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Original Article

Association of concomitant MASLD and hepatitis B virus with clinical prognosis in hepatocellular carcinoma after curative resection

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Abstract: The term "metabolic dysfunction-associated steatotic liver disease" (MASLD) was introduced to replace the term "nonalcoholic fatty liver disease". The prevalence of MASLD is increasing worldwide. The prevalence of concomitant MASLD and hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is also increasing. This study explored the effect of the coexistence of MASLD and HBV on clinicopathological features and long-term clinical prognoses in patients with MASLD-related and/or HBV-related HCC after curative hepatectomy. The study retrospectively collected the data of 653 patients with HCC who had undergone curative hepatectomy between 2011 and 2022. We assessed the association of histologically confirmed MASLD with HCC recurrence and mortality. Of 653 patients, 320 (49.0%), 103 (15.8%), and 230 (35.2%) had concomitant MASLD and HBV, MASLD only, and HBV only, respectively. The median follow-up period was 5.1 years. Patients with concomitant MASLD and HBV were at a significantly increased risk of HCC recurrence ($P = 0.013$ and $P = 0.041$) and mortality ($P = 0.044$ and $P = 0.026$) than those with MASLD or HBV alone. In multivariable analyses, concomitant MASLD and HBV, male sex, body mass index < 23, absence of antiviral therapy, and tumor size ≥ 5 cm were significantly associated with increased HCC recurrence. Concomitant MASLD and HBV, male sex, type 2 diabetes mellitus, serum aspartate aminotransferase ≥ 40 U/L, tumor size ≥ 5 cm, tumor cell differentiation II-III, microvascular invasion, lymph node invasion, and tumor recurrence were significantly associated with increased mortality. In conclusion, patients with concomitant MASLD and HBV are at a significantly greater risk of HCC recurrence and mortality after curative hepatectomy than those with MASLD or HBV alone.

Keywords: Metabolic dysfunction-associated steatotic liver disease, hepatitis B virus, hepatocellular carcinoma, recurrence, mortality

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1-3]. In Taiwan, HCC is often caused by viral or alcohol-related diseases [4, 5]. Recent advances in treatments for chronic hepatitis B

virus (HBV) and hepatitis C virus (HCV) infections have reduced the proportion of HCC cases caused by these viruses [6]. Despite advancements in diagnosis and treatment approaches, the risk of HCC recurrence and mortality after resection remains high, with recurrence and mortality rates exceeding 50% within 5 years [7, 8]. Key prognostic factors for HCC recurrence after resection include tumor number and size, microvascular invasion, metabolic syndrome, cirrhosis, and Barcelona Clinic Liver Cancer (BCLC) stage [7, 9, 10].

The global incidence of nonalcoholic fatty liver disease (NAFLD) is increasing because of the increasing rates of metabolic disorders, such as insulin resistance, type 2 diabetes mellitus, dyslipidemia, obesity, and hypertension [11, 12]. In the Asia-Pacific region, the coexistence of NAFLD and HBV infection is an emerging clinical concern. The interaction between NAFLD and HBV has been shown to accelerate HCC development [13].

In Taiwan, where HBV is endemic, the prevalence of concurrent metabolic dysfunction-associated fatty liver disease (MAFLD) in HBV-related HCC is expected to increase. However, in previous international guidelines, NAFLD was defined by excluding secondary causes of hepatic steatosis, such as substantial alcohol consumption, HBV infection, and other factors; consequently, MAFLD and chronic hepatitis B (CHB) were not considered to coexist [14, 15]. Accordingly, data on the effect of MAFLD on HBV-related HCC, particularly in HBV-endemic regions with a high HCC prevalence, remain limited. Specifically, few studies have reported the influence of MAFLD on the pathological characteristics and outcomes of HBV-related HCC after curative resection [10, 16]. In 2020, the term "metabolic dysfunction–associated fatty liver disease" was introduced to replace NAFLD, reflecting the disease's association with metabolic dysfunction [17, 18]. MAFLD is currently recognized as the most prevalent chronic liver disease worldwide, driven by the increased prevalence of metabolic syndrome features [19, 20]. Additionally, the prevalence of MAFLD-related cirrhosis and HCC is increasing [21-26].

In 2023, a multisociety Delphi consensus redefined the classification of liver diseases, introducing the term "metabolic dysfunction-associated steatotic liver disease" (MASLD) to replace NAFLD and MAFLD [27]. MASLD is diagnosed by identifying hepatic steatosis and at least one cardiometabolic risk factor [27]. This updated definition allows for the coexistence of MASLD and HBV, which is particularly relevant in regions such as Taiwan, where HBV is endemic. Consequently, the incidence of concurrent MASLD and HBV-related HCC is expected to increase due to the increasing prevalence of MASLD and its broader diagnostic criteria.

Only one study has explored the effect of MASLD on the clinical prognosis of HBV-related HCC after curative hepatectomy [28]. The new definitions emphasize MASLD as a critical condition that can coexist with HBV, highlighting the need for further research in this area. Accordingly, the present study investigated the effect of MASLD and HBV coexistence on the clinicopathological features and long-term clinical outcomes of MASLD and/or HBV-related HCC after curative hepatectomy. The study focused on HBV-endemic countries with a high prevalence of HCC.

Materials and methods

Study design and ethics

This multicenter, retrospective, cross-sectional cohort study was conducted in Taiwan. The research was approved by the Institutional Review Board of E-DA Hospital. The requirement for informed consent was waived because of the minimal risk to participants and the study's retrospective design. Moreover, the study was conducted in accordance with the Declaration of Helsinki and the guidelines of the International Conference on Harmonization for Good Clinical Practice.

Study population

Data for this study were sourced from E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital. The data of patients with HCC treated between October 2011 and December 2022 were collected. The last follow-up time was October 31, 2023. Patients were included if they were diagnosed as having HBV infection, were diagnosed as having MASLD, underwent curative hepatectomy between 2011 and 2022, and had a pathology report of liver steatosis. Patients were excluded if they lacked a report of liver steatosis, were diagnosed as having HCV infection, consumed

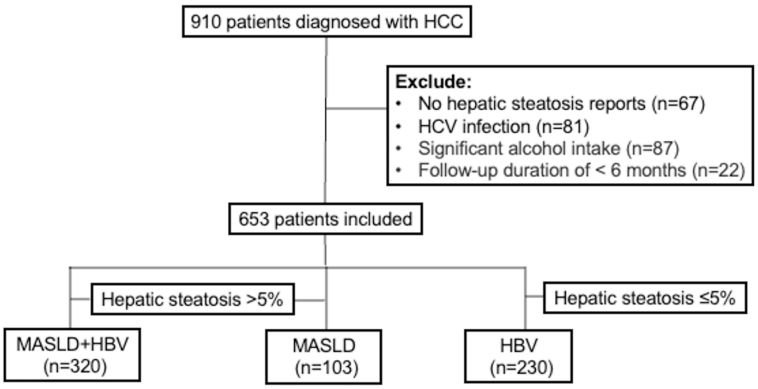

Figure 1. Flow chart of patient's selection.

a substantial amount of alcohol (> 210 g/week for men, > 140 g/week for women), or had less than 6 months of follow-up data. A flowchart of the patient enrollment process is illustrated in **Figure 1**. In total, 910 patients with HBV and/or MASLD underwent surgical resection for HCC. Of these patients, 67 were excluded owing to the lack of a report of liver steatosis, 81 were excluded owing to having HCV, 87 were excluded owing to substantial alcohol consumption, and 22 were excluded owing to the lack of at least 6 months of follow-up data. Consequently, 653 patients with complete liver steatosis data were eligible for analysis (**Figure 1**).

Data collection

Patient data were retrospectively collected from medical records at the time of surgery. Data were collected on sex, age, body mass index (BMI), type 2 diabetes mellitus status, hypertension, dyslipidemia, alcohol intake, smoking history, serum biochemistry, tumor markers, hepatitis B markers, and HBV DNA level. Data on the pathological features of resected tumors were also collected (i.e., tumor number, tumor size, macrovascular invasion, microvascular invasion, lymph node invasion, tumor cell differentiation, histological grade, and cirrhosis).

Study outcomes

The primary and secondary endpoints were HCC recurrence and overall mortality after surgery, respectively. The follow-up time was defined as the time from the date of inclusion to the date of death, the last follow-up, or the end of the study (October 31, 2023), whichever was earliest. The recurrence time was defined as the time from the date of inclusion to the date of HCC operation, the date of death, the last follow-up, or the end of the study (October 31, 2023), whichever was earliest. HCC recurrence was established on the basis of histology or at least two typical HCC imaging methods, as outlined by the HCC guidelines of the American Association for the Study of Liver Disease [3].

Definition

MASLD diagnosis requires evidence of hepatic steatosis (> 5%) and at least one of the following five cardiometabolic risk factors: (1) a BMI of ≥ 23 kg/m^2 for Asian populations or a waist circumference of > 94 cm for men or > 80 cm for women; (2) a diagnosis or treatment of type 2 diabetes mellitus, fasting serum glucose level of ≥ 5.6 mmol/L (100 mg/dL), 2-hour postload glucose level of ≥ 7.8 mmol/L (140 mg/dL), or HbA1c level of ≥ 5.7% (39 mmol/mol); (3) a blood pressure level of ≥ 130/85 mmHg or treatment with specific antihypertensive drugs; (4) a plasma triglyceride level of ≥ 1.70 mmol/L (150 mg/dL) or treatment with lipid-lowering medications; or (5) a plasma HDL cholesterol level of < 1.0 mmol/L (40 mg/dL) for men or < 1.3 mmol/L (50 mg/dL) for women, treatment with lipid-lowering medications, or exclusion of other causes of steatosis, including exclusion of excessive alcohol consumption (> 210 g/week for men, > 140 g/week for women) [27].

HCC staging was conducted in accordance with BCLC guidelines [29]. Tumor differentiation was graded histologically using the modified nuclear grading scheme developed by Edmondson and Steiner [3]. Liver cirrhosis was diagnosed on the basis of an Ishak fibrosis score of 5-6 in nontumor tissues [30]. Type 2 diabetes mellitus was diagnosed in accordance with criteria set by the American Diabetes Association [31].

Statistical analysis

Continuous data are expressed as means and standard deviations (SDs), and categorical data are expressed as numbers and percentages.

Normally distributed continuous variables were compared using Student's *t* test, and the Wilcoxon rank-sum test was applied for comparisons of two groups when continuous variables were not normally distributed. A chi-square test was used to compare categorical variables. Cumulative HCC recurrence and mortality rates were evaluated using the Kaplan-Meier method. Because patients who have died are no longer at risk for HCC recurrence, competing risk analyses were conducted to evaluate cumulative HCC recurrence while accounting for mortality. Both univariable and multivariable analyses were used to identify risk factors for HCC recurrence and mortality. Multivariable analyses were conducted using Cox proportional regression models for HCC. $P < 0.05$ indicated statistical significance. All analyses were performed using Statistical Package for Social Sciences (version 23.0; Chicago, IL, USA).

Results

Patient characteristics

Of 653 eligible patients, 320 (49.0%) had HCC with concomitant MASLD and HBV, 103 (15.8%) had HCC with MASLD only, and 230 (35.2%) had HCC with HBV only. The demographic and clinicopathological characteristics of the study patients are presented in **Table 1**. Notably, 555 (85%) patients were men. The mean (SD) age was 60 (10) years. HCC recurrence occurred in 287 (44.0%) patients, and mortality occurred in 277 (42.4%) patients. Additionally, 26.9% of the patients received a diagnosis of type 2 diabetes mellitus, and 27.9% of the patients had dyslipidemia. One-fourth of the patients had liver cirrhosis. Regarding tumor stage, 85.5% and 79.5% of the patients' tumors were classified as BCLC stage 0-A and tumor-node-metastasis (TNM) stage I-II, respectively.

Effect of concomitant MASLD and HBV on clinical prognosis of HCC after surgical resection

After a mean follow-up period of 5.1 years, 167 (52.2%), 32 (31.1%), and 88 (38.3%) patients with concomitant MASLD and HBV, MASLD only, and HBV only, respectively, experienced HCC recurrence (**Table 1**). The cumulative incidence of HCC recurrence was significantly higher among patients with concomitant MASLD and HBV than among those with MASLD only ($P = 0.013$) or HBV only ($P = 0.041$; **Figure 2A**). HCC recurrence did not differ significantly between the patients with MASLD only and those with HBV only ($P = 0.312$; **Figure 2A**). Moreover, 159 (49.7%), 36 (35%), and 82 (35.7%) patients with concomitant MASLD and HBV, MASLD only, and HBV only, respectively, experienced mortality (**Table 1**). The cumulative incidence of mortality was significantly higher among patients with concomitant MASLD and HBV than among those with MASLD only ($P = 0.044$) or HBV only ($P = 0.026$; **Figure 2B**). Mortality did not differ significantly between the patients with MASLD only and those with HBV only ($P = 0.733$; **Figure 2B**). These results indicate that patients with concomitant MASLD and HBV are at significantly increased risk of HCC recurrence and mortality when compared with those with MASLD or HBV alone.

HCC recurrence risk factors in patients who had undergone hepatectomy

A Cox proportional hazards model was used to summarize the prognostic factors for HCC recurrence (**Table 2**). Univariate analysis results revealed that sex, BMI, type 2 diabetes mellitus status, dyslipidemia, surface antigen of HBV, HBV DNA level, antiviral therapy, tumor size, microvascular invasion, lymph node invasion, TNM stage, BCLC stage, and etiology were significant risk factors for HCC recurrence (**Table 2**). Multivariable analysis results indicated that male sex (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.15-2.42, $P = 0.008$), tumor size ≥ 5 cm (HR: 1.35; 95% CI, 1.06-1.72, $P = 0.022$), and concomitant MASLD and HBV (HR: 1.62; 95% CI, 1.13-2.33, $P = 0.007$) were also significant risk factors for HCC recurrence. However, BMI ≥ 23 (HR: 0.56; 95% CI, 0.41-0.76, $P < 0.001$) and antiviral therapy (HR: 0.74; 95% CI, 0.56-0.95, $P = 0.021$) were significantly associated with lower HCC recurrence rates.

Kaplan-Meier analysis results revealed that patients with concomitant MASLD and HBV had a significantly higher risk of HCC recurrence than did those with MASLD only ($P = 0.013$) or HBV only ($P = 0.041$; **Figure 2A**). For patients with concomitant MASLD and HBV, the 1-, 5-, and 10-year cumulative HCC recurrence rates were 11.2%, 42.8%, and 68.2%, respectively. By contrast, those with MASLD only had 1-, 5-, and 10-year cumulative HCC recurrence rates of 2.9%, 36.0%, and 42.9%, respectively, and

Table 1. Demographic data of all patients

Characteristics	Total cohort (n = 653)	MASLD+HBV (n = 320)	MASLD (n = 103)	HBV (n = 230)	*P*-value*
Gender (male)	555 (85.0)	285 (89.1)	85 (82.5)	185 (80.4)	0.015
Age (years)	60 (10)	60 (10)[a]	67 (8)[c]	55 (11)[b]	< 0.001
BMI (kg/m^2)	24.8 (3.8)	26.1 (3.2)	26.0 (3.5)[c]	22.4 (3.6)[b]	0.018
Hypertension, present	339 (47.9)	191 (59.7)	56 (54.4)[c]	66 (28.7)[b]	< 0.001
Diabetes, present	147 (26.9)	102 (31.9)[a]	45 (43.7)[c]	29 (12.6)[b]	< 0.001
Dyslipidemia, present	182 (27.9)	96 (30.0)[a]	48 (46.6)[c]	38 (16.5)[b]	< 0.001
Alcohol, present	86 (13.2)	48 (15.0)[a]	5 (4.8)[c]	38 (16.5)	< 0.001
Smoking, present	110 (16.8)	66 (20.6)[a]	8 (7.8)[c]	36 (15.7)	0.008
AST (IU/L)	49 (39)	43 (24)	49 (36)[c]	57 (53)[b]	0.002
ALT (IU/L)	49 (44)	47 (41)	44 (36)	53 (50)	0.713
Total bilirubin (mg/dL)	0.8 (0.5)	0.8 (0.5)	0.8 (0.5)	0.8 (0.5)	0.928
Albumin (g/dL)	4.2 (0.3)	4.3 (0.3)	4.2 (0.3)	4.2 (0.4)[b]	0.598
Platelet count (×10^3/mL)	190 (74)	192 (70)	200 (71)[c]	182 (81)[b]	0.012
INR	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.934
α-fetoprotein (ng/mL)	8399 (50988)	4454 (27750)	7031 (34958)	14500 (75663)[b]	0.048
ALBI grade (I)	552 (84.5)	282 (88.1)	86 (83.5)	184 (80.0)[b]	0.032
ICG (%)	11.4 (6.7)	11.6 (6.9)	11.5 (5.9)	11.0 (6.6)	0.835
HBsAg-positive	550 (84.2)	320 (100)[a]	0 (0)[c]	230 (100)	< 0.001
HBeAg-positive	100 (15.3)	57 (17.8)[a]	0 (0)[c]	43 (18.7)	< 0.001
Baseline HBV DNA (log^{10} IU/mL)	6.8 (7.5)	5.7 (7.2)[a]	0 (0)[c]	7.1 (7.8)	< 0.001
Baseline HBV DNA, detectable	304 (46.6)	174 (54.4)[a]	0 (0)[c]	130 (56.5)	< 0.001
Antiviral therapy-positive	430 (65.8)	256 (80.0)[a]	0 (0)[c]	174 (75.7)	< 0.001
Ishak score	2.9 (2.0)	2.8 (2.0)[a]	2.3 (1.9)[c]	3.1 (2.0)	0.002
Liver cirrhosis, present	161 (24.7)	77 (24.1)	15 (14.6)	69 (30.0)	0.010
Child-Pugh class A	644 (98.6)	315 (98.4)	102 (90.0)	227 (98.7)	0.896
Operative margin (> 1 cm)	457 (70.0)	232 (72.5)	71 (68.9)	154 (67.0)	0.364
Tumor cell differentiation, I	61 (9.3)	30 (9.4)	11 (10.7)	20 (8.7)	0.847
Macrovascular invasion, present	73 (11.2)	32 (10.0)	13 (12.6)	28 (12.2)	0.640
Microvascular invasion, present	199 (30.5)	104 (32.5)	27 (26.2)	68 (29.6)	0.451
Lymph node invasion, present	22 (3.4)	13 (4.1)	2 (1.9)	7 (3.0)	0.551
Tumor number, single	591 (90.5)	293 (91.6)	95 (92.2)	203 (88.3)	0.346
Tumor size (cm)	5.2 (3.4)	5.0 (3.1)[a]	6.0 (3.6)[c]	5.1 (3.7)	0.036
Tumor size, < 5 cm	384 (58.8)	190 (59.4)[a]	50 (48.5)[c]	144 (62.2)	0.053
TNM stage I-II	519 (79.5)	249 (77.8)	85 (82.5)	185 (80.4)	0.553
BCLC stage 0-A	560 (85.5)	282 (88.1)	88 (85.4)	190 (82.6)	0.188
Recurrence	287 (44.0)	167 (52.2)[a]	32 (31.1)	88 (38.3)[b]	< 0.001
Recurrence time	4.3 (3.2)	4.5 (3.2)	4.2 (3.1)	4.2 (3.4)	0.687
Mortality	277 (42.4)	159 (49.7)[a]	36 (35.0)	82 (35.7)[b]	0.001
Follow up time	5.1 (3.3)	5.1 (3.3)	5.2 (3.2)[c]	5.0 (3.5)	0.523

Data shown as mean (standard deviation) or number (%); MASLD: Metabolic dysfunction-associated steatotic liver disease; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: international normalized ratio; ALBI grade: Albumin-bilirubin grade; HBsAg: Hepatitis B Surface Antigen; HBeAg: Hepatitis B e Antigen; HBV: Hepatitis B Virus; BCLC stage: Barcelona clinic liver cancer; Marker a: *P*-value < 0.05, HBV+MASLD *vs.* MAFLD; b: *P*-value < 0.05, HBV+MASLD *vs.* HBV; c: *P*-value < 0.05, MASLD *vs.* HBV; *P*-value is used by Student's *t* tests, Wilcoxon rank-sum statistics or Chi-squared tests. *: *P*-value is used by one-way ANOVA test among three groups.

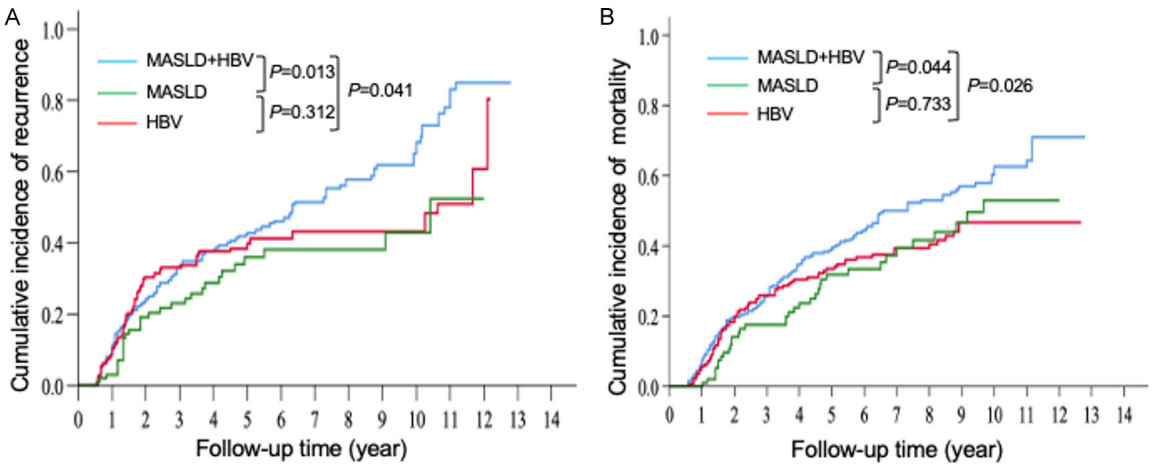

Figure 2. The cumulative incidences of hepatocellular carcinoma recurrence and mortality after surgical resection. The cumulative incidences of HCC recurrence according to different etiologies (A). Patients with concomitant MASLD and HBV significantly increased the incidence of HCC recurrence compared to those with MASLD or HBV alone. The cumulative incidences of mortality according to different etiologies (B). Patients with concomitant MASLD and HBV significantly increased the incidence of mortality compared to those with MASLD or HBV alone.

those with HBV only had 1-, 5-, and 10-year cumulative HCC recurrence rates of 8.4%, 38.4%, and 43.2%, respectively (**Figure 2A**).

In the competing risk analysis, patients with concomitant MASLD and HBV still had a significantly higher risk of HCC recurrence than did those with MASLD only ($P = 0.019$) or HBV only ($P = 0.031$; **Figure 3**). For patients with concomitant MASLD and HBV, the 1-, 5-, and 10-year cumulative HCC recurrence rates were 3.1%, 26.4%, and 54.9%, respectively, whereas these rates were 1.5%, 20.4%, and 23.5%, respectively, for those with MASLD only and 4.2%, 21.7%, and 29%, respectively, for those with HBV only (**Figure 3**).

Mortality risk factors in patients who had undergone hepatectomy

A Cox proportional hazards model was used to summarize the prognostic factors for mortality (**Table 3**). Univariate analysis results demonstrated that sex, BMI, type 2 diabetes mellitus, hypertension, dyslipidemia, serum aspartate aminotransferase, alpha-fetoprotein, Hepatitis B e Antigen, Ishak score, tumor number, tumor size, tumor cell differentiation, macrovascular invasion, microvascular invasion, lymph node invasion, TNM stage, BCLC stage, recurrence, and etiology were significant risk factors for mortality (**Table 3**). Multivariable analysis results revealed that male sex (HR: 1.66; 95% CI: 1.09-2.52, $P = 0.019$), type 2 diabetes mellitus (HR: 1.54; 95% CI, 1.13-2.09, $P = 0.006$), serum aspartate aminotransferase ≥ 40 U/L (HR: 1.34; 95% CI, 1.02-1.76, $P = 0.033$), tumor size ≥ 5 cm (HR: 1.56; 95% CI, 1.19-2.05, $P < 0.001$), tumor cell differentiation II-III (HR: 3.63; 95% CI, 1.89-6.95, $P < 0.001$), microvascular invasion (HR: 1.51; 95% CI, 1.21-2.05, $P = 0.007$), lymph node invasion (HR: 2.29; 95% CI, 1.28-4.09, $P = 0.005$), tumor recurrence (HR: 2.79; 95% CI, 2.14-3.66, $P < 0.001$), and concomitant MASLD and HBV (HR: 1.45; 95% CI, 1.01-2.08, $P = 0.046$) were significant risk factors for mortality.

The Kaplan-Meier analysis revealed that patients with concomitant MASLD and HBV had a significantly higher risk of mortality than did those with MASLD only ($P = 0.044$) or HBV only ($P = 0.026$; **Figure 2B**). For patients with concomitant MASLD and HBV, the 1-, 5-, and 10-year cumulative mortality rates were 7.6%, 38.7%, and 60.2%, respectively, whereas these rates were 0%, 31.8%, and 53.0%, respectively, for those with MASLD only and 5.8%, 33.5%, and 46.7%, respectively, for those with HBV only (**Figure 2B**).

Discussion

This study analyzed the data of 653 patients with MASLD and/or HBV who had undergone curative resection for HCC. The median follow-up period was 5.1 years. The study explored the effect of concurrent MASLD and HBV on long-

Table 2. Univariate and multivariate Cox regression analyses predicting hepatocellular carcinoma recurrence in the all hepatocellular carcinoma patients after surgical resection

Characteristics	HCC recurrence			
	Univariate analyses		Multivariate analyses	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender, Female vs. Male	1.53 (1.07-2.18)	0.019	1.66 (1.15-2.42)	0.008
Age (years), < 60 vs. ≥ 60	0.94 (0.75-1.19)	0.620		
BMI (kg/m^2), < 23 vs. ≥ 23	0.78 (0.61-0.99)	0.045	0.56 (0.41-0.76)	< .001
Diabetes Mellitus, No vs. Yes	1.32 (1.01-1.72)	0.039	1.21 (0.88-1.63)	0.233
Hypertension, No vs. Yes	1.23 (0.98-1.56)	0.079		
Hyperlipidemia, No vs. Yes	1.28 (0.97-1.65)	0.042	1.16 (0.79-1.57)	0.429
Alcohol, No vs. Yes	1.27 (0.96-1.62)	0.059		
Smoking, No vs. Yes	0.98 (0.73-1.32)	0.898		
AST (IU/L), < 40 vs. ≥ 40	1.25 (0.95-1.61)	0.055		
ALT (IU/L), < 40 vs. ≥ 40	1.16 (0.91-1.46)	0.224		
Total Bilirubin (mg/dl), < 1.2 vs. ≥ 1.2	1.09 (0.95-1.35)	0.398		
Albumin (g/dl), < 3.5 vs. ≥ 3.5	0.95 (0.53-1.70)	0.871		
Platelet count (×10^3/ml), < 150K vs. ≥ 150K	0.99 (0.78-1.27)	0.953		
INR, < 1.0 vs. ≥ 1.0	0.95 (0.73-1.33)	0.899		
AFP (ng/dl), < 200 vs. ≥ 200	1.17 (0.90-1.53)	0.252		
ALBI grade I vs. II-III	0.97 (0.70-1.32)	0.823		
HBsAg, Positive vs. Negative	1.46 (1.01-2.11)	0.044	1.15 (0.71-1.86)	0.571
HBeAg, Positive vs. Negative	0.84 (0.60-1.17)	0.838		
Serum HBV DNA, detectable vs. undetectable	1.27 (1.01-1.60)	0.045	1.08 (0.83-1.41)	0.591
Antiviral therapy, No vs. Yes	0.68 (0.53-0.88)	0.004	0.74 (0.56-0.95)	0.021
Ishak score, 0-4 vs. 5-6	1.13 (0.95-1.38)	0.379		
Liver cirrhosis, No vs. Yes	1.47 (1.13-1.92)	0.004		
Child-Pugh class, A vs. B	1.74 (0.77-3.9)	0.182		
Operative margin (cm), < 1.0 vs. ≥ 1.0	1.08 (0.83-1.38)	0.578		
Tumor number, Single vs. Multiple	1.42 (0.97-2.04)	0.076		
Tumor size (cm), < 5 vs. ≥ 5	1.54 (1.22-1.94)	< .001	1.35 (1.06-1.72)	0.022
Tumor cell differentiation I vs. II-III	1.21 (0.79-1.85)	0.388		
Macrovascular invasion, No vs. Yes	1.14 (0.79-1.62)	0.496		
Microvascular invasion, No vs. Yes	1.36 (1.05-1.76)	0.017	1.18 (0.89-1.55)	0.249
Lymph node invasion, No vs. Yes	3.07 (1.71-5.51)	< .001	1.89 (0.99-3.56)	0.051
TNM stage, I-II vs. III-IV	1.55 (1.18-2.04)	0.002	1.29 (0.93-1.81)	0.122
BCLC stage, 0-A vs. B-C	1.43 (1.03-2.01)	0.035	1.04 (0.72-1.51)	0.848
Etiology, MASLD+HBV vs. HBV	1.61 (1.11-2.36)	0.013	1.62 (1.13-2.33)	0.007
Etiology, MASLD+HBV vs. MASLD	1.23 (0.82-1.85)	0.312	1.19 (0.82-1.58)	0.556

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: international normalized ratio; ALBI grade: Albumin-bilirubin grade; HBsAg: Hepatitis B Surface Antigen; HBeAg: Hepatitis B e Antigen; HBV: Hepatitis B Virus; BCLC stage: Barcelona clinic liver cancer; MAFLD: Metabolic associated fatty liver disease.

term clinical prognoses after curative hepatectomy for HCC. Notably, patients with concomitant MASLD and HBV were significantly more likely to experience HCC recurrence and mortality when compared with those with MASLD only or HBV only, even after relevant demographic and clinical characteristics were accounted for. According to our review of the literature, this study is the first to demonstrate that among patients with HCC, those with concurrent MASLD (as per the newly defined criteria) and HBV have significantly worse clinical outcomes following hepatectomy than do those with MASLD or HBV alone.

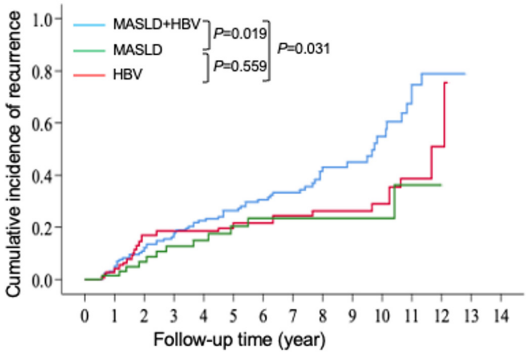

Figure 3. The cumulative incidences of hepatocellular carcinoma recurrence after surgical resection after competing risk analysis. Patients with concomitant MASLD and HBV significantly increased the incidence of HCC recurrence compared to those with MASLD or HBV alone after competing risk analysis.

MASLD has been significantly associated with increased overall survival but not recurrence-free survival in patients who underwent curative resection for HBV-related early-stage HCC (BCLC stage 0 or A) [28]. The present study revealed that patients with concurrent MASLD and HBV were at a significantly higher risk of HCC recurrence and mortality when compared with those with MASLD or HBV alone. Our study showed that patients with concurrent MASLD and HBV were at a significantly greater risk of HCC recurrence than those with HBV only. Our study also showed that patients with concurrent MASLD and HBV were at a significantly greater risk of HCC recurrence than those with MASLD only. Our study examined clinical prognoses across a broader range of disease stages than did other studies.

Several studies have examined the effects of metabolic dysfunction and fatty liver disease on clinical outcomes in patients with HBV-related HCC after surgery. Some studies have suggested that MAFLD is a risk factor for HCC recurrence, especially among patients with HBV-related HCC who have undergone hepatectomy. Our study findings are consistent with those of other relevant studies, suggesting that MAFLD increases the risk of HCC recurrence among patients with HBV-related HCC [16, 32-35]. A meta-analysis reported that patients (especially Asian patients) with NAFLD-related HCC have shorter survival after cancer recurrence [36]. Another study demonstrated that MAFLD is not associated with HCC recurrence [37]. Our study findings are consistent with those of several studies reporting that MASLD is a significant risk factor for HCC recurrence in patients with HBV-related HCC after curative hepatectomy. Some studies have suggested that MAFLD has a protective effect on the clinical prognosis of patients with overall survival, especially in the context of HBV-related HCC after hepatectomy. Some studies have shown that among patients who underwent hepatectomy for HCC, those with both MAFLD and HBV lived longer than did those with only HBV. Our study is different from other studies suggesting MAFLD improves overall survival outcomes among patients with HBV-related HCC [36, 38]. The negative effects of fatty liver disease on overall survival differ by study population. Our study revealed that patients with both MASLD and HBV had lower overall survival rates than did those with HBV only, similar to the findings of other studies [34, 35, 39]. Xue et al. observed that concurrent MAFLD was correlated with a lower rate of overall survival in patients with HBV-related HCC [40]. Yun et al. reported that MAFLD was significantly associated with poorer survival outcomes [16]. These findings highlight the complexity of the association among metabolic dysfunction, fatty liver disease, HBV, and HCC, suggesting that factors such as population demographics and study design influence study results. Huang et al. indicated that concurrent MASLD was associated with higher rates of HBsAg seroclearance and seroconversion in patients with HBV infection [41]. This suggests that hepatic steatosis may facilitate favorable outcomes in HBV. A negative association between MASLD and clinical outcomes was observed in the context of HCC. Comorbidities such as obesity, type 2 diabetes mellitus, dyslipidemia, and liver steatosis increase the risk of an adverse clinical prognosis, adding to the complexity of these associations. Possible explanations include MASLD creating a different immune environment in the liver, affecting tumor progression, and metabolic alterations like lipid acumination, insulin resistance and changes in adipokines impacting tumor growth. I Additionally, metabolic dysfunctions characteristic of MASLD along with a cellular inflammatory environment marked by oxidative stress, endoplasmic reticulum stress, and cytokine imbalance are likely to exacerbate the hepatocarcinogenic potential of HBV. Furthermore, several signaling pathways have

Table 3. Univariate and multivariate Cox regression analyses predicting mortality in the hepatocellular carcinoma patients after surgical resection

Characteristics	Mortality			
	Univariate analyses		Multivariate analyses	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender, Female vs. Male	1.77 (1.21-2.62)	0.004	1.66 (1.09-2.52)	0.019
Age (years), < 60 vs. ≥ 60	0.78 (0.77-1.24)	0.841		
BMI (kg/m^2), < 23 vs. ≥ 23	0.73 (0.57-0.93)	0.011	0.78 (0.56-1.08)	0.144
Diabetes Mellitus, No vs. Yes	1.63 (1.26-2.11)	< .001	1.54 (1.13-2.09)	0.006
Hypertension, No vs. Yes	1.42 (1.12-1.79)	0.004	1.32 (0.97-1.78)	0.075
Hyperlipidemia, No vs. Yes	1.35 (1.09-1.62)	0.039	1.24 (0.98-1.71)	0.068
Alcohol, No vs. Yes	1.31 (0.95-1.81)	0.096		
Smoking, No vs. Yes	1.11 (0.83-1.49)	0.488		
AST (IU/L), < 40 vs. ≥ 40	1.81 (1.42-2.31)	< .001	1.34 (1.02-1.76)	0.033
ALT (IU/L), < 40 vs. ≥ 40	1.21 (0.96-1.53)	0.115		
Total Bilirubin (mg/dl), < 1.2 vs. ≥ 1.2	1.16 (0.97-1.48)	0.298		
Albumin (g/dl), < 3.5 vs. ≥ 3.5	0.79 (0.45-1.39)	0.416		
Platelet count (×10^3/ml), < 150K vs. ≥ 150K	0.88 (0.69-1.12)	0.291		
INR, < 1.0 vs. ≥ 1.0	0.92 (0.78-1.07)	0.469		
AFP (ng/dl), < 200 vs. ≥ 200	1.55 (1.21-2.01)	0.001	1.24 (0.91-1.69)	0.181
ALBI grade I vs. II-III	0.98 (0.97-1.34)	0.993		
HBsAg, Positive vs. Negative	1.29 (0.91-1.84)	0.149		
HBeAg, Positive vs. Negative	1.31 (1.01-1.69)	0.048	1.34 (0.95-1.89)	0.103
Serum HBV DNA, detectable vs. undetectable	1.08 (0.85-1.37)	0.515		
Antiviral therapy, Yes vs. No	1.29 (0.95-1.83)	0.227		
Ishak score, 0-4 vs. 5-6	1.38 (1.03-1.86)	0.032	1.35 (0.98-1.83)	0.061
Liver cirrhosis, No vs. Yes	1.16 (0.88-1.53)	0.304		
Child-Pugh class, A vs. B	2.06 (0.92-4.63)	0.081		
Operative margin (cm), < 1.0 vs. ≥ 1.0	1.01 (0.78-1.31)	0.953		
Tumor number, Single vs. Multiple	1.59 (1.13-2.25)	0.009	1.31 (0.86-1.99)	0.311
Tumor size (cm), < 5 vs. ≥ 5	2.16 (1.71-2.74)	< .001	1.56 (1.19-2.05)	0.001
Tumor cell differentiation I vs. II-III	3.28 (1.75-6.17)	< .001	3.63 (1.89-6.95)	< .001
Macrovascular invasion, No vs. Yes	1.86 (1.36-2.54)	< .001	0.98 (0.63-1.46)	0.842
Microvascular invasion, No vs. Yes	1.85 (1.44-2.38)	< .001	1.51 (1.21-2.04)	0.007
Lymph node invasion, No vs. Yes	5.14 (3.16-8.34)	< .001	2.29 (1.28-4.09)	0.005
TNM stage, I-II vs. III-IV	1.92 (1.47-2.51)	< .001	1.37 (0.98-1.93)	0.065
BCLC stage, 0-A vs. B-C	2.22 (1.65-2.98)	< .001	1.45 (0.99-2.11)	0.052
Recurrence, Yes vs. No	3.06 (2.37-3.94)	< .001	2.79 (2.14-3.66)	< .001
Etiology, MASLD+HBV vs. HBV	1.62 (1.09-2.35)	0.025	1.45 (1.01-2.08)	0.046
Etiology, MASLD+HBV vs. MASLD	1.07 (0.72-1.58)	0.733	1.03 (0.61-1.55)	0.885

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: international normalized ratio; ALBI grade: Albumin-bilirubin grade; HBsAg: Hepatitis B Surface Antigen; HBeAg: Hepatitis B e Antigen; HBV: Hepatitis B Virus; BCLC stage: Barcelona clinic liver cancer; MAFLD: Metabolic associated fatty liver disease.

been reported to be deregulated in HCC. These are the subject of considerable interest as a means to identify therapeutic targets, particularly those involving cell proliferation, apoptosis and metabolism. Further research is required to elucidate the mechanisms underlying these observations [42]. Our study, along with others, indicates that fatty liver disease negatively affects clinical outcomes in patients with HCC.

Our study has several limitations. First, selection bias may be present. Second, we were not

able to establish any causal associations. Third, we excluded patients with HCV; therefore, whether MASLD interacts with HCV in the same way it interacts with HBV is unknown. Our study findings should be validated in other cohorts. Future largely prospective studies are warranted to address this study's limitations and to provide a more comprehensive assessment of MASLD's role in HCC.

Conclusion

Among patients with HCC who had undergone hepatectomy, those with concomitant MASLD and HBV were at a significantly increased risk of HCC recurrence and mortality than those with MASLD or HBV alone. Accordingly, MASLD should be considered in the clinical management and prognostic assessment of HBV-related HCC. Further research is necessary to confirm these findings and investigate the mechanisms underlying the adverse or protective effects of MASLD.

Disclosure of conflict of interest

None.

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References

[1] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J and Finn RS. Hepatocellular carcinoma. Nat Rev Dis Primers 2021; 7: 6.

[2] McGlynn KA, Petrick JL and El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology 2021; 73 Suppl 1: 4-13.

[3] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR and Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723-750.

[4] Tsai MC, Yang SS, Lin CC, Wang WL, Hsu YC, Chen YS, Hu JT, Lin JY, Yu ML and Lin CW. Association of heavy alcohol intake and ALDH2 rs671 polymorphism with hepatocellular carcinoma and mortality in patients with hepatitis B virus-related cirrhosis. JAMA Netw Open 2022; 5: e2223511.

[5] Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, Hsu CC, Lo GH, Chen YS, Yen YC, Hu JT, Yu ML, Lee PH, Lin JT and Yang SS. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. J Hepatol 2013; 58: 730-735.

[6] Kulik L and El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019; 156: 477-491, e471.

[7] Tabrizian P, Jibara G, Shrager B, Schwartz M and Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg 2015; 261: 947-955.

[8] Lin CW, Chen YS, Lin CC, Lee PH, Lo GH, Hsu CC, Hsieh PM, Koh KW, Chou TC, Dai CY, Huang JF, Chuang WL, Chen YL and Yu ML. Autophagy-related gene LC3 expression in tumor and liver microenvironments significantly predicts recurrence of hepatocellular carcinoma after surgical resection. Clin Transl Gastroenterol 2018; 9: 166.

[9] Zheng J, Kuk D, Gonen M, Balachandran VP, Kingham TP, Allen PJ, D'Angelica MI, Jarnagin WR and DeMatteo RP. Actual 10-year survivors after resection of hepatocellular carcinoma. Ann Surg Oncol 2017; 24: 1358-1366.

[10] Lin YP, Lin SH, Wang CC, Lin CC, Chen DW, Chuang CH, Huang PY, Hung CH, Yang SY, Cho WR, Chen YS and Tsai MC. Impact of MAFLD on HBV-related stage 0/A hepatocellular carcinoma after curative resection. J Pers Med 2021; 11: 684.

[11] Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE and Loomba R. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023; 77: 1797-1835.

[12] Le P, Chaitoff A, Rothberg MB, McCullough A, Gupta NM and Alkhouri N. Population-based trends in prevalence of nonalcoholic fatty liver disease in US adults with type 2 diabetes. Clin Gastroenterol Hepatol 2019; 17: 2377-2378.

[13] Shen S and Pan L. Effect of metabolic dysfunction-associated fatty liver disease on the risk of hepatocellular carcinoma in patients with

chronic hepatitis B: a systematic review and meta-analysis. Exp Ther Med 2024; 27: 99.
[14] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388-1402.
[15] Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, Fan J, Goh KL, Hamaguchi M, Hashimoto E, Kim SU, Lesmana LA, Lin YC, Liu CJ, Ni YH, Sollano J, Wong SK, Wong GL, Chan HL and Farrell G. Asia-Pacific working party on non-alcoholic fatty liver disease guidelines 2017-Part 1: definition, risk factors and assessment. J Gastroenterol Hepatol 2018; 33: 70-85.
[16] Yun B, Ahn SH, Oh J, Yoon JH and Kim BK. Prognostic impact of MAFLD following surgical resection of hepatitis B virus-related hepatocellular carcinoma: a nationwide cohort study. Cancers (Basel) 2022; 14: 5002.
[17] Eslam M, Sanyal AJ and George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020; 158: 1999-2014, e1991.
[18] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Jarvinen H, Fan JG, Gronbaek H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V and George J. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020; 73: 202-209.
[19] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J and Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11-20.
[20] Powell EE, Wong VW and Rinella M. Non-alcoholic fatty liver disease. Lancet 2021; 397: 2212-2224.
[21] Conci S, Cipriani F, Donadon M, Marchitelli I, Ardito F, Famularo S, Perri P, Iaria M, Ansaloni L, Zanello M, La Barba G, Patauner S, Pinotti E, Molfino S, Germani P, Romano M, Sciannamea I, Ferrari C, Manzoni A, Troci A, Fumagalli L, Delvecchio A, Floridi A, Memeo R, Chiarelli M, Crespi M, Zimmitti G, Griseri G, Antonucci A, Zanus G, Tarchi P, Baiocchi GL, Zago M, Frena A, Ercolani G, Jovine E, Maestri M, Valle RD, Grazi GL, Romano F, Giuliante F, Torzilli G, Aldrighetti L and Ruzzenente A; He.RC.O.Le.S Group. Hepatectomy for metabolic associated fatty liver disease (MAFLD) related HCC: propensity case-matched analysis with viral- and alcohol-related HCC. Eur J Surg Oncol 2022; 48: 103-112.
[22] D'Silva M, Cho JY, Han HS, Yoon YS, Lee HW, Lee JS, Lee B and Kim M. Long-term surgical outcomes of Non alcoholic fatty liver disease associated hepatocellular carcinoma. Surg Oncol 2022; 41: 101730.
[23] Xiong KG, Lin TS, Kong JF, Lin QB, Chen LF and Ke KY. Impact of MAFLD on the complications after hepatectomy in patients with HBV-related hepatocellular carcinoma. Medicine (Baltimore) 2023; 102: e33062.
[24] Geh D, Manas DM and Reeves HL. Hepatocellular carcinoma in non-alcoholic fatty liver disease-a review of an emerging challenge facing clinicians. Hepatobiliary Surg Nutr 2021; 10: 59-75.
[25] Yamaoka K, Saitoh S, Kinowaki K, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Suzuki F, Suzuki Y, Arase Y, Ikeda K, Fukusato T and Kumada H. Clinicopathological assessment of steatohepatitic hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2022; 46: 101799.
[26] Xiong KG, Ke KY, Chen LF, Kong JF, Lin TS, Lin QB, Lin S and Zhu YY. The impact of metabolic dysfunction-associated fatty liver disease on the prognosis of patients with hepatocellular carcinoma after radical resection. Hepatobiliary Pancreat Dis Int 2023; 22: 366-372.
[27] Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byrne CD, Castro Narro GE, Chowdhury A, Cortez-Pinto H, Cryer DR, Cusi K, El-Kassas M, Klein S, Eskridge W, Fan J, Gawrieh S, Guy CD, Harrison SA, Kim SU, Koot BG, Korenjak M, Kowdley KV, Lacaille F, Loomba R, Mitchell-Thain R, Morgan TR, Powell EE, Roden M, Romero-Gomez M, Silva M, Singh SP, Sookoian SC, Spearman CW, Tiniakos D, Valenti L, Vos MB, Wong VW, Xanthakos S, Yilmaz Y, Younossi Z, Hobbs A, Villota-Rivas M and Newsome PN; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023; 78: 1966-1986.
[28] Huynh CN, Tsai YC, Tsai MJ, Tsai CJ, Wang CC, Lin CC, Yen YH, Hung CH, Kuo YH, Tai WC, Hu TH and Tsai MC. Impact of concurrent MASLD on early-stage HCC following curative resection in chronic hepatitis B. Am J Cancer Res 2024; 14: 4567-4579.
[29] Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, Kelley RK, Galle PR,

Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C and Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022; 76: 681-693.

[30] European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.

[31] American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care 2017; 40 Suppl 1: S11-S24.

[32] Lee YB, Ha Y, Chon YE, Kim MN, Lee JH, Park H, Kim KI, Kim SH, Rim KS and Hwang SG. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019; 25: 52-64.

[33] Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, Chan HL, To KF and Wong VW. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017; 32: 667-676.

[34] Choi HSJ, Brouwer WP, Zanjir WMR, de Man RA, Feld JJ, Hansen BE, Janssen HLA and Patel K. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2020; 71: 539-548.

[35] Peleg N, Issachar A, Sneh Arbib O, Cohen-Naftaly M, Braun M, Leshno M, Barsheshet A and Shlomai A. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. JHEP Rep 2019; 1: 9-16.

[36] Su JY, Deng ZJ, Teng YX, Koh YX, Zhang WG, Zheng MH, Xie S, Huo RR, Chen CJ, Ma L and Zhong JH. Prognosis after hepatic resection of patients with hepatocellular carcinoma related to non-alcoholic fatty liver disease: meta-analysis. BJS Open 2023; 7: zrac167.

[37] Lim CT, Goh GBB, Li H, Lim TK, Leow WQ, Wan WK, Azhar R, Chow WC and Kumar R. Presence of hepatic steatosis does not increase the risk of hepatocellular carcinoma in patients with chronic hepatitis B over long follow-up. Microbiol Insights 2020; 13: 1178636120918878.

[38] Liu L, Xie S, Teng YX, Deng ZJ, Chen K, Liu HT, Huo RR, Liang XM, Guo PP, Yang DL, Ma L, Xiang BD, Li LQ and Zhong JH. Outcomes of liver resection for metabolic dysfunction-associated fatty liver disease or chronic hepatitis B-related HCC. Front Oncol 2022; 11: 783339.

[39] Wang X, Wei S, Wei Y, Wang X, Xiao F, Feng Y and Zhu Q. The impact of concomitant metabolic dysfunction-associated fatty liver disease on adverse outcomes in patients with hepatitis B cirrhosis: a propensity score matching study. Eur J Gastroenterol Hepatol 2023; 35: 889-898.

[40] Xue J, Wang QX, Xiao HM, Shi MJ, Xie YB, Li S, Lin M and Chi XL. Impact of metabolic dysfunction associated fatty liver disease on the prognosis of patients with hepatitis B virus-related hepatocellular carcinoma based on propensity score matching analysis. Cancer Manag Res 2022; 14: 2193-2202.

[41] Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liu CH, Liao SH, Hong CM, Lan TY, Yang HC, Liu CJ, Chen PJ and Kao JH. Metabolic dysfunction-associated steatotic liver disease facilitates hepatitis B surface antigen seroclearance and seroconversion. Clin Gastroenterol Hepatol 2024; 22: 581-590, e586.

[42] Huang SC and Liu CJ. Chronic hepatitis B with concurrent metabolic dysfunction-associated fatty liver disease: challenges and perspectives. Clin Mol Hepatol 2023; 29: 320-331.