Clinical and Translational Oncology (2026) 28:215–228
https://doi.org/10.1007/s12094-025-03981-3

RESEARCH ARTICLE

Tumor size larger than 6.5 cm and microvascular invasion are comparable prognosticators for hepatocellular carcinoma: a multi-institutional observational study

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Received: 11 May 2025 / Accepted: 16 June 2025 / Published online: 10 July 2025

Abstract

Background Recent study showed that T1 hepatocellular carcinoma (HCC) > 6.5 cm had survivals comparable to T2 tumors. Nevertheless, the differential impact between tumor size > 6.5 cm and microvascular invasion (mVI) on survival of HCC was rarely discussed. The current study aimed to compare the specific impact of tumor size > 6.5 cm and mVI on the survival outcome of HCC after liver resections.

Methods Operated HCC patients were identified from the Chang Gung Research Database (CGRD), and the patients with T1bN0M0 or pT2N0M0 tumors were enrolled. The survivals of patients with either tumor size > 6.5 cm, mVI, or multiple tumors were compared.

Results From 2002 to 2018, a total of 3449 patients who underwent surgery for T1bN0M0 or T2N0M0 HCC were identified from the CGRD. After excluding cases who died within 30 days of surgery (n = 31), Kaplan–Meier survival analysis discovered that tumor > 6.5 cm without mVI had survivals similar to those of solitary tumor > 2 cm with mVI. Cox regression multivariate analysis further demonstrated that tumor size > 6.5 cm and mVI were independent poor prognostic factors for both mortality and tumor recurrence after surgery. Subgroup analysis further discovered that the presence of both tumor size > 6.5 cm and mVI substantially compromised survivals after liver resection.

Conclusion Our study demonstrated that tumor size larger than 6.5 cm and mVI are comparable prognosticators for HCC. In addition, the presence of these two adverse factors significantly worsens HCC survival outcomes compared to the presence of either factor alone. Further studies are warranted to validate our findings.

Keywords Chang Gung research database · Hepatocellular carcinoma · Hepatoma · Liver resection · Microvascular invasion · Prognosis · Tumor size > 6.5 cm

Abbreviations

AASLD	American association for the study of liver diseases
AFP	α-Fetoprotein
aHR	Adjusted HR
AJCC	American joint committee on cancer
ALBI	Albumin-bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APASL	Asian pacific association for the study of the liver
BCLC	Barcelona clinic liver cancer
CGMH	Chang Gung memorial hospital
CGRD	Chang Gung research database
CI	Confidence interval
DFS	Disease-free survival
EASL	European association for the study of the liver
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICD-9-CM	International classification of diseases, 9th revision, clinical modification
ICD-10-CM	International classification of diseases, 10th revision, clinical modification
ICD-O-3	International classification of diseases for oncology, 3rd edition
ICG-15	Indocyanine green retention test at 15 min

Extended author information available on the last page of the article

IDI	Integrated discrimination improvement
INR	International normalize ratio
IRB	Institutional review board
mVI	Microvascular invasion
NLR	Neutrophil to lymphocyte ratio
NRI	Net reclassification improvement
OS	Overall survival
PNI	Prognostic nutritional index
SD	Standard deviation
TLCA	Taiwan liver cancer association
TNM	Tumor/node/metastasis

Introduction

Hepatocellular carcinoma (HCC) is a fatal malignancy and ranks as the sixth most prevalent cancer globally [1, 2]. It results in over 7300 fatalities in Taiwan on a yearly basis [3]. While surgical resection has proven to be an efficient treatment for specific patients, merely 30–40% of individuals qualify for hepatectomy at the time of diagnosis [4]. Despite notable improvements in surveillance programs, diagnostic methods, surgical procedures, and postoperative management, the recurrence rate of HCC following curative treatment remains relatively high. Approximately 60% of patients experience HCC relapse after curative treatment, and tumor recurrence further complicates overall long-term survival [5, 6]. Given the low resectability rate and high recurrence rate, it is paramount to ascertain prognostic factors capable of predicting tumor relapse and survival following liver resection. Individuals deemed at elevated risk for recurrence or worse prognosis may undergo neoadjuvant therapy, rigorous postoperative monitoring, or novel adjuvant therapy to prevent or detect recurrence at an earlier stage, thereby enhancing the likelihood of prolonged survival.

Numerous efforts have been made to search for risk factors associated with HCC recurrence and worse survival [7]. Among them, vascular invasion (VI) has been demonstrated as the most robust indicator for tumor recurrence/progression and overall survival. The American Joint Committee on Cancer (AJCC) Tumor/Node/Metastasis (TNM) staging manual therefore incorporated both microvascular invasion (mVI) and macrovascular invasion (MVI) into the latest 8th edition of HCC staging system [8, 9]. However, this edition did not consider the influence of tumor size on the outcome of HCC. Previous studies have demonstrated that tumor diameter, in addition to vascular invasion, was also an important prognostic factor for HCC [10–15]. Our recent study further identified that a solitary tumor > 6.5 cm without mVI, although categorized as a T1b disease based on the AJCC 8th edition, had survival outcomes compatible with those of T2 tumors [16]. These findings imply that tumor size is indeed a significant prognostic factor and should be assessed alongside mVI during routine practice. Nevertheless, the differential impact between tumor size > 6.5 cm and mVI on the survival outcome of HCC was rarely discussed. The current study, as a result, aimed to compare the specific impact of tumor size > 6.5 cm and mVI on the survival outcome of HCC after liver resections.

Material and methods

Data source

The study utilized the Chang Gung Research Database (CGRD), a comprehensive repository of electronic medical records maintained by Chang Gung Memorial Hospital (CGMH) across multiple medical centers and hospitals in Taiwan. Initially established for administrative and insurance purposes, the CGRD provides detailed data on patient demographics, diagnoses, treatments, and outcomes, encompassing a significant portion of Taiwan's healthcare services. It includes extensive records from outpatient, emergency, and inpatient visits. A notable feature of the CGRD is its cancer registry, which contains meticulously curated data on diagnoses, staging, treatment modalities, recurrence, and mortality. All entries in the cancer registry are manually verified, ensuring high reliability [17]. Both the International Classification of Diseases, 9th and 10th revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes and the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) are used in the CGRD. For personal privacy, individual identities are protected by encryption. The medical information is prospectively digitized and stored in the CGRD and is amenable to researchers conducting large-scale retrospective analysis. This level of accuracy and comprehensiveness makes the CGRD an invaluable resource for clinical research [14, 18, 19]. The database's extensive coverage of Taiwan's medical landscape—encompassing 20% of all cancer patient data and approximately 34% of outpatient information—further highlights its utility as a robust resource for healthcare research.

Study design and population

Figure 1 illustrates the study flow chart. From January 2002 to December 2018, a total of 36,470 patients diagnosed with HCC were identified from the CGRD. Among them, 5583 patients underwent liver resection for their HCC. After excluding patients who were not pT1N0M0 or pT2N0M0 disease (n = 1242), who had a solitary tumor ≤ 2 cm (n = 890), who had an incorrect Child–Pugh score (n = 2), and who died within 30 days of surgery (n = 31), a total of 3418 patients were identified. Among them, 496 patients were found to have multiple tumors none greater than 5 cm

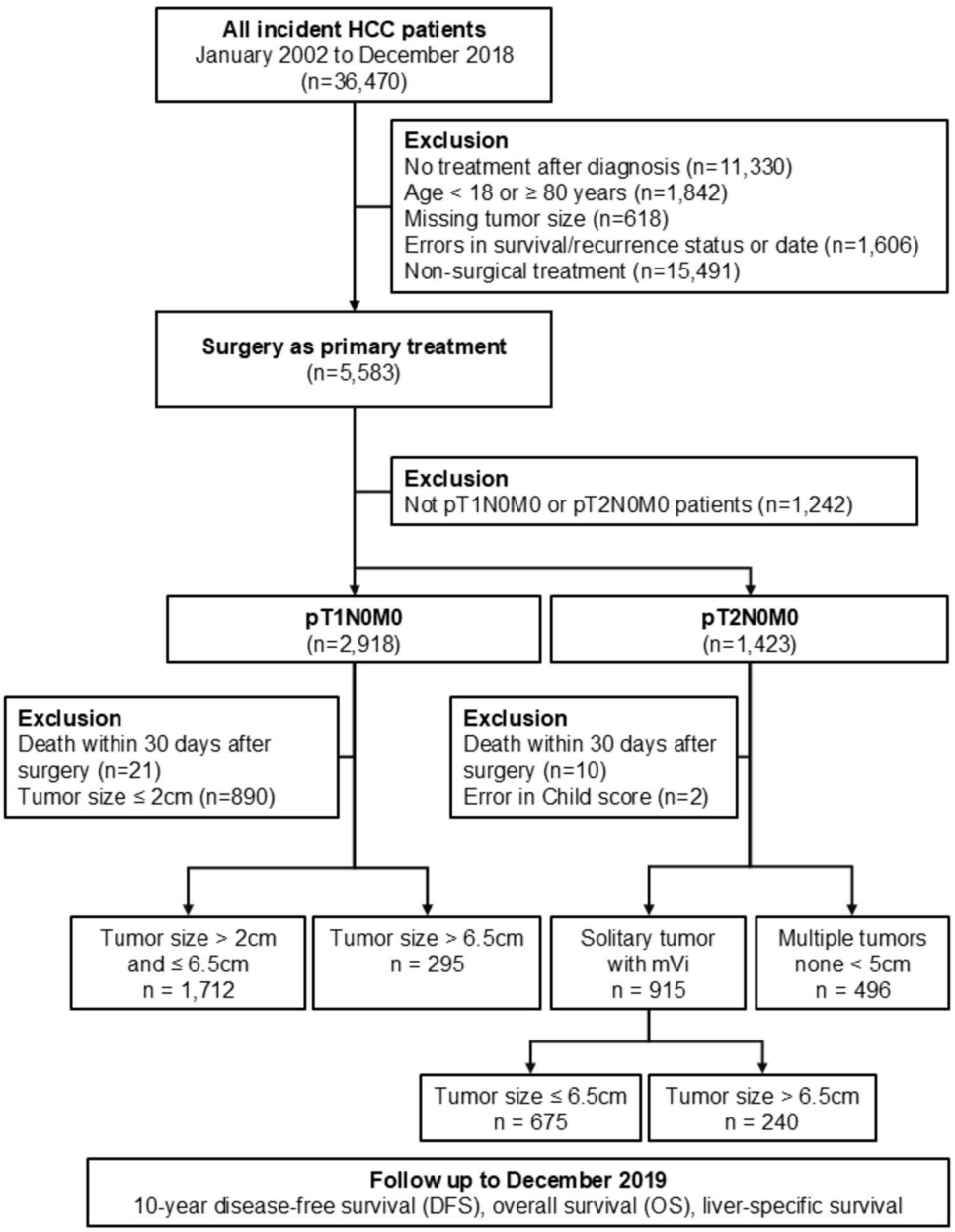

Fig. 1 Flow diagram of the current study. HCC patients diagnosed from 2002 to 2018 were retrieved from the CGRD database (n = 36,470). Those who received non-surgical treatment, who had missing data, who were not pT1N0M0 or pT2N0M0 disease, who had solitary tumor ≤ 2 cm, who had incorrect Child–Pugh score, and who died within 30 days of surgery were excluded from further analysis. The survivals of 496 patients who had multiple tumors none greater than 5 cm in diameter were then compared with the remaining 2922 patients who had solitary HCC larger than 2 cm

in diameter. The survival outcomes of these patients were then compared with those of the remaining 2922 patients who had solitary HCC larger than 2 cm. This cohort of 2922 patients was further analyzed based on tumor size and the presence of mVI. For tumor size, we adopted a cutoff value of 6.5 cm based on a previous report indicating that T1b tumors larger than 6.5 cm were associated with significantly worse survival outcomes compared to smaller T1b tumors [16]. The survivals of these tumors were, in contrast, similar to those of T2 tumors. The specific impact of tumor size > 6.5 cm and mVI on survival outcomes in HCC was subsequently examined. This study was approved by the Institutional Review Board of CGMH (IRB No: 201900800B0C501).

Outcome assessment and statistical analysis

Overall survival (OS) was adopted as the primary outcome while disease-free survival (DFS) and liver-specific survival were adopted as the secondary outcomes in the current study. The first date of definitive diagnosis of HCC, defined as the date of surgery in the current study, was designated as the index date. DFS was defined as the period between the index date and the date of the first documented clinical recurrence or the end of the year 2019. OS was defined as the duration between the index date and the date of all-cause mortality or the end of the year 2019. Liver-specific survival spanned the period between the index date and the date of liver-related mortality or

the end of the year 2019. The liver-related causes encompassed tumor recurrence, metastasis, and decompensated liver cirrhosis related to HCC progression.

The demographic characteristics were described as means with standard deviations (SD) for continuous variables and numbers with percentages for categorical variables. Kaplan–Meier analysis was conducted to estimate the 10-year overall survival (OS), disease-free survival (DFS), and liver-specific survival. Next, univariate and multivariate Cox regression analyses were performed to determine the crude and adjusted hazard ratios (aHRs) of individual prognostic covariates, including tumor size > 6.5 cm and mVI. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were carried out to investigate the predictive capability of combining tumor size > 6.5 cm and mVI for all-cause mortality and tumor recurrence after liver resection for solitary HCC. The freeware Konstanz information miner (KNIME) and the commercial statistical software STATA (StataCorp. 2019. Stata Statistical Software: release 16. College Station, TX: StataCorp LLC) were employed to process and analyze the data [20]. All statistics with *P*-values < 0.05 were regarded as statistically significant.

Results

Patient demographics

The baseline characteristics of 2922 subjects who had solitary HCC larger than 2 cm were summarized in Table 1. Stratified by the tumor size, 2387 patients had tumor ≤ 6.5 cm, and 535 patients had tumor > 6.5 cm. The majority of patients were male (78.4%) with similar distribution across both size groups ($P = 0.42$). More than 50% of the patients were over 60 years ($P = 0.10$). The prevalence of diabetes and hypertension was comparable between the two groups ($P = 0.14$ and 0.091, respectively). While HBV infection accounted for nearly 50% of patients in both size groups, there was significantly more HCV infection when the tumors were ≤ 6.5 cm (24.2% *vs.* 8.6%, $P < 0.001$). The presence of liver cirrhosis was also higher in patients with smaller tumors (47.6% *vs.* 23.6%, $P < 0.001$). The occurrence of mVI, on the other hand, was significantly more frequent in tumors > 6.5 cm (44.9% *vs.* 28.3%, $P < 0.001$). Biochemical profiles revealed significantly higher α-fetoprotein (AFP) levels and liver function indicators in the > 6.5 cm group, including elevated AST, ALT, and albumin-bilirubin (ALBI) grade ($P < 0.001$, $P = 0.005$, and $P < 0.001$ respectively). The nutritional and inflammatory markers were both unfavorable in the > 6.5 cm group (all $P < 0.001$).

Survival outcome

Figure 2 illustrated the Kaplan–Meier OS curves of patients with either solitary tumor > 6.5 cm without mVI, solitary tumor > 2 cm with mVI, or multiple tumors none greater than 5 cm in diameter. The median follow-up duration was 51.4 months, and the median OS for these three groups were 115.5, 107.5, and 90.7 months, respectively (overall log-rank test, $P = 0.231$). There was no significant difference between individual groups in terms of OS (Fig. 2A). As for liver-specific survival, while there was no difference between solitary tumor > 6.5 cm without mVI and solitary tumor > 2 cm with mVI (median survivals both not reached, $P = 0.244$), the median survival of solitary tumor > 6.5 cm without mVI was significantly longer than that of multiple tumors none greater than 5 cm (not reached *vs.* 119.0 months, $P = 0.043$). The liver-specific survival was comparable between solitary tumor > 2 cm with mVI and multiple tumors none greater than 5 cm ($P = 0.213$) (Fig. 2B). The Kaplan–Meier DFS curves were further depicted in Fig. 2C. The estimated DFS was comparable between solitary tumor > 6.5 cm without mVI and solitary tumor > 2 cm with mVI (median DFS 50.7 and 51.9 months, respectively, $P = 0.548$). Nevertheless, the DFS was significantly impaired in patients with multiple tumors none greater than 5 cm in diameter (median DFS 29.2 months, $P = 0.001$ against solitary tumor > 6.5 cm without mVI and < 0.001 against solitary tumor > 2 cm with mVI).

Risk factors for mortality and tumor recurrence

Table 2 summarized risk factors for all-cause mortality after hepatectomy for solitary HCC larger than 2 cm. Multivariate analysis demonstrated that mVI (adjusted hazard ratio [aHR]: 1.65, 95% CI 1.27–2.15, $P < 0.001$), tumor size > 6.5 cm (aHR: 1.53, 95% CI 1.11–2.09, $P = 0.009$), male gender (aHR: 1.79, 95% CI 1.36–2.37, $P < 0.001$), age ≥ 65 years (aHR: 1.80, 95% CI 1.37–2.37, $P < 0.001$), cirrhosis (aHR: 1.46, 95% CI 1.12–1.92, $P = 0.006$), hemoglobin ≤ 10 g/dL (aHR: 2.31, 95% CI 1.51–3.54, $P < 0.001$), and platelet count ≤ 100×10^3/uL (aHR: 1.54, 95% CI 1.03–2.32, $P = 0.038$) were independent poor prognostic factors for all-cause mortality after surgery. Additionally, an ALBI grade of II/III was associated with higher mortality risk compared to grade I (aHR: 1.72, 95% CI 1.21–2.47, $P = 0.003$).

Similarly, the independent prognostic factors associated with liver-specific mortality included mVI (aHR: 1.67, 95% CI 1.23–2.27, $P = 0.001$), tumor size > 6.5 cm (aHR: 1.66, 95% CI 1.16–2.39, $P = 0.006$), male gender (aHR: 1.72, 95% CI 1.14–2.58, $P = 0.009$), age ≥ 65 years (aHR: 1.47, 95% CI 1.07–2.03, $P = 0.019$), cirrhosis (aHR: 1.58, 95% CI 1.15–2.15, $P = 0.004$), hemoglobin ≤ 10 g/dL (aHR: 3.00,

Table 1 Baseline characteristics of subjects with solitary hepatocellular carcinoma (HCC) larger than 2 cm undergoing liver resections

	Total (n = 2922)	≤ 6.5 cm (n = 2387)	> 6.5 cm (n = 535)	p-value
Demographics				
Gender (n,(%))				
Female	632 (21.6%)	523 (21.9%)	109 (20.3%)	0.42
Male	2291 (78.4%)	1864 (78.1%)	426 (79.6%)	
Age group (n,(%))				
−40	211 (7.2%)	161 (6.7%)	50 (9.3%)	0.10
41–60	1226 (41.9%)	1011 (42.4%)	215 (40.1%)	
61-	1486 (50.8%)	1215 (50.9%)	270 (50.5%)	
DM (n,(%))	746 (25.5%)	623 (26.1%)	123 (23.0%)	0.14
Hypertension (n,(%))	1108 (37.9%)	888 (37.2%)	220 (41.1%)	0.091
Chronic hepatitis (n,(%))				**< 0.001**
HBV	1428 (48.9%)	1169 (49.0%)	259 (48.4%)	
HCV	624 (21.3%)	578 (24.2%)	46 (8.6%)	
HBV + HCV	156 (5.3%)	131 (5.5%)	25 (4.7%)	
Lifestyles (n,(%))				
Cigarette smoking	331 (11.3%)	272 (11.4%)	59 (11.0%)	0.81
Alcohol consumption	306 (10.5%)	244 (10.2%)	62 (11.6%)	0.35
Betel nut	88 (3.0%)	69 (2.9%)	19 (3.6%)	0.42
Child-Turcot-Pugh classification (n,(%))				
A	1648 (98.2%)	1376 (98.6%)	272 (96.1%)	**0.003**
B	30 (1.8%)	19 (1.4%)	11 (3.9%)	
Liver cirrhosis (n,(%))				
No	976 (56.4%)	756 (52.4%)	220 (76.4%)	**< 0.001**
Yes	755 (43.6%)	687 (47.6%)	68 (23.6%)	
Tumor size (mean (SD), mm)	4.8 (3.5)	3.6 (1.2)	10.3 (4.8)	**< 0.001**
mVI (n,(%))	915 (31.3%)	675 (28.3%)	240 (44.9%)	**< 0.001**
Medications (n,(%))				
Anti-HCV/HBV therapy	217 (7.4%)	207 (8.7%)	10 (1.9%)	**< 0.001**
Metformin	174 (6.0%)	148 (6.2%)	26 (4.9%)	0.24
Aspirin	129 (4.4%)	98 (4.1%)	31 (5.8%)	0.086
Biochemical profiles (mean (SD))				
α-Fetoprotein, ng/mL	3610.0 (57,613.1)	695.8 (4943.0)	16,723.8 (134,060.3)	**< 0.001**
ICG-15, %	9.1 (7.9)	9.4 (8.0)	7.9 (7.4)	**< 0.001**
Albumin, g/dL	4.1 (0.5)	4.1 (0.5)	4.0 (0.6)	**< 0.001**
Hgb, g/dL	13.6 (1.9)	13.7 (1.9)	13.2 (2.1)	**< 0.001**
Platelet, 10^3/μL	183.0 (70.2)	173.1 (62.6)	223.8 (84.0)	**< 0.001**
INR	1.1 (0.1)	1.1 (0.1)	1.1 (0.2)	**0.045**
AST, U/L	61.4 (106.0)	55.7 (92.9)	86.3 (147.9)	**< 0.001**
ALT, U/L	64.7 (105.5)	62.0 (95.3)	76.5 (141.1)	**0.005**
Total bilirubin, mg/dL	0.9 (0.6)	0.9 (0.6)	0.9 (0.7)	0.27
ALBI grade				
Grade 1 (lowest risk)	1694 (58.0%)	1383 (57.9%)	311 (58.1%)	**< 0.001**
Grade 2	734 (25.1%)	562 (23.5%)	172 (32.1%)	
Grade 3 (highest risk)	35 (1.2%)	21 (0.9%)	14 (2.6%)	
Missing	459 (15.7%)	421 (17.6%)	38 (7.1%)	
PNI				
Normal	1067 (36.5%)	881 (36.9%)	186 (34.8%)	**< 0.001**
Mild	584 (20.0%)	463 (19.4%)	121 (22.6%)	
Mod to severe	356 (12.2%)	263 (11.0%)	93 (17.4%)	
Serious	226 (7.7%)	157 (6.6%)	69 (12.9%)	

Table 1 (continued)

	Total (n = 2922)	≤ 6.5 cm (n = 2387)	> 6.5 cm (n = 535)	p-value
Missing	689 (23.6%)	623 (26.1%)	66 (12.3%)	
NLR (mean (SD))	4.2 (5.6)	3.9 (5.1)	5.2 (7.0)	**< 0.001**

ALBI grade ALBI (albumin-bilirubin) grade, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DM* diabetes mellitus, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *Hgb* hemoglobin, *ICG-15* indocyanine green retention test at 15 min, *INR* international normalized ratio, *mVI* microvascular invasion, *NLR* neutrophil–lymphocyte ratio, *PNI* prognostic nutritional index, *SD* standard deviation

Values in bold are statistically significant (p < 0.05)

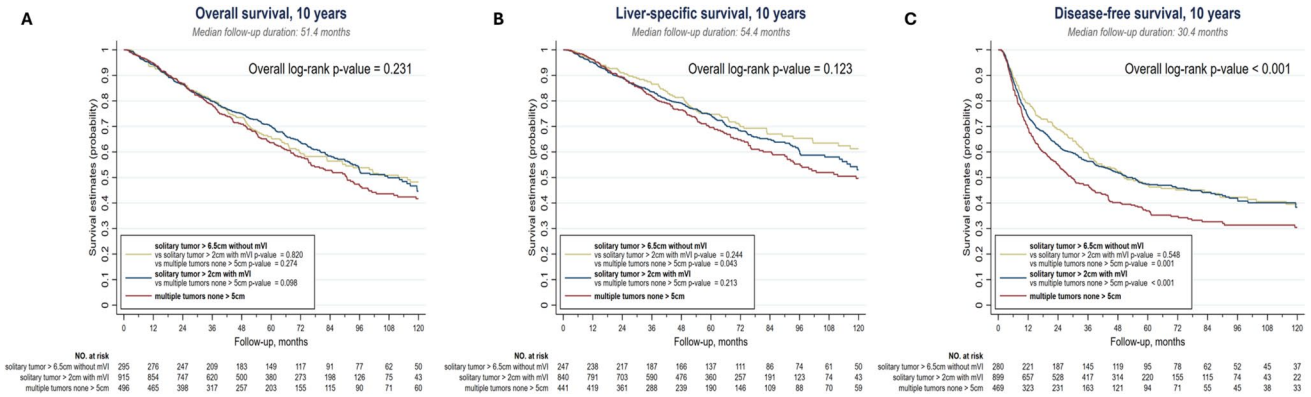

Fig. 2 Kaplan–Meier survival curves of solitary tumor > 6.5 cm without mVI, solitary tumor > 2 cm with mVI, and multiple tumors none greater than 5 cm in diameter. **A** Overall-survival (OS), **B** liver-specific survival, and **C** disease-free survival (DFS)

95% CI 1.88–4.80, $P < 0.001$), and ALBI grade II/III (aHR: 1.97, 95% CI 1.32–2.94, $P = 0.001$) (Table 3).

As for risk factors correlated with tumor recurrence, multivariate analysis demonstrated that mVI (aHR: 1.41, 95% CI 1.16–1.72, $P = 0.001$), tumor size > 6.5 cm (aHR: 1.52, 95% CI 1.18–1.95, $P = 0.001$), male gender (aHR: 1.31, 95% CI 1.02–1.70, $P = 0.037$), cirrhosis (aHR: 1.63, 95% CI 1.33–2.00, $P < 0.001$), smoking (aHR: 1.50, 95% CI 1.17–1.92, p = 0.001), HCV infection (aHR: 1.40, 95% CI 1.10–1.77, p = 0.006), hemoglobin ≤ 10 g/dL (aHR: 1.56, 95% CI 1.08–2.26, p = 0.019), and ALBI grade II/III (aHR: 1.76, 95% CI 1.33–2.32, p < 0.001) were significant prognosticators for tumor recurrence after liver resection for solitary HCC > 2 cm (Table 4).

Survival impact of tumor size > 6.5 cm and mVI

Figure 3 further analyzed the survivals of different HCC subgroups. Based on tumor size cutoff of 6.5 cm and mVI, four distinct subgroups of solitary HCC were shown. These included solitary tumor 2–6.5 cm without mVI, solitary tumor 2–6.5 cm with mVI, solitary tumor > 6.5 cm without mVI, and solitary tumor > 6.5 cm with mVI. The median follow-up duration was 60.9 months, and the median OS for these four subgroups were not reached, 119.3, 115.5, and 79.9 months, respectively (overall log-rank test, $P < 0.001$, Fig. 3A). While solitary tumor 2–6.5 cm without mVI enjoyed the longest OS and solitary tumor > 6.5 cm with mVI had the worst OS, the OS of solitary tumor 2–6.5 cm with mVI and solitary tumor > 6.5 cm without mVI were similar. The post hoc analysis further revealed that solitary tumor 2–6.5 cm with mVI and solitary tumor > 6.5 cm without mVI had comparable OS ($P = 0.171$). Table 5 summarized the pairwise comparisons of these log-rank tests. The liver-specific survivals of these four subgroups were next depicted in Fig. 3B. With a median follow-up of 62.8 months, the median liver-specific survivals were all not reached for solitary tumor 2–6.5 cm without mVI, solitary tumor 2–6.5 cm with mVI, and solitary tumor > 6.5 cm without mVI. The median liver-specific survival was only 93.1 months for solitary tumor > 6.5 cm with mVI (overall log-rank test, $P < 0.001$). The liver-specific survivals were comparable between solitary tumor 2–6.5 cm with mVI and solitary tumor > 6.5 cm without mVI ($P = 0.924$) (Table 5). As for DFS, after a median follow-up of 61.8 months, solitary tumor 2–6.5 cm without mVI enjoyed the longest median DFS of 95 months. Solitary tumor > 6.5 cm with mVI, in contrast, had a median DFS of only 32.3 months. Solitary tumor 2–6.5 cm with mVI and solitary tumor > 6.5 cm without mVI, on the other hand, had an intermediate median DFS

Table 2 Univariate and multivariate analyses of risks factors for all-cause mortality after hepatectomy for solitary, > 2 cm hepatocellular carcinoma

Variables	Univariable		Multivariable	
	HR (95% CI)	p-value	aHR (95% CI)	p-value
mVI no	1 (reference)			
Yes	1.46 (1.27, 1.67)	< 0.001	1.65 (1.27, 2.15)	< 0.001
Tumor size ≤ 6.5 cm	1 (reference)			
> 6.5 cm	1.64 (1.41, 1.92)	< 0.001	1.53 (1.11, 2.09)	0.009
Gender female	1 (reference)			
Male	1.96 (1.72, 2.22)	< 0.001	1.79 (1.36, 2.37)	< 0.001
Age < 65 y/o	1 (reference)			
≥ 65 y/o	2.01 (1.77, 2.28)	< 0.001	1.80 (1.37, 2.37)	< 0.001
Cirrhosis no	1 (reference)			
Yes	1.55 (1.27, 1.89)	< 0.001	1.46 (1.12, 1.92)	0.006
Diabetes mellitus no	1 (reference)			
Yes	1.32 (1.15, 1.52)	< 0.001	1.09 (0.79, 1.50)	0.620
Hypertension no	1 (reference)			
Yes	1.22 (1.08, 1.39)	0.002	1.00 (0.76, 1.33)	0.981
Smoking no	1 (reference)			
Yes	1.12 (0.90, 1.40)	0.321	1.12 (0.80, 1.57)	0.507
Alcohol no	1 (reference)			
Yes	0.98 (0.76, 1.25)	0.843	1.29 (0.92, 1.83)	0.143
HBs Ag negative	1 (reference)			
Positive	0.70 (0.62, 0.80)	< 0.001	0.76 (0.56, 1.03)	0.077
Hepatitis C virus negative	1 (reference)			
Positive	1.29 (1.13, 1.48)	< 0.001	1.16 (0.86, 1.58)	0.331
Albumin (vs. > 3.5 (g/dL)	1 (reference)			
≤ 3.5	1.59 (1.33, 1.90)	< 0.001	0.72 (0.47, 1.10)	0.131
Hemoglobin (> 10 (g/dL)	1 (reference)			
≤ 10	1.90 (1.46, 2.47)	< 0.001	2.31 (1.51, 3.54)	< 0.001
Platelet > 100 (10^3/uL)	1 (reference)			
≤ 100	1.91 (1.59, 2.30)	< 0.001	1.54 (1.03, 2.32)	0.038
INR (≤ 1.4)	1 (reference)			
> 1.4	1.61 (0.84, 3.08)	0.152	0.68 (0.27, 1.69)	0.406
ALT (≤ 108 (U/L))	1 (reference)			
> 108	1.16 (0.96, 1.41)	0.117	0.71 (0.45, 1.10)	0.126
Bilirubin total (≤ 1.5 (mg/dL))	1 (reference)			
> 1.5	1.59 (1.27, 2.00)	< 0.001	1.24 (0.80, 1.92)	0.333
α-fetoprotein ≤ 400 (ng/mL))	1 (reference)			
> 400	1.11 (0.91, 1.35)	0.297	1.08 (0.77, 1.52)	0.645
ALBI grade (I)	1 (reference)			
II/III	1.73 (1.50, 1.99)	< 0.001	1.72 (1.21, 2.47)	0.003
PNI (normal/mild)	1 (reference)			
moderate/serious	1.70 (1.46, 1.98)	< 0.001	1.36 (0.93, 1.99)	0.113
Antiviral therapy in HBV or HCV (no)	1 (reference)			
Yes	0.83 (0.64, 1.09)	0.178	1.22 (0.76, 1.95)	0.407

of 57.5 and 50.7 months, respectively. (overall log-rank test, $P < 0.001$) (Fig. 3C). The DFS of solitary tumor 2–6.5 cm with mVI was equivalent to that of solitary tumor > 6.5 cm without mVI ($P = 0.682$) (Table 5). Moreover, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analyses confirmed that the addition of tumor size > 6.5 cm to mVI could significantly enhance the predictive capability of mVI for all-cause mortality and tumor recurrence after liver resection for solitary HCC (all $P < 0.05$) (Supplementary Table 1 and 2).

Table 3 Univariate and multivariate analyses of risks factors for liver-specific mortality after hepatectomy for solitary, > 2 cm hepatocellular carcinoma

Variables	Univariable		Multivariable	
	HR (95% CI)	*p* value	aHR (95% CI)	*p* value
mVi no	1 (reference)			
Yes	1.62 (1.38, 1.90)	< 0.001	1.67 (1.23, 2.27)	0.001
Tumor size ≤ 6.5 cm	1 (reference)			
> 6.5 cm	1.61 (1.34, 1.93)	< 0.001	1.66 (1.16, 2.39)	0.006
Gender female	1 (reference)			
Male	1.05 (0.88, 1.26)	0.587	1.72 (1.14, 2.58)	0.009
Age < 65 y/o	1 (reference)			
≥ 65 y/o	1.78 (1.53, 2.07)	< 0.001	1.47 (1.07, 2.03)	0.019
Cirrhosis no	1 (reference)			
Yes	1.65 (1.31, 2.08)	< 0.001	1.58 (1.15, 2.15)	0.004
Diabetes mellitus no	1 (reference)			
Yes	1.25 (1.06, 1.49)	0.010	0.78 (0.52, 1.18)	0.242
Hypertension no	1 (reference)			
Yes	1.23 (1.05, 1.43)	0.009	1.00 (0.72, 1.39)	0.990
Smoking no	1 (reference)			
Yes	1.14 (0.88, 1.48)	0.315	1.00 (0.67, 1.48)	0.991
Alcohol no	1 (reference)			
Yes	1.06 (0.81, 1.40)	0.662	1.37 (0.92, 2.02)	0.120
HBs Ag negative	1 (reference)			
Positive	0.78 (0.67, 0.91)	0.001	0.81 (0.57, 1.15)	0.236
Hepatitis C virus negative	1 (reference)			
Positive	1.31 (1.12, 1.54)	0.001	1.15 (0.80, 1.66)	0.448
Albumin (vs. > 3.5 (g/dL)	1 (reference)			
≤ 3.5	1.62 (1.31, 2.00)	< 0.001	0.73 (0.45, 1.19)	0.206
Hemoglobin (> 10 (g/dL)	1 (reference)			
≤ 10	1.95 (1.44, 2.64)	< 0.001	3.00 (1.88, 4.80)	< 0.001
Platelet > 100 (10^3/uL)	1 (reference)			
≤ 100	2.10 (1.70, 2.61)	< 0.001	1.58 (0.99, 2.52)	0.053
INR (≤ 1.4)	1 (reference)			
> 1.4	1.35 (0.62, 2.95)	0.448	0.45 (0.14, 1.46)	0.185
ALT (≤ 108 (U/L))	1 (reference)			
> 108	1.31 (1.05, 1.63)	0.016	0.74 (0.45, 1.21)	0.229
Bilirubin total (≤ 1.5 (mg/dL))	1 (reference)			
> 1.5	1.73 (1.34, 2.25)	< 0.001	1.24 (0.76, 2.03)	0.387
α-fetoprotein ≤ 400 (ng/mL))	1 (reference)			
> 400	1.08 (0.86, 1.36)	0.519	1.07 (0.72, 1.58)	0.735
ALBI grade (I)	1 (reference)			
II/III	1.81 (1.53, 2.14)	< 0.001	1.97 (1.32, 2.94)	0.001
PNI (normal/mild)	1 (reference)			
moderate/serious	1.70 (1.41, 2.04)	< 0.001	1.21 (0.78, 1.87)	0.406
Antiviral therapy in HBV or HCV (no)	1 (reference)			
Yes	1.01 (0.76, 1.35)	0.921	1.40 (0.85, 2.29)	0.184

Discussion

According to the 8th edition of AJCC TNM staging system for HCC, solitary tumor greater than 2 cm without vascular invasion, regardless of tumor size, are all categorized as T1 lesions [8, 9]. In other words, the treatment recommendation and prognosis are expected to be similar among these solitary lesions. Nevertheless, our previous study demonstrated that large stage I HCC had significantly worse OS and DFS than smaller tumors after surgery [14]. Other studies have also indicated that tumor size did influence patient survival and should be considered in our conventional staging

Table 4 Univariate and multivariate analyses of risks factors for recurrence after hepatectomy for solitary, > 2 cm hepatocellular carcinoma

Variables	Univariable		Multivariable	
	HR (95% CI)	*p* value	aHR (95% CI)	*p* value
mVi no	1 (reference)			
Yes	1.37 (1.22, 1.54)	< 0.001	1.41 (1.16, 1.72)	0.001
Tumor size ≤ 6.5 cm	1 (reference)			
> 6.5 cm	1.43 (1.25, 1.64)	< 0.001	1.52 (1.18, 1.95)	0.001
Gender female	1 (reference)			
Male	1.04 (0.91, 1.18)	0.586	1.31 (1.02, 1.70)	0.037
Age < 65 y/o	1 (reference)			
≥ 65 y/o	1.49 (1.34, 1.66)	< 0.001	1.21 (0.97, 1.50)	0.084
Cirrhosis no	1 (reference)			
Yes	1.65 (1.42, 1.93)	< 0.001	1.63 (1.33, 2.00)	< 0.001
Diabetes mellitus no	1 (reference)			
Yes	1.11 (0.98, 1.25)	0.097	0.90 (0.70, 1.16)	0.423
Hypertension no	1 (reference)			
Yes	1.05 (0.95, 1.18)	0.340	0.87 (0.70, 1.08)	0.194
Smoking no	1 (reference)			
Yes	1.21 (1.02, 1.43)	0.030	1.50 (1.17, 1.92)	0.001
Alcohol no	1 (reference)			
Yes	0.85 (0.70, 1.04)	0.121	0.88 (0.67, 1.16)	0.374
HBs Ag negative	1 (reference)			
Positive	0.85 (0.77, 0.95)	0.004	0.97 (0.77, 1.23)	0.818
Hepatitis C virus negative	1 (reference)			
Positive	1.35 (1.20, 1.51)	< 0.001	1.40 (1.10, 1.77)	0.006
Albumin (vs. > 3.5 (g/dL)	1 (reference)			
≤ 3.5	1.44 (1.24, 1.68)	< 0.001	0.83 (0.58, 1.18)	0.296
Hemoglobin (> 10 (g/dL)	1 (reference)			
≤ 10	1.48 (1.17, 1.86)	0.001	1.56 (1.08, 2.26)	0.019
Platelet > 100 (10^3/uL)	1 (reference)			
≤ 100	1.59 (1.34, 1.89)	< 0.001	1.17 (0.83, 1.63)	0.373
INR (≤ 1.4)	1 (reference)			
> 1.4	1.10 (0.59, 2.04)	0.770	0.67 (0.29, 1.52)	0.338
ALT (≤ 108 (U/L))	1 (reference)			
> 108	1.26 (1.07, 1.48)	0.006	0.80 (0.57, 1.12)	0.194
Bilirubin total (≤ 1.5 (mg/dL))	1 (reference)			
> 1.5	1.32 (1.07, 1.63)	0.010	1.00 (0.68, 1.46)	0.990
α-fetoprotein ≤ 400 (ng/mL))	1 (reference)			
> 400	1.09 (0.92, 1.29)	0.336	0.91 (0.70, 1.18)	0.461
ALBI grade (I)	1 (reference)			
II/III	1.56 (1.39, 1.76)	< 0.001	1.76 (1.33, 2.32)	< 0.001
PNI (normal/mild)	1 (reference)			
Moderate/serious	1.50 (1.32, 1.71)	< 0.001	0.94 (0.69, 1.28)	0.704
Antiviral therapy in HBV or HCV (no)	1 (reference)			
Yes	0.87 (0.70, 1.09)	0.225	1.01 (0.72, 1.42)	0.935

systems [10–12]. To identify those patients at risks, our recent study proposed that T1 HCC could be further classified as: T1a: solitary tumor ≤ 2 cm with or without vascular invasion, T1b: solitary tumor > 2 cm but ≤ 6.5 cm without vascular invasion, and T1c: solitary tumor > 6.5 cm without vascular invasion. We demonstrated that the DFS and OS of T1c HCC were similar to those of T2 HCC patients [16]. These findings imply that tumor size is indeed a significant prognostic factor and should be assessed alongside other adverse risk factors for HCC during our clinical practice.

Microvascular invasion, or mVI, is one of these adverse risk factors and, when present, is considered to represent

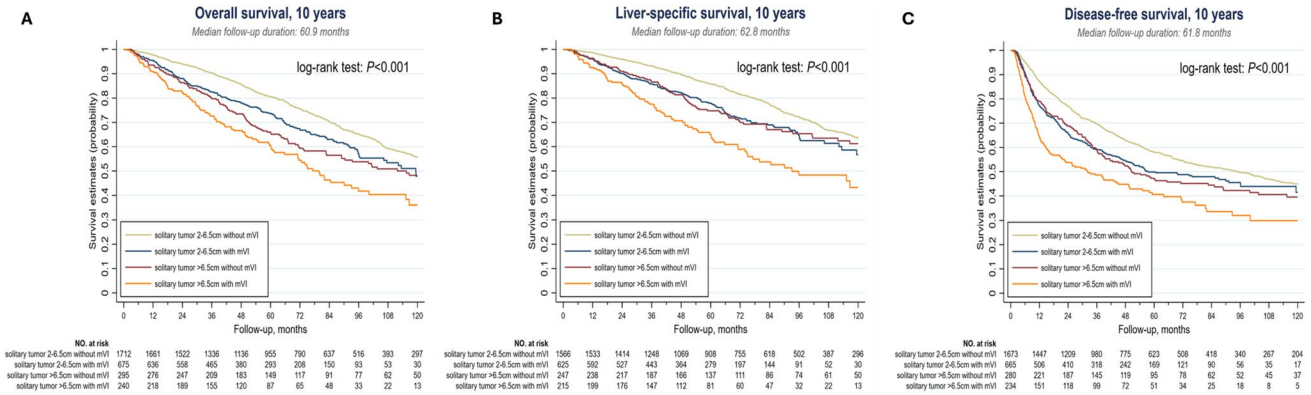

Fig. 3 Kaplan–Meier survival curves of 4 distinct HCC subgroups, solitary tumor 2–6.5 cm without mVI, solitary tumor 2–6.5 cm with mVI, solitary tumor > 6.5 cm without mVI, and solitary tumor > 6.5 cm with mVI. **A** Overall-survival (OS), **B** liver-specific survival, and **C** disease-free survival (DFS)

Table 5 Pairwise log-rank test between mVI and tumor size for solitary HCC after liver resection

Overall survival				
Log-rank *P*	2–6.5 cm without mVI	2–6.5 cm with mVI	> 6.5 cm without mVI	> 6.5 cm with mVI
2–6.5 cm without mVI	1	< 0.001	< 0.001	< 0.001
2–6.5 cm with mVI	< 0.001	1	0.171	< 0.001
> 6.5 cm without mVI	< 0.001	0.171	1	0.031
> 6.5 cm with mVI	< 0.001	< 0.001	0.031	1
Liver-specific survival				
Log-rank *P*	2–6.5 cm without mVI	2–6.5 cm with mVI	> 6.5 cm without mVI	> 6.5 cm with mVI
2–6.5 cm without mVI	1	< 0.001	0.011	< 0.001
2–6.5 cm with mVI	< 0.001	1	0.924	< 0.001
> 6.5 cm without mVI	0.011	0.924	1	0.002
> 6.5 cm with mVI	< 0.001	< 0.001	0.002	1
Disease-free survival				
Log-rank *P*	2–6.5 cm without mVI	2–6.5 cm with mVI	> 6.5 cm without mVI	> 6.5 cm with mVI
2–6.5 cm without mVI	1	< 0.001	0.002	< 0.001
2–6.5 cm with mVI	< 0.001	1	0.682	< 0.001
> 6.5 cm without mVI	0.002	0.682	1	0.007
> 6.5 cm with mVI	< 0.001	< 0.001	0.007	1

a T2 disease by the 8th edition of AJCC TNM staging system for HCC [21]. Since T2 stage comprises not only solitary tumor > 2 cm with mVI but also multiple tumors none greater than 5 cm in diameter, it would be of great clinical significance to examine the individual impact of tumor size > 6.5 cm and mVI on HCC survival outcomes to establish a more appropriate staging system and treatment recommendation. The current study, by examining one of the largest and most comprehensive clinical databases worldwide, is the first English-language study to date to discover that tumor size > 6.5 cm and mVI were comparable prognosticators for HCC (Fig. 2). To further corroborate our findings, we performed Cox regression multivariate analysis and found that tumor size > 6.5 cm and mVI were both independent prognostic factors for tumor recurrence, liver-specific mortality, and all-cause mortality after liver resection. By conducting IDI and NRI analyses, we again demonstrated that tumor size > 6.5 cm was an indispensable prognostic variable. The addition of tumor size > 6.5 cm to mVI significantly enhanced the predictive capability of mVI for all-cause mortality and tumor recurrence after liver resection for HCC.

In our previous study, we identified that solitary tumor > 6.5 cm without vascular invasion had survivals

similar to those of T2 lesions [16]. However, that study did not examine the outcome between T2 subcategories, namely, solitary tumor > 2 cm with mVI and multiple tumors none greater than 5 cm in diameter. In this regard, the current study is the first to demonstrate that, although OS and liver-specific OS were comparable between solitary tumor > 2 cm with mVI and multiple tumors none greater than 5 cm, the DFS was significantly impaired in patients with multiple tumors (Fig. 2). Our findings indicate that although solitary tumor > 2 cm with mVI and multiple tumors none greater than 5 cm were both allocated as T2 stage, a substantial difference in terms of tumor recurrence can still be observed. This may be attributed to the fact that multiple tumors, even if all less than 5 cm, signified either multicentric occurrence or intrahepatic metastasis. Since intrahepatic metastasis usually developed secondary to vascular invasion, "multiple tumors none greater than 5 cm" included within the T2 stage may comprise a subgroup more advanced than microvascular invasion alone [22]. This unbalanced stage allocation may explain the results identified in the current study. A subclassification within stage T2 is therefore indicated. In short, we propose that tumor size > 6.5 cm should be integrated with mVI to constitute stage T2a, while multiple tumors none greater than 5 cm should account for a more advanced subgroup, T2b.

It has been mentioned that in large HCC, pathologists may underestimate the disease severity such as mVI due to inadequate sampling [23, 24]. Indeed, given huge tumor volume, it is possible that sectioning for pathological examination may not cover the entire specimen, potentially leading to false-negative results. However, since larger tumor size is widely recognized as a risk factor for mVI [25, 26], it is theoretically reasonable to consider it as a more advanced disease, regardless of status of mVI on the final pathology report. In other words, we should thoroughly consider upgrading HCC with larger tumor size into a higher tumor stage. Other the other hand, due to their potential correlation, it is important to emphasize that tumor size > 6.5 cm and mVI are comparable in prognostic strength, but not identical or equal risk factors.

Moreover, the current study discovered that tumor size > 6.5 cm and mVI were not only comparable prognosticators but also synergistic unfavorable prognostic factors that, when both present, substantially compromised HCC survivals. The OS, liver-specific OS and DFS were all significantly reduced for tumors > 6.5 cm with mVI compared to either tumor > 6.5 cm or with mVI (Fig. 3 and Table 5). This novel finding has provided surgical oncologists with paramount implications: the presence of multiple equivalent adverse factors does not lead to an outcome equivalent to the presence of single adverse factors. In contemporary treatment guidelines—including those from APASL, EASL, AASLD, BCLC, and TLCA—tumor size and mVI are not currently incorporated into treatment allocation or staging systems [27–33]. Although the presence of a large tumor or mVI may not directly influence the choice of primary treatment modality, these factors may have significant implications for postoperative surveillance strategies and the consideration of adjuvant therapy. In the recently updated results of the phase III IMbrave050 study, adjuvant administration of atezolizumab and bevacizumab did not significantly reduce the incidence of early recurrence following curative surgery [34]. We believe this may be partially attributable to suboptimal selection criteria for identifying high-risk patients. Based on the findings of the current study, patients with both tumor size > 6.5 cm and mVI exhibit markedly elevated recurrence rates and reduced survival outcomes. Therefore, we propose that such patients be classified as a high-risk subgroup, warranting the use of adjuvant systemic therapy and intensive postoperative monitoring to improve oncologic outcomes. Further studies are warranted to validate this risk stratification approach and its therapeutic implications.

In the current study, the frequency of HCV infection and liver cirrhosis differed between tumors ≤ 6.5 cm and > 6.5 cm. Tumors ≤ 6.5 cm were significantly associated with a higher prevalence of HCV infection and liver cirrhosis compared to larger tumors. We believe this disparity may be attributed to different screening strategies. Patients with HCV infection typically require definitive antiviral treatment and frequent post-treatment follow-ups, allowing HCC to be detected at a smaller size. Similarly, since liver cirrhosis usually develops in the context of HCV infection, the higher incidence of cirrhosis in tumors ≤ 6.5 cm may be linked to the increased prevalence of HCV infection in these patients.

Despite notable findings, this study has several limitations. First, the data were derived from a hospital-based database and cancer registry, which lacked access to more detailed descriptive variables such as performance status, postoperative complications, and pathological details such as margin width. These variables could not be analyzed consequently. Second, some T2 lesions, such as bilobar tumors or cases with more than three tumors, were typically not treated surgically. As a result, the survival outcomes presented here may overestimate the overall prognosis associated with all T2 lesions. Third, patients with impaired liver function often cannot tolerate major liver resection, which is typically required for larger tumors to achieve an adequate safety margin. An insufficient surgical margin may therefore worsen the prognosis of patients with tumors larger than 6.5 cm. A well-designed trial recruiting patients with same safety margin is needed to validate our findings. Moreover, since mVI is typically identified only after liver resection, the findings and implications of the current study may not be directly applicable to non-surgical patients. Therefore, the development of non-invasive surrogates for mVI is essential to support clinical decision-making in this population. Next,

while potential recall bias was minimized by prospectively registering daily clinical data into the CGRD, referral bias remained unavoidable since CGMHs serve as the largest tertiary care center in Taiwan [35, 36]. Lastly, as this study primarily relied on data from a single country, the patient population was relatively homogeneous. The absence of an external validation cohort encompassing diverse ethnic groups was another limitation. Validation using HCC datasets from countries with more heterogeneous populations would strengthen the findings. Future studies incorporating external validation cohorts are essential to confirm and generalize our results.

Conclusion

In conclusion, our CGRD-based study demonstrated that tumor size larger than 6.5 cm and mVI are comparable prognosticators for HCC. Due to significantly higher risks of recurrence and death, tumor size > 6.5 cm should be integrated with mVI into the same stage to further optimize the current staging system. In addition, we discovered that the presence of these two adverse factors significantly worsens HCC survival outcomes compared to the presence of either factor alone. As a result, patients with both size > 6.5 cm and mVI should undergo adjuvant therapy to optimize oncological outcomes. Further studies are warranted to validate our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12094-025-03981-3.

Acknowledgements We are grateful to all our colleagues in the Division of General Surgery, Department of Surgery, Linkou, Keelung, Chiayi, and Kaohsiung Chang Gung Memorial Hospitals for patient care and data maintenance. We also appreciate the support from Department of Cancer Center, Linkou Chang Gung Memorial Hospital, and Graduate Institute of Clinical Medical Sciences, Chang Gung University for their technical assistance.

Author contributions Conceptualization, Chao-Wei Lee, Hsing-Yu Chen, and Hsin-I Tsai; Data curation, Ming-Chin Yu and Hsing-Yu Chen; Formal analysis, Chao-Wei Lee and Hsing-Yu Chen; Funding acquisition, Chao-Wei Lee and Hsing-Yu Chen; Investigation, Chao-Wei Lee, Ming-Chin Yu, and Chih-Chi Wang; Methodology, Ming-Chin Yu, Chih-Chi Wang, and Wei-Chen Lee; Project administration, Chao-Wei Lee; Resources, Ming-Chin Yu, Wei-Chen Lee, and Chih-Chi Wang; Software, Jason Chia-Hsun Hsieh, Chiao-En Wu, Po-Ting Lin, Bo-Huan Chen, and Sheng-Fu Wang; Supervision, Chih-Chi Wang, Wei-Chen Lee, and Ming-Chin Yu; Validation, Chih-Chi Wang and Wei-Chen Lee; Visualization, Jason Chia-Hsun Hsieh and Chiao-En Wu; Writing–original draft, Chao-Wei Lee; Writing–review & editing, Hsin-I Tsai, Po-Ting Lin, Bo-Huan Chen, Sheng-Fu Wang, and Hsing-Yu Chen.

Funding This study was supported by Chang Gung Memorial Hospital (CGRPG1Q0011 and CMRPG3P0541), the Ministry of Health and Welfare (MOHW113-CMAP-M-113-000003-B and MOHW113-CMAP-M-113-000002-D), and the National Science and Technology Council in Taiwan (MOST111-2320-B-182-035-MY3).

Data availability All data generated or analyzed during the study are included in this published article. Raw data may be requested from the authors with the permission of the institution.

Declarations

Conflict of interest Hsing-Yu Chen, Hsin-I Tsai, Ming-Chin Yu, Wei-Chen Lee, Chih-Chi Wang, Jason Chia-Hsun Hsieh, Chiao-En Wu, Po-Ting Lin, Bo-Huan Chen, Sheng-Fu Wang, and Chao-Wei Lee have no conflicts of interest or financial ties to disclose

Ethical approval and consent to participate This study was approved by the Institutional Review Boards (CGMH IRB No: 201900800B0C501) of CGMH. For retrospective study, informed consent was waived according to our institutional guidelines.

Consent for publication Not applicable.

References

1. Lee CW, Chan KM, Tsai HI, Hsieh YC, Lin CY, Kuo YC, et al. Hepatic resection for hepatocellular carcinoma in the octogenarian: is it justified? Aging. 2019;11(5):1537–50.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
3. Department of Health ROC. Statistics of cause of death in Taiwan 2021. Executive Yuan, Republic of China. 2022.
4. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet (London, England). 2012;379(9822):1245–55.
5. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg. 2000;232(1):10–24.
6. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. World J Gastroenterol. 2015;21(4):1207–15.
7. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int. 2009;29(4):502–10.
8. Edge SB, Byrd DR, Carducci MA, Compton CC, Fritz A, Greene F. AJCC cancer staging manual. New York: Springer; 2017.

9. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
10. Abdel-Rahman O. Assessment of the discriminating value of the 8th AJCC stage grouping for hepatocellular carcinoma. HPB (Oxford). 2018;20(1):41–8.
11. Fang KC, Kao WY, Su CW, Chen PC, Lee PC, Huang YH, et al. The prognosis of single large hepatocellular carcinoma was distinct from Barcelona clinic liver cancer stage A or B: the role of albumin-bilirubin grade. Liver cancer. 2018;7(4):335–58.
12. Zhong JH, Pan LH, Wang YY, Cucchetti A, Yang T, You XM, et al. Optimizing stage of single large hepatocellular carcinoma: A study with subgroup analysis by tumor diameter. Medicine. 2017;96(15): e6608.
13. Shindoh J, Kobayashi Y, Kawamura Y, Akuta N, Kobayashi M, Suzuki Y, et al. Microvascular invasion and a size cutoff value of 2 cm predict long-term oncological outcome in multiple hepatocellular carcinoma: reappraisal of the American joint committee on cancer staging system and validation using the surveillance, epidemiology, and end-results database. Liver cancer. 2020;9(2):156–66.
14. Lee CW, Yu MC, Wang CC, Lee WC, Tsai HI, Kuan FC, et al. Liver resection for hepatocellular carcinoma larger than 10 cm: A multi-institution long-term observational study. World J Gastrointest Surg. 2021;13(5):476–92.
15. Wang YY, Zhong JH, Xu HF, Xu G, Wang LJ, Xu D, et al. A modified staging of early and intermediate hepatocellular carcinoma based on single tumour >7 cm and multiple tumours beyond up-to-seven criteria. Aliment Pharmacol Ther. 2019;49(2):202–10.
16. Lee C-W, Tsai H-I, Yu M-C, Wang C-C, Lee W-C, Yeh T-S, et al. A proposal for T1 subclassification in hepatocellular carcinoma: reappraisal of the AJCC 8th edition. Hepatology Int. 2022. https://doi.org/10.1007/s12072-022-10422-8.
17. Chiang CJ, Wang YW, Lee WC. Taiwan's nationwide cancer registry system of 40 years: past, present, and future. J Formos Med Assoc. 2019;118(5):856–8.
18. Shao SC, Chan YY, Kao Yang YH, Lin SJ, Hung MJ, Chien RN, et al. The Chang Gung research database-a multi-institutional electronic medical records database for real-world epidemiological studies in Taiwan. Pharmacoepidemiol Drug Saf. 2019;28(5):593–600.
19. Tsai MS, Lin MH, Lee CP, Yang YH, Chen WC, Chang GH, et al. Chang Gung research database: A multi-institutional database consisting of original medical records. Biomed J. 2017;40(5):263–9.
20. Berthold MR, Cebron N, Dill F, Gabriel TR, Kötter T, Meinl T, et al. KNIME—the Konstanz information miner: version 2.0 and beyond. SIGKDD Explor Newsl. 2009;11(1):26–31.
21. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth editon AJCC Cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
22. Nakashima O, Kojiro M. Recurrence of hepatocellular carcinoma: multicentric occurrence or intrahepatic metastasis? A viewpoint in terms of pathology. J Hepatobiliary Pancreat Surg. 2001;8(5):404–9.
23. Li LJ, Wu CQ, Ye FL, Xuan Z, Zhang XL, Li JP, et al. Histopathological diagnosis of microvascular invasion in hepatocellular carcinoma: Is it reliable? World J Gastroenterol. 2025;31(5):98928.
24. Hu HT, Wang Z, Kuang M, Wang W. Need for normalization: the non-standard reference standard for microvascular invasion diagnosis in hepatocellular carcinoma. World J Surg Oncol. 2018;16(1):50.
25. Wang L, Jin YX, Ji YZ, Mu Y, Zhang SC, Pan SY. Development and validation of a prediction model for microvascular invasion in hepatocellular carcinoma. World J Gastroenterol. 2020;26(14):1647–59.
26. Yanhan W, Lianfang L, Hao L, Yunfeng D, Nannan S, Fanfan L, et al. Effect of microvascular invasion on the prognosis in hepatocellular carcinoma and analysis of related risk factors: a two-center study. Front Surg. 2021;8:733343.
27. Cho Y, Kim BH, Park JW. Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: An Asian perspective comparison. Clin Mol Hepatol. 2023;29(2):252–62.
28. European Associaton for the Study of the Liver. EASL clinical practice guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025;82(2):315–74.
29. Taddei TH, Brown DB, Yarchoan M, Mendiratta-Lala M, Llovet JM. Critical update: AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2025. https://doi.org/10.1097/hep.0000000000001269.
30. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922–65.
31. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681–93.
32. Lau G, Obi S, Zhou J, Tateishi R, Qin S, Zhao H, et al. APASL clinical practice guidelines on systemic therapy for hepatocellular carcinoma-2024. Hep Intl. 2024;18(6):1661–83.
33. Teng W, Wang HW, Lin SM. Management consensus guidelines for hepatocellular carcinoma: 2023 update on surveillance, diagnosis, systemic treatment, and posttreatment monitoring by the Taiwan liver cancer association and the gastroenterological society of Taiwan. Liver Cancer. 2024;13(5):468–86.
34. Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet (London, England). 2023;402(10415):1835–47.
35. Sedgwick P. What is recall bias? BMJ. 2012;344((may23 1)):e3519-e.
36. Sedgwick P. Retrospective cohort studies: advantages and disadvantages. BMJ British Med J. 2014; 348.https://doi.org/10.1136/bmj.g1072.

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