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ORIGINAL RESEARCH

Novel Preoperative Type IV Collagen to Predict the Risk of Hepatocellular Carcinoma in Patients with Hepatitis B Virus-Related Cirrhotic Portal Hypertension After Laparoscopic Splenectomy and Azygoportal Disconnection

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Purpose: Although laparoscopic splenectomy and azygoportal disconnection (LSD) can significantly decrease portal vein pressure and even the incidence of hepatocellular carcinoma (HCC) in patients with cirrhotic portal hypertension (CPH), postoperative HCC inevitably occurs in certain patients. The purpose of this study was to seek a novel preoperative non-invasive predictive indicator to predict the occurrence of postoperative HCC.

Patients and Methods: From April 2012 to April 2022, we collected clinical data of 178 hepatitis B virus (HBV)-related CPH patients. Based on inverse treatment probability weighting, candidate variables for predicting postoperative HCC were determined by means analysis. Then, a novel preoperative non-invasive prediction indicator (ie, type IV collagen-alpha fetoprotein-fibrosis-4 score [IVAF-FIB-4]) was established based on candidate variables, and its predictive ability was explored.

Results: Postoperative HCC occurred in 9 (5.1%) patients. Correlation analyses showed that the IVAF-FIB-4 had a significant positive correlation with HCC ($r = 0.835$, $P < 0.001$). IVAF-FIB-4 showed a high accuracy (the area under the receiver operating characteristic curve: 0.939, 95% confidence interval [CI]: 0.818–1.000; sensitivity: 88.9%; specificity: 93.5%). At the end of follow-up, the incidence density of HCC in patients with IVAF-FIB-4 (1) was significant higher than that in patients with IVAF-FIB-4 (0) (138.1/1000 vs 1.1/1000 person-years; rate ratio: 130.475, 95% CI: 16.318–1043.227). In logistic regression, IVAF-FIB-4 was an independent risk factor for HCC (odds ratio: 668.000, 95% CI: 53.895–8279.541; $P < 0.001$).

Conclusion: IVAF-FIB-4 is a novel preoperative noninvasive predictive indicator for predicting postoperative HCC in HBV-related CPH patients after LSD, with satisfactory predictive ability.

Keywords: liver fibrotic markers, splenectomy, azygoportal disconnection, hepatocellular carcinoma, risk

Introduction

Liver cancer is one of the most common malignant tumors worldwide, and the most common histological type is hepatocellular carcinoma (HCC).[1,2] One of the most important causes of HCC is liver cirrhosis, which can be caused by a variety of factors. Virus-related cirrhosis is most prevalent in Asia, especially hepatitis B virus (HBV). The annual incidence of HCC in patients with HBV-related cirrhosis is 3%–6%, which is the main cause of HCC in China.[3,4] At present, there are about 350 million HBV-infected people in the world, and every year, over 500,000 people die from diseases associated with HBV, including liver cirrhosis and liver cancer.[5]

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In clinical practice, the decompensated period of cirrhosis is accompanied by clinical manifestations such as low liver function, portal hypertension, splenomegaly, and hypersplenism.[6,7] Due to its advantages of less trauma, faster recovery, and less inflammatory interference, laparoscopic splenectomy and azygoportal disconnection (LSD) has gradually become the ideal surgical modality for the treatment of these decompensated patients with cirrhotic portal hypertension (CPH) in Asia. Unfortunately, although LSD can improve the liver function, and portal vein pressure, and even decrease the incidence of HCC,[8–10] some patients inevitably develop HCC due to the background of liver fibrosis and cirrhosis.

Implementing HCC surveillance is important because it is the only way to identify HCC at an early stage, thereby reducing disease-related morbidity and mortality.[11] However, identifying which patients may or may not require close HCC surveillance is an important but unresolved issue in our clinical practice. Therefore, it is necessary to find a simple and effective method to assess and predict the risk of HCC for CPH patients. If high-risk HCC groups can be identified in advance, and then receive regular checkups, potential HCC can be detected as early as possible and treated in time.

Currently, as advanced non-invasive fibrotic indicators, laminin (LN), type IV collagen (C-IV), hyaluronidase (HA), procollagen type III (PC-III), and fibrosis-4 score (FIB-4) have aroused extensive clinical attention. These indicators have been found to be significantly associated with the progression of liver fibrosis in patients with chronic liver disease.[12–14] It is well known that severe liver fibrosis is closely related to the occurrence and development of HCC.[15–17] Then, whether these indicators are also related to the occurrence and development of HCC, relevant research is rare. In addition, as an important indicator for the diagnosis and efficacy monitoring of liver cancer, it is unclear whether serum alpha fetoprotein (AFP) is related to the occurrence of HCC after LSD. Therefore, the aim of this study was to seek a novel preoperative non-invasive predictive indicator to predict the occurrence of postoperative HCC after LSD and explore its predictive ability.

Materials and Methods

Study Population

From April 2012 to April 2022, We collected clinical data of 468 CPH patients with gastroesophageal variceal bleeding and secondary hypersplenism in our hepatobiliary pancreatic center. The exclusion criteria: age <18 years; any cancer before treatment; Child–Pugh class C; cirrhosis not caused by HBV; treatment with transjugular intrahepatic portosystemic shunt or liver transplantation; the first variceal bleeding treatment was not LSD; perioperative death; simple splenectomy or azygoportal disconnection; pregnancy; human immunodeficiency virus infection; uncontrolled diabetes or hypertension; and computed tomography image was not consistent with the manifestations of liver cirrhosis. In addition, we also excluded the patients with HBV DNA viral load ≥100 IU/mL at postoperative months (POM) 3 to ensure the comparability of postoperative HBV management in each patient. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, and the Medical Ethics Committee of Clinical Medical College of Yangzhou University approved the study. This retrospective study was based on the existing data in the hospital database and did not involve intervention on patients; therefore, an exemption for informed consent of patients was obtained from the ethics committee.

Data Extraction

Considering the influence of different etiologies on the occurrence of liver cancer, in order to allow better homogeneity in etiology between the groups, this study only included HBV-related CPH patients. All patients were successfully treated with LSD in our previous study, we had reported the specific implementation methods for LSD and intraoperative autologous cell retrieval.[18] The general population data of patients collected included age, gender, body mass index (BMI), and year of treatment. The clinical characteristics data of all patients included preoperative Child-Pugh classification, FIB-4, portal vein thrombus, diabetes, hypertension, spleen diameter, portal vein diameter, splenic vein diameter, white blood cell count (WBC), platelet count (PLT), hemoglobin (HGB), alanine aminotransferase (ALT), plasma albumin (ALB), total bilirubin (TBIL), creatinine (Cr), blood urea nitrogen (BUN), international normalized ratio (INR), AFP, LN, C-IV, HA, and PC-III. Considering the continuous enrollment of new patients, as well as the uncertainty of patient loss to follow-up and death, we use the incidence density to describe the occurrence of HCC. Our retrospective follow-up period was 11 years, and the follow-up endpoint of patients was HCC or death.

Preoperative Non-Invasive Predictive Indicator

Candidate variables for predicting postoperative HCC were determined by means analysis before and after weighting, and the cutoff value of candidate indicators was determined by calculating Youden's index (sensitivity+specificity-1).[19] In this study, AFP, FIB-4, and C-IV were candidate indicators, and the cutoff values were 2.08, 6.92, and 73.95, respectively. Then, a novel non-invasive predictive indicator, type IV collagen-alpha fetoprotein-fibrosis-4 score (IVAF-FIB-4) was obtained by combining these three indicators. When C-IV level ≥73.95 μg/L, AFP level ≥2.08 ng/mL, and FIB-4 ≥6.917 were met at the same time, the novel indicator was assigned a value of 1, and the other cases were assigned a value of 0. Then, the patients were divided into IVAF-FIB-4 (0) and IVAF-FIB-4 (1) groups.

Statistical Analysis

When using observational clinical data to infer causality, if the effect of covariates between groups is not considered, the causal relationship between treatment factors and effects will be distorted, and causal inference will be biased. In order to better understand the correlation between liver fibrotic markers and the occurrence of HCC, we used inverse treatment probability weighting (IPTW) to reduce the confounding bias between groups and make the covariates between groups reach relatively balanced.[20]

Means between groups were compared using independent samples *t*-test, Mann–Whitney *U*-test or chi-square test, combined with IPTW. Continuous variables are reported as mean (standard deviation) or median (interquartile range), and categorical variables were reported as frequencies and percentages. Receiver operating characteristic (ROC) curves, the area under the ROC curve (AUC), and correlation analysis were used to evaluate the predictive ability of these indicators. When the AUC value is 0.5 to 0.7, it means low accuracy, 0.7 to 0.9 means certain accuracy, and greater than 0.9 means high accuracy. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS 25.0 software (IBM Corp., Armonk, NY, USA) and R software (version 4.2.2).

Results

The enrollment process is shown in Figure 1. A total of 178 HBV-related CPH patients with gastroesophageal variceal bleeding and secondary hypersplenism were enrolled in the study. The mean follow-up time was 67.6 months. At the end of the follow-up, 9 patients developed postoperative HCC, and the time ranged from 4 to 72 months, with an average time of 31.5 months and a median time of 14 months. Additionally, according to whether HCC occurred after LSD, the patients were divided into HCC group (n = 9) and non-HCC group (n = 169).

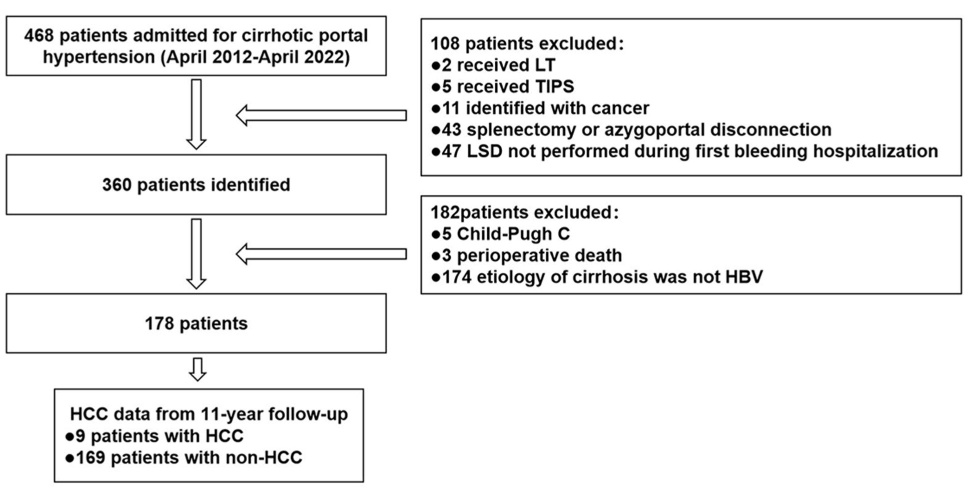


Figure 1 CONSORT diagram.

Notes: CONSORT figure adapted from Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *PLoS Med*. 2010;7(3): e1000251.[21] Copyright: © 2010 Schulz et al. Creative Commons Attribution License.

Comparison of HCC and Non-HCC Groups in Terms of Demographics and Clinical Characteristics

As shown in Supplementary Table 1, there were no significant differences in HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb between the non-HCC group and the HCC group (all $P > 0.05$). Additionally, LN, HA, PC-III, and FIB-4 had no significant differences between HCC and non-HCC groups before IPTW (all $P > 0.05$; Table 1). After weighting for gender, age, year of treatment, BMI, cirrhotic etiology, hypertension, diabetes, Child-Pugh classification, portal vein thrombosis, longitudinal diameter of the spleen, portal vein diameter, splenic vein diameter, WBC, PLT, HGB, TBIL, ALB, ALT, INR, Cr, and BUN, the differences in LN, HA, PC-III between HCC and non-HCC groups were still not

Table 1 Demographic and Preoperative Clinical Characteristics Between Non-HCC and HCC Groups in Unadjusted and IPTW Adjusted Population

Characteristics	Unadjusted			IPTW Adjusted		
	Non-HCC	HCC	*P*	Non-HCC	HCC	*P*
	N = 169	N = 9		N = 177.6	N = 160	
Age (years)	52.02 ± 10.33	53.89 ± 8.84	0.595	52.12 ± 10.40	56.77 ± 7.20	0.183
Gender			0.726			0.669
Male	112 (66.3)	7 (77.8)		118.7 (66.8)	89.3 (55.8)	
Female	57 (33.7)	2 (22.2)		58.9 (33.2)	70.8 (44.2)	
Year of treatment			0.371			0.603
2012–2016	77 (45.6)	6 (66.7)		82.7 (46.6)	55.9 (34.9)	
2017–2022	92 (54.4)	3 (33.3)		94.8 (53.4)	104.1 (65.1)	
Hypertension			0.369			0.185
No	142 (84.0)	6 (66.7)		147.6 (83.1)	87.4 (54.6)	
Yes	27 (16.0)	3 (33.3)		30.0 (16.9)	72.6 (45.4)	
Diabetes			0.070			0.506
No	143 (84.6)	5 (55.6)		147.8 (83.2)	114.2 (71.4)	
Yes	26 (15.4)	4 (44.4)		29.7 (16.8)	45.8 (28.6)	
Portal vein thrombosis			0.596			0.830
No	151 (89.3)	7 (77.8)		157.9 (88.9)	145.6 (91.0)	
Yes	18 (10.7)	2 (22.2)		19.6 (11.1)	14.4 (9.0)	
Child-Pugh Classification			0.600			0.789
A	107 (63.3)	7 (77.8)		113.4 (63.9)	111.9 (70.0)	
B	62 (36.7)	2 (22.2)		64.2 (36.1)	48.1 (30.0)	
BMI	23.82 ± 3.27	23.70 ± 4.44	0.914	23.83 ± 3.27	23.71 ± 2.31	0.846
Splenic vein diameter (mm)	11.94 ± 3.11	10.39 ± 3.22	0.146	11.89 ± 3.11	11.72 ± 1.76	0.748
Longitudinal diameter of spleen (mm)	178.75 ± 28.04	168.11 ± 45.72	0.287	178.25 ± 28.25	164.07 ± 32.33	0.227
Portal vein diameter (mm)	13.82 ± 2.29	13.51 ± 2.14	0.689	13.82 ± 2.29	13.47 ± 2.20	0.755
WBC (× 10^9/L)	2.29 ± 0.76	2.21 ± 0.73	0.772	2.28 ± 0.76	2.00 ± 0.68	0.373
HGB (g/L)	106.92 ± 18.56	109.44 ± 17.58	0.690	107.01 ± 18.53	104.61 ± 12.31	0.590
PLT (× 10^9/L)	51.34 ± 14.71	56.11 ± 18.68	0.351	51.52 ± 14.77	52.76 ± 13.32	0.840
ALT (U/L)	25.41 ± 15.19	22.22 ± 8.89	0.534	25.28 ± 15.08	21.74 ± 6.15	0.101
INR	1.32 ± 0.17	1.31 ± 0.14	0.780	1.32 ± 0.17	1.28 ± 0.09	0.113
BUN (mmol/L)	5.81 ± 2.42	6.52 ± 3.27	0.401	5.86 ± 2.46	5.18 ± 3.08	0.650

(*Continued*)

Table 1 (Continued).

Characteristics	Unadjusted			IPTW Adjusted		
	Non-HCC	HCC	*P*	Non-HCC	HCC	*P*
	N = 169	N = 9		N = 177.6	N = 160	
Cr (umol/L)	80.44 ± 19.52	80.56 ± 16.35	0.986	80.43 ± 19.53	76.97 ± 15.29	0.620
LN (μg/L)	31.44 (15.93–53.16)	46.78 (23.55–49.95)	0.467	31.42 (15.87–53.20)	35.48 (23.11–46.88)	0.245
C-IV (μg/L)	37.01 (24.45–54.45)	95.53 (87.63–115.38)	<0.001	36.80 (24.30–54.48)	77.61 (66.27–91.05)	<0.001
HA (μg/L)	78.20 (50.00–128.66)	104.50 (82.99–246.79)	0.094	78.13 (50.20–128.86)	82.92 (81.62–251.28)	0.600
PC-III (μg/L)	37.69 (24.48–54.52)	46.26 (36.94–50.22)	0.266	37.50 (24.45–54.43)	38.28 (36.78–41.88)	0.417
AFP (ng/mL)	2.30 (1.34–3.95)	4.44 (3.09–10.04)	0.015	2.30 (1.34–3.91)	3.32 (2.59–7.17)	0.044
FIB-4	5.97 (4.15–8.54)	7.70 (7.22–7.79)	0.050	5.96 (4.13–8.48)	7.23 (7.17–8.91)	0.021

Notes: Data shown as mean ± standard deviation, number (percentages), or median (interquartile range), as indicated.
Abbreviations: HCC, hepatocellular carcinoma; IPTW, inverse treatment probability weighting; BMI, body mass index; WBC, white blood cells; HGB, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; INR, international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; LN, laminin; C-IV, type IV collagen; HA, hyaluronidase; PC-III, procollagen type III; AFP, alpha fetoprotein; FIB-4, fibrosis-4 score.

statistically significant (all $P > 0.05$), but the difference in FIB-4 became statistically significant ($P = 0.021$). Nevertheless, whether the relevant covariates were weighted or not, the C-IV and AFP were significantly different between the two groups (all $P < 0.05$).

The ROC and Correlation Analysis of Candidate Variables and Non-Invasive Predictive Indicator

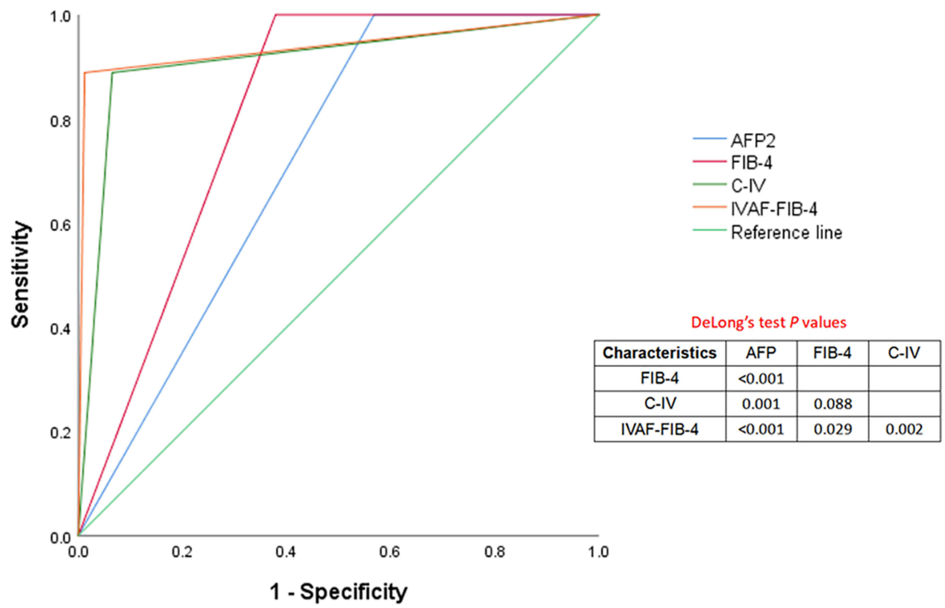
As shown in Table 2, we performed a correlation analysis of HCC with candidate variables and IVAF-FIB-4. The results showed that IVAF-FIB-4 had the highest positive correlation with the occurrence of HCC (r = 0.835, $P < 0.001$), followed by C-IV (r = 0.585, $P < 0.001$), FIB-4 (r = 0.277, $P < 0.001$), and AFP (r = 0.192, $P = 0.010$).

We performed an ROC analysis of AFP, FIB-4, C-IV, and IVAF-FIB-4 to determine their clinical value for predicting postoperative HCC (Figure 2). In contrast, IVAF-FIB-4 (AUC: 0.930, 95% confidence interval [CI]: 0.812–1.000; $P <$ 0.001) showed the highest accuracy in predicting postoperative HCC, with an associated sensitivity of 88.9% and specificity of 97.0%. Followed by C-IV (AUC: 0.912, 95% CI: 0.791–1.000; $P < 0.001$), FIB-4 (AUC: 0.811, 95% CI: 0.725–0.896; $P = 0.002$) and AFP (AUC: 0.716, 95% CI: 0.597–0.835; $P = 0.029$). In addition, the performance of ROC curve was compared by DeLong's test, IVAF-FIB-4 had statistical significance compared with C-IV, FIB-4, and AFP, respectively (all $P < 0.05$; Figure 2).

Table 2 Correlation Analysis of HCC with C-IV, AFP, FIB-4, and IVAFP-FIB-4

Characteristics	Correlation Coefficient	*P*
C-IV (μg/L) (cutoff value: 73.95)	0.585	<0.001
AFP (ng/mL) (cutoff value: 2.08)	0.192	0.010
FIB-4 (cutoff value: 6.92)	0.277	<0.001
IVAF-FIB-4*	0.835	<0.001

Notes: *IVAF-FIB-4: When C-IV level ≥73.95 μg/L, AFP level ≥2.08 ng/mL, and FIB-4 ≥6.917 were met at the same time, the indicator was assigned a value of 1, and the other cases were assigned a value of 0.
Abbreviations: C-IV, type IV collagen; AFP, alpha fetoprotein; FIB-4, fibrosis-4 score; IVAFP-FIB-4, type IV collagen-alpha fetoprotein-fibrosis-4 score.



Characteristics	AFP	FIB-4	C-IV
FIB-4	<0.001		
C-IV	0.001	0.088	
IVAF-FIB-4	<0.001	0.029	0.002

Characteristics	AUC	95% CI	*P*	Sensitivity (%)	Specificity (%)
AFP	0.716	0.597-0.835	0.029	100.0	43.2
FIB-4	0.811	0.725-0.896	0.002	100.0	62.1
C-IV	0.912	0.791-1.000	<0.001	88.9	93.5
IVAF-FIB-4	0.930	0.812-1.000	<0.001	88.9	97.0

Figure 2 Receiver operating characteristic curve analysis to assess the accuracy of candidate variables and the non-invasive predictive indicator in discriminating patients with and without HCC.

Incidence of HCC at the End of Follow-Up

All patients were divided into IVAF-FIB-4 (0) and IVAF-FIB-4 (1) groups according to the preoperative non-invasive predictive indicator, their mean follow-up times were 67.5 months and 69.5 months, respectively. As shown in Figure 3, at the end of the follow-up, among the all patients, 5.1% (9/178) developed postoperative HCC, while 0.6% (1/168) in patients with IVAF-FIB-4 (0) and 80.0% (8/10) in patients with IVAF-FIB-4 (1). In addition, the incidence densities of

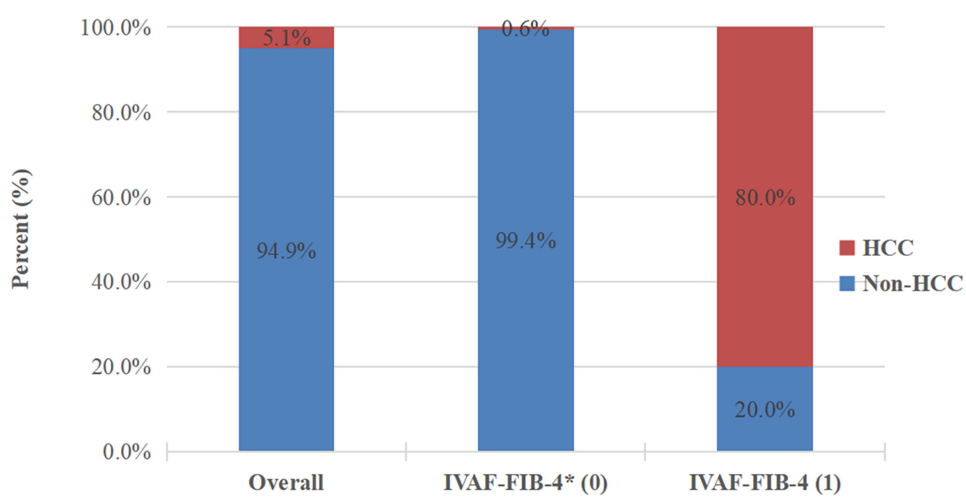


Figure 3 The proportion of occurrence of HCC in HBV-related CPH patients with different groups. (*IVAF-FIB-4: When C-IV level ≥73.95 μg/L, AFP level ≥2.08 ng/mL, and FIB-4 ≥6.917 were met at the same time, the indicator was assigned a value of 1, and the other cases were assigned a value of 0.

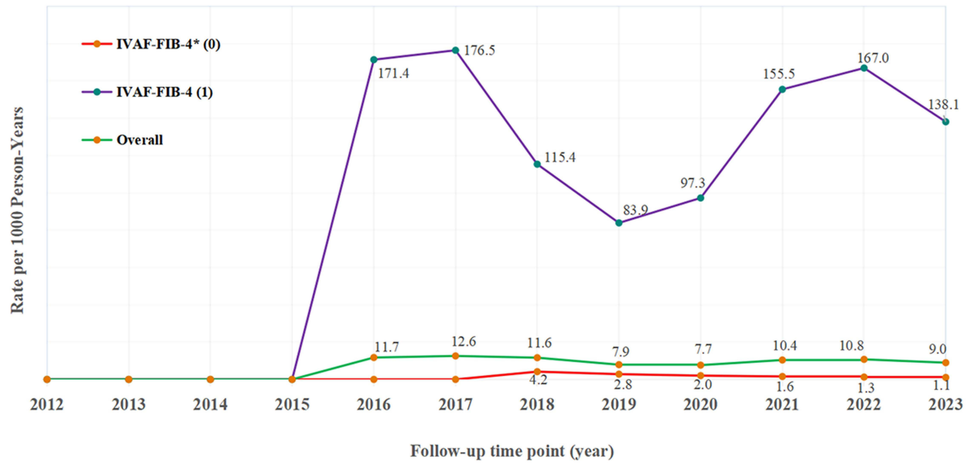


Figure 4 The incidence density of HCC in HBV-related CPH patients with different groups. (*IVAF-FIB-4: When C-IV level ≥73.95 μg/L, AFP level ≥2.08 ng/mL, and FIB-4 ≥6.917 were met at the same time, the indicator was assigned a value of 1, and the other cases were assigned a value of 0.

HCC among HBV-related CPH patients during the follow-up period are shown in Figure 4. At the end of follow-up, the incidence density of HCC in patients with IVAF-FIB-4 (1) was significant higher than that in patients with IVAF-FIB-4 (0) (138.1/1000 vs 1.1/1000 person-years; rate ratio: 130.475, 95% CI: 16.318–1043.227).

Independent Risk Predictors of HCC Incidence

Before IPTW, the results of logistic regression analysis showed that compared with IVAF-FIB-4 (0), IVAF-FIB-4 (1) was an independent risk factor for postoperative HCC (odds ratio: 668.000, 95% CI: 53.895–8279.541; $P < 0.001$; Table 3). After weighting for gender, age, year of treatment, BMI, cirrhotic etiology, hypertension, diabetes, Child-Pugh classification, portal vein thrombosis, longitudinal diameter of the spleen, portal vein diameter, splenic vein diameter, WBC, PLT, HGB, TBIL, ALB, ALT, INR, Cr, and BUN, the results of logistic regression analysis still showed that IVAF-FIB-4 (1) was an independent risk factor for postoperative HCC (odds ratio: 3244.565, 95% CI: 316.198–33293.081; $P < 0.001$; Table 3).

Discussion

It is well known that liver fibrosis is a major risk for HCC, and the more serious the degree of liver fibrosis, the higher the risk of HCC.[15–17] The most serious degree of liver fibrosis is cirrhosis, and about 85–95% of HCC patients suffer from cirrhosis.[22] Much of the literature has reported that C-IV is positively correlated with the progression of liver fibrosis.[12–14] C-IV is an important component of the normal extracellular matrix (ECM), which is also the main component of the liver interstitial basement membrane. C-IV will occur in the serum when the basement membrane is formed or destroyed.[23,24]

MMP-2 and MMP-9 are the members of the matrix metalloproteinase (MMPs) family. Many studies have shown that MMPs, as important enzymes currently known to degrade ECM, play an important role in promoting tumor angiogenesis,

Table 3 Logistic Regression Analysis of Occurrence of HCC in Unadjusted and IPTW Adjusted Population

Characteristics	Unadjusted		IPTW Adjusted	
	OR [95% CI]	*P*	OR [95% CI]	*P*
IVAF-FIB-4* (1/0)	668.000 (53.895–8279.541)	<0.001	3244.565 (316.198–33,293.081)	<0.001

Notes: *IVAF-FIB-4: When C-IV level ≥73.95 μg/L, AFP level ≥2.08 ng/mL, and FIB-4 ≥6.917 were met at the same time, the indicator was assigned a value of 1, and the other cases were assigned a value of 0.

Abbreviations: HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval; C-IV, type IV collagen; AFP, alpha fetoprotein; FIB-4, fibrosis-4 score; IVAFP-FIB-4, type IV collagen-alpha fetoprotein-fibrosis-4 score.

metastasis, and invasion.[25–27] MMP-2 and MMP-9 are considered as potential biomarkers in the process of tumorigenesis, as well as key effectors of ECM remodeling and important potential targets for anti-tumor therapy.[28,29] The ECM degradation caused by MMPs will lead to an increased C-IV level in serum.[30] Therefore, logically, C-IV level in serum may be positively correlated with the risk of tumor.

In this study, the increase in C-IV level in serum reflects the progression of liver fibrosis, on the one hand, and, on the other hand, it may also be due to the early activation of MMPs in patients, which makes basement membrane catabolism active, resulting in an increase in serum C-IV level. The expression of MMP-2/9 is reported to be associated with the progression of liver cancer.[31] So, the increased C-IV level in serum may suggest important information for the early HCC development in liver cirrhosis patients, which needs to be further explored in future studies.

In addition, FIB-4 has been confirmed by many studies to have the ability to assess the degree of liver fibrosis in patients with chronic liver disease.[32,33] Some scholars have indicated that in a cohort of non-cirrhotic patients with chronic HBV infection, a higher FIB-4 was associated with an increased risk of HCC.[34,35] For a long time, AFP has been considered as a biomarker for the clinical diagnosis and prognosis of HCC. Moreover, some scholars have confirmed the cancer-promoting role of AFP in the development of HCC using AFP deficient mouse models. Based on these findings, the combination of C-IV, AFP, and FIB-4 may be a good potential predictor for the occurrence of HCC.

In Asia, the benefits of LSD in the treatment of patients with CPH have been increasingly recognized. LSD can not only improve liver reserve function but also reduce portal vein pressure and the risk of gastroesophageal variceal bleeding.[8,9] In addition, LSD even reduced the incidence of postoperative HCC.[10] However, some CPH patients after LSD still inevitably progress to HCC. Therefore, in order to seek certain markers that can better predict postoperative HCC after LSD, we explored the relationship between non-invasive predictive indicator and postoperative HCC.

In this study, we found that C-IV, AFP, and FIB-4 were potential markers to predict postoperative HCC after LSD. A novel non-invasive predictive indicator (ie, IVAF-FIB-4) resulting from combining these three indicators was an independent risk factor for postoperative HCC with satisfactory diagnostic accuracy and reasonable predictive performance. Its AUC value was 0.939, with associated sensitivity of 88.9% and specificity of 98.8%. The logistic regression analysis showed that the likelihood of postoperative HCC in patients with IVAF-FIB-4 (1) was 668 times than that in patients with IVAF-FIB-4 (0). After weighting by IPTW, the risk was increased to 3244.565 times. In addition, at the end of follow-up, the 11-year HCC incidence density in patients with IVAF-FIB-4 (1) was significantly higher than that in patients with IVAF-FIB-4 (0) (138.1/1000 vs 1.1/1000 person-years). These phenomena indicate that when the patients have C-IV ≥73.95 μg/L, AFP ≥2.08 ng/mL, or FIB-4 ≥6.917 conditions, we should pay appropriate attention. And when the patient has IVAF-FIB-4 (1) condition, we should pay more attention, in order to detect problems as early as possible and intervene in a timely manner.

The present study has several limitations. First, the sample size of this research is not big enough, mainly because liver fibrotic markers in the early stage were not tested in our department. Second, this is a retrospective study. Prospective and multi-center studies are needed to verify the findings of this study in the future. Thirdly, the patients were regularly followed up every three months within 1 year after LSD. Then, after one year, the follow-up interval is usually half a year, some patients may have developed HCC without noticing during the follow-up interval. Fourth, this study focuses on HBV-related CPH patients after LSD, and whether its finding is fit for all cirrhosis patients needs to be further investigated. Finally, the detection of HBsAg, HBeAb, HBcAb, and other indicators in our hospital were only qualitative measurements, and the concentration value cannot be obtained. We hope to increase the quantitative detection of these indicators in future prospective studies.

Conclusion

To the best of our knowledge, this is the first report on the exploration of a non-invasive predictive indicator for postoperative HCC in HBV-related CPH patients after LSD. This study found that C-IV ≥73.95 μg/L, AFP ≥2.08 ng/mL, and FIB-4 ≥6.917 were all potential indicators to predict postoperative HCC after LSD. It is worth noting that the non-invasive predictive indicator based (ie, IVAF-FIB-4) on these three indicators showed a very satisfactory predictive ability for occurrence of postoperative HCC in HBV-related CPH patients after LSD. Therefore, in clinical practice, we can identify HBV-related CPH patients with a high risk of postoperative HCC in advance, and then strengthen the regular checkups for these patients, so as to facilitate early detection of HCC and timely treatment, thereby bringing better survival benefits to these patients.

Abbreviations

LSD, laparoscopic splenectomy and azygoportal disconnection; HCC, hepatocellular carcinoma; CPH, cirrhotic portal hypertension; HBV, hepatitis B virus; LT, Liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt; C-IV, type IV collagen; IPTW, inverse treatment probability weighting; LN, laminin; HA, hyaluronidase; PC-III, procollagen type III; AFP, alpha fetoprotein; FIB-4, fibrosis-4 score; IVAF-FIB-4, type IV collagen-alpha fetoprotein-fibrosis-4 score; POM, postoperative months; BMI, body mass index; WBC, white blood cells; HGB, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; INR, international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; ROC, Receiver operating characteristic; AUC, area under the receiver operating characteristic curve; ECM, extracellular matrix; MMPs, matrix metalloproteinase; OR, odds ratio.

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Disclosure

The authors report no conflicts of interest in this work.

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