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Original Article

Impact of concurrent MASLD on early-stage HCC following curative resection in chronic hepatitis B

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Abstract: In 2023, a new nomenclature, metabolic dysfunction-associated steatotic liver disease (MASLD), replaced the term non-alcoholic fatty liver disease (NAFLD). With the global rise in MASLD prevalence, concurrent MASLD and chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC) are becoming increasingly common. This study aimed to evaluate the clinical impact of concurrent MASLD on long-term survival outcomes in patients with CHB-related early-stage HCC following curative resection. This retrospective study included patients diagnosed with CHB-related early-stage HCC who underwent curative hepatectomy between January 2010 and December 2019. We examined the association between histologically confirmed MASLD and clinical outcomes, with overall survival (OS) and recurrence-free survival (RFS) calculated using the Kaplan-Meier method and compared using the log-rank test. Of 587 eligible patients, 275 (46.8%) were diagnosed with concurrent MASLD. Patients with concurrent MASLD had a higher prevalence of diabetes, hypertension, body mass index (BMI) > 23 kg/m^2, a lower proportion of AFP > 200 ng/ml, and microvascular invasion compared to those without MASLD. After a median follow-up of 66 months, patients with concurrent MASLD exhibited a lower risk of death (HR: 0.57, 95% CI: 0.34-0.95, P = 0.030) but no significant difference in HCC recurrence rates. Subgroup analysis revealed significantly higher OS in females, individuals with BMI ≥ 23 kg/m^2, and non-cirrhotic patients (all P < 0.05). In conclusion, concurrent MASLD is associated with improved survival in patients with CHB-related HCC following curative resection, particularly in females, those with BMI ≥ 23 kg/m^2, and non-cirrhotic patients.

Keywords: CHB, hepatocellular carcinoma, resection, recurrence, metabolic dysfunction-associated steatotic liver disease (MASLD)

Introduction

Hepatocellular carcinoma (HCC) represents a significant global health challenge, ranking as the sixth most diagnosed and third most lethal cancer worldwide in 2020 and the second leading cause of premature cancer death [1, 2]. The burden of HCC varies across regions, driven by a range of risk factors including chronic viral infections, metabolic disorders, and lifestyle factors. Chronic hepatitis B (CHB), particularly endemic in Asia, is a significant risk factor for HCC [3, 4]. Despite advancements in treatment, including enhanced surgical techniques and patient selection, the risk of HCC recurrence after resection remains high, with rates reaching up to 70% at five years [5, 6]. Key prognostic factors for recurrence include tumor size, differentiation, presence of multiple lesions, microvascular invasion, alpha-fetoprotein (AFP) levels, and satellite nodules [5, 7].

In parallel, the global incidence of non-alcoholic fatty liver disease (NAFLD) is rising, driven by the increasing rates of obesity and related metabolic disorders such as insulin resistance, dys-

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lipidemia, central obesity, and hypertension [6, 8]. NAFLD affects an estimated 25-30% of adults globally [9, 10]. The coexistence of NAFLD and CHB, especially in the Asia-Pacific region, underscores a growing clinical concern. The interaction between CHB and NAFLD accelerates HCC development through several mechanisms [11]. NAFLD contributes to increased oxidative stress, insulin resistance, and chronic inflammation, all of which exacerbate liver damage caused by CHB. This combination of viral-induced hepatocyte injury and metabolic stress creates a synergistic environment that accelerates hepatocarcinogenesis [11]. Kupffer cell activation, mitochondrial dysfunction, and the imbalance of adipokines (such as leptin and adiponectin) further promote hepatic inflammation and fibrosis, creating an environment conducive to carcinogenesis. Additionally, insulin resistance in NAFLD leads to elevated insulin-like growth factors, which stimulate hepatocyte proliferation and inhibit apoptosis, further accelerating the risk of HCC in patients with CHB [12]. However, prior to 2020, international guidelines have excluded secondary causes of hepatic steatosis, such as CHB, from the NAFLD definition [13, 14]. This exclusion criterion contributed to limited research on the impact of NAFLD on HBV-related HCC.

In recent years, NAFLD classification has evolved significantly, leading to the adoption of new terminology. In 2020, the term Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) was introduced [15, 16], and more recently, in 2023, a multisociety Delphi consensus further refined the classification to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). These changes aimed to address the limitations of previous NAFLD terminology [17, 18]. The diagnosis of MASLD as defined in the Delphi consensus document, involves identifying hepatic steatosis and at least one of the following cardiometabolic risk factors [18]. With the increasing prevalence of MASLD and new definitions permitting the coexistence of CHB and MASLD, the incidence of cases featuring concurrent MASLD and CHB-related HCC is increasing. Several studies have assessed the impact of MAFLD on patients with CHB-related HCC following curative resection [19-21]. However, to date, no studies have investigated the impact of newly defined MASLD on the outcomes of HBV-related HCC following curative resection.

The evolving definitions now recognize MASLD as a significant condition that can coexist with CHB, highlighting the need for updated research in this area. Therefore, this study aimed to evaluate the clinicopathological characteristics and outcomes of HBV-related HCC following curative resection in patients with and without MASLD.

Materials and methods

Study design and ethics

This was a multicenter, cross-sectional, retrospective study in Taiwan. The Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital approved the study (IRB number: 201901103B0), and the requirement for informed consent was waived owing to the study's retrospective design and minimal risk to participants.

Study population

Data for this study were sourced from the Chang Gung Research Database (CGRD) maintained by Chang Gung Memorial Hospital (CGMH), the largest private hospital system in Taiwan. We conducted a retrospective review of CGRD and collected data from patients with HCC treated between January 2010 and December 2019.

The inclusion criteria for this study were: (1) patients were diagnosed with HBV infection only, confirmed by the presence of hepatitis B surface antigen and negative hepatitis C antibody; (2) patients with early-stage HCC classified as Barcelona Clinic Liver Cancer (BCLC) stage 0 or A; (3) patients who underwent curative liver resection between 2010 and 2019 at KCGRD and had a pathologic hepatic steatosis report.

The exclusion criteria for this study were: (1) patients lacking a hepatic steatosis report; (2) patients consuming significant amounts of alcohol; (3) patients who had undergone liver transplantation; (4) patients with a follow-up period of less than 3 months. A flow diagram depicting the patient selection process is presented in **Figure 1**.

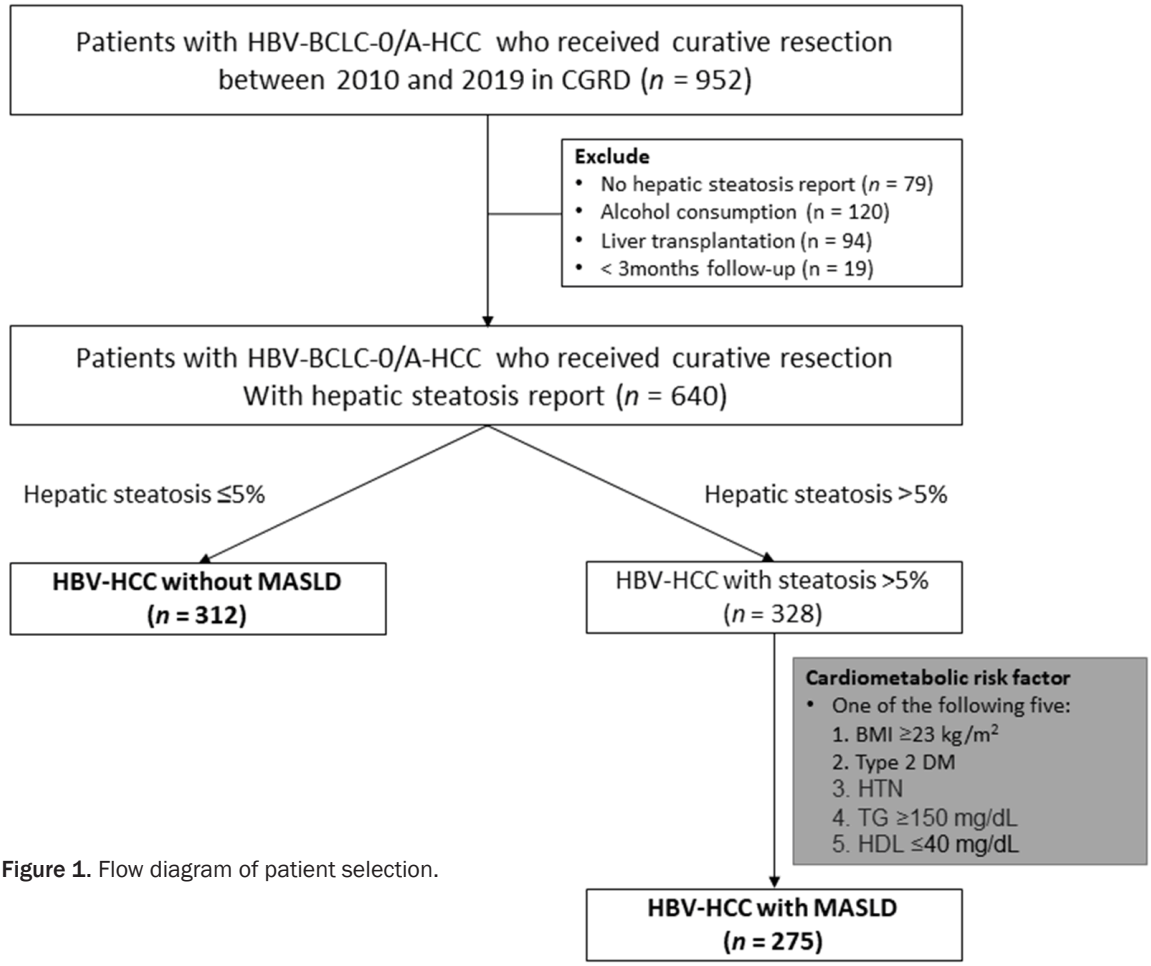

Figure 1. Flow diagram of patient selection.

Data collection

Patient data were retrospectively collected from medical records at the time of surgery. This included details on age, sex, BMI, presence of type 2 diabetes mellitus (T2DM), hypertension (HTN), alcohol use, smoking history, serum biochemistry, hepatitis B markers, and HBV DNA (with a detection limit of 20 IU/mL, using the Roche COBAS TaqMan system; Roche Molecular System, Branchburg, NJ, USA). Additionally, the histological characteristics of the resected tumor were noted, including satellite nodules, capsule invasion, microvascular invasion, tumor differentiation, histological grade, and cirrhosis.

Study outcomes

The primary outcome measured was RFS, which was defined as the period from the date of surgery to the first recurrence of HCC. The secondary outcome was OS, defined as the duration from the date of surgery to death, liver transplantation, or the last follow-up. The follow-up was concluded on December 31, 2020.

Definition

The diagnosis of MASLD requires evidence of hepatic steatosis (> 5%) along with at least one of the following five cardiometabolic risk factors: (1) BMI ≥ 23 kg/m^2 for asian populations, or waist circumference > 94 cm for males, > 80 cm for females; (2) diagnosis or treatment of type 2 diabetes, or fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL), or 2-hour post-load glucose ≥ 7.8 mmol/L (140 mg/dL), or HbA1c ≥ 5.7% (39 mmol/mol); (3) blood pressure ≥ 130/85 mmHg, or treatment with specific antihypertensive drugs; (4) plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL), or treatment with lipid-lowering medications; (5) plasma HDL-cholesterol < 1.0 mmol/L (40 mg/dL) for males,

< 1.3 mmol/L (50 mg/dL) for females, or treatment with lipid-lowering medications and excluding other causes of steatosis including ruling out excessive alcohol consumption (> 210 g/week for male, > 140 g/week for females) [18].

HCC was diagnosed based on histopathological reports of surgically resected tumor tissues and in accordance with the criteria set forth by the practice guidelines of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [22, 23]. HCC staging was conducted according to the Barcelona Clinic Liver Cancer (BCLC) guidelines [24]. Tumor differentiation was graded histologically using the modified nuclear grading scheme developed by Edmondson and Steiner, and tumors were categorized as well-differentiated, moderately differentiated, or poorly differentiated [22]. Liver cirrhosis was identified by an Ishak fibrosis score of 5-6 in non-tumor tissues [23]. T2DM was diagnosed according to the criteria set by the American Diabetes Association (ADA) [25].

Statistical analysis

Statistical analyses were conducted using the SPSS software (version 23.0; IBM Corp., Armonk, NY, USA) for Windows. Continuous variables were represented as means with standard deviations, while categorical variables were reported as frequencies and percentages. The association between RFS and OS was evaluated using Kaplan-Meier survival curves, with comparisons made using the log-rank test. Cox proportional hazards regression models were applied for both univariate and multivariate analyses to determine the hazard ratios (HR) for RFS and OS. Statiscical significance was set at $P < 0.05$.

Results

Patient characteristics

From January 2010 to December 2019, 952 patients with HBV-BCLC stage 0 or A HCC underwent primary curative hepatectomy at KCGRD. Of these, we excluded 79 patients lacking hepatic steatosis reports, 120 patients with significant alcohol consumption, 94 patients who had liver transplants, and 19 patients with follow-up periods of less than three months. Consequently, 640 patients with complete hepatic steatosis data were eligible for analysis (**Figure 1**). Among these, 275 patients were classified as having HCC with MASLD (MASLD group), whereas 312 patients had HCC without MASLD (non-MASLD group).

Table 1 provides an overview of baseline clinicopathological characteristics of the study population. The mean age of the patients was 56.7 years, with a predominantly male representation (81.5%). The median tumor diameter was 2.7 cm, and all patients were classified as having either BCLC stage 0 (27.5%) or stage A (72.5%) HCC. Additionally, 23.2% of the patients were diagnosed with diabetes before undergoing surgery and 47.4% had cirrhosis. Significant differences were observed between MASLD and non-MASLD groups. Patients with MASLD had a higher mean BMI than those without MASLD ($P < 0.001$). The prevalence of diabetes mellitus ($P < 0.001$), hypertension ($P = 0.003$), and elevated serum ALT levels ($P = 0.002$) was also higher in the MASLD group. Furthermore, a higher percentage of patients in the MASLD group had BMI ≥ 23 kg/m^2 ($P < 0.001$) and BMI ≥ 30 kg/m^2 ($P < 0.001$). Platelet counts < 150 × 10^3/μL were less common in the MASLD group ($P < 0.001$), and these patients had slightly higher albumin levels ($P = 0.005$) and a marginally better albumin-bilirubin (ALBI) score ($P = 0.029$). Additionally, microvascular invasion was less frequent in the MASLD group ($P = 0.011$) and was associated with a lower incidence of AFP > 200 ng/mL ($P = 0.003$).

Impact of MASLD on the outcomes of HBV-HCC

After a mean follow-up period of 65 months, the impact of MASLD on the outcomes of HBV-related HCC following liver resection was evaluated. Among the patients studied, 98 (35.6%) with MASLD experienced HCC recurrence compared with 108 (34.6%) without MASLD, showing no significant difference in recurrence rates ($P = 0.796$) (**Figure 2A**). Additionally, there was no significant difference in early and late HCC recurrence (Figure S1). However, mortality was significantly lower in the MASLD group, with 26 patients (9.5%) compared to 47 patients (15.1%) in the non-MASLD group ($P = 0.021$) (**Figure 2B**). Among the mortality cases, 47

Table 1. Characteristics of the CHB patients with early-stage HCC with or without MASLD who underwent curative resection

	CHB with MASLD (n = 275)	CHB without MASLD (n = 312)	*P* value
Age (years), mean ± SD	56.8 ± 10.6	56.6 ± 11.4	0.809
Male, n (%)	231 (84.0)	247 (79.2)	0.133
Diabetes mellitus, n (%)	83 (30.2)	53 (17.0)	< 0.001
Hypertension, n (%)	106 (38.5)	84 (27.0)	0.003
BMI, mean ± SD	26.5 ± 3.2	23.8 ± 3.4	< 0.001
MBI ≥ 23 kg/m^2, n (%)	243 (89.3)	171 (56.6)	< 0.001
MBI ≥ 30 kg/m^2, n (%)	40 (14.7)	13 (4.3)	< 0.001
Platelets < 150 10^3/μL, n (%)	78 (29.1)	142 (47.5)	< 0.001
Albumin (g/dL); mean ± SD	4.3 ± 0.5	4.2 ± 0.5	0.005
AST, (U/L); mean ± SD	36.8 ± 20.6	35.4 ± 20.5	0.419
ALT (UL); mean ± SD	46.7 ± 40.8	37.8 ± 29.2	0.002
Total bilirubin (mg/dL), mean ± SD	0.8 ± 0.4	0.8 ± 0.3	0.099
ALBI score, mean ± SD	-2.9 ± 0.6	-2.8 ±0.5	0.029
Liver cirrhosis, n (%)	128 (46.5)	155 (49.7)	0.448
HBV DNA			0.649
Undetectable	47 (43.9)	75 (46.0)	
< 2000 IU/mL	12 (11.2)	23 (14.1)	
≥ 2000 IU/mL	48 (44.9)	65 (39.9)	
NUCs treatment	120 (43.6)	143 (45.8)	0.867
Child-Pugh grade, n (%)			0.754
A	262 (99.2)	295 (99.0)	
B	2 (0.8)	3 (1.0)	
BCLC stage, n (%)			0.633
0	78 (28.4)	83 (26.6)	
A	197 (71.6)	229 (73.4)	
AFP > 10 ng/mL, n (%)	127 (47.0)	162 (53.8)	0.106
AFP > 200 ng/mL, n (%)	41 (15.2)	76 (25.2)	0.003
Tumor size (cm)[a]; mean ± SD	2.7 ± 1.1	2.7 ± 1.0	0.968
Tumor size > 2 cm, n (%)	204 (74.2)	232 (74.4)	0.961
Tumor number, n (%)			0.343
Single	238 (86.5)	278 (89.1)	
Multiple	37 (13.5)	34 (10.9)	
MVI, n (%)	66 (24.1)	105 (33.7)	0.011
Hepatic steatosis > 5%, n (%)	275 (100.0)	83 (26.6)	< 0.001
Recurrence, n (%)	98 (35.6)	108 (34.6)	0.796
Death, n (%)	26 (9.5)	47 (15.1)	0.040
Follow-up duration (months)	67.3 ± 32.6	62.8 ± 32.2	0.863

Data are expressed as mean ± standard deviation (SD) or n (%). Abbreviations: CHB, chronic hepatitis B; MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; NUCs, nucleos(t)ide analogs; BCLC, Barcelona clinical liver cancer; MVI, microvascular invasion. [a]Diameter of the largest tumor nodule.

(64.4%) died from liver-related causes, and 26 (35.6%) died from non-liver-related causes. The cumulative incidence of non-liver-related mortality was lower in the MASLD group compared to those without MASLD (P = 0.008) (**Figure 2D**). However, there was no significant difference in liver-related mortality (**Figure 2C**). These findings highlight the significant associa-

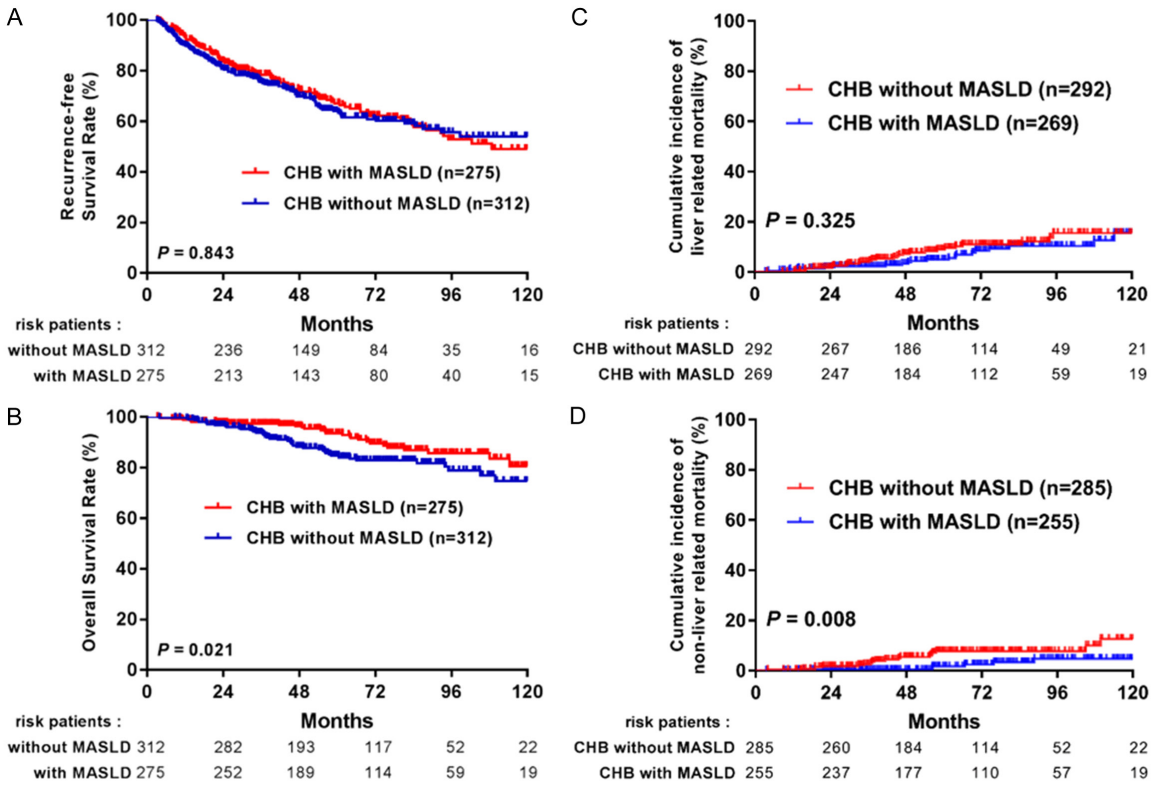

Figure 2. RFS (A), OS (B), cumulative incidence of liver related (C) and non-liver related mortality (D) after curative resection in patients with HBV-related HCC with or without MASLD.

tion between MASLD and improved overall survival, especially in non-liver related mortality, while the recurrence rates remained unaffected.

Factors associated with HCC recurrence

The stepwise Cox proportional hazard model in **Table 2** summarizes the prognostic factors associated with HCC recurrence in the study cohort. The variables identified as statistically significant in the multivariable analysis ($P < 0.05$) were older age (HR, 1.49; 95% confidence interval (CI), 1.11-1.99, $P = 0.008$), elevated AFP levels (HR, 1.55; 95% CI, 1.10-2.18, $P = 0.013$), liver cirrhosis (HR, 1.99; 95% CI, 1.47-2.70, $P < 0.001$), tumor size greater than 2 cm (HR, 1.59; 95% CI, 1.10-2.29, $P = 0.014$), and multiple tumors (HR, 1.50; 95% CI, 1.02-2.19, $P = 0.037$). Conversely, MASLD was not associated with the risk of HCC recurrence (HR, 0.97; 95% CI, 0.74-1.28, $P = 0.843$).

Factors associated with overall survival

As shown in **Table 3**, the multivariate analysis identified several independent risk factors associated with OS in the study cohort. Older age (HR, 1.03; 95% CI, 1.01-1.05, $P = 0.020$), elevated AFP levels (HR, 2.04; 95% CI, 1.06-3.91, $P = 0.033$) and the presence of liver cirrhosis (HR, 2.10; 95% CI, 1.23-3.59, $P = 0.007$) were significantly associated with an increased risk of mortality. Additionally, classification as BCLC stage A compared to stage 0 (HR, 1.99; 95% CI, 1.01-3.90, $P = 0.046$) and microvascular invasion (MVI) (HR, 1.82; 95% CI, 1.13-2.91, $P = 0.013$) were associated with increased mortality. Importantly, the presence of MASLD was associated with a significantly lower risk of overall mortality (HR, 0.57; 95% CI, 0.34-0.95, $P = 0.030$), suggesting a protective effect. Other factors such as sex, hypertension, diabetes mellitus, BMI, tumor size, and tumor number were not significantly associated with overall survival in the multivariate analysis.

MASLD subgroup analysis

Subgroup analyses were conducted to compare OS in HBV-HCC patients with and without MASLD based on various clinical characteristics. These analyses revealed significant differ-

Table 2. Prognostic factors associated with HCC recurrence

Variable	Comparison	Univariable		Multivariable	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	> 60 vs. ≤ 60	1.39 (1.06-1.83)	0.018	1.49 (1.11-1.99)	0.008
Sex	Male vs. Female	1.09 (0.76-1.57)	0.624		
Hypertension	Yes vs. No	1.20 (0.91-1.60)	0.203		
Diabetes mellitus	Yes vs. No	1.50 (1.11-2.03)	0.008		
BMI (kg/m^2)	≥ 23 vs. < 23	0.80 (0.59-1.07)	0.134		
AFP (ng/mL)	≥ 10 vs. < 10	1.54 (1.11-2.15)	0.010	1.55 (1.10-2.18)	0.013
Platelet (10^3/μL)	< 150 vs. ≥ 150	1.32 (0.99-1.76)	0.052		
Liver cirrhosis	Yes vs. No	2.13 (1.60-2.83)	< 0.001	1.99 (1.47-2.70)	< 0.001
HBV DNA (IU/mL)	≥ 2000 vs. < 2000	1.12 (0.65-1.63)	0.920		
NUCs treatment	Yes vs. No	0.96 (0.72-1.26)	0.745		
BCLC stage	A vs. 0	1.62 (1.16-2.28)	0.005		
Tumor size (cm)	≥ 2 vs. < 2	1.57 (1.11-2.22)	0.012	1.59 (1.10-2.29)	0.014
Tumor number	Multiple vs. Single	1.47 (1.02-2.11)	0.040	1.50 (1.02-2.19)	0.037
MVI	Yes vs. No	1.16 (0.86-1.56)	0.326		
MASLD	Yes vs. No	0.97 (0.74-1.28)	0.843		

HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; BMI, body mass index; NUCs, nucleos(t)ide analogs; MVI, microvascular invasion; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 3. Prognostic factors associated with overall mortality

Variable	Comparison	Univariable		Multivariable	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	Per 1 increase	1.02 (1.00-1.04)	0.049	1.03 (1.01-1.05)	0.020
Sex	Male vs. Female	1.12 (0.62-2.05)	0.703		
Hypertension	Yes vs. No	1.28 (0.79-2.06)	0.317		
Diabetes mellitus	Yes vs. No	1.16 (0.68-1.98)	0.584		
BMI (kg/m^2)	≥ 23 vs. < 23	0.84 (0.50-1.39)	0.491		
AFP (ng/mL)	≥ 10 vs. < 10	2.37 (1.24-4.50)	0.009	2.04 (1.06-3.91)	0.033
Platelet (10^3/μL)	< 150 vs. ≥ 150	2.07 (1.27-3.37)	0.004		
Liver cirrhosis	Yes vs. No	2.29 (1.39-3.78)	0.001	2.10 (1.23-3.59)	0.007
HBV DNA (IU/mL)	≥ 2000 vs. < 2000	1.49 (0.77-2.70)	0.182		
NUCs treatment	Yes vs. No	1.54 (0.97-2.47)	0.069		
BCLC stage	A vs. 0	1.90 (1.02-3.52)	0.043	1.99 (1.01-3.90)	0.046
Tumor size (cm)	≥ 2 vs. < 2	1.65 (0.89-3.07)	0.111		
Tumor number	Multiple vs. Single	1.35 (0.74-2.46)	0.332		
MVI	Yes vs. No	1.82 (1.13-2.91)	0.013		
MASLD	Yes vs. No	0.57 (0.36-0.93)	0.023	0.57 (0.34-0.95)	0.030

HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; BMI, body mass index; NUCs, nucleos(t)ide analogs; MVI, microvascular invasion; MASLD, metabolic dysfunction-associated steatotic liver disease.

ences between the subgroups. Specifically, patients with MASLD demonstrated significantly higher OS than those without MASLD among females (P = 0.035, **Figure 3A**), individuals with a BMI ≥ 23 kg/m^2 (P = 0.013, **Figure 3B**), and non-cirrhotic patients (P = 0.02, **Figure 3C**).

Discussion

This study aimed to evaluate the clinical impact of concurrent MASLD on the prognosis of CHB-related HCC following curative resection. In a comprehensive multicenter analysis, we evaluated 587 consecutive patients who underwent

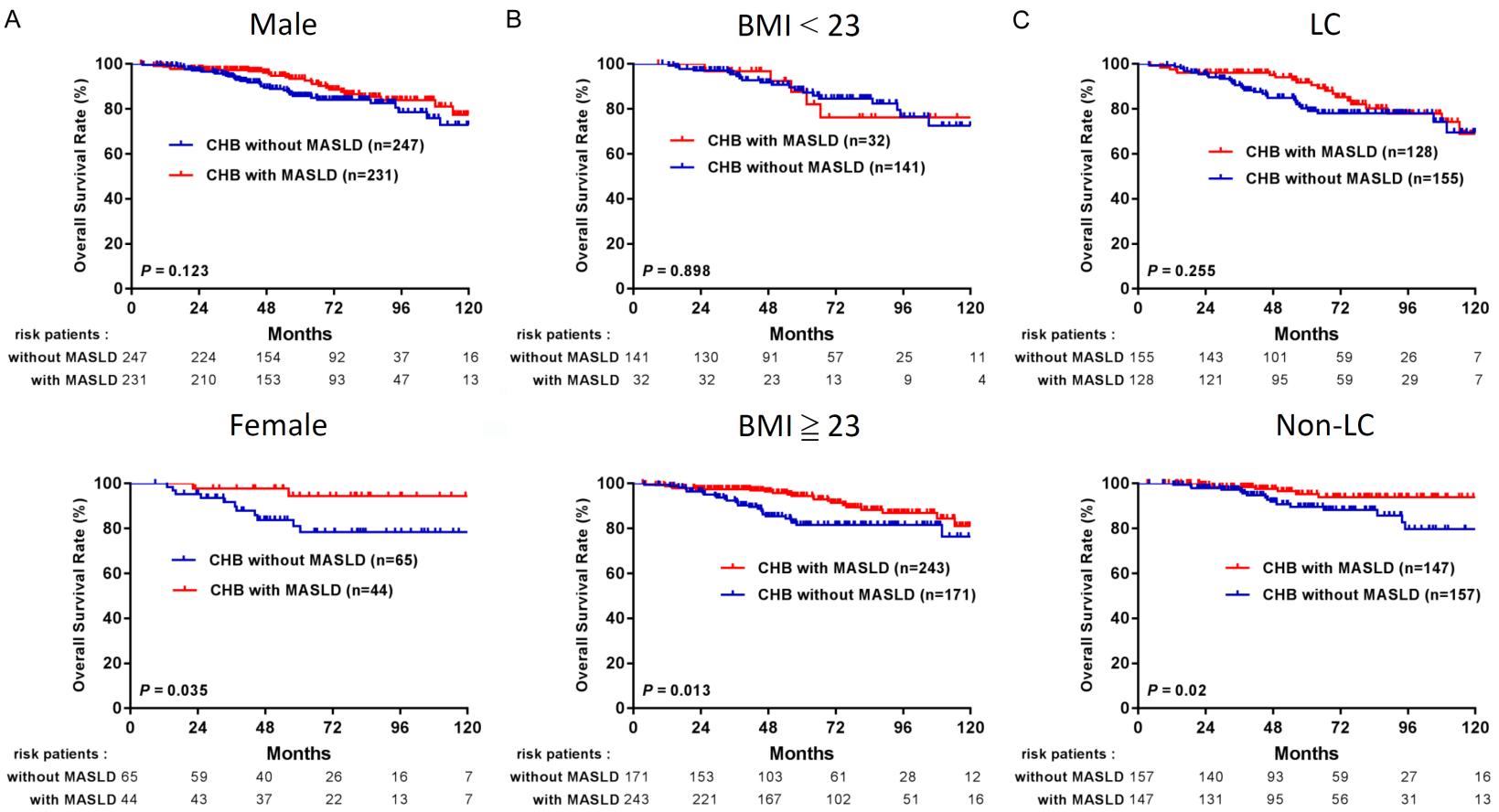

Figure 3. Comparisons of OS in HBV-HCC with or without MASLD stratified by (A) gender (B) BMI, and (C) liver cirrhosis.

curative resection for HBV-related early-stage HCC (BCLC stage 0 or A) and categorized them into the MASLD and non-MASLD groups, with a median follow-up of 66 months. Our primary finding indicates that while MASLD was significantly associated with increased OS, it did not significantly affect RFS. To the best of our knowledge, this is the first study to investigate the association between the newly defined criteria for MASLD and outcomes of CHB-related HCC following curative resection.

Several previous studies have evaluated the impact of fatty liver disease and metabolic dysfunction (NAFLD and MAFLD patient groups) on the prognosis of patients with CHB-related HCC. Some studies have suggested that MAFLD has a protective effect on the prognosis of patients with HCC, particularly in the context of CHB. Our study aligns with most previous research suggesting a better prognosis for HCC patients with fatty liver disease, particularly regarding overall survival. The study by Kong et al. suggested that MAFLD may be a protective factor for OS in patients with HCC after hepatectomy but does not improve RFS. However, they found that overweight patients had better RFS than those in the lean/normal weight group [20]. Similarly, a the study by Lin et al. evaluating the impact of MAFLD on HBV-related HCC after curative resection found no significant differences in HCC recurrence or death/liver transplantation between MAFLD and non-MAFLD patients; however, those with MAFLD appeared to have better recurrence-free survival [21]. A meta-analysis by Su et al. suggests that NAFLD-related HCC patients potentially have longer overall and recurrence-free survival compared to those with HCC from other etiologies, particularly in the Asian population [26]. Liu et al. found that patients with HCC associated with MAFLD had improved long-term survival after curative liver resection compared to those with CHB/MAFLD or CHB alone [27].

However, the protective effects of fatty liver disease vary among different study populations. Xiong et al. found that concurrent MAFLD was associated with an increased incidence of complications after radical resection in patients with HCC, particularly in those with MAFLD and T2DM [28]. Similarly, Xue et al. found that concurrent MAFLD, especially in cases with two or more metabolic components, was associated with a higher risk of poor prognosis in patients with HBV-related HCC [29]. Yun et al. demonstrated that MAFLD was significantly associated with poorer outcomes in terms of HCC recurrence and all-cause mortality following surgical resection of HBV-related HCC [30]. In contrast to previous studies, our study is the first to evaluate the impact of pathologically proven MASLD on HCC following curative resection. Hepatic steatosis can be detected using serum biomarkers, imaging techniques, or histology; however, pathological diagnosis remains the gold standard and is more reliable. We assessed hepatic steatosis based on the pathological evaluation of the resected non-tumor tissues, which is more accurate than the imaging or fatty liver index methods used in most published studies. However, these discrepancies highlight the complexity of the relationship between CHB, metabolic dysfunction, fatty liver disease, and HCC outcomes, suggesting that factors such as population differences and study design significantly influence the results. For instance, hepatic steatosis in patients with CHB may suppress HBV viral activity, resulting in reduced liver damage and a higher rate of HBsAg seroclearance. Huang et al. found that in untreated HBeAg-negative CHB patients in Taiwan, concurrent MASLD was associated with higher rates of HBsAg seroclearance and seroconversion [31]. This suggests that MASLD may facilitate favorable outcomes in the context of CHB, in contrast to the negative associations found in the context of HCC. However, comorbidities such as diabetes mellitus or obesity increase the risk of adverse liver outcomes, adding to the complexity of these relationships [32].

The findings of our study suggest that the presence of MASLD may confer a survival benefit, particularly in OS, in patients with CHB-related early-stage HCC following curative resection. Despite the new terminology and diagnostic criteria, our study, along with other studies, indicated that fatty liver disease (NAFLD, MAFLD, or MASLD) continues to have a protective effect on the prognosis of HCC patients. This observation aligns with some of the existing literature suggesting a protective role of MASLD in the prognosis of patients with HCC, although the precise mechanisms remain unclear. In our study, MASLD was associated with a lower

degree of microvascular invasion (24.1% vs. 33.7%, $P = 0.011$) and lower AFP levels (15.2% vs. 25.2%, $P = 0.003$), both of which are indicators of a less aggressive tumor biology and better prognosis. Additionally, despite the presence of comorbidities, patients with MASLD exhibited better liver function markers, such as higher albumin levels and lower ALBI scores. These factors may enhance patient's ability to tolerate surgery and recover more effectively postoperatively. Possible explanations include MASLD creating a different immune environment in the liver, affecting tumor progression, and metabolic alterations such as insulin resistance and changes in adipokines impacting tumor growth [33]. However, these hypotheses require further investigation.

Although our study showed improved OS, the RFS rates did not differ significantly between patients with and without MASLD. Specifically, during the median follow-up period of 66 months, the incidence of HCC recurrence was 35.6% in the MASLD group and 34.6% in the non-MASLD group ($P = 0.796$). These findings align with previous studies that also observed no significant disparities in recurrence rates between patients with and without fatty liver disease following curative resection [20, 21, 26]. The precise mechanisms by which MASLD differentially affects OS without significantly altering RFS in patients with HCC remain unclear. However, it is hypothesized that the coexistence of MASLD and CHB may synergistically amplify the risk of HCC [34]. Metabolic dysfunctions characteristic of MASLD, including insulin resistance and dyslipidemia, along with a proinflammatory environment marked by cytokine imbalance and oxidative stress, are likely to exacerbate the hepatocarcinogenic potential of CHB [11]. The intricate pathogenesis of MASLD in HCC patients could be a contributing factor to this phenomenon [33, 35]. In our study, it was observed that MASLD patients generally demonstrated better liver function at the time of HCC diagnosis, as evidenced by higher albumin levels and more favorable ALBI scores compared to their counterparts without MASLD. Further research is required to elucidate the mechanisms underlying these observations.

In our study, subgroup analyses were conducted to compare OS in HBV-HCC patients with and without MASLD based on various clinical characteristics. These analyses revealed significant differences between the subgroups. Specifically, patients with MASLD demonstrated significantly higher OS than those without MASLD among females ($P = 0.035$), individuals with BMI $\geq$ 23 kg/m^2 ($P = 0.013$), and non-cirrhotic patients ($P = 0.020$). Among these subgroups, BMI is not only a critical determinant of prognosis but also one of the five cardiometabolic risk factors in the diagnostic criteria for MASLD [18]. Our results reveal that individuals with MASLD and a BMI $\geq$ 23 kg/m^2 show significantly improved overall survival compared to those with a lower BMI. This observation is consistent with numerous studies that have identified BMI as an important prognostic factor for HCC. For instance, a study from Taiwan indicated that a higher BMI correlates with better survival rates in patients with HCC, potentially due to better nutritional reserves and overall health status [36]. Similarly, a study in Korea found that overweight males experienced better OS than normal-weight males, especially among those treated with transarterial chemoembolization (TACE), highlighting the protective role of higher BMI in specific treatment contexts [37]. Furthermore, several studies have highlighted the varying prognoses of patients with MAFLD based on BMI. Lean-MAFLD is an independent risk factor for post-hepatectomy complications and HCC recurrence in patients with HBV-HCC, indicating a poorer prognosis [19, 21]. Conversely, MAFLD in overweight patients (BMI $\geq$ 23 kg/m^2) is associated with improved 1-year, 3-year, and 5-year recurrence-free survival rates after hepatectomy, suggesting a better prognosis for these patients [20]. Taken together, the impact of MASLD on HBV-HCC outcomes after resection is complex, with different subgroups exhibiting different outcomes. In the future, it will be necessary to analyze specific subgroups to better understand the impact of MASLD on HCC.

Our study had several inherent limitations. First, as a retrospective study, there is potential for selection bias and a limited ability to establish causal relationships. However, the risk of bias was minimized as most patients were consistently followed by the same physicians, with regular assessments and HCC screening every 3-6 months. Second, we only included patients with HBV-related early-stage

HCC; therefore, it remains to be seen whether MASLD has a similar impact on HCC caused by other etiologies or on advanced HCC. Therefore, our results need to be validated in other cohorts and in Western countries. Finally, not all data were available from electronic medical records, such as the HOMA-IR index, lipid profile, or waist circumference, leading to the exclusion of some patients. Future prospective studies with larger patient cohorts are needed to address these limitations and to provide a more comprehensive understanding of MASLD's role.

Conclusion

In conclusion, our study found that concurrent MASLD is associated with improved overall survival in patients with CHB-related HCC following curative resection, especially in females, individuals with a BMI ≥ 23 kg/m^2, and non-cirrhotic patients. These findings highlight the importance of considering the MASLD in the clinical management and prognostic assessment of CHB-related HCC. Further research is necessary to confirm these results and to explore the mechanisms underlying the protective effects of MASLD.

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Disclosure of conflict of interest

None.

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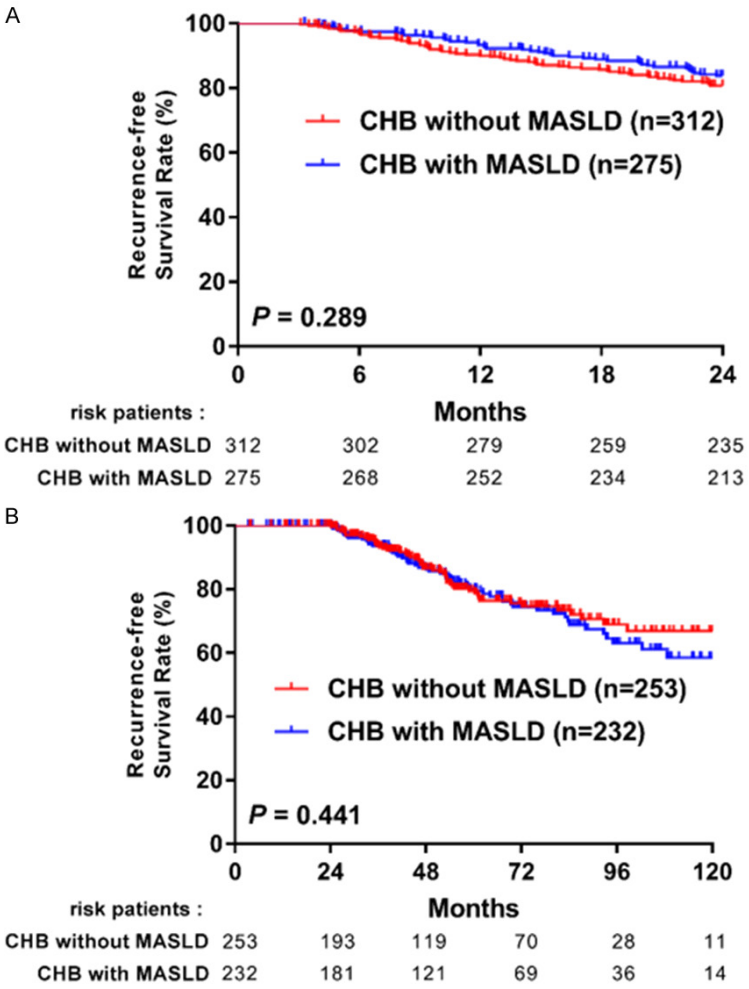

Figure S1. Early RFS (A) and late RFS (B) after curative resection in patients with HBV-related HCC with or without MASLD.