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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Association of Preoperative Hypercoagulability with Poor Prognosis in Hepatocellular Carcinoma Patients with Microvascular Invasion After Liver Resection: A Multicenter Study

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ABSTRACT

Background. Microvascular invasion (MVI) predicts poor prognosis in patients with hepatocellular carcinoma (HCC). HCC patients with hypercoagulability are prone to develop thrombosis; however, the relationship between preoperative coagulability state, as reflected by the international normalized ratio (INR) level, and MVI remains unclear.

Methods. From January 2009 to December 2012, HCC patients who underwent R0 liver resection (LR) from four cancer centers entered into this study. The overall survival (OS) and recurrence-free survival (RFS) rates were compared using the Kaplan–Meier method and Cox regression analysis.

Results. Of the 2509 HCC patients who were included into this study, 1104 were found to have MVI in the resected specimens. These patients were divided into the low (n = 151), normal (n = 796), and high (n = 157) INR subgroups based on the preoperative INR levels. The low INR subgroup had a significantly higher incidence of MVI than the normal or high INR subgroups (61.6% vs. 41.6% vs. 44.6%; $p < 0.001$). HCC patients with MVI were significantly more likely to have a low preoperative INR level ($p < 0.001$); the INR level ($p < 0.001$) was an independent risk factor of OS and RFS. HCC patients with MVI in the low INR subgroup had significantly worse RFS and OS than the normal or high INR subgroups (median RFS 13.5 vs. 20.2 vs. 21.6 months, $p < 0.001$; median OS 35.5 vs. 59.5 vs. 57.0 months, $p < 0.001$).

Conclusions. Preoperative hypercoagulability was associated with poor long-term prognosis in HCC patients with MVI after R0 LR.

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related death worldwide.[1,2] Liver resection (LR) is still the first-line treatment for the early and intermediate stages of HCC.[3,4] Unfortunately, the 5-year recurrence rates after R0 LR still range as high as 70–80%, which seriously limits the long-term prognosis of HCC patients.[5]

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Microvascular tumor invasion (MVI), a vital poor prognostic factor, occurs in 15–57% of HCC patients[6] and is commonly associated with early tumor recurrence within 1 year of LR. Recent studies reported that hepatitis B virus (HBV) infection and active HBV replication were associated with the development of MVI,[7,8] while another study demonstrated the preoperative factors associated with MVI included large tumor diameter, multiple nodules, incomplete capsule, α-fetoprotein (AFP) level $\geq$ 20 ng/mL, platelet count $\leq 100 \times 10^3/\mu L$, HBV DNA load $\geq 10^4$ IU/mL, and a typical dynamic pattern of tumors on contrast-enhanced magnetic resonance imaging (MRI).[9] However, many other significant factors related to increased incidences of MVI and survival outcomes are still unknown.

Many cancer patients are in a hypercoagulability state, and venous thromboembolic events can be the first presentation of cancer.[10] Recent studies suggested multiple and often interrelated mechanisms in HCC patients can tip the hemostatic balance towards hypercoagulability.[11,12] MVI has been reported to have a similar underlying pathophysiological mechanism to develop diffuse intravascular coagulation (DIC),[13,14] with formation of thromboembolism in the microvasculature under microscopy. To our knowledge, no information is available on the preoperative coagulability state, as reflected by the international normalized ratio (INR) level in HCC patients, correlating with the incidence of MVI and long-term survival outcomes.

This study aimed to assess the association between preoperative INR levels and the incidences of MVI and long-term overall survival (OS) outcomes in patients with HCC and MVI after R0 LR.

METHODS

Patients

A retrospective study was conducted on HCC patients who underwent R0 LR from January 2009 to December 2012 from four major cancer centers—the Eastern Hepatobiliary Surgery Hospital (EHBH) of Shanghai, the Affiliated Hospital of Binzhou Medical College (AHBMC) of Shandong, LongYan First Hospital (LYFH) of Fujian, and Wenzhou People's Hospital (WZPH) of Zhejiang. The clinical and pathological data of these patients were retrospectively analysed, and patients were divided into three groups according to preoperative INR levels.

This study was approved by the Institutional Ethics Committee of the EHBH AHBMC, LYFH, and WZPH. Informed consent was obtained from all patients for their data to be used for research.

Inclusion and Exclusion Criteria

The inclusion criteria were patients with HCC with (1) good liver function and a Child–Pugh A or B7 score $\leq$ 7; (2) complete preoperative serological data and contrast-enhanced computed tomography (CT) or MRI of the abdomen; (3) R0 LR as an initial treatment with no residual tumors left, based on gross inspection and histological examination of the resection specimens; (4) histopathological diagnosis of HCC; (5) a detailed search for MVI in the resected specimens by two experienced pathologists; (6) no macrovascular invasion or extrahepatic metastasis; and (7) complete serological, pathological, and clinical data on follow-up. The exclusion criteria were (1) a history of other cancers; (2) incomplete clinical data; and (3) preoperative anticoagulation therapy. The diagnostic criteria of MVI were the presence of tumor cells in a portal vein, hepatic vein, or large capsular vessel of the surrounding hepatic tissues lined by endothelium that was visible only on microscopy.[15,16]

Preoperative and Postoperative Investigations

Routine preoperative investigations included imaging and serological tests. All patients underwent a standard liver imaging protocol [3,4] that included abdominal ultrasonography, contrast-enhanced MRI and/or CT scan of the abdomen, and plain radiography or non-contrast CT scan of the chest. All radiological examinations were reviewed by two experienced radiologists. Routine preoperative laboratory investigations included complete blood counts, liver and renal function tests, hepatitis B and C serology, HBV DNA load, and serum AFP level. The preoperative investigation of the coagulability state included INR, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB). The INR level from the last examination within 3 days before surgery was chosen as the indicator for data analysis. Routine postoperative investigations included histopathology and immunohistochemical studies. The diagnosis of MVI was only determined by histologic examination of the resected surgical specimens. Other pathological indexes used in this study included tumor diameter (maximum diameter), number of tumors, tumor encapsulation, and cirrhosis. The histopathological evaluations were performed by two independent and experienced pathologists who were blinded to the clinical data.

Liver Resection

R0 LR was performed using the techniques that have been described in detail previously.[15,17] Curative LR,

defined as complete removal of macroscopic nodules with a microscopically tumor-free resection margin, was carried out in patients in good general condition, with tumor nodules on imaging studies being technically resectable, and with adequate liver remnant volume and functional reserve. Intraoperative ultrasonography was performed routinely to assess the number and size of lesions and the relationship of the tumors to the vascular structures. Pringle's maneuver was routinely used, with a clamp/unclamp cycle of 10 min/5 min.

Follow-Up and Endpoints

Patients were regularly followed-up. Investigations during the follow-up visits included serum AFP, liver function, abdominal ultrasonography, and contrast-enhanced CT once every 2–3 months for the first year and then once every 6 months until death or dropout from the follow-up system. The diagnosis of tumor recurrence was based on raised serum AFP levels, ultrasound scanning, MRI, and CT. When tumor recurrence was diagnosed, patients were subjected to appropriate treatments, such as percutaneous ethanol injection, radiofrequency ablation, transarterial chemoembolization (TACE), or LR, depending on the general condition of the patient, the liver functional reserve, and the pattern of tumor recurrence.

The primary endpoints of this study were recurrence-free survival (RFS) and OS. RFS was calculated from the date of R0 LR to the date when tumor recurrence was first diagnosed, while OS was calculated from the date of R0 LR to the date of the patient's death or date of last follow-up.

Statistical Analysis

Continuous variables, reported as median [interquartile range (IQR)], were compared using the Mann–Whitney test; normally distributed variables, reported as mean (standard deviation), were compared using Student's t test; and categorical data, presented as frequency (%), were compared using the Chi square test or Fisher's exact test. OS or RFS curves were generated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses were assessed using the Cox proportional hazards stepwise model. Factors with a p value < 0.05 on univariate analysis were incorporated into the multivariate analysis. Multivariate Cox regression analysis with a stepwise selection was performed to detect independent predictors of RFS and OS (the entry criteria for selection into the final multivariate model was $p < 0.05$). Survival curves of RFS and OS were calculated using the Kaplan–Meier method and compared using the log-rank test. Median survival times and their 95% confidence intervals (CIs) were reported. The data analyzes were performed using SPSS software version 24.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

The 2509 HCC patients in this study (Fig. 1) were divided into two groups according to whether or not they had MVI (n = 1405 in the non-MVI group; n = 1104 in the MVI group). The baseline characteristics of all HCC patients are reported in electronic Supplementary Table 1. HCC patients with MVI were further subdivided into three subgroups according to preoperative INR. The other variables among the three subgroups showed no significant difference (Table 1).

Association of Preoperative International Normalized Ratio (INR) Levels with Incidences of Microvascular Invasion (MVI) in Hepatocellular Carcinoma (HCC) Patients

HCC patients in the low INR subgroup had a significantly higher incidence of MVI than the normal or high INR subgroups (61.6% vs. 41.6% vs. 44.6%; $p < 0.001$) [electronic supplementary Table 2]. Of the 1405 patients in the non-MVI group, 94 (6.7%), 1116 (79.4%), and 195 (13.9%) patients were included in the low, normal, and high INR subgroups, respectively. Furthermore, of the 1104 patients in the MVI group, 151 (13.7%), 796 (72.1%), 157 (14.2%) patients were included in the low, normal, and high INR subgroups, respectively. Patients with HCC and MVI were significantly more likely to have a low preoperative INR level than those with no MVI ($p < 0.001$).

Univariate and Multivariate Cox Regression Analyses on Survival Outcomes in HCC Patients with MVI

Univariate and multivariate Cox regression analyses demonstrated that the INR level ($p < 0.001$), number of tumors ($p = 0.002$), satellite nodules ($p < 0.001$), AFP ($p = 0.002$), tumor diameter ($p < 0.001$), ALT ($p = 0.004$), and PT ($p < 0.001$) were independent risk factors of OS in HCC patients with MVI (Table 2), while INR level ($p < 0.001$), sex ($p = 0.013$), number of tumors ($p = 0.005$), satellite nodules ($p < 0.001$), AFP ($p = 0.001$), tumor diameter ($p < 0.001$), and PT ($p < 0.001$) were independent risk factors of RFS in these patients (Table 3). Univariate and multivariate Cox regression analyses on survival outcomes in all HCC

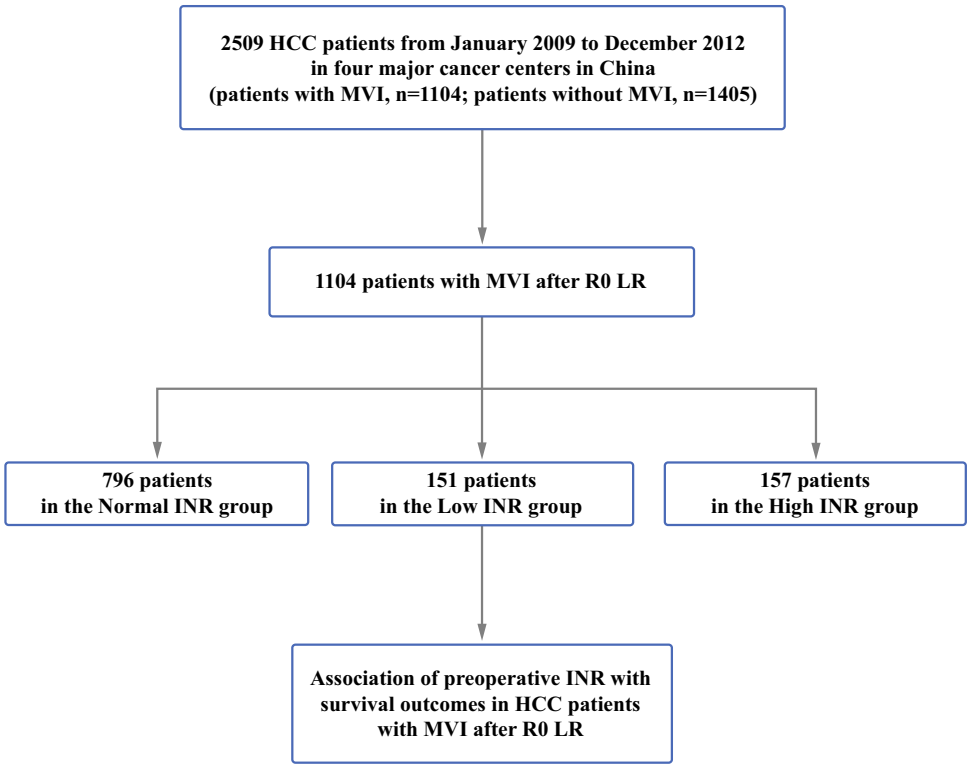


FIG. 1 Selection of HCC patients for inclusion in the study. *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *LR* liver resection, *INR* international normalized ratio

patients are shown in electronic supplementary Tables 3 and 4.

Survival Analysis in HCC Patients with MVI Among the Low, Normal, and High INR Subgroups

The three subgroups of patients who had MVI, but with different preoperative INR levels, showed significantly different RFS and OS rates ($p < 0.001$) (Fig. 2). The low INR subgroup had significantly worse 1-, 3-, and 5-year RFS rates than the normal or high INR subgroups (1 year: 52.2% vs. 62.9% vs. 59.8%; 3 years: 35.8% vs. 38.3% vs. 34.8%; 5 years: 13.0% vs. 25.9% vs. 25.6%; median RFS 13.5 vs. 20.2 vs. 21.6 months, $p < 0.001$) (Fig. 2a). For the OS rates of these three subgroups of patients, the low INR subgroup had significantly worse 1-, 3-, and 5-year OS rates than the normal or high INR subgroups (1 year: 78.3% vs. 83.9% vs. 82.7%; 3 years: 48.9% vs. 64.3% vs. 61.0%; 5 years: 35.3% vs. 49.6% vs. 47.9%; median OS 35.5 vs. 59.5 vs. 57.0 months, $p < 0.001$) (Fig. 2b). There were no significant differences in the RFS and OS rates between the normal and high INR groups.

DISCUSSION

The presence of MVI significantly worsens long-term survival outcomes in HCC patients after R0 LR.[15,18,19] MVI can only be diagnosed under microscopic examination of the resected specimens. It starts as a microvascular tumor thrombus, which can embolize through the portal and hepatic venous systems as tumor cells or emboli.[20,21] Previous studies reported the incidence of MVI to be correlated with a high preoperative HBV DNA level, tumor size, incomplete capsule, and antiviral treatment.[7,9] A coagulability state, especially hypercoagulability, is associated with a high incidence of vascular complications in HCC patients, especially in portal vein thrombosis.[10,11] Whether hypercoagulability can promote the formation of MVI in capillaries and influence the postoperative prognosis of these patients is unknown.

This study of a large-scale, multicentre cohort of patients is the first to report on the association between hypercoagulability and the incidence of MVI, and to explore whether HCC patients with MVI and a low INR level have worse long-term survival outcomes after R0 LR.

The presence of MVI has been repeatedly shown in recent studies to be one of the most vital poor prognostic factors of early recurrence and OS after curative LR for HCC.[18–22] Even in small HCCs of < 3 cm, MVI is still a poor prognostic indicator.[22–24] MVI can be predicted using preoperative data,[8,23] although the prediction is nothing near to 100% accurate. Nomograms, based on preoperative serological indexes or preoperative radiomic data, showed favourable predictions on MVI status in patients with HCC.[9,25] Other studies reported that new imaging techniques or characteristic manifestations could preoperatively

TABLE 1 Clinicopathological features of HCC patients with MVI (n = 1104)

Variables	INR low (N = 151)	INR normal (N = 796)	INR high (N = 157)	p value
Age (years)				
< 50	75 (49.67)	372 (46.73)	75 (47.77)	0.796
≥ 50	76 (50.33)	424 (53.27)	82 (52.23)	
Sex				
Male	120 (79.47)	688 (86.43)	130 (82.80)	0.064
Female	31 (20.53)	108 (13.57)	27 (17.20)	
HBsAg				
Yes	125 (82.78)	671 (84.30)	120 (76.43)	0.057
No	26 (17.22)	125 (15.70)	37 (23.57)	
Ascites				
Yes	20 (13.25)	61 (07.66)	16 (10.19)	0.068
No	131 (86.75)	735 (92.34)	141 (89.81)	
No. of tumors				
Single	125 (82.78)	658 (82.66)	126 (80.25)	0.761
Multiple	26 (17.22)	138 (17.34)	31 (19.75)	
Satellite nodules				
Yes	36 (23.84)	192 (24.12)	29 (18.47)	0.305
No	115 (76.16)	604 (75.88)	128 (81.53)	
AFP (μg/L)				
< 400	83 (54.97)	453 (56.91)	84 (53.50)	0.698
≥ 400	68 (45.03)	343 (43.09)	73 (46.50)	
Tumor diameter				
< 5	55 (36.42)	375 (47.11)	71 (45.22)	0.054
≥ 5	96 (63.58)	421 (52.89)	86 (54.78)	
Encapsulation				
Yes	119 (78.81)	619 (77.76)	127 (80.89)	0.678
No	32 (21.19)	177 (22.24)	30 (19.11)	
Cirrhosis				
Yes	89 (58.94)	533 (66.96)	127 (80.89)	< 0.001
No	62 (41.06)	263 (33.04)	30 (19.11)	
TBIL (μg/L)				
< 17.1	119 (78.81)	573 (71.98)	103 (65.61)	0.036
≥ 17.1	32 (21.19)	223 (28.02)	54 (34.39)	
DBIL (μg/L)				
< 6.8	126 (83.44)	606 (76.13)	90 (57.32%)	< 0.001
≥ 6.8	25 (16.56)	190 (23.87)	67 (42.68)	
ALB	44.9 (39.6–50.2)	42.6 (41.1–44.1)	38.6 (37.7–39.5)	0.038
ALT	66.4 (36.8–95.9)	58.0 (52.8–63.2)	164.5 (98.5–230.6)	< 0.001
AST	45.3 (32.6–58.0)	79.0 (64.6–93.4)	361.6 (174.4–548.9)	< 0.001
CR	67.6 (65.2–70.0)	70.5 (69.0–72.0)	69.8 (65.1–74.4)	0.332
PT	10.8 (10.7–11.0)	12.4 (12.1–12.8)	13.6 (13.4–14.0)	< 0.001
PLT	196.0 (182.6–209.5)	159.8 (154.4-165.2)	132.3 (121.4–143.3)	< 0.001

Data are expressed as n (%) or median (IQR)

HBsAg hepatitis B surface antigen, *AFP* α-fetoprotein, *TBIL* total bilirubin, *DBIL* direct bilirubin, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CR* creatinine, *PT* prothrombin time, *PLT* platelet, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *INR* international normalized ratio, *IQR* interquartile range

TABLE 2 Univariate and multivariate analysis of overall survival of HCC patients with MVI (n = 1104)

Characteristics	Univariate analysis				Multivariate analysis			
	HR	95% CI		p value	HR	95% CI		p value
INR								
Low versus normal	1.463	1.125	1.904	0.005	2.281	1.498	3.475	< 0.001
Age (years)								
< 50 versus ≥ 50	0.953	0.783	1.159	0.630				
Sex								
Male versus female	0.910	0.688	1.204	0.510				
HBsAg								
Positive versus negative	1.132	0.839	1.527	0.418				
Ascites								
Yes versus no	1.340	0.914	1.964	0.134				
No. of tumors								
Single versus multiple	1.677	1.320	2.131	< 0.001	1.636	1.204	2.221	0.002
Satellite nodules								
Yes versus no	2.210	1.805	2.705	< 0.001	1.665	1.301	2.131	< 0.001
AFP (μg/L)								
< 400 versus ≥ 400	1.781	1.462	2.169	< 0.001	1.476	1.151	1.893	0.002
Tumor diameter, cm								
< 5 versus ≥ 5	2.498	2.016	3.094	< 0.001	1.106	1.076	1.137	< 0.001
Encapsulation								
Yes versus no	0.783	0.625	0.981	0.033				
Cirrhosis								
Yes versus no	1.107	0.889	1.378	0.364				
TBIL (μmol/L)								
< 17.1 versus ≥ 17.1	1.003	1.001	1.005	0.017				
DBIL (μg/L)								
< 6.8 versus ≥ 6.8	1.004	1.001	1.007	0.016				
ALB (mg/mL)	0.987	0.973	1.001	0.071				
ALT (U/L)	1.001	1.000	1.002	0.050	1.002	1.001	1.003	0.004
AST (U/L)	1.002	1.000	1.004	0.041				
CR	1.001	0.996	1.007	0.599				
PT (s)	0.999	0.979	1.019	0.922	1.647	1.395	1.945	< 0.001
PLT (10^9/L)	1.000	0.999	1.002	0.405				

HBsAg hepatitis B surface antigen, *AFP* α-fetoprotein, *TBIL* total bilirubin, *DBIL* direct bilirubin, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CR* creatinine, *PT* prothrombin time, *PLT* platelet, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *INR* international normalized ratio, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

screen HCC patients with MVI with high effectiveness and sensitivity.[26–29] Some factors that are possibly related to the incidence of MVI have not yet been clearly defined. Cancer patients can develop a hypercoagulability state, and venous thromboembolic events can be the first clinical manifestation of cancer.[10,30,31] As the liver synthesizes most coagulation factors and regulatory proteins that are part of the hemostatic control mechanisms, a severe derangement of liver function can result in thrombotic complications.[32] There are multiple and often interrelated mechanisms through which HCC can tip the hemostatic balance towards hypercoagulability;[33–35] however, whether hypercoagulability, as reflected by a low INR level, could promote early microvascular invasion in HCC is still unknown.

In our study, HCC patients who had a low INR level, reflecting on a hypercoagulability state, had a significantly higher incidence of MVI than patients with a normal or high INR level (61.6% vs. 41.6% vs. 44.6% of patients with MVI in the low, normal, and high INR groups; $p < 0.001$). These findings suggest that a hypercoagulability state promoted the incidence of MVI with early vascular metastasis in HCC. In addition, patients with HCC

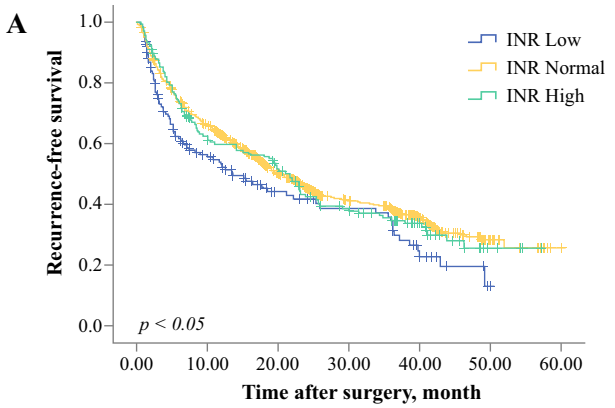
TABLE 3 Univariate and multivariate analysis of recurrence-free survival of HCC patients with MVI (n = 1104)

Characteristics	Univariate analysis				Multivariate analysis			
	HR	95% CI		p value	HR	95% CI		p value
INR								
Low versus normal	1.344	1.073	1.683	0.010	1.934	1.347	2.777	< 0.001
Age (years)								
< 50 versus ≥ 50	0.892	0.756	1.053	0.178				
Sex								
Male versus female	0.835	0.652	1.069	0.153	0.683	0.506	0.922	0.013
HBsAg								
Positive versus negative	1.168	0.903	1.511	0.238				
Ascites								
Yes versus no	1.683	1.217	2.327	0.002				
No. of tumors								
Single versus multiple	1.502	1.220	1.849	< 0.001	1.474	1.126	1.929	0.005
Satellite nodules								
Yes versus no	2.028	1.700	2.419	< 0.001	1.681	1.352	2.090	< 0.001
AFP (μg/L)								
< 400 versus ≥ 400	1.423	1.204	1.682	< 0.001	1.415	1.145	1.749	0.001
Tumor diameter (cm)								
< 5 versus ≥ 5	1.744	1.469	2.071	< 0.001	1.085	1.057	1.114	< 0.001
Encapsulation								
Yes versus no	0.957	0.823	1.229	0.957				
Cirrhosis								
Yes versus no	1.103	0.917	1.327	0.299				
TBIL (μmol/L)								
< 17.1 versus ≥ 17.1	1.003	1.001	1.006	0.017				
DBIL (μg/L)								
< 6.8 versus ≥ 6.8	1.004	1.001	1.008	0.025				
ALB (mg/mL)	0.997	0.992	1.003	0.359				
ALT (U/L)	1.000	0.999	1.001	0.624				
AST (U/L)	1.002	1.000	1.004	0.041				
CR (U/L)	1.000	0.994	1.005	0.884				
PT (s)	1.004	0.990	1.019	0.584	1.406	1.211	1.632	< 0.001
PLT (10^9/L)	1.000	0.999	1.001	0.693				

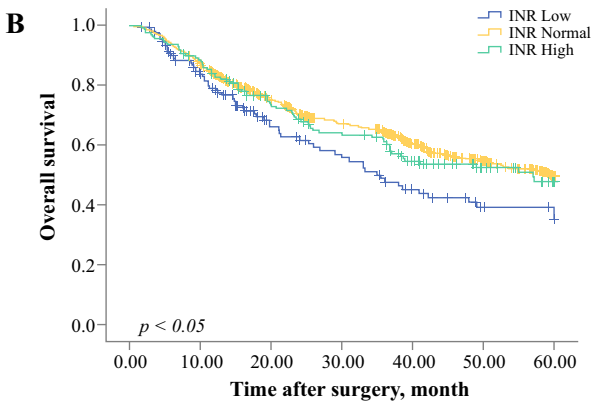
HBsAg hepatitis B surface antigen, *AFP* α-fetoprotein, *TBIL* total bilirubin, *DBIL* direct bilirubin, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CR* creatinine, *PT* prothrombin time, *PLT* platelet, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *INR* international normalized ratio, *RFS* recurrence-free survival, *HR* hazard ratio, *CI* confidence interval

and MVI were significantly more likely to have a low preoperative INR level with a hypercoagulability state than those with no MVI (13.7% vs. 6.7%; $p < 0.001$), indicating that the presence of MVI could conversely promote the formation of a hypercoagulability state in HCC patients. The pathophysiology of an HCC-associated hypercoagulability state has only recently been studied in depth.[36] The incidence of MVI and hypercoagulability state existed side by side and played an important role together. Previous studies reported the rebalanced and unstable hemostatic status of cirrhosis can easily be tipped towards by the development of HCC.[11,12] Our study uncovered the association between hypercoagulability state and the incidence of MVI in HCC patients; however, the concrete underlying mechanisms need to be further studied.

A recent study reported that elevated plasma FIB levels in patients who are in a hypercoagulability state were associated with poor prognosis in patients with HCC.[33] Our study demonstrated that a hypercoagulability state may promote the incidence of MVI, and the presence of MVI significantly worsens long-term survival outcomes in HCC patients. Thus, the poor prognosis in HCC patients with



INR Low	151	67	35	26	10	0	0
INR Normal	796	511	308	191	102	20	2
INR High	157	92	75	50	27	4	0



INR Low	151	109	60	48	34	22	18
INR Normal	796	388	525	424	335	240	162
INR High	157	137	101	85	64	39	24

FIG. 2 Kaplan–Meier analysis for the **a** RFS and **b** OS rates in HCC patients with MVI after R0 LR among the low, normal, and high INR subgroups. **a** RFS for patients among the low, normal, and high INR subgroups (151 vs. 796 vs. 157 patients) after R0 LR ($p < 0.001$), **b** OS for patients among the low, normal, and high INR subgroups (151 vs. 796 vs. 157 patients) after R0 LR ($p < 0.001$). *INR* international normalized ratio, *RFS* recurrence-free survival, *OS* overall survival, *HCC* hepatocellular carcinoma, *MVI* microvascular invasion, *LR* liver resection

elevated plasma FIB levels likely resulted from a high incidence of MVI. In our study, univariate and multivariate Cox regression analyses demonstrated INR level ($p < 0.001$) was an independent risk factor of OS and RFS. HCC patients with MVI in the low INR subgroup had significantly worse RFS and OS than those in the normal or high INR subgroups. Prophylactic anticoagulation is a standard practice used to prevent potentially life-threatening thrombosis in cancer patients.[37] Aspirin, as an anticoagulant drug, could lower the HCC risk and improve prognosis in HCC patients.[38,39] Our study demonstrated that HCC patients with MVI in the normal or high INR subgroups exhibited better prognosis, which may serve as preliminary evidence to support the use of anticoagulation therapy in HCC patients with MVI after hepatectomy. Such a suggestion should be tested in well-developed, randomized controlled trials using a large sample size.

There are some limitations in this retrospective study. First, potential biases exist, and, second, the mechanisms of hypercoagulability in the formation of MVI were not studied. Third, the vast majority of these patients had a background of HBV infection. Whether the results obtained in this study can be extrapolated to HCV-related or alcohol-related HCC is not certain.

CONCLUSIONS

Our study demonstrated that preoperative hypercoagulability, as reflected by the INR level, was associated with the incidence of MVI and poor survival outcomes in HCC patients with MVI after hepatectomy. A low INR level was a prognostic predictor in identifying high-risk patients with poor long-term survival outcomes. Our results added to the existing and growing evidence that anticoagulation therapy may be useful for HCC patients with MVI.

AUTHOR CONTRIBUTIONS S-QC, WYL, X-PZ, M-CW: Conception and design. S-QC: Financial support. FZ, C-QZ, Y-RH, KW, Z-TC, Z-HC: Provision of study materials or patients. X-PZ, Z-HW: Collection and assembly of data. X-PZ, T-FZ: Data analysis and interpretation. X-PZ, WYL: Manuscript writing. All authors: Final approval of manuscript.

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