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Prognostic comparison between LNM and MaVI of hepatocellular carcinoma: a multicenter population-based propensity scores matching study

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Abstract

Background Hepatocellular carcinoma (HCC) with lymph node metastases (LNM) is an uncommon neoplasm and has an ambivalent prognosis compared to the common type of HCC with macrovascular invasion (MaVI).

Methods In this study, the clinical data of patients were extracted from Surveillance, Epidemiology, and End Results (SEER) and Southeast Big Data Institute of Hepatobiliary Health, Mengchao Hepatobiliary Hospital of Fujian Medical University. The K-M survival curve described overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) between LNM and MaVI. Prognostic factors were identified by univariate and multivariate Cox regression analysis. Additionally, propensity score matching (PSM) was performed to minimize the potential confounding factors to facilitate a more reliable conclusion.

Results A total of 3,326 HCC patients were included in our study. In the SEER cohort, after PSM, the 1-, 3-, and 5-year OS rates were 41.1%, 13.8%, and 8.8% in Group LNM and 28.3%, 11.0%, and 7.1% in Group MaVI ($p < 0.001$). The 1-, 3-, and 5-year CSS rates were 46.5%, 17.6%, and 12.0% in Group LNM and 32.2%, 14.3%, and 9.7% in Group MaVI ($p < 0.001$). Multivariate Cox analysis showed that LNM had better OS (HR = 0.79, 95% CI = 0.71–0.89, $p < 0.001$) and CSS (HR = 0.78, 95% CI = 0.70–0.88, $p < 0.001$) compared to MaVI. In the hospital cohort, the 1-, 3-, and 5-year OS rates were 57.5%, 42.6%, and 36.3% in Group LNM and 56.3%, 27.4%, and 14.3% in Group MaVI ($p = 0.038$). The 1-, 3-, and 5-year RFS rates were 40.7%, 32.3%, and 23.5% in Group LNM and 28.9%, 13.0%, and 5.7% in Group MaVI ($p = 0.015$). Multivariate Cox analysis revealed similar OS (HR = 0.83, 95% CI = 0.57–1.23, $p = 0.361$) and CSS (HR = 0.76, 95% CI = 0.53–1.10, $p = 0.142$) between LNM and MaVI.

Conclusion This study found that the current HCC AJCC TNM staging system cannot accurately distinguish the prognosis of LNM and MaVI patients. For patients undergoing hepatectomy, HCC with LNM may obtain a better

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prognosis than that of HCC with MaVI. Future research requires additional clinical data to further corroborate this finding.

Keywords Hepatocellular carcinoma, Macrovascular invasion, Lymph node metastases, Prognosis, AJCC TNM staging

Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer and the fourth leading cause of cancer-related deaths worldwide, with approximately 841,000 new cases and 782,000 deaths annually [1]. Despite the widespread application of screening programs and improvements in diagnostic imaging [2, 3], many HCC patients still present with advanced HCC initially or developed into advanced in the future because of high relapse and lacking effective curative treatment [4]. The incidence has been reported to be 1.7–2.2% [5, 6] and 44.0-62.2% [7], respectively, in HCC with lymph node metastases (LNM) and macrovascular invasion (MaVI).

LNM and MaVI reflecting tumor characteristics and burden are two important prognosis factors in advanced HCC. For HCC, the staging of LNM and MaVI are different in various staging systems. According to the latest American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) Staging System for HCC, MaVI is staged IIIB, and LNM is staged IVA [8]. Based on Barcelona Clinic Liver Cancer (BCLC) staging system, LNM and MaVI are regarded as BCLC C [9]. According to China liver cancer staging (CNLC), MaVI is CNLC IIIa and LNM is CNLC IIIb [10]. TNM stage by liver Cancer Study Group of Japan criteria (LCSGJ) place LNM and MaVI into the same stage together namely stage IV-A [11].

At present, due to the rare incidence of LNM, there are few studies to explore the profile of HCC LNM [4, 12–14], and the prognosis of LNM and MaVI still needs further clarification. Therefore, we conducted a retrospective study using the Surveillance, Epidemiology, and End Results (SEER) database and Southeast Big Database including three medical centers to compare the prognosis between LNM and MaVI in advanced HCC.

Materials and methods

Object and eligibility

SEER cohort

Data for 2,575 HCC patients involved in this study were extracted from Incidence - SEER Research Plus Data,17 Registries by SEER*stat (version 8.4.3). The SEER database is publicly accessible and does not require approval from the ethics institutional review board. The study cohort presents clinical features and survival data for HCC patients with MaVI or LNM. Patient information inclusion criteria: [1] Patients diagnosed with HCC (histologic type ICD-O-3 Hist/behave, malignant = 8170–8175) [2]. The "AJCC 7th edition TNM stage" is described as LNM (T1-3aN1M0) or MaVI (T3bN0M0) [3]. Complete information on follow-up visits. The exclusion criteria are as follows: [1] Survival = 0 or unknown [2]. Other AJCC 8th edition TNM stage. All patients were divided into two groups: Group LNM (T1-3aN1M0), and Group MaVI (T3bN0M0). The screening process for patients is shown in Fig. 1A.

Hospital cohort

751 patients from Southeast Big Database. Patients who underwent liver resection for HCC from January 2009 to December 2014 at three hospitals including Mengchao Hepatobiliary Hospital of Fujian Medical University, Eastern Hepatobiliary Surgery Hospital, and the First Afflicted Hospital of Fujian Medical University. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (ethical approval number: 2021_111_01). At the same time, this study has obtained the exemption of informed consent application from the Ethics Committee of Mengchao Hepatobiliary Hospital of Fujian Medical University. The inclusion criteria included: (1) Primary HCC; (2) HCC with LNM (T1-3aN1M0) or MaVI (T3bN0M0); (3) Without distant metastasis and bile duct tumor thrombus; (4) 18 year ≤ Age ≤ 85 year; (5) complete clinicopathological data and follow up information. Patients who had a history of accompany with other cancer, had incomplete data, lost to follow-up within 30 days after operation were excluded from the analysis. All patients were divided into two groups: Group LNM (T1-3aN1M0), and Group MaVI (T3bN0M0). The screening process for patients is shown in Fig. 1B.

Definition of lymph node metastasis and macrovascular invasion

MaVI (T3bN0M0) and LNM (T1-3aN1M0) were defined based on the AJCC 7th edition TNM staging information provided in the SEER database and postoperative pathological data.

Data collection and processing

Information of SEER cohort were extracted: age, sex, race, marital status, T stage, N stage, M stage, tumor size, AFP, surgery, radiotherapy, chemotherapy, cause of death, survival status, and survival months. Information of hospital cohort were extracted: age, sex, AFP, PLT, ALB, TBIL, ALBI grade, AJCC TNM staging, tumor margin,

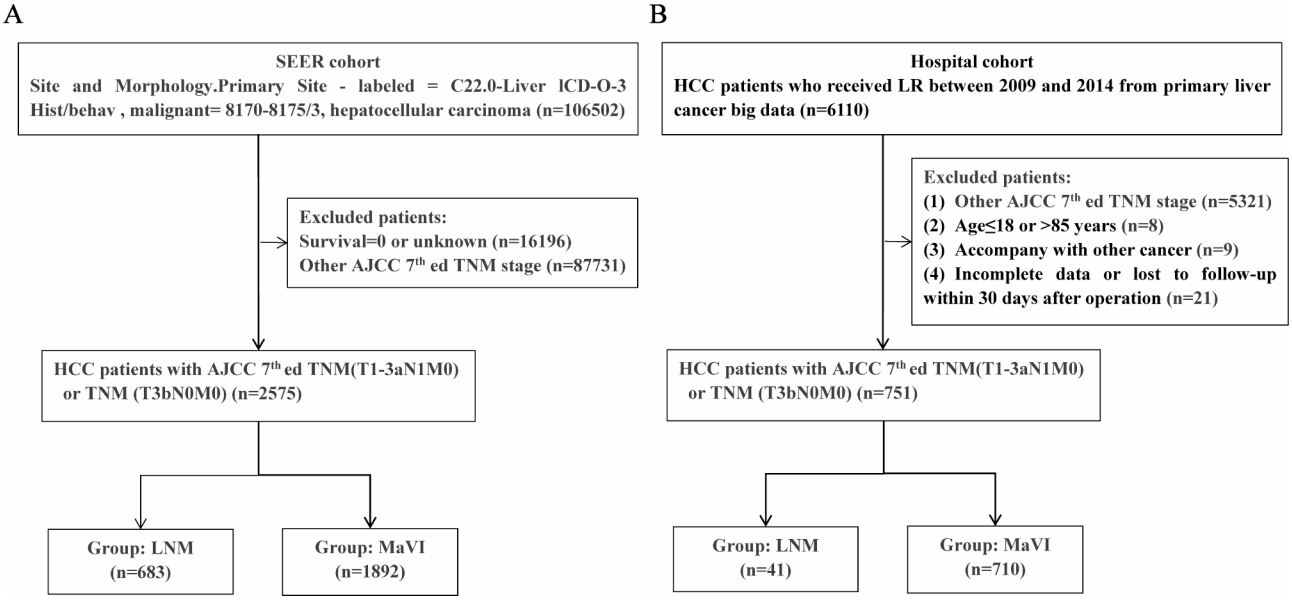

Fig. 1 The flow chart of selected patients. (**A**): SEER cohort; (**B**): Hospital cohort. Abbreviations: ICD, international classification of disease; LNM, lymph node metastasis; MaVI, macrovascular invasion; AJCC, American Joint Committee on Cancer; TNM, Tumor-Node-Metastasis

tumor size, tumor number, MVI, tumor differentiation, tumor capsule, liver cirrhosis, postoperative TACE, postoperative AVT, survival status, and survival months.

Propensity score matching

Propensity score matching (PSM) was developed to reduce any bias in patient selection. Possible unbalanced variables in baseline between LNM and MaVI groups were matched by a one-to-one ratio nearest neighbor match with a caliber of 0.4.

Follow up

For hospital cohort, patients were followed up every three months for the first two years after hospital discharge and then every 3–6 months thereafter. The follow-up assessments included liver function tests, AFP measurements, and abdominal ultrasound. If there was a clinical suspicion of tumor recurrence, contrast-enhanced CT or MRI was conducted.

Statistical analysis

Continuous variables were presented as mean (standard deviation) and continuous variables as number (%). Continuous variables were used t test or Wilcoxon rank sum test and categorical variables were used Chi-square or Fisher exact tests for comparative analysis in our study. Kaplan-Meier method was used to draw the survival curve, the COX regression was used for univariate and multivariate analysis, and the corresponding Hazard Ratio (HR) and 95% Confidence interval (CI) were analyzed. PSM is performed by the ratio (1:1). $P < 0.050$ (three-sided) was considered statistically significant. Our statistical analyses were performed with R version 4.0.4 (http://www.r-project.org/).

Results

Demographic and clinicopathological characteristics

In SEER cohort, there were 683 cases of LNM (26.52%) and 1,892 cases of MaVI (73.48%). Of these patients, 2,088 cases (81.09%) were male, 1,595 cases (61.94%) age > 60 years, 1,816 cases (70.52%) were white people, 342 cases (13.28%) were black people, 417 cases (16.19%) were other races; 1,299 cases (50.45%) marital status were married, 566 cases (21.98%) marital status were single and 710 cases (27.57%) marital status were others, 2,181 cases (84.70%) alpha-fetoprotein were positive, 812 cases (31.53%) tumor size < 5 cm, 1,042 cases (40.47%) tumor size = 5–10 cm, 721 cases (28.00%) tumor size > 10 cm, 179 cases (6.95%) performed surgery for primary site, 356 cases (13.83%) performed radiation, 1,283 cases (49.83%) performed chemotherapy. 2,134 cases (82.87%) cause of death was HCC. For SEER cohort, before PSM, there were differences in terms of AFP, tumor size, radiation, and chemotherapy ($p < 0.05$). These variables were included as covariates for matching. Although differences in marital status and race remained after PSM, the proportions were similar. Compared to the differences in treatment, AFP, and tumor size, the impact of these two variables was relatively small. The baseline characteristics of each group are shown in Table 1. In hospital cohort, the baseline characteristics of each group are shown in Table 2.

Table 1 Comparison of demographic and clinicopathological characteristics between patients with LNM and MaVI in the SEER cohort

Variables	Before PSM			After PSM		
	LNM (*N* = 683)	MaVI (*N* = 1892)	*p*-value	LNM (*N* = 682)	MaVI (*N* = 682)	*p*-value
Sex						
Female	140 (20.5%)	347 (18.3%)	0.239	140 (20.5%)	118 (17.3%)	0.147
Male	543 (79.5%)	1545 (81.7%)		542 (79.5%)	564 (82.7%)	
Age, years						
< 60	255 (37.3%)	725 (38.3%)	0.683	255 (37.4%)	257 (37.7%)	0.955
≥ 60	428 (62.7%)	1167 (61.7%)		427 (62.6%)	425 (62.3%)	
Marital status						
Single	160 (23.4%)	406 (21.5%)	0.117	160 (23.5%)	144 (21.1%)	0.034
Married	355 (52.0%)	944 (49.9%)		354 (51.9%)	327 (47.9%)	
Others	168 (24.6%)	542 (28.6%)		168 (24.6%)	211 (30.9%)	
Race						
White	499 (73.1%)	1317 (69.6%)	0.167	498 (73.0%)	497 (72.9%)	0.038
Black	88 (12.9%)	254 (13.4%)		88 (12.9%)	113 (16.6%)	
Others	96 (14.1%)	321 (17.0%)		96 (14.1%)	72 (10.6%)	
AFP						
Negative	146 (21.4%)	248 (13.1%)	< 0.001	145 (21.3%)	145 (21.3%)	1.000
Positive	537 (78.6%)	1644 (86.9%)		537 (78.7%)	537 (78.7%)	
Tumor size						
< 5 cm	265 (38.8%)	547 (28.9%)	< 0.001	264 (38.7%)	258 (37.8%)	0.935
= 5–10 cm	276 (40.4%)	766 (40.5%)		276 (40.5%)	282 (41.3%)	
> 10 cm	142 (20.8%)	579 (30.6%)		142 (20.8%)	142 (20.8%)	
Surgery						
No	639 (93.6%)	1757 (92.9%)	0.601	638 (93.5%)	624 (91.5%)	0.181
Yes	44 (6.4%)	135 (7.1%)		44 (6.5%)	58 (8.5%)	
Radiation						
No	617 (90.3%)	1602 (84.7%)	< 0.001	616 (90.3%)	622 (91.2%)	0.640
Yes	66 (9.7%)	290 (15.3%)		66 (9.7%)	60 (8.8%)	
Chemotherapy						
No	318 (46.6%)	974 (51.5%)	0.031	318 (46.6%)	324 (47.5%)	0.786
Yes	365 (53.4%)	918 (48.5%)		364 (53.4%)	358 (52.5%)	
Died of HCC						
No	132 (19.3%)	309 (16.3%)	0.085	132 (19.4%)	117 (17.2%)	0.326
Yes	551 (80.7%)	1583 (83.7%)		550 (80.6%)	565 (82.8%)	

Abbreviations: HCC, hepatocellular carcinoma; MaVI, macrovascular invasion; LNM, lymph node metastasis; AFP, alpha-fetoprotein; PSM, propensity score matching

Survival analyzes

In SEER cohort, K-M survival cures showed the OS and CSS. To reduce differences in baseline characteristics, we conducted propensity score matching (PSM) according to the results of Table 1 (AFP, tumor size, radiation, and chemotherapy). Before PSM, The OS rates at 1-year, 3-year, and 5-year were 41.2%, 13.8%, and, 8.8%, respectively, in Group LNM and 26.7%, 9.9%, and 6.6%, respectively, in Group MaVI (Fig. 2A). The CSS rates at 1-, 3-year and 5-year were 46.6%, 17.5%, and, 12.0% respectively, in Group LNM, 30.5%, 12.8%, and 9.2%, in Group MaVI (Fig. 2B). After PSM, The OS rates at 1-year, 3-year, and 5-year were 41.1%, 13.8%, and, 8.8%, respectively, in Group LNM and 28.3%, 11.0%, and 7.1%, respectively, in Group MaVI (Fig. 3A). The CSS rates at 1-, 3-year and 5-year were 46.5%, 17.6%, and, 12.0% respectively, in Group LNM, 32.2%, 14.3%, and 9.7%, in Group MaVI (Fig. 3B). Subgroup analysis based on treatment showed that in the surgery and chemotherapy groups, patients with LNM had better OS and CSS than those with MaVI. No significant difference was observed in OS and CSS between the two radiotherapy groups (Fig. S1). In the AFP-positive group, LNM patients had better OS and CSS than MaVI patients. In the AFP-negative group, LNM patients had better OS, and although CSS showed no statistical significance, the survival trend favored LNM over MaVI (Fig. S2). Subgroup analysis based on tumor diameter showed that in patients with tumors smaller than 5 cm, LNM patients had better OS and CSS than MaVI patients, while no difference in OS and CSS was found in patients with tumors larger than 5 cm (Fig. S3).

Table 2 Comparison of demographic and clinicopathological characteristics between patients with LNM and MaVI in the hospital cohort

Variables	LNM (*N* = 41)	MaVI (*N* = 710)	*P*-value
Age, year			
≤ 60	34 (82.9%)	614 (86.5%)	0.682
> 60	7 (17.1%)	96 (13.5%)	
Gender			
Female	4 (9.8%)	75 (10.6%)	1.000
Male	37 (90.2%)	635 (89.4%)	
AFP, ng/mL			
≤ 400	23 (56.1%)	267 (37.6%)	0.028
> 400	18 (43.9%)	443 (62.4%)	
PLT, 109/L			
≤ 100	4 (9.8%)	108 (15.2%)	0.467
> 100	37 (90.2%)	602 (84.8%)	
TBIL,μmol/L			
≤ 20	37 (90.2%)	585 (82.4%)	0.279
> 20	4 (9.8%)	125 (17.6%)	
WBC			
Mean (SD)	6.37 (1.83)	5.80 (2.10)	0.062
ALB			
Mean (SD)	39.9 (3.81)	41.5 (3.61)	0.013
GGT			
Mean (SD)	134 (125)	175 (192)	0.054
ALP			
Mean (SD)	112 (59.3)	121 (77.6)	0.322
ALBI grade			
Grade 1	25 (61.0%)	497 (70.0%)	0.432
Grade 2	16 (39.0%)	211 (29.7%)	
Grade 3	0 (0%)	2 (0.3%)	
Surgical margin, cm			
< 1	33 (80.5%)	654 (92.1%)	0.021
≥ 1	8 (19.5%)	56 (7.9%)	
Tumor diameter, cm			
≤ 5	10 (24.4%)	119 (16.8%)	0.295
> 5	31 (75.6%)	591 (83.2%)	
Tumor number			
Single	29 (70.7%)	484 (68.2%)	0.865
Multiple	12 (29.3%)	226 (31.8%)	
MVI			
No	20 (48.8%)	98 (13.8%)	< 0.001
Yes	21 (51.2%)	612 (86.2%)	
Satellite nodule			
No	19 (46.3%)	218 (30.7%)	0.055
Yes	22 (53.7%)	492 (69.3%)	
Liver cirrhosis			
No	15 (36.6%)	144 (20.3%)	0.022
Yes	26 (63.4%)	566 (79.7%)	
Edmondson grade			
I-II	4 (9.8%)	10 (1.4%)	0.001
III-IV	37 (90.2%)	700 (98.6%)	
Tumor capsule			
Complete	7 (17.1%)	43 (6.1%)	0.017
Uncomplete	13 (31.7%)	303 (42.7%)	
None	21 (51.2%)	364 (51.3%)	

Table 2 (continued)

Variables	LNM (*N* = 41)	MaVI (*N* = 710)	*P*-value
Blood transfusion, ml			
No	34 (82.9%)	535 (75.4%)	0.361
Yes	7 (17.1%)	175 (24.6%)	
Bleeding loss, ml			
< 800	37 (90.2%)	580 (81.7%)	0.238
≥ 800	4 (9.8%)	130 (18.3%)	
AVT			
No	23 (56.1%)	398 (56.1%)	1.000
Yes	18 (43.9%)	312 (43.9%)	
TACE			
No	23 (56.1%)	428 (60.3%)	0.713
Yes	18 (43.9%)	282 (39.7%)	

Abbreviations: AFP, alpha fetoprotein; PLT, platelet count; TBIL, total bilirubin; WBC, white blood cell; ALB, albumin; GGT, glutamyl transpeptidase; ALP, alkaline phosphatase; ALBI, Albumin-Bilirubin; MVI, microvascular invasion; AVT, antiviral treatment; TACE, transhepatic arterial chemotherapy and embolization

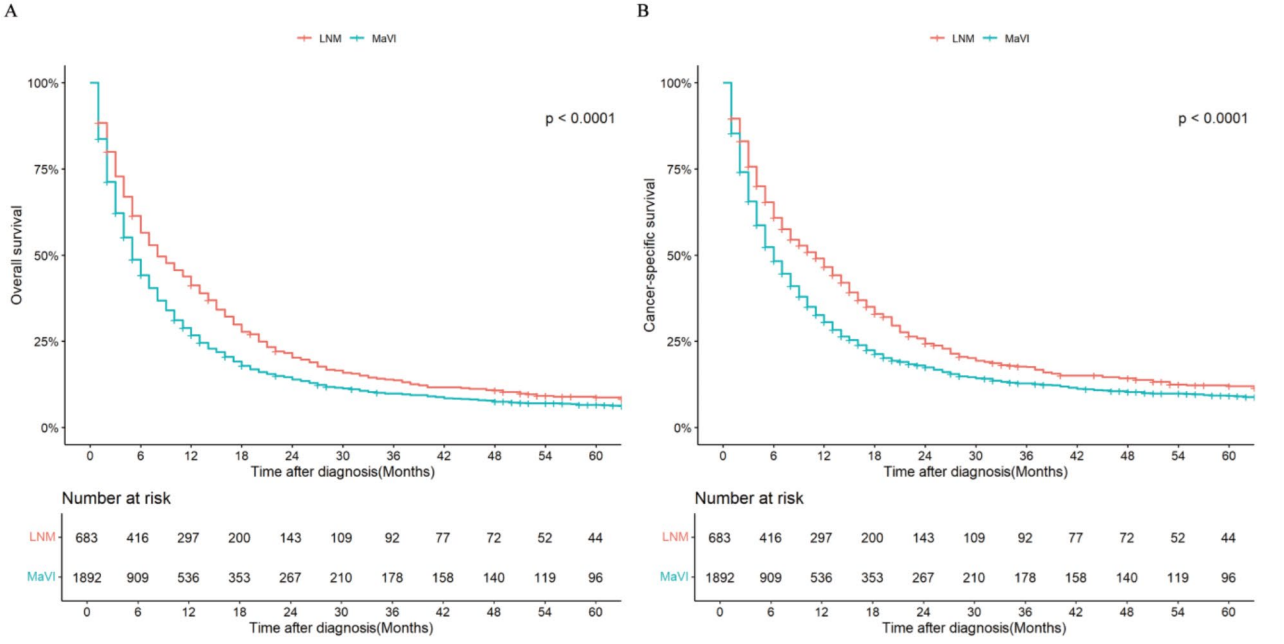

Fig. 2 Overall survival and cancer-specific survival in SEER cohort before PSM. LNM, lymph node metastasis; MaVI, macrovascular invasion; PSM, propensity score matching. **A**: overall survival; **B**: cancer-specific survival

In hospital cohort, K-M survival cures showed the OS and RFS. The OS rates at 1-year, 2-year, and 3-year were 57.50%, 48.70%, and, 42.60%, respectively, in Group LNM and 56.30%, 39.60%, and 27.40%, respectively, in Group MaVI (Fig. 4A). The RFS rates at 1-, 2-year and 3-year were 40.70%, 32.30%, and, 32.30% respectively, in Group LNM, 28.90%, 18.80%, and 13.00%, in Group MaVI (Fig. 4B).

Univariate and multivariate analyze

Before PSM, in SEER cohort, the univariate and multivariate Cox analyses for determining the risk factors associated with OS and CSS were shown in Table S1-S2. Multivariate analysis identified LNM as the type of HCC-related OS (LNM: HR = 0.79, 95%CI = 0.72–0.87, reference = MaVI, $p < 0.001$) and CSS (LNM: HR = 0.79, 95%CI = 0.71–0.87, reference = MaVI, $p < 0.001$). Other independent prognostic factors associated with OS and CSS were AFP, tumor size, receiving treatments (surgery, radiation, and chemotherapy).

After PSM, in SEER cohort, the univariate and multivariate Cox analyses for determining the risk factors associated with OS and CSS were shown in Tables 3 and 4. Multivariate analysis identified LNM as the type of HCC-related OS (LNM: HR = 0.79, 95%CI = 0.71–0.89, reference = MaVI, $p < 0.001$) and CSS (LNM: HR = 0.78,

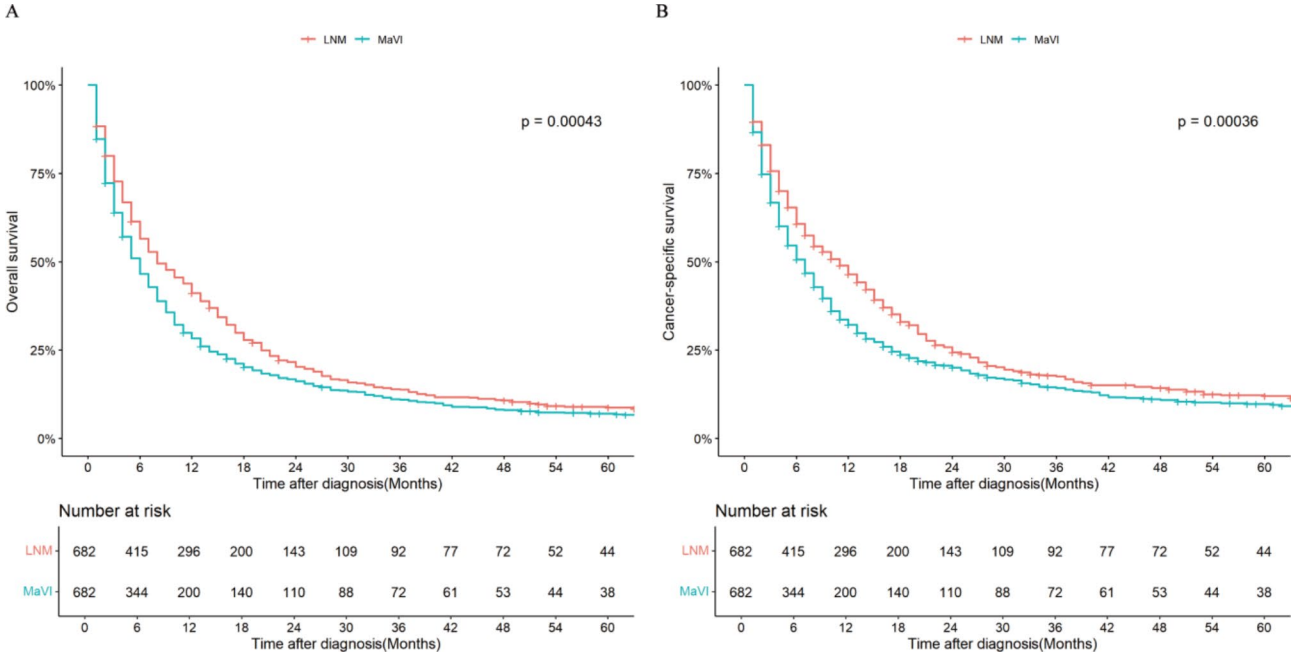

Fig. 3 Overall survival and cancer-specific survival in SEER cohort after PSM. LNM, lymph node metastasis; MaVI, macrovascular invasion; PSM, propensity score matching. **A**: overall survival; **B**: cancer-specific survival

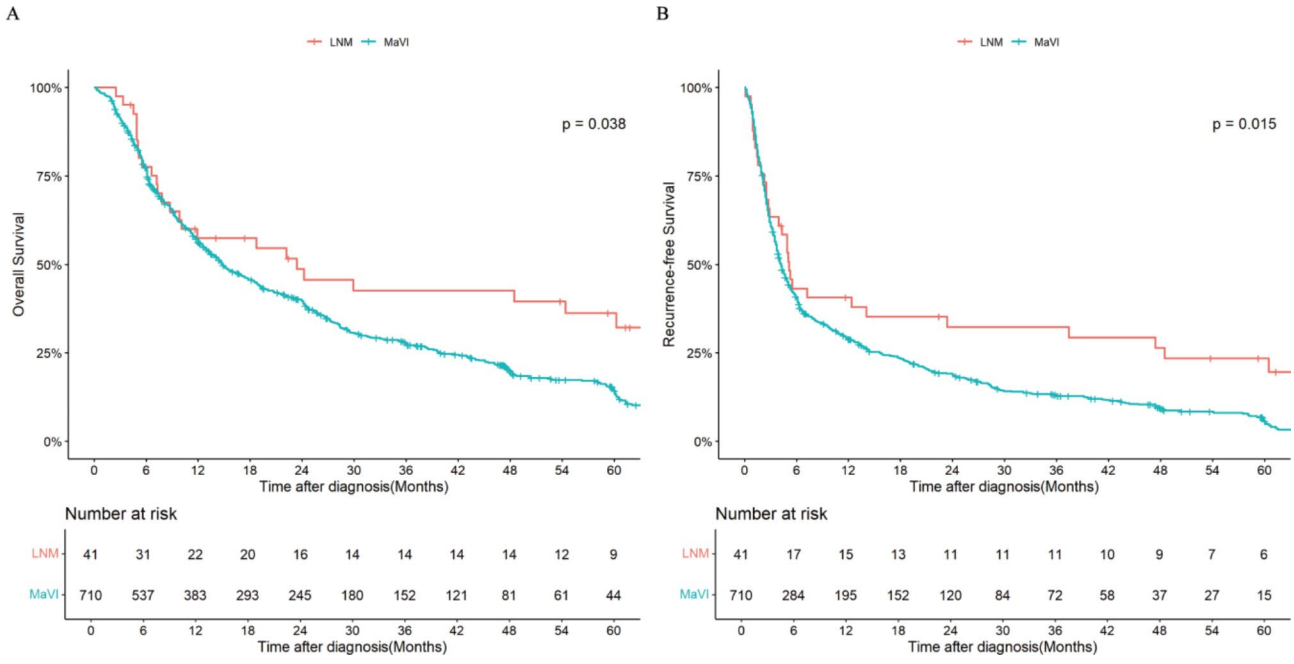

Fig. 4 Comparison of overall survival (**A**) and recurrence-free survival (**B**) between HCC with LNM and MaVI who underwent surgery in hospital cohort. Abbreviations: HCC, hepatocellular carcinoma; LNM, lymph node metastasis; MaVI, macrovascular invasion

95%CI = 0.70–0.88, reference = MaVI, $p < 0.001$). Other independent prognostic factors associated with OS and CSS were AFP, tumor size, receiving treatments (surgery, radiation, and chemotherapy).

In hospital cohort, the univariate and multivariate Cox analyses for determining the risk factors associated with OS and RFS were shown in Tables 5 and 6. Multivariate cox analysis identified LNM as the type of HCC-related OS (LNM: HR = 0.83, 95%CI = 0.57–1.23, $p = 0.261$, reference = MaVI) and RFS (LNM: HR = 0.76, 95%CI = 0.53–1.10, $p = 0.142$, reference = MaVI). Other independent prognostic factors associated with OS were tumor diameter (HR = 1.56, 95%CI = 1.24–1.96, $p < 0.001$), liver cirrhosis (HR = 1.29, 95%CI = 1.05–1.59, $p = 0.017$),

Table 3 Uni- and multivariate Cox regression analysis of risk factors of overall survival after PSM in the SEER cohort

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Sex, Female vs. Male	0.92(0.80–1.06)	0.253	/	/
Age, years ≥ 60 vs. < 60	1.07(0.95–1.20)	0.275	/	/
Race, Black vs. White	0.93(0.80–1.09)	0.382	/	/
Race, Other vs. White	0.75(0.63–0.90)	0.002	/	/
Marital status, Married vs. Single	0.98(0.85–1.13)	0.780	/	/
Marital status, Other vs. Single	1.16(0.99–1.35)	0.069	/	/
Tumor size, cm 5–10 cm vs. < 5 cm	1.34(1.18–1.52)	< 0.001	1.36(1.20–1.54)	< 0.001
Tumor size, cm > 10 cm vs. < 5 cm	1.49(1.28–1.73)	< 0.001	1.73(1.48–2.01)	< 0.001
AFP, Positive vs. Negative	1.47(1.28–1.69)	< 0.001	1.42(1.24–1.63)	< 0.001
Surgery, Yes vs. No	0.33(0.26–0.43)	< 0.001	0.28(0.22–0.36)	< 0.001
Radiation, Yes vs. No	0.68(0.56–0.83)	< 0.001	0.55(0.45–0.67)	< 0.001
Chemotherapy, Yes vs. No	0.64(0.57–0.72)	< 0.001	0.61(0.54–0.68)	< 0.001
Group, LNM vs. MaVI	0.82(0.73–0.91)	< 0.001	0.79(0.71–0.89)	< 0.001

Abbreviations: HCC, hepatocellular carcinoma; MaVI, macrovascular invasion; LNM, lymph node metastasis; HR, hazard ratio; CI, confidence interval; PSM, Propensity score matching

Table 4 Uni- and multivariate Cox regression analysis of risk factors of cancer-special survival after PSM in the SEER cohort

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Sex, Female vs. Male	0.92(0.79–1.07)	0.290	/	/
Age, years ≥ 60 vs. < 60	1.08(0.96–1.22)	0.194	/	/
Race, Black vs. White	0.91(0.77–1.08)	0.269	/	/
Race, Other vs. White	0.76(0.63–0.91)	0.003	/	/
Marital status, Married vs. Single	0.97 (0.83–1.12)	0.663	/	/
Marital status, Other vs. Single	1.13 (0.96–1.33)	0.155	/	/
Tumor size, cm 5–10 cm vs. < 5 cm	1.40(1.22–1.60)	< 0.001	1.42(1.24–1.62)	< 0.001
Tumor size, cm > 10 cm vs. < 5 cm	1.55(1.32–1.81)	< 0.001	1.79(1.52–2.10)	< 0.001
AFP, Positive vs. Negative	1.48 (1.28–1.71)	< 0.001	1.43(1.24–1.65)	< 0.001
Surgery, Yes vs. No	0.33(0.26–0.43)	< 0.001	0.28(0.22–0.36)	< 0.001
Radiation, Yes vs. No	0.69(0.56–0.85)	< 0.001	0.56(0.45–0.69)	< 0.001
Chemotherapy, Yes vs. No	0.68(0.61–0.77)	< 0.001	0.64(0.57–0.73)	< 0.001
Group, LNM vs. MavI	0.81(0.72–0.91)	< 0.001	0.78(0.70–0.88)	< 0.001

Abbreviations: HCC, hepatocellular carcinoma; MaVI, macrovascular invasion; LNM, lymph node metastasis; HR, hazard ratio; CI, confidence interval; PSM, Propensity score matching

tumor capsule (HR = 1.66, 95%CI = 1.13–2.45, $p = 0.010$, uncomplete vs. complete; HR = 2.21, 95%CI = 1.49–3.28, $p < 0.001$, none vs. complete), receiving AVT (HR = 0.74, 95%CI = 0.62–0.88, $p = 0.001$), receiving TACE (HR = 0.74, 95%CI = 0.62–0.87, $p < 0.001$). Other independent prognostic factors associated with RFS were age (HR = 0.99, 95%CI = 0.98-1.00, $p = 0.003$), tumor diameter (HR = 1.27, 95%CI = 1.03–1.57, $p = 0.025$), tumor capsule (HR = 1.52, 95%CI = 1.08–2.13, $p = 0.016$, none vs. complete), receiving TACE (HR = 0.69, 95%CI = 0.58–1.10, $p < 0.001$).

Discussions

Advanced hepatocellular carcinoma (HCC) is a serious disease because of high relapse and lacking effective curative treatment [1]. Several HCC patients are initially presented with advanced HCC or develop into advanced stages in the future [4]. The stage of the tumor is an essential factor in planning the therapeutic approach and in prognosis evaluation [15, 16]. Staging of LNM and MaVI are different in different staging systems at present [8–11]. There are some reasons for this discrepancy may be as follows: firstly, HCC is a highly heterogeneous disease, and the prognostic differences are driven by various biological characteristics [17]. LNM and MaVI represent two distinct biological behaviors, and the underlying mechanisms remain unclear. With the advent of targeted and immunotherapies, the immune profiling of HCC is actively being explored [18]. Our study provides valuable insights for further investigation into the differences in the immune microenvironment underlying these two distinct biological behaviors. Secondly, the etiology of HCC varies by region [19]. In Asia, particularly in China, Japan, and Korea, hepatitis B virus (HBV) infection is the primary risk factor for HCC. In contrast, in Western

Table 5 Uni- and multivariate Cox regression analysis of risk factors of overall survival in the hospital cohort

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age, year	1.00 (0.99-1.00)	0.389	/	/
Gender, Male vs. Female	1.09 (0.83–1.43)	0.537	/	/
AFP, ng/mL > 400 vs. ≤ 400	1.26 (1.06–1.49)	0.007	1.14 (0.96–1.36)	0.136
PLT, 10^9/L > 100 vs. ≤ 100	0.91 (0.73–1.14)	0.412	/	/
TBIL, μmol/L > 20 vs. ≤ 20	1.14 (0.92–1.42)	0.231	/	/
WBC, 10^9/L	0.98 (0.94–1.02)	0.351	/	/
ALB, g/L	0.98 (0.96-1.00)	0.091	/	/
GGT, IU/L	1.00 (1.00–1.00)	0.527	/	/
ALP, IU/L	1.00 (1.00–1.00)	0.282	/	/
ALBI grade				
Grade 2 vs. Grade 1	1.01 (0.85–1.21)	0.891	/	/
Grade 3 vs. Grade 1	1.09 (0.15–7.78)	0.931	/	/
Surgical margin, **cm ≥ 1 vs. < 1**	0.77 (0.57–1.04)	0.083	/	/
Tumor diameter, **cm > 5 vs. ≤ 5**	1.59 (1.27–1.99)	0.000	1.56 (1.24–1.96)	< 0.001
Tumor number Multiple vs. Single	1.26 (1.06–1.50)	0.009	1.13 (0.93–1.37)	0.213
MVI Yes vs. No	1.55 (1.23–1.96)	0.000	1.05 (0.81–1.36)	0.732
Satellite nodule Yes vs. No	1.36 (1.14–1.63)	0.001	1.05 (0.85–1.30)	0.622
Liver cirrhosis Yes vs. No	1.32 (1.08–1.62)	0.008	1.29 (1.05–1.59)	0.017
Edmondson grade, **III-IV vs. I-II**	1.57 (0.84–2.93)	0.158	/	/
Tumor capsule				
Uncomplete vs. Complete	1.84 (1.26–2.70)	0.002	1.66 (1.13–2.45)	0.010
None vs. Complete	2.52 (1.72–3.67)	0.000	2.21 (1.49–3.28)	< 0.001
Blood transfusion, **ml Yes vs. No**	1.19 (0.99–1.44)	0.062	/	/
Bleeding loss, **ml ≥ 800 vs. < 800**	1.14 (0.93–1.41)	0.199	/	/
AVT, **Yes vs. No**	0.68 (0.58–0.80)	0.000	0.74 (0.62–0.88)	0.001
TACE, **Yes vs. No**	0.70 (0.59–0.83)	0.000	0.74 (0.62–0.87)	< 0.001
Group, LNM vs. MaVI	0.67 (0.46–0.98)	0.039	0.83 (0.57–1.23)	0.361

Abbreviations: AFP, alpha fetoprotein; PLT, platelet count; TBIL, total bilirubin; WBC, white blood cell; ALB, albumin; GGT, glutamyl transpeptidase; ALP, alkaline phosphatase; ALBI, Albumin-Bilirubin; MVI, microvascular invasion; AVT, antiviral treatment; TACE, transhepatic arterial chemotherapy and embolization

countries, hepatitis C virus (HCV) infection, alcoholic liver disease, and non-alcoholic fatty liver disease are the main risk factors. Thirdly, Differences in economic development and healthcare levels across regions may contribute to discrepancies in staging systems. Lastly, HCC with isolated LNM is relatively rare in clinical practice, and there is a lack of clinical evidence regarding such cases. Thus, we conducted this study to compare the prognosis between LNM and MaVI in advanced HCC.

Based on this study, we found that HCC with LNM had better OS and CSS than MaVI. It is inconsistent with the current AJCC TNM Staging System and China liver cancer staging (CNLC). But it is agreed with the TNM Staging System of LCSGJ. Several studies had come up with a similar result that LNM may have better survival than MaVI. By Jean-Nicolas Vauthey et al. found that the survival of patients with lymph node involvement matched that of patients with major vascular invasion ($P = 0.30$) [15]. A Japanese nationwide survey that included a total of 14,872 patients showed that there was no significant difference in the prognosis between stage IVAnon-n1(included MaVI but not LNM) and stage n1(included LNM) [20]. An analysis of 8,828 patients in a single medical center showed that no significant difference was demonstrated in stages IIIB, IVA, and IVB [21]. BCLC staging system is the authoritative staging system in the field of HCC. But it doesn't furtherly provide a prognosis stratification for advanced HCC with LNM and MaVI. Some studies point out that HCC patients with BCLC-C can be markedly heterogeneous with varying prognoses [22, 23]. Our study provided relatively accuracy prognosis information for advanced HCC with LNM and MaVI which is supplementation for the BCLC Staging System. And the impacts of LNM and MaVI on the prognosis can provide more evidence for precise staging in the future. In addition, we have reviewed and compiled previous prognostic studies on LNM or MaVI (Table S3).

Subgroup analysis revealed that in patients undergoing surgery, chemotherapy, and those with tumor diameters smaller than 5 cm, HCC with LNM had better OS and CSS than MaVI However, we found no survival difference between the two groups in patients with larger tumor diameters or those receiving radiation therapy. In patients receiving radiation therapy, there was no

Table 6 Uni- and multivariate Cox regression analysis of risk factors of recurrence-free survival in the hospital cohort

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age, year	0.99 (0.98-1.00)	0.004	0.99 (0.98-1.00)	0.003
Gender, Male vs. Female	1.03 (0.81–1.33)	0.793		
AFP, ng/mL > 400 vs. ≤ 400	1.17 (1.00-1.37)	0.045	1.06 (0.90–1.25)	0.472
PLT, 10^9/L > 100 vs. ≤ 100	0.93 (0.75–1.15)	0.518	/	/
TBIL, μmol/L > 20 vs. ≤ 20	1.02 (0.83–1.25)	0.882	/	/
WBC, 10^9/L	0.99 (0.96–1.03)	0.668	/	/
ALB, g/L	1.02 (1.00-1.04)	0.118	/	/
GGT, IU/L	1.00 (1.00–1.00)	0.633	/	/
ALP, IU/L	1.00 (1.00–1.00)	0.629	/	/
ALBI grade				
Grade 2 vs. Grade 1	0.85 (0.72–1.01)	0.064	/	/
Grade 3 vs. Grade 1	0.53 (0.07–3.75)	0.522	/	/
Surgical margin, **cm ≥ 1 vs. < 1**	0.84 (0.64–1.11)	0.228	/	/
Tumor diameter, **cm > 5 vs. ≤ 5**	1.32 (1.08–1.62)	0.007	1.27 (1.03–1.57)	0.025
Tumor number Multiple vs. Single	1.22 (1.04–1.44)	0.016	1.08 (0.90–1.30)	0.388
MVI Yes vs. No	1.49 (1.20–1.85)	0.000	1.12 (0.89–1.43)	0.334
Satellite nodule Yes vs. No	1.36 (1.15–1.61)	0.000	1.13 (0.92–1.38)	0.234
Liver cirrhosis Yes vs. No	1.25 (1.03–1.51)	0.023	1.18 (0.97–1.43)	0.102
Edmondson grade, **III-IV vs. I-II**	1.43 (0.81–2.54)	0.218	/	/
Tumor capsule				
Uncomplete vs. Complete	1.55 (1.11–2.14)	0.009	1.39 (1.00-1.94)	0.051
None vs. Complete	1.83 (1.33–2.52)	0.000	1.52 (1.08–2.13)	0.016
Blood transfusion, **ml Yes vs. No**	1.15 (0.96–1.37)	0.119	/	/
Bleeding loss, **ml ≥ 800 vs. < 800**	1.14 (0.93–1.38)	0.200	/	/
AVT, **Yes vs. No**	0.86 (0.74-1.00)	0.052	/	/
TACE, **Yes vs. No**	0.70 (0.60–0.81)	0.000	0.69 (0.58–0.80)	< 0.001
Group, LNM vs. MaVI	0.65 (0.46–0.92)	0.017	0.76 (0.53–1.10)	0.142

Abbreviations: AFP, alpha fetoprotein; PLT, platelet count; TBIL, total bilirubin; WBC, white blood cell; ALB, albumin; GGT, glutamyl transpeptidase; ALP, alkaline phosphatase; ALBI, Albumin-Bilirubin; MVI, microvascular invasion; AVT, antiviral treatment; TACE, transhepatic arterial chemotherapy and embolization

survival difference between the two groups, which may be due to the higher sensitivity of MaVI lesions to radiotherapy compared to primary tumors and LNM [24–26]. In patients with larger tumor diameters, there was also no survival difference between the groups, which may be attributed to the prognostic impact of tumor burden caused by tumor size, outweighing the biological characteristics. This is similar to previous studies which found that in patients with larger tumors, MVI status did not affect prognosis [27, 28].

In previous studies, the prognosis of local advanced HCC is poor and the efficacy of treatment of local advanced HCC is still not satisfactory [29, 30]. In our study, the median OS is only 6 months for all patients and we found that most patients (diagnosed with HCC during 2010–2015 years) with LNM or MaVI received chemotherapy as the major treatment. But with the development of drugs, more and more evidences show that local advanced HCC patients receiving positively treatment can prolong long-term survival [31–33]. However, because of the heterogeneity of HCC, patients with different pathological features may respond differently to treatment [29, 30]. Thus, the analysis of LNM and MaVI on the prognosis can provide more evidence for individualized treatment of patients with local advanced HCC in the future.

There are some limitations to our study. Firstly, for non-surgical patients, TNM staging primarily relies on clinical follow-up data combined with typical imaging features (CT & MRI) or pathological biopsy results. Secondly, due to the regional nature of SEER data, further validation of external data from various other regions is necessary. Finaly, due to the deletion of a small number of missing variables in the SEER database during the matching analysis, this may introduce a certain degree of bias.

In conclusion, current HCC TNM staging system cannot accurately distinguish the prognosis of LNM and MaVI patients. For patients undergoing hepatectomy, HCC with LNM may obtain a better prognosis than that of HCC with MaVI. Future research requires additional clinical data to further corroborate this finding.

Abbreviations

HCC Hepatocellular carcinoma
LNM Lymph node metastasis

MaVI	Macrovascular invasion
AJCC	American joint committee on cancer
TNM	Tumor-node-metastasis
ICD	International classification of disease
AFP	Alpha fetoprotein
PLT	Platelet count
TBIL	Total bilirubin
WBC	White blood cell
ALB	Albumin
GGT	Glutamyl transpeptidase
ALP	Alkaline phosphatase
ALBI	Albumin-bilirubin
MVI	Microvascular invasion
AVT	Antiviral treatment
TACE	Transhepatic arterial chemotherapy and embolization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Not applicable.

Author contributions
Jinyu Zhang and Jianxing Zeng contributed to the study's design. Jinyu Zhang, Yifan Chen and Peng Ye performed the data analyses, interpretation, and modifed of the manuscript. Jinyu Zhang, Qionglan Wu contributed to data collection. Jianxing Zeng and Jingfeng Liu provided administrative and financial support. All authors read and approved the final manuscript.

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Data availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (ethical approval number: 2021_111_01). At the same time, this study has obtained the exemption of informed consent application from the Ethics Committee of Mengchao Hepatobiliary Hospital of Fujian Medical University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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