

Early Recurrence of Hepatocellular Carcinoma in Patients without Microscopic Vascular Invasion: Clinicopathological Characteristics and Risk Factors

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Purpose: Early recurrence of hepatocellular carcinoma (HCC) is not uniformly associated with microscopic vascular invasion (MVI). This study aims to identify the clinical and pathological factors associated with early recurrence in HCC patients without MVI.

Methods: A retrospective cohort study was conducted on 69 patients who underwent hepatectomy for HCC at the University Medical Center Ho Chi Minh city. All patients were microscopically confirmed as MVI-negative. Clinical and subclinical data, along with tumor recurrence within 24 months post-surgery were collected. Microscopic features of both tumor and non-tumor liver tissue were assessed using Hematoxylin-Eosin-stained slides.

Results: The majority of patients were male (78.3%) and had cirrhosis (72.5%). The early recurrence rate was 31.9%, with most recurrences occurring between 6- and 18-month post-surgery. Independent factors for early tumor recurrence included preoperative treatment with Transarterial Chemoembolization (TACE) or Radiofrequency Ablation (RFA) (HR = 8.63, 95% CI = 1.45–51.38), tumor size > 5 cm (HR = 3.82, 95% CI = 1.17–12.42), and HCV infection (HR = 4.61, 95% CI = 1.41–15.1).

Conclusion: The pathogenesis and pattern of early tumor recurrence in MVI-negative HCC differ from that in MVI-positive cases. Identifying risk factors, such as HCV infection, tumor size, and preoperative locoregional therapy, may aid in optimizing treatment strategies and postoperative surveillance.

Keywords: hepatocellular carcinoma, microvascular invasion, early recurrence, risk factor, clinical characteristics, pathological characteristics

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies worldwide, accounting for approximately 80% of primary liver cancer and contributing to over 700,000 deaths annually.^{1,2} The incidence and mortality rates of HCC are closely associated with the prevalence of chronic liver diseases, particularly viral hepatitis, cirrhosis, and non-alcoholic fatty liver disease.³ Due to its heterogeneity in etiology, molecular characteristics, and clinical behavior, HCC remains a challenging malignancy to manage.⁴

The primary treatment modalities for HCC include surgical resection, liver transplantation, local ablative therapies, and systemic therapies. However, the prognosis for HCC patients remains poor, primarily due to the high rate of tumor recurrence.⁵ Early recurrence, within two years after curative treatment, is common and associated with unfavorable outcomes. This early recurrence is often attributed to intrahepatic metastasis, but may also result from multicentric tumor development, underlying liver disease, and tumor invasion at the resection margin.⁶

Several clinicopathological factors have been identified as predictors of early recurrence in HCC patients, including tumor size, multifocality, histological grade, vascular invasion, serum alpha-fetoprotein levels, and liver function parameters. Among these, microscopic vascular invasion (MVI) is recognized as one of the most important independent risk factors leading to early recurrence and reduced overall survival.⁶ MVI refers to the microscopic presence of tumor cells within blood vessels in either the tumor or adjacent liver parenchyma. MVI has been reported in approximately 30–60% of HCC patients undergoing surgical resection or liver transplantation.^{7,8}

While MVI-positive patients are at high risk of recurrence, early recurrence can still occur in MVI-negative cases.⁹ Identifying risk factors for recurrence among HCC patients with negative MVI can facilitate the detection of high-risk patients who could benefit from closer surveillance and adjuvant therapies post-treatment. Therefore, this study aims to determine the clinical and pathological factors associated with early recurrence in HCC patients without MVI who have undergone surgical resection and to analyze the clinical and pathological determinants influencing this recurrence.

Materials and Methods

Patient Selection and Data Collection

This retrospective cohort study included all 69 hCC patients without MVI who underwent liver resection at the University Medical Center, Ho Chi Minh City between January 2018 and December 2018. Patients were excluded if tissue samples were inadequate for histopathological evaluation, or if they were lost to follow-up immediately after surgery, or if the final diagnosis was not HCC (Figure 1).

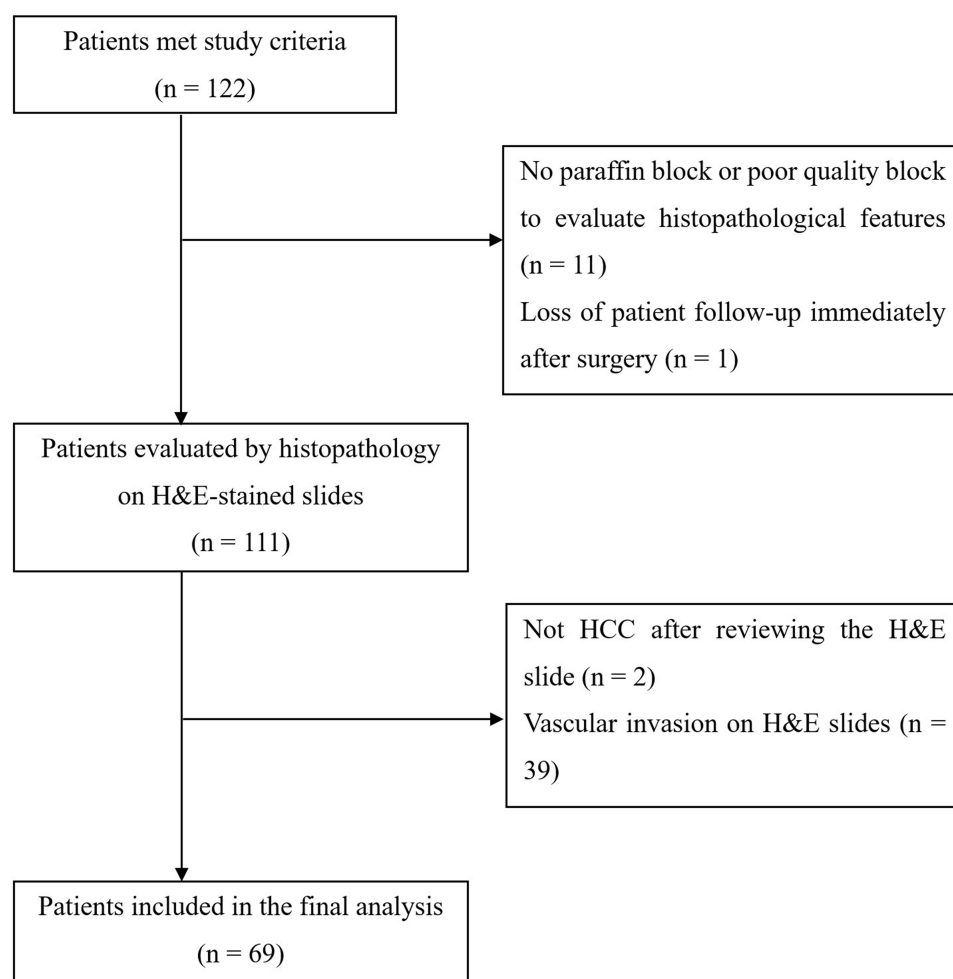


Figure 1 Flowchart of patient selection.

All clinical, paraclinical and follow-up data were extracted from electronic medical records. Patients were followed every 3–6 months for 24 months postoperatively, including abdominal ultrasound and serum AFP measurement at each visit. If any abnormalities were detected, such as elevated AFP levels or suspicious ultrasound findings, patients underwent a contrast-enhanced CT scan of the abdomen. When new lesions exhibited typical imaging features of HCC, the case was reviewed in a multidisciplinary tumor board composed of oncologists, radiologists, pathologists, and surgeons. The diagnosis of tumor recurrence was based on the consensus of this multidisciplinary discussion and was documented in the electronic medical records. In this study, early recurrence was defined as HCC recurrence confirmed by the tumor board and occurring within 24 months after surgery, consistent with definitions used in previous studies.^{6,10,11}

Pathological Assessment

Tumor characteristics, including size, Edmondson-Steiner grade, histological subtype (classified according to the 2019 WHO classification),¹² necrosis, mitotic index, and MVI were assessed. MVI was defined as the presence of clusters of tumor cells within a vascular lumen lined by endothelium, identified on hematoxylin and eosin (H&E) stained sections. For each case, all tumor-containing blocks (typically three to five per case) were examined. All cases were reviewed by the same pathologist to ensure consistency in MVI evaluation.

Non-tumor liver tissue, sampled at least 1 cm from the tumor margin, was evaluated for inflammation and fibrosis using the Ishak-Knodell scoring system,¹³ and steatosis was categorized as none (<5%), mild (5–33%), moderate (34–66%), or severe (>67%).

Statistical Analysis

Statistical analyses were performed using Stata software. Continuous and categorical variables were summarized as means $\pm$ standard deviations and frequencies/percentages, respectively. Univariate and multivariate Cox regression analyses were conducted to identify factors associated with early recurrence. Variables with a p-value < 0.1 in univariate analysis or those considered clinically relevant were included in the multivariate model. Due to the retrospective nature of the study, missing data were present for some variables. However, since the missingness was likely not completely at random and the overall sample size was relatively small, we did not apply any imputation methods. Instead, patients with complete data for all selected covariates were included in the multivariate analysis. We did not apply automated selection procedures such as stepwise, backward, or forward selection. Instead, we used a manual approach to construct a parsimonious multivariate model based on variables with univariate significance. Given that our study was exploratory in nature and not designed to test a specific hypothesis, the multivariate analysis was intended to describe potential associations rather than to formally test hypotheses. A p-value < 0.05 was considered statistically significant.

Results

Among the 69 patients included in the analysis, 22 (31.9%) experienced tumor recurrence within two years post-surgery, while 47 (68.1%) remained recurrence-free. Most recurrences occurred between 6 and 18 months. The recurrence rate over time is illustrated in [Figure 2](#).

Clinical and Paraclinical Characteristics

The clinical and laboratory characteristics of the cohort are summarized in [Table 1](#). The majority of patients were male (78.3%), with a mean age of 56.9 ± 12.8 years. Most had ALBI grade 1 (66.2%) with normal AST (85.3%) and ALT (80.9%) levels. AFP levels exceeded 200 ng/mL in one-third of cases. Patients with advanced BCLC stage at surgery had a more than four-fold increased risk of early recurrence compared to those with early-stage disease (HR = 4.23, 95% CI = 1.82–9.87, $p < 0.001$). A marginally statistical difference was observed in HCV infection where a recurrence group had a higher proportion of HCV infection compared to the non-recurrence group (47.4% vs 25.6%, $p = 0.080$). No statistically significant differences were found in other clinical characteristics among patients with early recurrence and those without early recurrence.

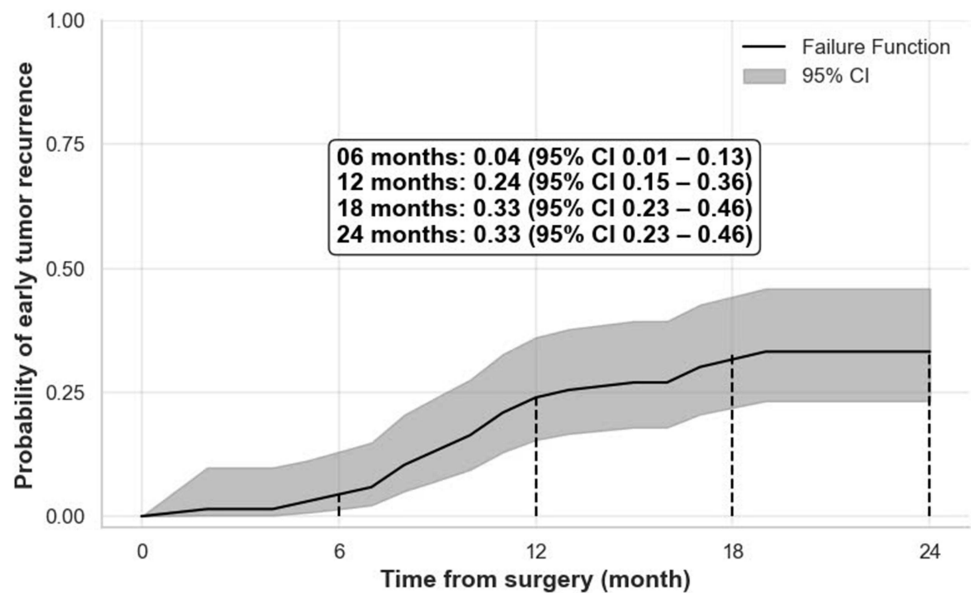


Figure 2 Probability of tumor recurrence in patients after HCC surgery.

Histopathological Features

The histopathological characteristics of the tumor and non-tumor liver tissue are presented in Table 2. Tumor size >5 cm was observed in approximately 25% of cases and were significantly associated with early recurrence (HR = 3.24, 95% CI = 1.38–8.00, $p = 0.007$). Conventional HCC histology was predominant, with over 70% of cases lacking adverse histological features such as necrosis and high mitotic rate. Most HCCs developed in cirrhotic livers, with a significant percentage of hepatitis. HCV-infected patients had a higher tendency to develop cirrhosis (89.5% vs 61.5%, $p = 0.059$). However, non-tumor liver characteristics were not associated with early recurrence.

Table 1 The Association Between Clinical Features and Early Tumor Recurrence in Surgery HCC Patients

Factors	Total n (%)	Tumor Recurrence			
		Yes (n = 22) n (%)	No (n = 47) n (%)	HR (95 CI)	p
Age (Year)					
Mean (SD)	56.9 ± 12.8	55.1 ± 12.7	60.9 ± 12.4	1.03 (1.00–1.07)	0.071
≥ 65	19 (27.5)	9 (40.9)	10 (21.3)	2.07 (0.88–4.85)	0.094
< 65	50 (72.5)	13 (59.1)	37 (78.7)	I	
Sex					
Female	15 (21.7)	6 (27.3)	9 (19.2)	1.55 (0.60–3.95)	0.363
Male	54 (78.3)	16 (72.7)	38 (80.8)	I	
ALBI score					
Mean (SD)	−2.7 ± 0.4	−2.7 ± 0.4	− 2.7 ± 0.4	1.07 (0.33–3.44)	0.915
> −2.6	23 (33.8)	7 (31.8)	16 (34.8)	0.90 (0.37–2.21)	0.821
≤ −2.6	45 (66.2)	15 (68.2)	30 (65.2)	I	
Hb (g/dL)					
Mean (SD)	14.3 ± 1.5	14.3 ± 1.6	14.3 ± 1.2	1.00 (0.97–1.02)	0.820
> 11.4	44 (93.6)	22 (100)	44 (93.6)		
≤ 11.4	3 (6.4)	0	3 (6.4)		

(Continued)

Table 1 (Continued).

Factors	Total n (%)	Tumor Recurrence			
		Yes (n = 22) n (%)	No (n = 47) n (%)	HR (95 CI)	p
WBC (G/L)					
Mean (SD)	8.9 ± 4.3	8.6 ± 4.3	9.4 ± 4.2	1.02 (0.94–1.11)	0.627
> 8.65	24 (34.8)	11 (50.0)	13 (27.7)	1.49 (0.80–2.76)	0.206
≤ 8.65	45 (65.2)	11 (50.0)	34 (72.3)	1	
PLT (G/L)					
Mean (SD)	213.2 ± 68.4	211.0 ± 75.1	218.0 ± 52.7	1.00 (0.99–1.01)	0.710
> 225	22 (31.9)	8 (36.4)	14 (29.8)	1.20 (0.50–2.87)	0.677
≤ 225	47 (68.1)	14 (63.6)	33 (70.2)	1	
GGT (U/L)					
Mean (SD)	87.0 ± 65.6	84.5 ± 66.0	93.3 ± 67.5	1.00 (0.99–1.01)	0.975
> 50	24 (63.2)	7 (63.6)	17 (63.0)	1.09 (0.32–3.73)	0.891
≤ 50	14 (36.8)	4 (36.4)	10 (37.0)	1	
PT (s)					
Mean (SD)	12.6 ± 1.1	12.7 ± 1.1	12.5 ± 1.3	0.85 (0.59–1.26)	0.434
> 13	27 (40.3)	8 (38.1)	19 (41.3)	0.83 (0.34–1.99)	0.672
≤ 13	40 (59.7)	13 (61.9)	27 (58.7)	1	
AST (U/L)					
Median (IQR)	36.0 (27.0–53.5)	37.5 (26.2–64.8)	35.5 (29.2–46.5)	1.00 (1.00–1.01)	0.508
> 90	10 (14.7)	3 (13.6)	7 (15.2)	0.82 (0.24–2.76)	0.744
≤ 90	58 (85.3)	19 (86.4)	39 (84.8)	1	
ALT (U/L)					
Median (IQR)	35.5 (23.0–50.2)	28.5 (18.8–61.8)	36.5 (24.0–50.0)	1.00 (1.00–1.01)	0.380
> 60	13 (19.1)	6 (27.3)	7 (15.2)	1.48 (0.58–3.79)	0.412
≤ 60	55 (80.9)	16 (72.7)	39 (84.8)	1	
AFP (ng/mL)					
Median (IQR)	10.5 (3.7–217.2)	8.7 (2.3–10.9)	34.5 (4.5–489.8)	1.00 (1.00–1.00)	0.360
> 200	8 (25.0)	1 (10.0)	7 (31.8)	0.29 (0.04–2.32)	0.245
≤ 200	24 (75.0)	9 (90.0)	15 (68.2)	1	
HBsAg					
Positive	44 (74.6)	11 (64.7)	33 (78.6)	0.54 (0.20–1.47)	0.230
Negative	15 (25.4)	6 (35.3)	9 (21.4)	1	
Anti-HCV					
Positive	19 (32.8)	9 (47.4)	10 (25.6)	2.21 (0.89–5.44)	0.080
Negative	39 (67.2)	10 (52.6)	29 (74.4)	1	
BCLC stage					
B/C	19 (28.8)	12 (54.5)	7 (15.9)	4.23 (1.82–9.87)	<0.001
0/A	47 (71.2)	10 (45.5)	37 (84.1)	1	
Preoperative treatment					
Yes	3 (4.3)	2 (9.1)	1 (2.1)	2.70 (0.91–7.22)	0.073
No	66 (95.7)	20 (90.9)	46 (97.9)	1	

Note: Bold values indicate statistical significance at $p < 0.05$.

Abbreviations: ALBI, Albumin – Bilirubin; Hb, Hemoglobin; WBC, White Blood Cells; PLT, Platelets; GGT, Gamma-Glutamyl Transpeptidase; PT, Prothrombin Time; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; AFP, Alpha Fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Multivariate Analysis

Based on findings from [Tables 1](#) and [2](#), multivariate analysis was conducted to include patient age, HCV infection, BCLC stage, preoperative treatment, and tumor size. Preoperative treatment was the strongest predictor of early recurrence (HR = 8.63, 95% CI = 1.45–51.38, $p = 0.018$). Other independent risk factors included HCV infection (HR = 4.61, 95% CI =

Table 2 The Association Between Clinical Characteristics and Early Tumor Recurrence in Surgery HCC Patients

Factors	Total n (%)	Tumor Recurrence			
		Yes (n = 22) n (%)	No (n = 47) n (%)	HR (95% CI)	p
Tumor size (cm)					
Mean (SD)	3.8 ± 2.4	3.4 ± 2.3	4.6 ± 2.5	1.14 (1.01–1.28)	0.033
≥ 5	16 (23.2)	9 (40.9)	7 (14.9)	3.24 (1.38–8.00)	0.007
< 5	53 (76.8)	13 (59.1)	40 (85.1)	1	
HCC Subtype					
Conventional HCC	46 (66.7)	17 (77.3)	29 (61.7)	1	
Other subtypes	23 (33.3)	5 (22.7)	18 (38.3)	0.62 (0.23–1.67)	0.344
Tumor grade					
Grade 3–4	34 (49.3)	13 (59.1)	21 (44.7)	1.53 (0.65–3.57)	0.330
Grade 1–2	35 (50.7)	9 (40.9)	26 (55.3)	1	
Tumor necrosis					
Yes	16 (23.2)	4 (18.2)	12 (25.5)	0.75 (0.25–2.23)	0.609
No	53 (76.8)	18 (81.8)	35 (74.5)	1	
Mitotic count					
Median (IQR)	2.0 (1.0–5.0)	3.0 (2.0–4.0)	2.0 (1.0–6.0)	0.98 (0.90–1.06)	0.542
≥ 5	19 (27.5)	5 (22.7)	14 (29.8)	0.81 (0.30–2.19)	0.672
< 5	50 (72.5)	17 (77.3)	33 (70.2)	1	
HAI score					
Mean (SD)	9.8 ± 2.4	9.9 ± 2.5	9.8 ± 2.2	0.97 (0.82–1.15)	0.749
> 8	50 (72.5)	14 (63.6)	36 (76.6)	0.59 (0.25–1.40)	0.232
≤ 8	19 (27.5)	8 (36.4)	11 (23.4)	1	
Liver cirrhosis					
Yes	50 (72.5)	15 (68.2)	35 (74.5)	0.72 (0.29–1.77)	0.473
No	19 (27.5)	7 (31.8)	12 (25.5)	1	
Liver steatosis					
Moderate – Severe	12 (17.4)	5 (22.7)	7 (14.9)	1.37 (0.50–3.71)	0.540
No – Mild	57 (82.6)	17 (77.3)	40 (85.1)	1	

Note: Bold values indicate statistical significance at $p < 0.05$.

Abbreviations: HCC, Hepatocellular Carcinoma; HAI, Histology Activity Index.

1.41–15.1, $p = 0.012$) and tumor size >5 cm (HR = 3.82, 95% CI = 1.17–12.42, $p = 0.026$). Although BCLC stage was statistically significant in the univariate analysis (HR = 4.23, $p < 0.001$), it did not remain significant in the multivariate model (HR = 2.66, 95% CI = 0.96–7.39, $p = 0.061$) (Figure 3).

Discussion

Although microscopic vascular invasion (MVI) is a well-established predictor of early HCC recurrence,^{14–16} HCC patients without MVI may also have high risk of early recurrence. In this study, nearly one third of HCC patients without MVI had early recurrence, mostly between 6- and 18-month post-surgery. Independent prognostic factors were HCV infection, tumor size >5 cm, and preoperative local/regional treatment. Our findings align with prior studies. Sumie et al reported a 27.7% early recurrence rate in MVI-negative patients, with no recurrences in the first few months after the surgery, unlike MVI-positive patients who experienced rapid recurrence.¹⁷ Yu et al found a higher recurrence rate of 41.8% in MVI-negative patients, with over 20% recurring within three months.¹⁸ However, it should be noted that while Sumie's and our study's MVI status was assessed by a pathologist, Yu's study relied solely on information from the pathology report form and excluded cases where the MVI status was not reported.

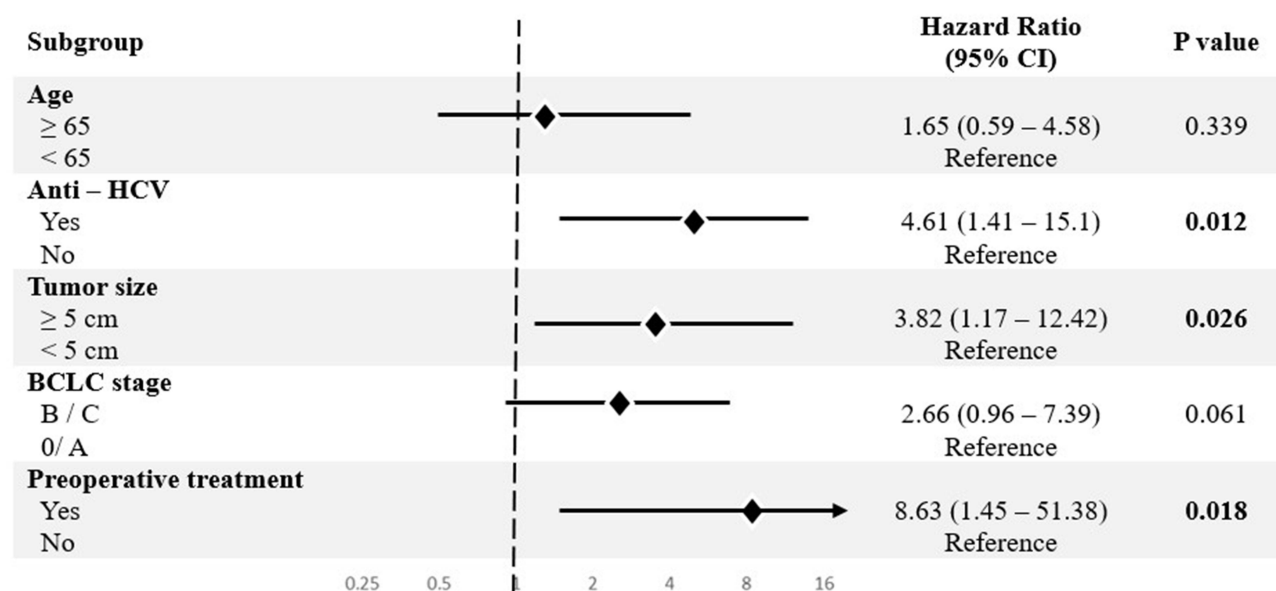


Figure 3 Multivariable Cox regression of factors independently associated with tumor recurrence.

Previous studies have shown that HCV infection is one of the significant risk factors for HCC development.¹⁹ In our study, HCV infection was identified as an independent risk factor for early recurrence among MVI-negative patients. This suggests that HCV may contribute directly to tumor recurrence through mechanisms beyond liver cirrhosis alone. Indeed, HCV-positive patients in our cohort had a higher prevalence of cirrhosis, which may partially mediate this association. However, chronic HCV infection itself has been implicated in hepatocarcinogenesis through sustained inflammation, immune evasion, and genomic instability.^{20,21} Previous studies have also raised concerns about recurrence risk following direct-acting antiviral (DAA) therapy, though this remains controversial.^{22,23} As we did not collect treatment data, we were unable to assess the potential impact of antiviral therapy in our cohort. Further studies incorporating both virological and treatment-related variables are needed to clarify the role of HCV in post-surgical recurrence. Tumor size is a well-known predictor of recurrence and survival in HCC patients. Larger tumors are associated with increased recurrence risk due to higher rates of poor differentiation, genetic alterations, and positive resection margins.^{24,25} In this study, tumor size >5 cm was identified as an independent risk factor for early recurrence (HR = 3.82, 95% CI = 1.17–12.42, $p = 0.026$). This result is consistent with Yu et al, who demonstrated a significant correlation between tumor size >5 cm and early recurrence (HR = 1.584, 95% CI = 1.295–1.937, $p < 0.001$).¹⁸ Conversely, Zhang et al found that while larger tumors were associated with recurrence, tumor size was not an independent prognostic factor.²⁴ Shehta et al also highlighted the increased likelihood of positive surgical margins in larger tumors, rising from 9.1% in tumors <5 cm to 23.3% in tumors >10 cm.²⁵ Due to the retrospective nature of our data and financial constraints, a comprehensive evaluation of tumor margin status was not feasible.

In our study, although only three patients received preoperative treatment, this was significantly increased recurrence risk. Preoperative interventions, such as trans-arterial chemoembolization (TACE) and radiofrequency ablation (RFA), may influence tumor biology by altering the microenvironment, increasing inflammatory cytokines (IL6, Th2), and promoting tumor progression through hypoxia-induced signaling pathways.^{26,27} Additionally, TACE/RFA selectively targets well-differentiated tumor cells, potentially leading to the survival of more aggressive tumor clones and the vascular dissemination of cancer cells may occur before treatment.^{28,29} Delays in surgery following preoperative treatment may also contribute to higher recurrence rates.³⁰ On the other hand, a meta-analysis by Zhou et al found no significant difference in recurrence or five-year survival between patients with and without preoperative TACE (32.1% vs 30.0%, $P = 0.17$; 40.2% vs 45.2%, $p = 0.37$, respectively).³¹ Although our analysis suggested an association between preoperative TACE/RFA and early recurrence, the number of patients who received this treatment in our cohort was limited. Therefore, the result should be interpreted with caution. Further studies with larger sample sizes are warranted to

confirm this finding and clarify the role of preoperative locoregional therapy in recurrence risk. Our findings highlight the importance of close monitoring of MVI-negative HCC patients, particularly during the high-risk period of 6–18 months after surgery. Preoperative TACE/RFA in surgically resectable cases, may negatively impact outcomes and should be considered with caution. Additionally, HCV status and tumor size should be factored into individualized treatment strategies. However, this study has several limitations. First, as a retrospective analysis, comprehensive clinical data were not available for all patients. Second, MVI assessment is highly dependent on grossing and histological evaluation, which may introduce variability. Third, the relatively small sample size may limit the statistical power and generalizability of our results. Fourth, surgical margin status, a factor potentially associated with early recurrence, was not evaluated in our study due to limitations in histological documentation and retrospective data collection.

Conclusion

Early tumor recurrence in MVI-negative HCC was prevalent. This study identified HCV infection, tumor size, and preoperative treatment as independent factors influencing recurrence. Future prospective studies are needed to refine recurrence prediction models and optimize therapeutic approaches for MVI-negative HCC patients.

Ethical Approval

This study was approved by the ethics committee of University of Medicine and Pharmacy at Ho Chi Minh City (Approval number: 701/HĐĐĐ-ĐHYD, dated September 20, 2022). As this retrospective cohort study utilized de-identified patient data from an electronic system and involved no direct contact with participants, the requirement for informed consent was waived by the ethics committee. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Rumgay H, Ferlay J, de Martel C, et al. Global, regional and national burden of primary liver cancer by subtype. *Eur J Cancer*. 2022;161:108–118. doi:10.1016/j.ejca.2021.11.023
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA*. 2018;68(6):394–424. doi:10.3322/caac.21492
3. Suraweera D, Konyn P, Vu T, Saab S. Clinical epidemiology of chronic liver disease: hepatocellular carcinoma. In: Wong RJ, Gish RG, editors. *Clinical Epidemiology of Chronic Liver Diseases*. Cham: Springer International Publishing; 2019:229–249.
4. Raja A, Haq F. Molecular classification of hepatocellular carcinoma: prognostic importance and clinical applications. *J Cancer Res Clin Oncol*. 2022;148(1):15–29. doi:10.1007/s00432-021-03826-w
5. Abdelhamed W, El-Kassas M. Hepatocellular carcinoma recurrence: predictors and management. *Liver Res*. 2023;7(4):321–332. doi:10.1016/j.livres.2023.11.004

6. Nevola R, Ruocco R, Criscuolo L, et al. Predictors of early and late hepatocellular carcinoma recurrence. *World J Gastroenterol.* 2023;29(8):1243–1260. doi:10.3748/wjg.v29.i8.1243
7. Mao S, Yu X, Yang Y, et al. Preoperative nomogram for microvascular invasion prediction based on clinical database in hepatocellular carcinoma. *Sci Rep.* 2021;11(1):13999. doi:10.1038/s41598-021-93528-7
8. Wang W, Guo Y, Zhong J, et al. The clinical significance of microvascular invasion in the surgical planning and postoperative sequential treatment in hepatocellular carcinoma. *Sci Rep.* 2021;11(1):2415. doi:10.1038/s41598-021-82058-x
9. Zheng Z, Guan R, Jianxi W, et al. Microvascular invasion in hepatocellular carcinoma: a review of its definition, clinical significance, and comprehensive management. *J Oncol.* 2022;2022:9567041. doi:10.1155/2022/9567041
10. Lee HA, Lee YS, Kim BK, et al. Change in the recurrence pattern and predictors over time after complete cure of hepatocellular carcinoma. *Gut Liver.* 2021;15(3):420–429. doi:10.5009/gnl20101
11. Cha DI, Ahn SH, Lee MW, et al. Risk group stratification for recurrence-free survival and early tumor recurrence after radiofrequency ablation for hepatocellular carcinoma. *Cancers.* 2023;15(3):687. doi:10.3390/cancers15030687
12. Lokuhetty D, White VA, Watanabe R, Cree IA, World Health O; International Agency for Research on C. *Digestive System Tumours.* Fifth edition ed. International Agency for Research on Cancer Lyon: Lyon; 2019.
13. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol.* 1995;22(6):696–699. doi:10.1016/0168-8278(95)80226-6
14. Xing H, Zhang WG, Cescon M, et al. Defining and predicting early recurrence after liver resection of hepatocellular carcinoma: a multi-institutional study. *HPB.* 2020;22(5):677–689. doi:10.1016/j.hpb.2019.09.006
15. Jung SM, Kim JM, Choi GS, et al. Characteristics of early recurrence after curative liver resection for solitary hepatocellular carcinoma. *J Gastrointestinal Surg.* 2019;23(2):304–311. doi:10.1007/s11605-018-3927-2
16. Hong YM, Cho M, Yoon KT, et al. Risk factors of early recurrence after curative hepatectomy in hepatocellular carcinoma. *Tumour Biol.* 2017;39(10):1010428317720863. doi:10.1177/1010428317720863
17. Sumie S, Kuromatsu R, Okuda K, et al. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. *Ann Surg Oncol.* 2008;15(5):1375–1382. doi:10.1245/s10434-008-9846-9
18. Yu Y, Wang XH, Hu WJ, Chen DH, Hu ZL, Li SQ. Patterns, risk factors, and outcomes of recurrence after hepatectomy for hepatocellular carcinoma with and without microvascular invasion. *J Hepatocell Carcinoma.* 2024;11:801–812. doi:10.2147/JHC.S438850
19. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nature Reviews Disease Primers.* 2021;7(1):6. doi:10.1038/s41572-020-00240-3
20. Hung J-H, Teng C-F, Hung H-C, et al. Genomic instabilities in hepatocellular carcinoma: biomarkers and application in immunotherapies. *Ann Hepatol.* 2024;29(6). doi:10.1016/j.aohp.2024.101546
21. Vescovo T, Refolo G, Vitagliano G, Fimia GM, Piacentini M. Molecular mechanisms of hepatitis C virus–induced hepatocellular carcinoma. *Clin Microbiol Infect.* 2016;22(10):853–861. doi:10.1016/j.cmi.2016.07.019
22. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol.* 2016;65(4):727–733. doi:10.1016/j.jhep.2016.06.015
23. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol.* 2016;65(4):719–726. doi:10.1016/j.jhep.2016.04.008
24. Zhang H, Yuan SX, Dai SY, et al. Tumor size does not independently affect long-term survival after curative resection of solitary hepatocellular carcinoma without macroscopic vascular invasion. *World J Surg.* 2014;38(4):947–957. doi:10.1007/s00268-013-2365-2
25. Shehta A, Elsabbagh AM, Medhat M, et al. Impact of tumor size on the outcomes of hepatic resection for hepatocellular carcinoma: a retrospective study. *BMC Surg.* 2024;24(1):7. doi:10.1186/s12893-023-02296-w
26. Kim MJ, Jang JW, Oh BS, et al. Change in inflammatory cytokine profiles after transarterial chemotherapy in patients with hepatocellular carcinoma. *Cytokine.* 2013;64(2):516–522. doi:10.1016/j.cyto.2013.07.021
27. Wang Z, Li Q, Liang B. Hypoxia as a target for combination with transarterial chemoembolization in hepatocellular carcinoma. *Pharmaceuticals.* 2024;17(8):1057. doi:10.3390/ph17081057
28. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology.* 1998;27(6):1578–1583. doi:10.1002/hep.510270617
29. Ikeda K, Saitoh S, Tsubota A, et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. *Cancer.* 1993;71(1):19–25. doi:10.1002/1097-0142(19930101)71:1<19::aid-cnrcr2820710105>3.0.co;2-i
30. Wu CC, Ho YZ, Ho WL, Wu TC, Liu TJ, P'Eng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. *Br J Surg.* 1995;82(1):122–126. doi:10.1002/bjs.1800820141
31. Zhou Y, Zhang X, Wu L, et al. Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patients with resectable hepatocellular carcinoma. *BMC Gastroenterol.* 2013;13(1):51. doi:10.1186/1471-230X-13-51