.g., radiofrequency or microwave ablation); c. Transarterial chemoembolization (TACE); d. Systemic therapy (targeted therapy, immunotherapy, etc.); 3) Complete clinical data, including serum uric acid (UA) and prothrombin time (PT) within one week before treatment; 4) Complete clinicopathological and follow-up data. Inclusion criteria are: 1) Diagnosis of hepatocellular carcinoma (HCC) confirmed by pathological histology, cytology, or clinical criteria in the "Guidelines for Diagnosis and Treatment of Primary Liver Cancer"; 2) Severe cardiac or renal insufficiency; 3) Comorbidities or medication history affecting UA/PT; 4) Follow-up time less than 12 months or loss to follow-up. The study protocol was reviewed and approved by the Ethics Committee of Fujian Cancer Hospital (approval number: K2025-041-01), and due to the retrospective nature of the study, patient informed consent was waived.

Data Collection

Baseline data and laboratory indexes of the patients were collected by consulting the electronic medical record system. Baseline data included age, gender, history of hepatitis B virus infection, alcohol consumption history, vascular invasion status, CNLC staging, and presence of ascites. Laboratory indexes focused on pre-treatment serum UA and PT levels. UA was measured using the uricase-peroxidase method (Beckman Coulter AU5800 Series Chemistry Analyzer), and PT was determined by the coagulation method (Sysmex CS-5100 Fully Automatic Coagulation Analyzer). All tests were performed using the analyzer in our hospital's laboratory department, following standardized operating procedures and quality control protocols. Additionally, other prognostic indicators were collected, including alpha-fetoprotein (AFP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and alanine aminotransferase (ALT).

Outcome and Follow-up

The primary endpoint of this study is recurrence-free survival (RFS). RFS is defined as the time from the completion of treatment to either the first confirmation of tumor recurrence by imaging examination (contrast-enhanced CT/MRI) or death caused by hepatic carcinoma itself. The postoperative follow-up plan is as follows. In the first two years after treatment, contrast-enhanced CT/MRI and serum AFP tests will be conducted every 3 to 6 months. The median follow-up time is 19 months. The follow-up cutoff date is December 31, 2024.

Statistical analysis

All statistical analyses were performed using SPSS software version 29.0 (SPSS, IBM Corp., Armonk, NY, USA) and R language version 4.2.1 (R Foundation, Vienna, Austria). Continuous variables were described using the median and interquartile range (IQR), while categorical variables were expressed as frequency (percentage). This study converted UA and PT into binary variables by using receiver operating characteristic (ROC) curve analysis. The optimal cutoff value for predicting recurrence was determined by maximizing Youden's index, rather than relying on clinical reference values or medians. Univariate Cox proportional hazards regression analysis was conducted for all potential prognostic factors. Variables with $p < 0.1$ were then included in a multivariate Cox regression model. Based on this model, a prognostic nomogram was developed to identify independent risk factors affecting RFS. Results were expressed as hazard ratio (HR) and its 95% confidence interval (CI). Based on the optimal cutoff values, patients were divided into high and low UA groups, as well as long and short PT groups. Survival curves were plotted using the Kaplan-Meier method, and differences in RFS between groups were compared by the Log-rank test. The association between UA, PT, and AFP was analyzed using Spearman's rank correlation analysis, with a two-sided p-value < 0.05 considered statistically significant.

RESULTS

Baseline clinical characteristics and biomarker comparison in HCC patients by recurrence status

This study included 199 patients with hepatocellular carcinoma who received treatment; of these, 83 (41.7%) did not experience recurrence, while 116 (58.3%) did. Significant differences were observed between the recurrence and non-recurrence groups in fibrinogen-albumin ratio (FAR) (0.079 vs. 0.092, $p = 0.017$) and neutrophil-to-lymphocyte ratio (NLR) (2.216 vs. 2.531, $p = 0.047$). Differences in age (60.78 ± 10.09 years vs. 57.82 ± 11.25 years, $p = 0.057$) and uric acid (UA) levels (315.0 vs. 338.5 μmol/L, $p = 0.074$) approached statistical significance. No significant differences were found between the two groups regarding gender, history of alcohol consumption, history of HBV infection, vascular invasion, ascites, CNLC staging, prothrombin time (PT), ALT, and AFP levels ($p > 0.05$) (Table 1).

Analysis of Risk Factors for HCC Recurrence

Univariate Cox regression analysis showed that age (HR = 0.982, 95% CI: 0.965 - 1.000, $p = 0.046$), UA (HR = 1.477, 95% CI: 1.005 - 2.171, $p = 0.048$), (HR = 1.495, 95% CI: 1.001 - 2.258, $p = 0.047$), and NLY (HR = 1.026, 95% CI: 1.002 - 1.050, $p = 0.036$) were associated with non-recurrence survival. These factors were identified in patients. Multivariate Cox regression analysis showed that UA (HR = 1.486, 95% CI: 1.009 - 2.189, $p = 0.045$) and PT (HR = 1.510, 95% CI: 1.011 - 2.261, $p = 0.046$) were independent risk factors for recurrence-free survival after treatment of hepatic carcinoma (Table 2).

Development and validation of predictive models

The optimal cutoff values for UA and PT predicting recurrence were determined through ROC curve analysis (Figure 1). Based on this, Kaplan-Meier (KM) survival curves were constructed, indicating that patients with high UA levels and prolonged PT had significantly lower recurrence-free survival rates ($p < 0.05$) (Figure 2). Subsequently, a nomogram was constructed integrating multiple clinical parameters to predict the postoperative survival probability of patients (Figure 3). Time-dependent ROC analysis showed that the AUC values for predicting 1-year recurrence risk were 0.545 for UA and 0.455 for PT (Figure 4).

Analysis of correlation among main biological indicators

Spearman's correlation analysis showed no significant correlation between serum uric acid (UA) and alpha-fetoprotein (AFP) levels ($R = 0.072$, $p = 0.315$). Similarly, no significant correlation was found between prothrombin time (PT) and AFP levels ($R = 0.008$, $p = 0.912$). These results indicate that UA and PT, as prognostic factors for hepatocellular carcinoma, provide information independent of the traditional tumor marker AFP.

DISCUSSION

This study confirms, through rigorous retrospective analysis, that elevated serum uric acid (UA) levels and prolonged prothrombin time (PT) independently increase the risk of tumor recurrence in patients with hepatocellular carcinoma (HCC) after treatment. Multivariate Cox regression analysis showed that, after adjusting for various potential confounding factors such as age, tumor staging, and vascular invasion, UA (HR = 1.486, 95% CI: 1.009 - 2.189, $p = 0.045$) and PT (HR = 1.510, 95% CI: 1.011 - 2.261, $p = 0.046$) remained significantly associated with poor recurrence-free survival (RFS). This result is consistent with existing studies,

Table 1. Comparison of baseline clinical data between the relapse and non-relapse groups.

Characteristics	Non-recurrence group	Recurrence group	p-value
n	83	116	
Age (years), mean ± sd	60.78 ± 10.09	57.82 ± 11.25	0.057
Gender, n (%)			
Male	74 (37.2%)	101 (50.8%)	0.656
Female	9 (4.5%)	15 (7.5%)	
Alcohol history, n (%)			
Yes	31 (15.6%)	39 (19.6%)	0.587
No	52 (26.1%)	77 (38.7%)	
HBV infection history, n (%)			
Yes	68 (34.2%)	92 (46.2%)	0.646
No	15 (7.5%)	24 (12.1%)	
Vascular Invasion, n (%)			
No	34 (17.1%)	39 (19.6%)	0.289
Yes	49 (24.6%)	77 (38.7%)	
Ascites, n (%)			
No	70 (35.2%)	102 (51.3%)	0.465
Yes	13 (6.5%)	14 (7%)	
CNLC, n (%)			
I	20 (10.1%)	30 (15.1%)	0.750
III	35 (17.6%)	42 (21.1%)	
II	21 (10.6%)	36 (18.1%)	
IV	7 (3.5%)	8 (4%)	
UA (μmol/L), median (IQR)	315.0 (270.5, 382.0)	338.5 (299.5, 388.5)	0.074
PT (seconds), median (IQR)	12.60 (11.9, 13.35)	12.40 (11.80, 13.05)	0.146
ALT (U/L), median (IQR)	40 (25, 69)	39 (26, 57)	0.581
AFP (ng/mL), median (IQR)	48.8 (4.6, 1,741.5)	109.3 (8.9, 1,110.2)	0.561
FAR, median (IQR)	0.079 (0.065, 0.101)	0.092 (0.069, 0.122)	0.017
NLY, median (IQR)	2.216 (1.528, 2.944)	2.531 (1.711, 3.525)	0.047

Categorical variables are expressed as frequency (percentage). Continuous variables with a normal distribution are expressed as mean ± standard deviation. Variables that are not normally distributed are expressed as median (interquartile range). For statistical analysis, comparisons between groups are conducted using the chi-squared test, *t*-test, or Mann-Whitney U test. UA: Uric Acid, PT: Prothrombin time, ALT: Alanine aminotransferase, AFP: Alpha fetoprotein, FAR: Fibrinogen-albumin ratio, NLY: Neutrophil-lymphocyte ratio.

highlighting the importance of these biomarkers in clinical prognosis. Although the predictive model based on UA and PT shows moderate performance in the time-dependent ROC curve, with AUCs of 0.545 and 0.455 respectively, it does not significantly correlate with AFP. This suggests that the model may serve as an independent prognostic indicator. This finding indicates that these two easily accessible routine clinical tests can provide important information for postoperative risk stratification in HCC patients [12-14].

Our findings align with previous studies exploring the role of uric acid (UA) in cancer prognosis. Multiple meta-analyses confirm that elevated circulating UA is linked to poor prognosis in gastrointestinal cancers [15]. The potential mechanisms may involve several aspects. First, UA, as an endogenous danger signal, may promote the production of reactive oxygen species and activate the NLRP3 inflammasome. This leads to sustained oxidative stress and inflammation in the tumor microenvironment, which supports tumor cell survival and proliferation [16]. Second, experimental studies indicate that UA can directly promote tumor cell proliferation and invasiveness by activating specific signaling pathways, such as the AhR/p27/cyclin E pathway [17,18]. In addition, hyperuricemia often coexists with metabolic syndrome components like obesity and diabetes melli-

Table 2. Cox regression analysis of factors affecting recurrence-free survival in liver cancer patients.

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (years)	199	0.982 (0.965 - 1.000)	0.046	0.983 (0.965 - 1.001)	0.060
Gender	199				
Male	175	reference			
Female	24	1.108 (0.644 - 1.906)	0.711		
Alcohol history	199				
Yes	70	reference			
No	129	1.143 (0.777 - 1.680)	0.497		
HBV infection history	199				
Yes	160	reference			
No	39	1.026 (0.654 - 1.607)	0.912		
Vascular Invasion	199				
No	73	reference			
Yes	126	1.291 (0.878 - 1.898)	0.194		
Ascites	199				
No	172	reference			
Yes	27	0.869 (0.497 - 1.519)	0.622		
CNLC	199				
I	50	reference			
III	77	0.941 (0.589 - 1.503)	0.798		
II	57	0.974 (0.600 - 1.581)	0.914		
IV	15	0.832 (0.381 - 1.814)	0.643		
UA (μmol/L)	199	1.477 (1.005 - 2.171)	0.048	1.486 (1.009 - 2.189)	0.045
PT (seconds)	198	1.495 (1.001 - 2.258)	0.047	1.510 (1.011 - 2.261)	0.046
ALT (U/L)	199	1.000 (0.997 - 1.002)	0.876		
AFP (ng/mL)	199	1.000 (1.000 - 1.000)	0.498		
FAR	199	0.912 (0.222 - 3.745)	0.899		
NLY	199	1.026 (1.002 - 1.050)	0.036	1.019 (0.996 - 1.043)	0.099

Variables with $p < 0.1$ in univariate analysis are included in multivariate analysis. HR: Risk ratio, CI: Confidence interval.

tus. These conditions are known risk factors for hepatocellular carcinoma (HCC), suggesting that the adverse prognostic impact of hyperuricemia may partly arise from this comorbidity [19].

This study highlights the central role of hepatic reserve, as indicated by PT, in the prognosis of HCC. PT is a sensitive indicator of liver synthetic function, with its prolongation indicating varying degrees of hepatic insufficiency [20]. Poor liver function may increase recurrence risk through several mechanisms: first, by reducing the liver's ability to clear carcinogens; second, by impairing immune surveillance in hepatic cirrhosis, thus creating a "soil" for tumor regeneration; and third, prolonged PT may indicate systemic conditions like chronic inflammation and malnutrition [21]. The CAP risk scoring model, developed by Hayakawa et al., includes PT to predict postoperative mortality following liver resection, further confirming PT's prognostic value [22,23].

The clinical significance of this study lies in the validation that UA and PT are routine, inexpensive, and reliable serological indicators that can be easily promoted and implemented in medical institutions at all levels [24,25]. Integrating UA and PT into the existing prognosis evaluation system (such as the CNLC staging) helps refine risk stratification for patients. For high-risk patients identified by UA and PT, more aggressive follow-up strategies, such as shortening the interval for imaging re-examination, can be adopted. These patients may also be considered as potential beneficiaries of future exploratory adjuvant targeted or immunotherapy, providing a basis for personalized treatment [26-29].

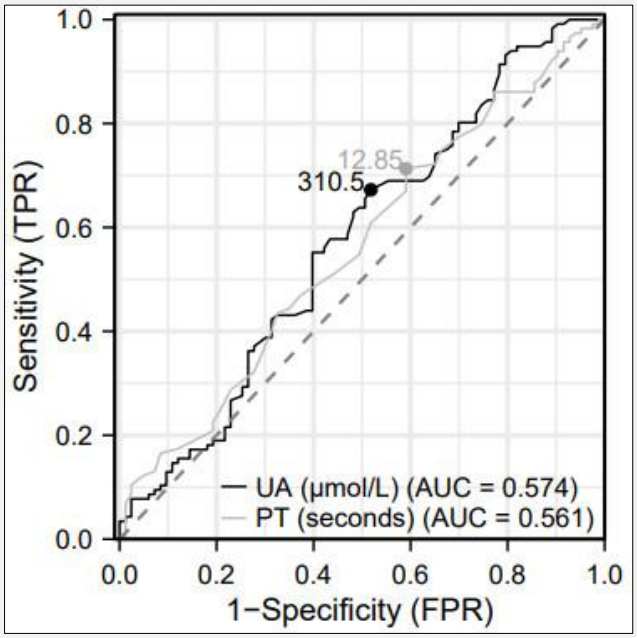

Figure 1. ROC curve of serum UA and PT predicting liver cancer recurrence.

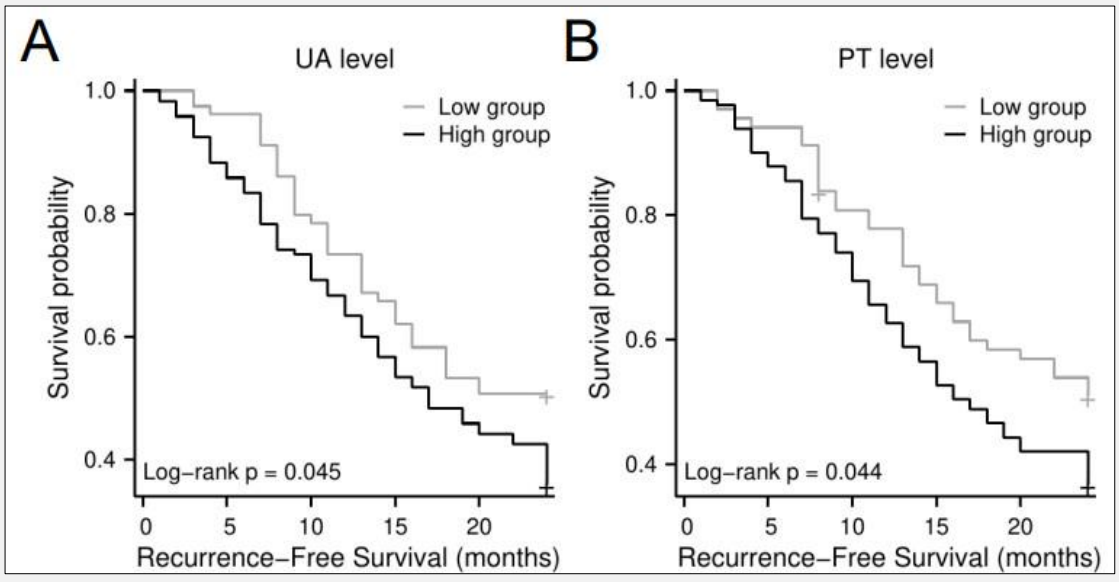

Figure 2. Recurrence-free survival Kaplan-Meier curve based on uric acid (UA) and prothrombin time (PT) levels.

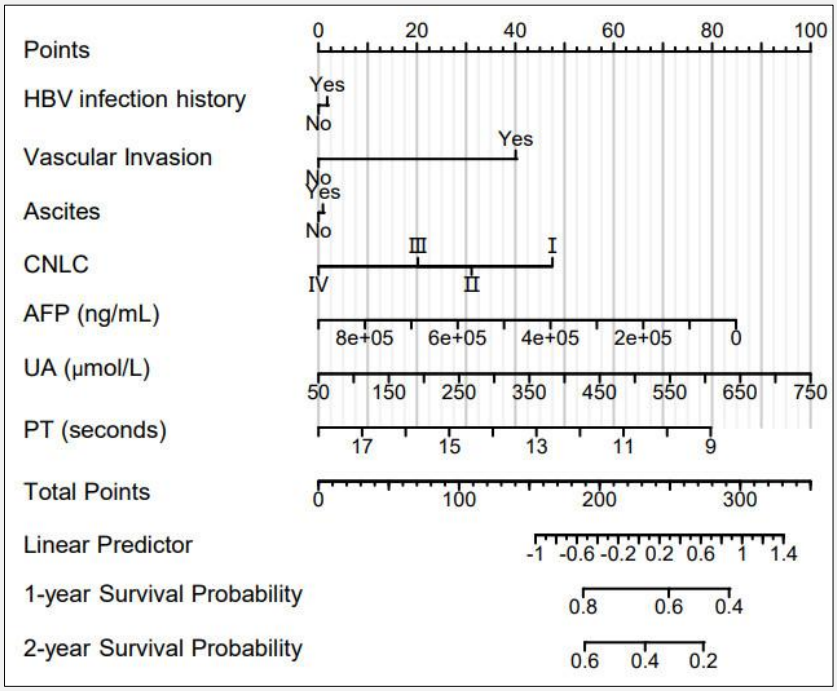

Figure 3. Shows a nomogram predicting the survival probability of hepatocellular carcinoma patients after treatment.

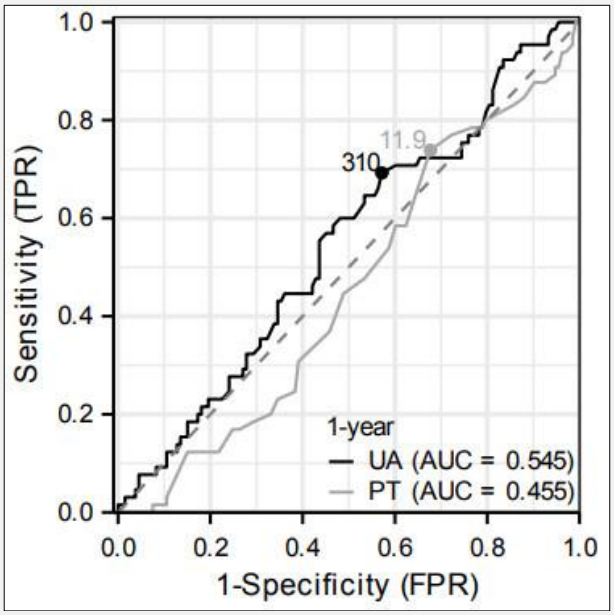

Figure 4. Time-dependent ROC curve analysis.

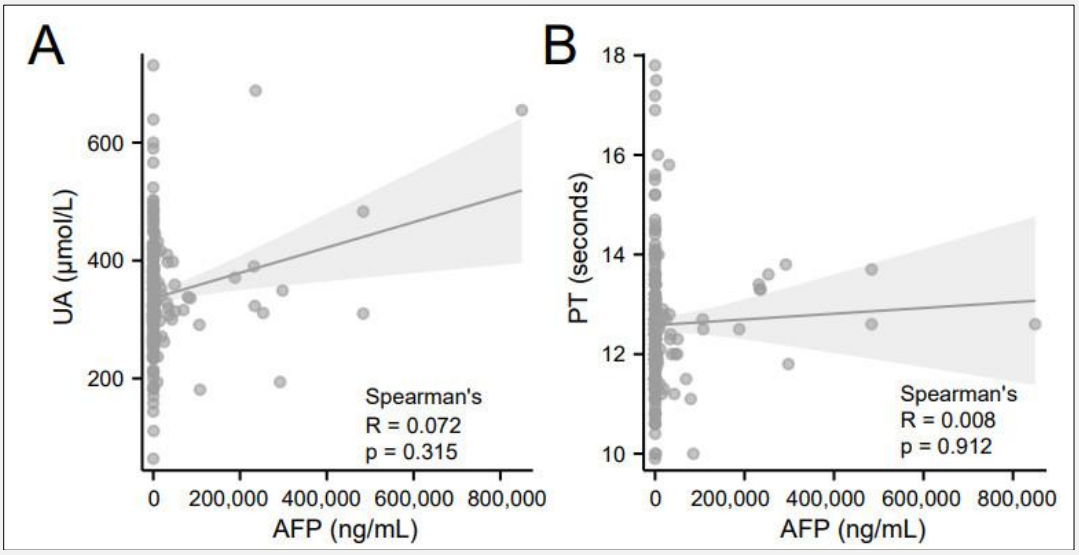

Figure 5. Correlation analysis of UA, PT, and AFP.

However, this study has several limitations that should be considered carefully when interpreting the results. First, as a single-center retrospective study, inherent selection bias and information bias in its design cannot be avoided [30]. Second, although the sample size (n = 199) meets certain statistical requirements, it may still be insufficient. This is especially true for some subgroup analyses, where statistical power might be inadequate. Such limitations could affect our ability to identify other potentially important factors [31]. Furthermore, the conclusions of this study lack validation from external cohorts. Their generalizability and reliability need further verification in prospective studies across different populations and centers. Finally, our exploration of the mechanisms by which UA and PT influence HCC recurrence remains limited to clinical associations and literature speculation. It lacks direct biological evidence from cell experiments, animal models, or more in-depth omics analyses [32]. For example, how UA affects liver cancer cell behavior via specific signaling pathways, and how the systemic inflammatory state behind PT prolongation regulates the microenvironment, are issues that require clarification through future basic research [33,34].

CONCLUSION

In conclusion, this study confirmed that serum UA and PT levels independently and effectively predict recurrence after comprehensive therapy for HCC. As routine biochemical indicators, they are cost-effective and easily implemented in clinical practice, offering significant value for improving postoperative risk stratification in HCC patients. Future research should validate these findings using multicenter, large-sample prospective cohorts. Additionally, basic experiments should explore the underlying molecular mechanisms. This approach will ultimately provide new strategies to intervene in these risk factors and improve patient prognosis.

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Availability of Data and Materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate:
The present study was approved by the Ethics Committee for Research and New Technologies of Fujian Provincial Cancer Hospital, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki, and its later amendments or

comparable ethical standards.

Declaration of Generative AI Use in Scientific Writing:
The authors used ChatGPT (OpenAI) to improve the grammar and clarity of the manuscript. The AI tool was not involved in the study design, data analysis, or interpretation of results. The authors take full responsibility for the final content.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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