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Developing a novel predictive model for identifying risk factors associated with being lost to follow-up among high-risk patients for recurrence following radical resection of hepatocellular carcinoma: the first report

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Abstract

Background Follow-up is essential especially for patients who are at a high risk of recurrence after radical resection of hepatocellular carcinoma (HCC). The aim of this study was to develop a predictive model aimed at identifying the risk factors associated with being lost to follow-up (LTFU) in high-risk patients for recurrence following radical resection of HCC.

Methods The retrospective study was conducted at our institution between October 2018 to May 2023. The patients who underwent radical liver resection for HCC and had high-risk factors for recurrence were categorized into an LTFU group and a control group. Multivariate logistic regression analysis was utilized to determine risk factors and construct a nomogram predictive model.

Results A total of 352 patients were included and subsequently classified into two distinct groups: the LTFU group ($n=123$, 34.94%) and the control group ($n=229$, 65.06%). Logistic regression analysis was then conducted to explore the potential associations between various factors and the occurrence of LTFU. The findings identified several independent risk factors for LTFU, including smoking (odds ratio, OR = 1.823, 95% confidence interval, CI 1.086–3.060, $p=0.023$); residing more than 200 km away from the hospital (OR = 1.857, 95% CI 1.105–3.121, $p=0.019$); having an unstable profession (OR = 1.918, 95% CI 1.112–3.311, $p=0.019$); and lacking medical insurance (OR = 5.921, 95% CI 1.747–20.071, $p=0.004$); the presence of liver cirrhosis (OR = 2.161, 95% CI 1.153–4.048, $p=0.016$); an operation time less than 240 min (OR = 2.138, 95% CI 1.240–3.688, $p=0.006$); and the absence of postoperative adjuvant therapy (OR = 2.641, 95% CI 1.504–4.637, $p=0.001$). Based on these seven significant factors, a main effects model

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was established, designated as the Wei-LTFU model, which achieved an area under the curve value of 0.744 (95% CI 0.691–0.798) in predicting the likelihood of LTFU.

Conclusion A main effects model, namely the Wei-LTFU model, incorporating the seven significant factors was formulated to predict the likelihood of LTFU occurrence, ultimately aiming to assist healthcare workers in developing effective strategies to improve follow-up outcomes for patients.

Keywords Hepatocellular carcinoma, Radical resection, Lost to follow-up, Recurrence, Model

Introduction

Hepatocellular carcinoma (HCC) is recognized as one of the most fatal cancers globally [1, 2, 3]. Many patients with HCC, especially those with early-stage and operable tumors, undergo radical resection as their primary treatment option [4]. However, recurrence remains a significant concern, particularly among those with high-risk factors [5, 6]. Therefore, regular follow-up is essential for early tumor recurrence detection and timely initiation of appropriate treatment interventions. Especially for HCC patients at high-risk for recurrence, early detection and treatment of recurrent lesions are crucial, making regular follow-up particularly important.

Numerous studies have shown that microvascular invasion (MVI), serum alpha-fetoprotein (AFP) levels greater than 400 ng/mL, poor tumor differentiation (E-S grade), a maximum tumor diameter exceeding 5 cm, and the number of tumors exceeding three are all high-risk factors for recurrence in HCC patients [7, 8, 9, 10, 11]. Prior research has highlighted the crucial role of consistent follow-up measures in effectively managing the recurrence rates of oncology patients. Additionally, it examines patient compliance issues and logistical constraints as potential factors contributing to patients becoming lost to follow-up (LTFU) [12]. Such instances of LTFU can significantly impede the prompt identification and management of tumor recurrence, potentially jeopardizing treatment efficacy and the overall quality of life for these patients [13, 14, 15]. Currently, the available research on the LTFU phenomenon among HCC patients who have undergone radical resection and high-risk factors for recurrence is lacking, and there exists a notable dearth of comprehensive and systematic predictive models to address this issue. Notably, we often overlook the profound influence that socioeconomic and psychological factors exert on patients' adherence to follow-up protocols.

Therefore, the objective of this study is to develop a comprehensive predictive model that aims to pinpoint the various risk factors associated with the LTFU status among HCC patients who have undergone radical resection and possess a high risk of recurrence. To achieve this goal, we conducted a retrospective analysis of medical records pertaining to HCC patients who underwent radical surgery at our institution. Our analysis was primarily directed towards examining tumor pathological features and patient serological characteristics, with the aim of determining their high-risk status for recurrence. In our study, we explored the independent risk factors that contribute to LTFU among these patients. Initially, we pinpointed the factors that were significantly correlated with LTFU and then crafted a predictive model, leveraging these identified factors. Finally, utilizing the predictive model's insights, we can employ targeted interventions in the future that hold significant value in swiftly identifying high-risk patients prone to becoming LTFU. This approach aims to enhance their treatment outcomes and ultimately to improve their overall quality of life. To the best of our knowledge, this is the first study dedicated to the development of an innovative predictive model, specifically designed to identify risk factors associated with being LTFU among high-risk patients for recurrence following radical resection of HCC.

Methods

Patients

We conducted a retrospective analysis of 525 HCC patients who underwent radical liver resection at Zhejiang Provincial People's Hospital spanning the period from October 2018 to May 2023. Drawing upon extensive prior research regarding recurrence factors in HCC patients [7, 8, 9, 10, 11], we identified the following criteria indicative of a high risk of recurrence: AFP levels exceeding 400 ng/ml, the presence of MVI, a maximum tumor diameter greater than 5 cm, a tumor count of more than 3, and an Edmondson-Steiner (E-S) grade of 3/4 for tumor differentiation. The exclusion criteria were stringent and encompassed the following: (1) patients who succumbed within the first year ($n = 32$), (2) those lacking the aforementioned high-risk factors for recurrence ($n = 129$), and (3) patients with incomplete or missing medical records ($n = 12$). After stringent screening, a total of 352 patients were ultimately included in the study, with 123 patients classified as being LTFU and 229 patients comprising the control group (Figure 1).

Clinical data

The study investigated a diverse set of 35 variables, encompassing clinical characteristics, pathological features, and sociological factors of the patients,

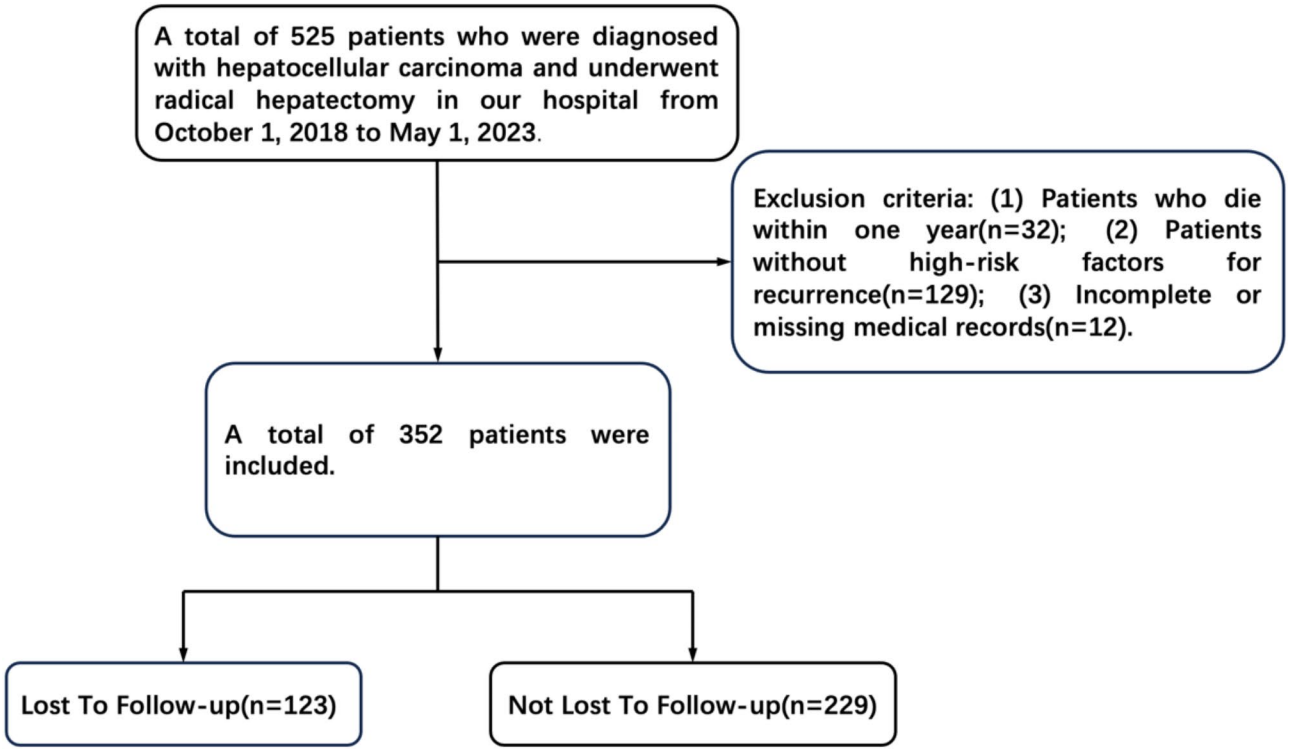

Fig. 1 Flowchart of patient selection

as comprehensively outlined in Table 1. To create the nomogram, we converted all risk factors into categorical variables. The variables incorporated in the analysis encompassed gender, age, body mass index (BMI), religion, smoking status, alcohol consumption, marital status, number of children, and type of residence, the GDP level of the patient's locality, distance from residence to hospital, educational attainment, occupation, medical insurance status, the presence of hypertension, diabetes mellitus, hepatitis B virus infection, liver cirrhosis, American Society of Anesthesiologists Physical Status, and serum levels of alanine aminotransferase, aspartate aminotransferase levels, alkaline phosphatase levels, glutamyltransferase levels, platelet count, hemoglobin concentration, albumin levels, serum cholesterol and triglyceride levels, total and direct bilirubin levels, time of operation, the presence of satellite nodules, Barcelona Clinic Liver Cancer (BCLC) staging, postoperative hospital stay, and postoperative adjuvant therapy.

Statistical analysis

Initially, the variables outlined in the study underwent dichotomization, with the categorical variables presented as frequencies and proportions. These were subsequently compared using chi-square tests or Fisher's exact tests, depending on the statistical appropriateness. Based on a cohort of 352 patients diagnosed with HCC who underwent radical hepatectomy and exhibited high recurrence risk factors, a nomogram was developed. During the entire study duration, we documented 123 cases of being LTFU. To mitigate the potential for overfitting, we ensured that the event per variable (EPV) ratio in our model remained at approximately 18. Initially, a univariate logistic regression analysis was performed, identifying variables with a P-value < 0.1. These variables were then subjected to Spearman correlation testing, and a correlation heatmap was generated to address any potential collinearity issues. Afterward, the identified variables were included in a multivariate logistic regression analysis, and those with a P-value < 0.05 were considered optimal candidates for constructing the predictive model. To evaluate the model's performance, receiver operating characteristic (ROC) curves and calibration curves were utilized, enabling the calculation of the area under the curve (AUC). Furthermore, decision curve analysis (DCA) was conducted to assess the clinical usefulness of the model. The net benefit curve in the DCA demonstrates the nomogram's clinical utility by comparing intervention benefits against two extremes: intervening in all or no patients. The net benefit curve shows that using the nomogram to identify high-risk patients provides a higher net benefit across a range of threshold probabilities, indicating that it is clinically useful for decision-making. All data processing and analyses were executed utilizing R version 4.3.0.

Table 1 Analysis of clinical and pathological characteristics among patients experiencing lost to follow-up (LTFU)

Variables	Controls($n=229$)	LTFU ($n=123$)	χ2	*P*
Gender			0.470	0.493
Man	191(83.4%)	99(80.5%)		
Women	38(16.6%)	24(19.5%)		
Age			0.420	0.517
≤ 60 years	120(52.4%)	60(48.8%)		
> 60 years	109(47.6%)	63(51.2%)		
BMI			0.402	0.526
< 24.0	126(55%)	72(58.5%)		
≥ 24.0	103(45%)	51(41.5%)		
Religions			2.018	0.155
No	216(94.3%)	111(90.2%)		
Yes	13(5.7%)	12(9.8%)		
Smoking			4.421	**0.036**
Yes	87(38%)	61(49.6%)		
No	142(62%)	62(50.4%)		
Drinking			2.501	0.114
Yes	72(31.4%)	49(39.8%)		
No	157(68.6%)	74(60.2%)		
Marital status			0.032	0.858
Not married	12(5.2%)	7(5.7%)		
Married	217(94.8%)	116(94.3%)		
Quantity of children			1.961	0.161
≤ 2	199(86.9%)	100(81.3%)		
>2	30(13.1%)	23(18.7%)		
Type of residence			11.627	**0.001**
City	104(45.4%)	33(26.8%)		
Countryside	125(54.6%)	90(73.2%)		
GDP level of the patients' residence			2.925	0.087
Less than 80,000 CNY	50(21.8%)	37(30.1%)		
More than 80,000 CNY	179(78.2)	86(69.9%)		
Distance from residence to hospital			9.170	**0.002**
≤ 200 km	148(64.6%)	59(48%)		
> 200 km	81(35.4%)	64(52%)		
Education level			0.576	0.448
Senior high school and below	212(92.6%)	111(90.2%)		
Above high school	17(7.4%)	12(9.8%)		
Profession			15.220	**< 0.001**
Stable	165(72.1%)	63(51.2%)		
Unstable	64(27.9%)	60(48.8%)		
Medical insurance			13.260	**< 0.001**
Insured	224(97.8%)	109(88.6%)		
Uninsured	5(2.2%)	14(11.4%)		
Hypertension			0.211	0.646
Yes	80(34.9%)	46(37.4%)		
No	149(65.1%)	77(62.6%)		
Diabetes			0.009	0.926
Yes	40(17.5%)	21(17.1%)		
No	189(82.5%)	102(82.9%)		
HBV infection			1.312	0.252
Yes	174(76%)	100(81.3%)		
No	55(24%)	23(18.7%)		
Liver cirrhosis			7.169	**0.007**

Table 1 (continued)

Variables	Controls($n=229$)	LTFU ($n=123$)	χ2	*P*
Yes	160(69.9%)	102(82.9%)		
No	69(30.1%)	21(17.1%)		
ASA classification			0.029	0.865
1/2	175(76.4%)	93(75.6%)		
3/4	54(23.6%)	30(24.4%)		
ALT			0.841	0.359
≤ 50 U/L	188(82.1%)	96(78%)		
> 50U/L	41(17.9%)	27(22%)		
AST			6.490	**0.011**
≤ 40 U/L	168(73.4%)	74(60.2%)		
> 40U/L	61(26.6%)	49(39.8%)		
ALP			4.129	**0.042**
≤ 125 U/L	179(78.2%)	84(68.3%)		
> 125U/L	50(21.8%)	39(31.7%)		
GGT			0.162	0.687
≤ 60 U/L	128(55.9%)	66(53.7%)		
> 60U/L	101(44.1%)	57(46.3%)		
PLT			0.049	0.825
<125*10^9/L	70(30.6%)	39(31.7%)		
≥ 125*10^9/L	159(69.4%)	84(68.3%)		
Hemoglobin			< 0.001	0.996
< 130 g/L	80(34.9%)	43(35%)		
≥ 130 g/L	149(65.1%)	80(65%)		
Serum albumin			2.686	0.101
< 40 g/L	140(61.1%)	86(69.9%)		
≥ 40 g/L	89(38.9%)	37(30.1%)		
Serum cholesterol			2.764	0.096
≤ 5.96 mmol/L	220(96.1%)	113(91.9%)		
> 5.96 mmol/L	9(3.9%)	10(8.1%)		
Serum TG			2.736	0.098
≤ 1.70 mmol/L	192(83.8%)	111(90.2%)		
> 1.70mmol/L	37(16.2%)	12(9.8%)		
TBIL			2.451	0.117
≤ 24μmol/ L	194(84.7%)	96(78%)		
> 24μmol/ L	35(15.3%)	27(22%)		
DBIL			0.340	0.560
≤ 6.80μmol/ L	204(89.1%)	112(91.1%)		
> 6.80μmol/ L	25(10.9%)	11(8.9%)		
Time of operation			2.884	0.089
<240 min	118(51.5%)	48(39%)		
≥ 240 min	111(48.5%)	75(61%)		
Satellite nodules			6.534	**0.011**
Yes	20(8.7%)	22(18.0%)		
No	209(91.3%)	100(82%)		
BCLC staging			0.918	0.338
0/A/B	171(74.7%)	86(69.9%)		
C/D	58(25.3%)	37(30.1%)		
PHS			3.218	0.073
< 7 days	79(34.5%)	31(25.5%)		
≥ 7 days	150(65.5%)	92(74.8%)		
Postoperative adjuvant therapy			11.046	**0.001**

Table 1 (continued)

Variables	Controls($n=229$)	LTFU ($n=123$)	χ2	*P*
Yes	181(79%)	77(62.6%)		
No	48(21%)	46(37.4%)		

Data are expressed as frequencies (percentages), otherwise indicated; The chi-squared (χ^2) test or Fisher's exact test is used to compare these data differences between groups. Abbreviations: BMI, body mass index; HBV hepatitis B virus, ASA American Society of Anesthesiologists, ALT alanine aminotransferase, AST aspartate aminotransferase, ALP alkaline phosphatase, GGT gamma-glutamyl transpeptidase, PLT platelet, TG triglycerides, TBIL total bilirubin, DBIL Direct bilirubin, BCLC Barcelona Clinic Liver Cancer, PHS Postoperative hospital stay

Follow-up

Following liver resection, all patients underwent outpatient or telephone follow-up. The follow-up schedule was set at every 3 months for the initial two years and then every 6 months thereafter. LTFU is defined as the absence of visits to the surgical department for a minimum of three consecutive months within the first year following surgery. The electronic medical records of enrolled patients were systematically gathered for analysis.

Ethics approval and consent to participate

This study adhered to the principles outlined in the Declaration of Helsinki and received approval (ZJPPHEC 2024O(222)) from the Institutional Review Board of Zhejiang Provincial People's Hospital. Due to the retrospective nature of the current study, the Institutional Review Board of Zhejiang Provincial People's Hospital waived the need of obtaining informed consent.

Results

Patients characteristics

During the study period, a total of 525 patients underwent radical liver resection at our hospital. However, 129 patients were excluded from the analysis due to various reasons: the absence of high-risk factors for hepatocellular carcinoma recurrence, death within one year ($n=32$), and incomplete or missing medical records ($n=12$). Subsequently, the final cohort comprised 352 patients, and their clinical, pathological, and sociodemographic characteristics are outlined in Table 1. Of these patients, 123 were LTFU within one year, resulting in a control group of 229 patients. Chi-square tests indicated statistically significant differences ($P<0.05$) in ten variables, including smoking status, type of residence, distance from residence to the hospital, profession, medical insurance coverage, the presence of liver cirrhosis, aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels, the presence of satellite nodules, and the receipt of postoperative adjuvant therapy. To note, in the LTFU group, the median duration of missed visits to the surgical department within the first year post-surgery was 9.4 months, with an interquartile range (IQR) of 6.65 to 10.6 months. This variability in the timing of LTFU highlights that patients experienced difference in care at different points during this critical period, emphasizing the need to address barriers to consistent follow-up adherence.

Univariate and multivariate logistic regression analysis

The findings of the univariate logistic regression analysis are presented in Table 2. As part of this study, we initially conducted a univariate logistic regression analysis on 35 potential influencing factors to initially screen for variables that are associated with the primary outcome.

This analysis process pinpointed 13 variables (Smoking, Type of residence, GDP level of patients' residence, Distance from residence to hospital, Profession, Medical insurance, Liver cirrhosis, Serum AST, Serum ALP, Time of operation, Satellite nodules, Postoperative hospital stay, Postoperative adjuvant therapy) with *P*-values less than 0.1, suggesting a noticeable association with the primary outcome data. To evaluate potential collinearity among categorical variables, we employed Spearman's rank correlation coefficient (Spearman's rho) for correlation analysis and subsequently generated a correlation heatmap (Figure 2) based on the results. Upon scrutinizing the heatmap, we noted that the highest Spearman's rank correlation coefficient among any pair of variables was 0.36. This indicates that there are no significant collinearity concerns among the categorical variables in our dataset. According to statistical conventions, an absolute correlation coefficient approaching or exceeding 0.7 is typically indicative of a strong collinear relationship between two variables. The absence of such high correlation values lays a solid foundation for conducting subsequent multivariable logistic regression analysis and model development. Based on the results of the screening and correlation analysis, we further explored the individual impacts of the 13 identified variables on the primary outcome data through multivariable logistic regression analysis. After rigorous statistical examination, we discovered that the *P*-values of seven variables—smoking, distance from residence to hospital, profession, medical insurance, liver cirrhosis, time of operation, and postoperative adjuvant therapy—were less than 0.05 (Table 3).

Establishment of nomogram

To visually represent and quantify the cumulative effect of seven variables (Smoking, Distance from residence to hospital, Profession, Medical insurance, Liver cirrhosis,

Table 2 Univariate logistic regression analysis for predicting being lost to follow-up (LTFU)

Parameter		OR (95% CI)	*P*
Gender	Male	1	0.494
	Female	1.219(0.692–2.145)	
Age	≤ 60 years	1	0.517
	> 60 years	1.156(0.746–1.792)	
BMI	< 24.0	1	0.526
	≥ 24.0	0.867(0.556–1.350)	
Religions	No	1	0.160
	Yes	1.796(0.796–4.067)	
Smoking	No	1	**0.036**
	Yes	1.606(1.031–2.501)	
Drinking	No	1	0.115
	Yes	1.444(0.915–2.279)	
Marital status	Not married	1	0.858
	Married	0.916(0.351–2.391)	
Quantity of children	≤ 2	1	0.163
	>2	1.526(0.842–2.763)	
Type of residence	City	1	**0.001**
	Countryside	2.269(1.409–3.653)	
GDP level of the patients' residence	More than 80,000 CNY	1	**0.088**
	Less than 80,000 CNY	1.540(0.937–2.531)	
Distance from residence to hospital	≤ 200 km	1	**0.003**
	> 200 km	1.982(1.269–3.095)	
Education level	Senior high school and below	1	0.449
	Above high school	1.348(0.622–2.923)	
Profession	Stable	1	**< 0.001**
	Unstable	2.455(1.556–3.867)	
Medical insurance	Insured	1	**0.001**
	Uninsured	5.754(2.021–16.385)	
Hypertension	No	1	0.646
	Yes	1.113(0.706–1.754)	
Diabetes	No	1	0.926
	Yes	0.973(0.544–1.738)	
HBV	No	1	0.253
	Yes	1.734(0.797–2.371)	
Liver cirrhosis	No	1	**0.008**
	Yes	2.095(1.211–3.623)	
ASA classification	1/2	1	0.865
	3/4	1.045(0.626–1.745)	
ALT	≤ 50 U/L	1	0.477
	> 50U/L	1.217(0.709–2.089)	
AST	≤ 40 U/L	1	**0.011**
	> 40U/L	1.824(1.146–2.903)	
ALP	≤ 125 U/L	1	**0.043**
	> 125U/L	1.662(1.016–2.720)	
GGT	≤ 60 U/L	1	0.688
	> 60U/L	1.095(0.705-1.700)	
PLT	≥ 125*10^9/L	1	0.825
	<125*10^9/L	1.055(0.657–1.692)	
Hemoglobin	≥ 130 g/L	1	0.996
	< 130 g/L	1.001(0.632–1.585)	
Albumin	≥ 40 g/L	1	0.102
	< 40 g/L	1.478(0.925–2.360)	

Table 2 (continued)

Parameter		OR (95% CI)	*P*
Serum cholesterol	≤ 5.96 mmol/L	1	0.103
	> 5.96 mmol/L	2.163(0.855–5.475)	
Serum TG	≤ 1.70 mmol/L	1	0.101
	> 1.70mmol/L	0.561(0.281–1.120)	
TBIL	≤ 24 umol/L	1	0.321
	> 24 umol/L	1.257(0.800-1.976)	
DBIL	≤ 6.80 umol/L	1	0.561
	> 6.80 umol/L	0.801(0.380–1.689)	
Time of operation	≥ 240 min	1	**0.090**
	<240 min	1.470(0.941–2.295)	
Satellite nodules	No	1	**0.012**
	Yes	2.299(1.199–4.407)	
BCLC staging	0/A/B	1	0.339
	C/D	1.268(0.779–2.064)	
PHS	< 7 days	1	**0.074**
	≥ 7 days	1.563(0.958–2.551)	
Postoperative adjuvant therapy	Yes	1	**0.001**
	No	2.253(1.388–3.657)	

Abbreviations: OR odds ratio, CI confidence interval, BMI body mass index, HBV hepatitis B virus, ASA American Society of Anesthesiologists, ALT alanine aminotransferase, AST aspartate aminotransferase, ALP alkaline phosphatase, GGT gamma-glutamyl transpeptidase, PLT platelet, TG triglycerides, TBIL total bilirubin, DBIL Direct bilirubin, BCLC Barcelona Clinic Liver Cancer, PHS Postoperative hospital stay

Time of operation, and Postoperative adjuvant therapy) on the primary predictive outcome, we developed a nomogram.

This graphical tool seamlessly integrates the analytical outcomes derived from a multivariable logistic regression model, translating the values of each variable into intuitive probability estimates for forecasting outcomes. Consequently, it offers a visual and comprehensible approach to assessing predictive risk across diverse combinations of variables. Using this methodology, the nomogram effectively portrays the contribution of each variable to the anticipated outcome, clearly delineating the varying degrees of predictive risk that stem from different permutations of variable values. Derived from the outcomes of rigorous multivariable logistic regression analysis, the nomogram graph ensures the accuracy and reliability of the predictive model. Equipped with this intuitive and pragmatic tool, clinicians can now conduct personalized risk assessments and predictions tailored to each patient's specific circumstances, ultimately guiding clinical decision-making processes (Figure 3).

Evaluation of predictive model

Once the nomogram was constructed, we thoroughly assessed its predictive performance. Initially, we generated a ROC curve and determined the AUC to quantitatively evaluate the model's efficacy in discriminating between actual and predicted outcomes. The analysis revealed an AUC of 0.744 (95% CI 0.691–0.798) for the nomogram, signifying excellent predictive accuracy (Figure 4). To further scrutinize the model's calibration, we constructed a calibration curve to assess the congruity between predicted and observed probabilities. This comparative evaluation of predicted and observed probabilities intuitively underscores the calibration performance of the model, thus ensuring reliability. Furthermore, to obtain a comprehensive assessment of the model's clinical efficacy, we performed DCA. DCA curves incorporate crucial factors like predictive accuracy, patient benefit, and medical costs, thereby offering robust guidance for clinical decision-making processes. By conducting DCA curve analysis, we delineated the net benefit of our model across various thresholds, empowering clinicians to make optimal decisions tailored to the unique circumstances of each patient.

Discussion

This study comprised a cohort of 352 patients diagnosed with HCC, constituting a relatively substantial sample size that bolsters the reliability and broad applicability of the findings. The research delves into risk factors associated with being LTFU following curative liver resection among HCC patients harboring high-risk features for recurrence, marking a pioneering endeavor in China. In oncology follow-up, we defined LTFU as missing three consecutive months from outpatient visits, which aligned with the typical 3-month HCC surveillance interval based on clinical consensus and prior studies [16, 17, 18]. This threshold captures potential gaps in postoperative monitoring where early recurrence may be undetected, enabling timely identification and intervention for high-risk patients. Besides, the first year post-hepatectomy is

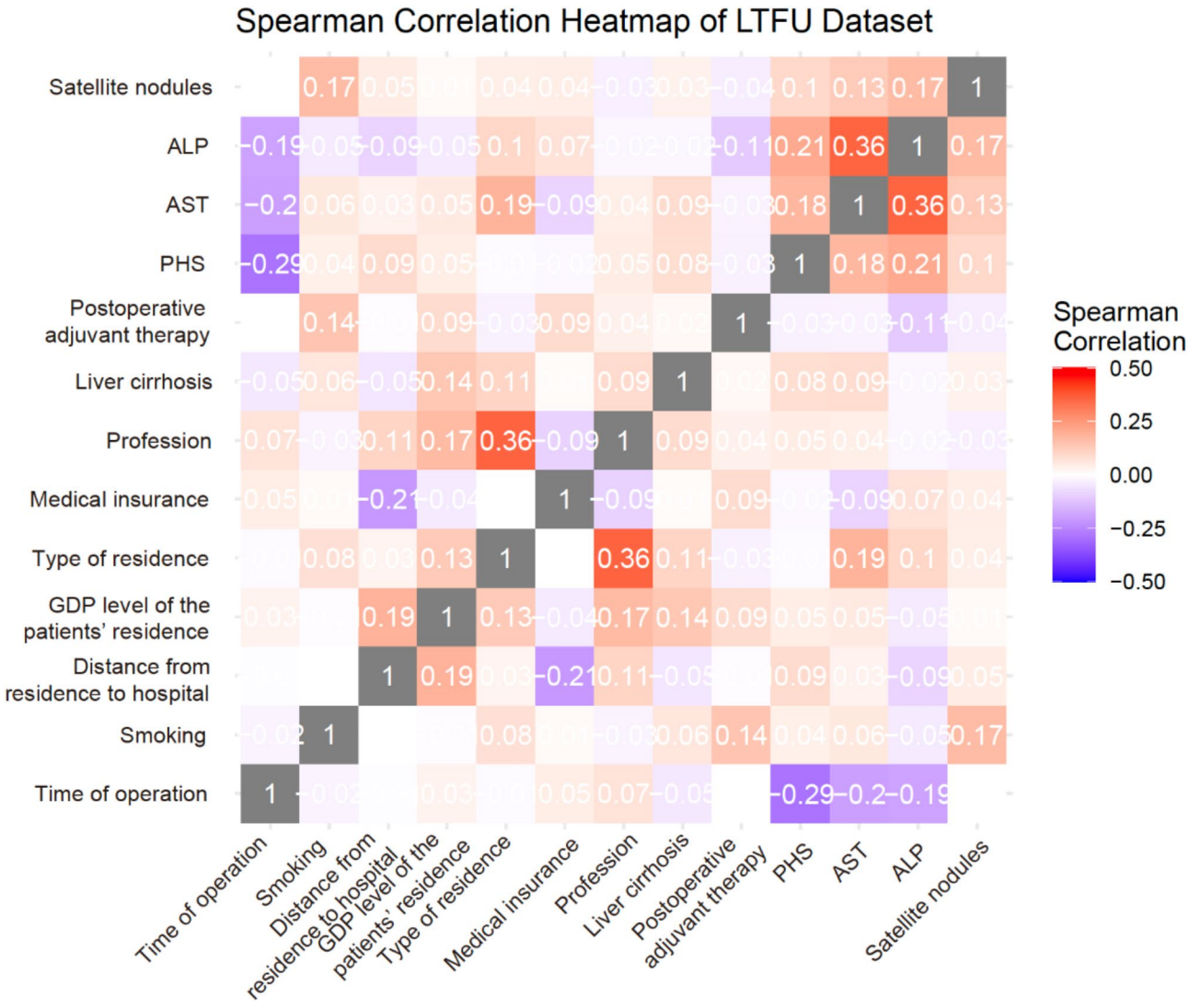

Fig. 2 Variable correlation coefficient matrix heatmap. This heatmap serves as a visual representation of the Spearman correlation coefficients among various clinical and pathological variables among patients diagnosed with hepatocellular carcinoma (HCC). The variables under analysis encompass time of operation, smoking status, distance from residence to hospital, GDP level of the patients' residence, type of residence, medical insurance, profession, liver cirrhosis, postoperative adjuvant therapy, postoperative hospital stay(PHS), aspartate aminotransferase (AST) levels, alkaline phosphatase (ALP) levels, and the occurrence of satellite nodules. The color gradient in this heatmap depicts the intensity and directionality of the correlations, with blue hues signifying negative correlations and red hues denoting positive correlations. In this study, the Spearman correlation coefficients range from −0.29 to 0.36, with higher absolute values indicating stronger correlations. This heatmap offers a comprehensive visualization of the intricate relationships among these various variables

crucial for monitoring HCC patients due to the highest risk of recurrence [19, 20], which independently predicts poor overall survival [21, 22]. Focusing on this period captures the most clinically relevant phase for LTFU, where missed visits may impact outcomes. Standardizing the follow-up to one year also minimizes confounding from varying durations. We have formulated a novel predictive Wei-LTFU model, taking into account seven risk factors, including smoking, residing more than 200 km away from the hospital, having an unstable profession, lacking medical insurance, suffering from liver cirrhosis, undergoing surgery with a duration of less than 240 min, and absence of postoperative adjuvant therapy.

The importance of preventing being LTFU

HCC is a malignancy marked by its high aggressiveness, tendency for frequent recurrence, and often dismal prognosis [10]. The continuity of follow-up plays a pivotal role in detecting HCC recurrence at an early stage, enabling prompt interventions. We firmly believe that consistent follow-up is imperative for patient survival, as timely diagnosis and treatment can effectively mitigate disease progression, particularly among HCC patients

Table 3 Multivariate logistic regression analysis for predicting being lost to follow-up (LTFU)

Parameter		OR (95% CI)	*P*
Smoking	No	1	**0.023**
	Yes	1.823(1.086–3.060)	
Type of residence	City	1	0.088
	Countryside	1.650(0.929–2.932)	
GDP level of the patients' residence	More than 80,000 CNY	1	0.794
	Less than 80,000 CNY	1.080(0.605–1.928)	
Distance from residence to hospital	≤ 200 km	1	**0.019**
	> 200 km	1.857(1.105–3.121)	
Profession	Stable	1	**0.019**
	Unstable	1.918(1.112–3.311)	
Medical insurance	Insured	1	**0.004**
	Uninsured	5.921(1.747–20.071)	
Liver cirrhosis	No	1	**0.016**
	Yes	2.161(1.153–4.048)	
Serum AST	≤ 40 U/L	1	0.393
	> 40U/L	1.291(0.719–2.319)	
Serum ALP	≤ 125 U/L	1	0.087
	> 125U/L	1.734(0.923–3.257)	
Time of operation	≥ 240 min	1	**0.006**
	<240 min	2.138(1.240–3.688)	
Satellite nodules	No	1	0.102
	Yes	1.833(0.887–3.787)	
PHS	< 7 days	1	0.187
	≥ 7 days	1.484(0.825–2.669)	
Postoperative adjuvant therapy	Yes	1	**0.001**
	No	2.641(1.504–4.637)	

Abbreviations: OR odds ratio, CI confidence interval, AST aspartate aminotransferase, ALP alkaline phosphatase, PHS Postoperative hospital stay

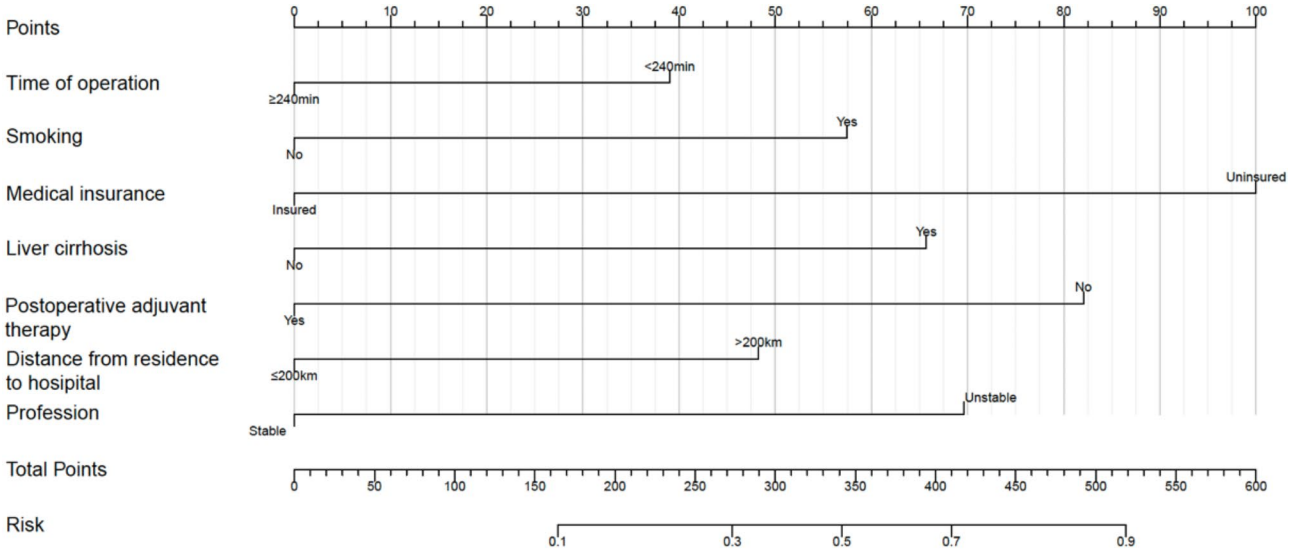

Fig. 3 Wei-LTFU nomogram for predicting being lost to follow-up probability. The Wei-LTFU nomogram consists of graph lines that include risk factors (time of operation, smoking status, medical insurance, liver cirrhosis, postoperative adjuvant therapy, distance from residence to hospital, and profession), individual scores (Points), total scores (Total Points), and event risk (lost to follow-up, LTFU). The line segment associated with each risk factor is adorned with a scale, portraying the span of potential values for that factor. The length of this line segment mirrors the extent to which that factor contributes to the outcome event. The "Points" segment, situated at the top of the graph, denotes the corresponding scores for risk factors at varying levels of values. The summation of all the individual scores ascribed to the risk factors results in the "Total Points," which corresponds to the " LTFU " metric at the graph's base. This metric serves as a representation of the predicted probability of being LTFU among patients diagnosed with hepatocellular carcinoma (HCC)

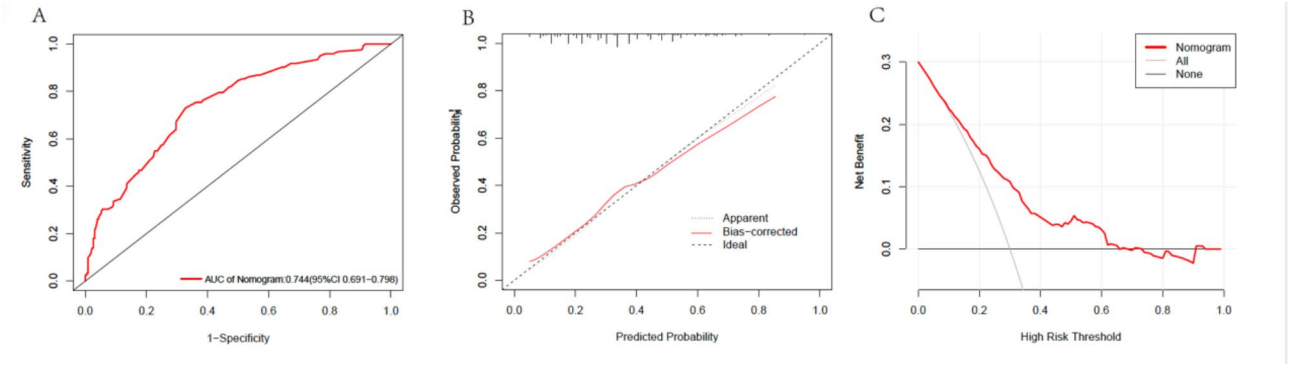

Fig. 4 ROC curves, calibration curves, and decision curve analysis (DCA). (**A**) ROC curves and the area under the curve (AUC) stood at 0.744, with a 95% confidence interval (CI) ranging from 0.691 to 0.798. ROC receiver operating characteristic. (**B**) Calibration Curve for the Nomogram: The x-axis depicts the risk estimated by the nomogram, while the y-axis signifies the number of patients experiencing lost to follow-up (LTFU). The diagonal dotted line represents the optimal prediction of an ideal model, and the apparent solid line indicates the actual performance of the nomogram. (**C**) Decision Curve Analysis (DCA) for predicting being LTFU: The black line signifies the scenario where no patient is predicted to experience LTFU, resulting in a net profit of 0. The gray line depicts the scenario where all patients are predicted to experience LTFU, and the net gain rate is represented by the slope of the downward-sloping line. The red line, however, represents the DCA curve of the current model, offering insights into the balance between benefits and harms in predicting being LTFU

harboring high-risk factors for recurrence. Prior research has incontrovertibly demonstrated that regular follow-up facilitates the early detection of recurrence, prompt intervention, an enhancement in survival rates, and adherence to treatment plans, ultimately mitigating the risks associated with disease progression [16]. To note, the primary objective of this study was not to directly compare recurrence and survival outcomes between high-risk and non-high-risk populations. Given the well-established clinical evidence [7, 8, 9, 10, 11], it is indeed predictable that the high-risk population would demonstrate a higher recurrence rate. While such comparative analyses could be valuable for future research directions, our current investigation specifically focuses on identifying and addressing the critical risk factors associated with LTFU within the high-risk population, which represents a significant gap in current clinical management strategies.

Independent risk factors for being LTFU

The analysis identified seven independent risk factors significantly associated with LTFU. In constructing the nomogram, the scale lengths for these variables were determined based on their relative contributions to the predictive model, as established through multivariate logistic regression analysis. Each variable was assigned a weighted score proportional to its regression coefficient, ensuring the nomogram accurately reflects the predictive significance of each factor in determining LTFU risk. To optimize clinical applicability, the scale lengths were standardized, enabling healthcare providers to rapidly and reliably assess individual patients' LTFU risk during routine clinical practice.

Smoking

Smoking is often intertwined with unhealthy lifestyle habits and a reduced sense of health awareness. Extensive research suggests that smokers tend to disregard health recommendations and preventive measures, including regular follow-up and health monitoring [23, 24, 25]. Additionally, smoking has been linked to various mental health challenges, such as anxiety and depression, which may further compromise adherence to treatment plans and follow-up appointments [26].

Such psychological issues can hinder patient compliance, ultimately resulting in decreased adherence to medical advice and recommendations [27]. Parallel research also posits that smokers may encounter discrimination or stigmatization in healthcare settings, thereby fostering reluctance and hesitation in returning for follow-up appointments [28]. The identification of smoking as an independent risk factor for being LTFU among HCC patients underscores the intricate entanglement of behavioral, psychological, and socio-economic dynamics in healthcare outcomes. This discovery underscores the paramount importance of tailored interventions directed towards smokers within the HCC patient cohort. Such initiatives, including psychological support, behavioral modification programs, and socio-economic assistance, are vital for bolstering follow-up compliance and ultimately optimizing health outcomes [6, 7, 8, 9].

Distance from residence to hospital exceeding 200 km

Our research underscores that residing over 200 km from the hospital serves as an independent risk factor for patients becoming LTFU. Notably, patients who reside further from the healthcare facility are more prone to missing appointments, a finding that aligns with previous

research in this area [29, 30, 31, 32]. Our hospital, a prominent tertiary institution situated in the provincial capital, caters to a substantial population of patients hailing from rural or remote regions. These patients often grapple with significant economic constraints, limited transportation alternatives, and inadequate access to medical resources. These challenges hinder their consistent attendance at follow-up appointments, leading to fewer scheduled check-ups and an increased likelihood of being LTFU [33, 34, 35].

Unstable profession

The instability of employment is often paralleled by financial uncertainty, posing significant economic stress for this demographic. This predicament often translates into difficulty sustaining the medical expenses associated with regular follow-up visits to the hospital. Research has revealed a strong correlation between financial hardships and patients' reluctance or inability to consistently attend follow-up appointments [36]. Moreover, individuals with unstable employment may be deprived of a reliable social support network, particularly in their work environment. This absence of support can diminish their motivation and capability to attend follow-up sessions. Previous studies underscore the pivotal role of social support in fostering healthy practices and compliance among patients [37]. Furthermore, unstable employment tends to exacerbate psychological stress, elevating anxiety levels and consequently augmenting the risk of being LFTU [38].

Lack of medical insurance

Patients who are uninsured must shoulder the entire financial burden of their medical expenses. The significant costs associated with treatment and follow-up care often render them unaffordable for many patients, prompting them to forego scheduled appointments [39]. Despite government initiatives aimed at ensuring near-universal health insurance coverage, the expenses incurred during follow-up medical care continue to pose a financial strain for those without insurance [40, 41]. In China's healthcare system, while medical services remain accessible through out-of-pocket payments, insurance coverage exerts significant influence on long-term treatment planning, particularly for costly interventions like liver cancer treatment. Uninsured patients often face substantial financial barriers that may compromise their adherence to follow-up schedules due to the associated costs. In contrast, insured patients are more likely to adhere to follow-up schedules, as their out-of-pocket expenses are reduced.

Liver cirrhosis

The condition of patients with cirrhosis is intricate, often coupled with various complications like ascites, bleeding, and hepatic encephalopathy. These comorbidities not only elevate patients' medical requirements but also amplify the complexity of their treatment, thereby hindering their adherence to regular follow-up appointments [42, 43]. The enduring pain and diminished quality of life stemming from cirrhosis intensify psychological distress among patients, predisposing them to anxiety and depression [44]. Furthermore, cirrhotic patients may be more vulnerable to issues like falls and cognitive impairments [45]. These obstacles have adverse effects on patients' health-related behaviors and medical adherence, ultimately increasing the likelihood of being LTFU.

Operation time less than 240 min

Intriguingly, a shorter duration of surgery, specifically under 240 min, is linked to a heightened risk of being LTFU. This apparent paradox aligns with prior research [46], and may stem from the assumption that simpler surgical interventions necessitate less rigorous post-surgical monitoring. Specifically, this counterintuitive finding may be explained by two potential aspects. First, patients with smaller tumors or less advanced disease—typically associated with shorter operative durations—may perceive a lower recurrence risk, thereby reducing their motivation for strict follow-up adherence. Second, prolonged surgical procedures are often associated with increased postoperative complication rates, which may necessitate more frequent hospital readmissions and subsequent follow-up visits [47]. Conversely, patients undergoing shorter procedures with fewer complications may consequently perceive less need for intensive monitoring.

Absence of postoperative adjuvant therapy

Some patients may lack comprehension of the additional treatment options available post-surgery or harbor doubts about their efficacy, leading them to forego postoperative adjunctive therapy. This reluctance could contribute to their reduced likelihood of actively engaging in follow-up appointments, thereby elevating the risk of being LTFU.

In summary, our study was aimed at identifying independent predictors associated with being LTFU, spanning clinical, pathological, and sociodemographic variables. To assess the model's efficacy, we employed visual methods such as ROC curve analysis, resulting in an AUC of 0.744, with a 95% CI ranging from 0.691 to 0.798. Furthermore, we utilized calibration curve analysis and DCA to evaluate the clinical relevance and utility of our model. Our findings indicate that our Wei-LTFU model demonstrates promising performance and has direct clinical applicability. Through individualized evaluations and

targeted interventions, we believe it holds the potential to significantly reduce the loss to follow-up rate among HCC patients, thereby enhancing the efficacy of follow-up management.

Conclusion

A main effects model, namely the Wei-LTFU model, incorporating the seven significant factors was formulated to predict the likelihood of LTFU occurrence, ultimately aiming to assist healthcare workers in developing effective strategies to improve follow-up outcomes for patients.

Limitations

However, it is important to acknowledge the limitations of this study. First, as a retrospective analysis conducted at a single medical center, it is susceptible to selection bias and information bias. Second, while our findings provide valuable insights into risk factors for LTFU in a high-risk HCC population, they may not fully represent the diversity of healthcare settings, patient demographics, or regional practices. For instance, variations in healthcare centers, insurance coverage, and cultural attitudes toward follow-up care could affect LTFU rates in different regions. Future studies are warranted to validate our nomogram in external cohorts and explore the impact of regional and systemic factors on LTFU. Third, although this study primarily focused on identifying LTFU risk factors and developing a predictive nomogram, its short follow-up duration limited analysis of recurrence or prognosis. Further exploration is essential to determine whether LTFU is associated with delayed recurrence detection and potentially poorer survival. Future long-term studies are needed to explore this aspect and clarify the clinical impact of LTFU. Fourth, although the level of discrimination is not perfect, the AUC value of 0.744 indicates that our model has reasonable discriminatory power for predicting LTFU, suitable for initial risk stratification in clinical practice. Indeed, the model is intended as a supplementary tool to guide clinical decision-making rather than a definitive diagnostic test. A risk probability threshold of 0.34 is recommended for identifying high-risk patients for optimal sensitivity and specificity in our cohort.

Abbreviations

AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
DCA	Decision curve analysis
EPV	Event per variable
HCC	Hepatocellular carcinoma
IQR	Interquartile range
LTFU	Lost to follow-up
MVI	Microvascular invasion
ROC	Receiver operating characteristic

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Not applicable.

Author contributions

Wei FQ, Yu ZC, Cao WL, Du CF, Liu J, and Peng LP reviewed related articles and developed the study; Wei FQ, Yu ZC, Cao WL, Du CF, Liu J, and Peng LP collected data, completed follow up and performed data analysis; Wei FQ, and Yu ZC wrote the article; Wei FQ edited the article.

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Data availability

The data gathered in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study adhered to the principles outlined in the Declaration of Helsinki and received approval (ZJPPHEC 2024O(222)) from the Institutional Review Board of Zhejiang Provincial People's Hospital. Due to the retrospective nature of the current study, the Institutional Review Board of Zhejiang Provincial People's Hospital waived the need of obtaining informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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