

Risk of *de novo* HCC in patients with MASLD following direct-acting antiviral-induced cure of HCV infection

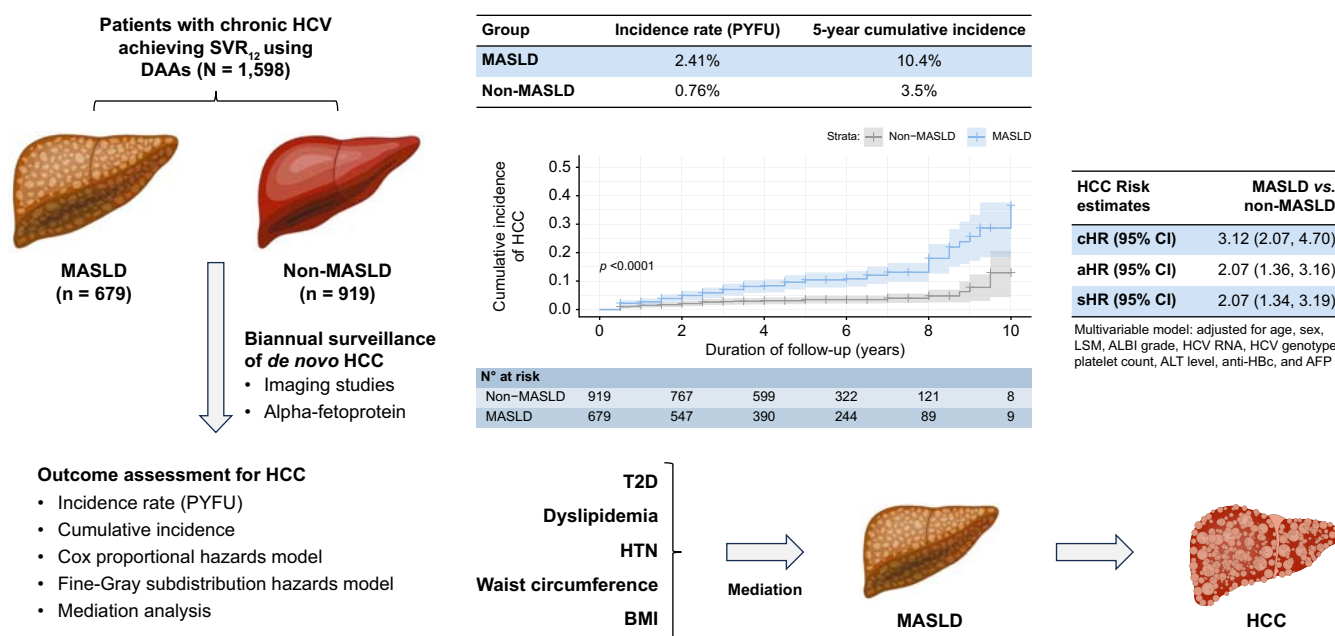
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Graphical abstract



Highlights

- Limited data exist regarding the long-term risk of *de novo* HCC among patients with MASLD following SVR₁₂ using DAAs.
- Patient with MASLD exhibit an approximately two-fold increased risk of *de novo* HCC compared to those without MASLD.
- MASLD significantly mediates CMRFs for increased risk of HCC development.
- Pharmacological interventions and proactive lifestyle modifications as well as vigilant HCC surveillance are required in this setting.

Impact and implications

The risk of *de novo* hepatocellular carcinoma (HCC) among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who have attained a sustained virologic response to direct-acting antivirals remains to be confirmed. In this study, recruiting 1,598 patients in Taiwan, individuals with MASLD had an approximately two-fold increased risk of *de novo* HCC compared to those without MASLD after achieving a sustained virologic response. MASLD significantly mediated cardiometabolic risk factors for HCC development. Our findings underscore the critical importance of pharmacological interventions and proactive lifestyle modifications to control cardiometabolic risk factors in patients with MASLD, as well as the need for vigilant HCC surveillance to ensure favorable outcomes following HCV eradication.

Risk of *de novo* HCC in patients with MASLD following direct-acting antiviral-induced cure of HCV infection

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Background & Aims: Data are limited on the risk of *de novo* hepatocellular carcinoma (HCC) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who have achieved sustained virologic response at off-treatment week 12 (SVR12) using direct-acting antivirals (DAAs) for HCV.

Methods: A total of 1,598 eligible patients received biannual alpha-fetoprotein (AFP) and liver imaging surveillance to detect *de novo* HCC after achieving SVR12. MASLD was defined as presence of controlled attenuation parameter (CAP) ≥ 248 dB/m and ≥ 1 cardiometabolic risk factor (CMRF). Cumulative HCC incidence was compared between patients with/without MASLD. We built univariable and multivariable Cox proportional hazards models to evaluate factors associated with HCC. Sensitivity analysis was performed using the Fine-Gray subdistribution hazards model. Additionally, we evaluated the mediation effect of MASLD on CMRFs and of CMRFs on MASLD for HCC using mediation analysis with bootstrapping.

Results: The incidence rate of HCC was 1.44 per 100 person-years of follow-up (95% CI 1.19–1.74). Patients with MASLD had a higher cumulative HCC incidence than those without MASLD (log-rank test, $p < 0.001$). Multivariable Cox regression analysis revealed that in addition to age, sex, liver stiffness measurement, platelet count, and AFP, MASLD (adjusted hazard ratio 2.07; 95% CI 1.36–3.16; $p < 0.001$) was independently associated with HCC. This finding was confirmed by the Fine-Gray model, which showed a subdistribution hazard ratio of 2.07 (95% CI 1.34–3.19, $p < 0.001$) for MASLD. MASLD significantly mediated CMRFs for HCC development.

Conclusion: After achieving SVR12, patients with MASLD exhibited an increased HCC risk compared to those without MASLD. Vigilant HCC surveillance and control of CMRFs to mitigate the effect of MASLD on HCC remain crucial for this population.

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Introduction

Despite a global decline in HCV prevalence due to the success of direct-acting antivirals (DAAs), chronic HCV infection remains a leading cause of cirrhosis, hepatocellular carcinoma (HCC), hepatic decompensation, and death.^{1,2} Sustained virologic response at off-treatment week 12 (SVR12) rates with pan-genotypic DAAs exceed 95% in diverse populations.³ While achieving SVR12 with DAAs improves the prognosis for most patients, individuals with concurrent liver diseases other than HCV may experience liver disease progression, offsetting the positive effects of viral eradication and leading to ongoing liver-related morbidity and mortality.

Recently, a multisociety Delphi consensus statement has introduced "metabolic dysfunction-associated steatotic liver disease (MASLD)" and "metabolic dysfunction-associated

steatohepatitis (MASH)", aiming to encompass the various etiologies of steatotic liver disease (SLD) while avoiding stigmatizing terminology.⁴ Accumulating evidence suggests a strong connection between HCV infection and MASLD.⁵ The mean prevalence of MASLD in HCV is approximately 55%, with variation from 40% to 86% depending on the local distribution of HCV genotypes and the presence of metabolic syndrome (MS). In HCV genotype 3, hepatic steatosis is directly induced by the virus through inhibition of microsomal triglyceride transfer protein, activation of peroxisome proliferator-activated receptor- α , and activation of sterol regulatory element-binding protein-1c.^{6–9} On the other hand, disruptions in host metabolism, including obesity and insulin resistance, are the primary contributors to hepatic steatosis in non-HCV genotype 3 infections.¹⁰

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While viral proteins may directly interact with the host cell to contribute to cancer development, HCV can indirectly accelerate hepatic fibrosis and inflammation, and extrahepatic manifestations, particularly MS, further increasing the cancer risk.^{11,12} Meta-analyses have shown that untreated HCV infection, when accompanied by concurrent obesity, type 2 diabetes (T2D), and hepatic steatosis, is associated with a three to four-fold higher risk of advanced hepatic fibrosis and HCC development.^{13,14} Furthermore, studies have indicated that T2D and pre-diabetic insulin resistance may independently increase the risk of HCC, regardless of the presence of HCV infection or cirrhosis.^{15,16}

Data regarding the role of MASLD and its contributing factors on HCC in patients who achieve SVR12 after antiviral treatment for HCV are conflicting. While the presence of hepatic steatosis and T2D have been shown to increase the risk of HCC development among patients following interferon (IFN)-based or DAA treatment, studies have shown divergent effects on HCC risk among patients exhibiting different stages of hepatic fibrosis.^{17–20} Intriguingly, BMI, one of the primary contributing factors of MASLD, also demonstrated equivocal effects on the HCC risk among patients achieving HCV eradication.^{17,20} Given the limited and inconsistent knowledge regarding the impact of MASLD on the risk of HCC in patients with HCV after achieving SVR12 with DAAs, we conducted a multicenter study to provide a more comprehensive understanding of how MASLD and the various contributing factors may influence the risk of HCC in these patients.

Materials and methods

Patients

We conducted a retrospective analysis of a cohort that was prospectively evaluated for the risk of *de novo* HCC at nine academic centers in Taiwan. This cohort comprised patients aged ≥ 18 years who received IFN-free DAAs for chronic HCV infection between January 2014 and October 2023. Chronic HCV infection was defined as having HCV antibody (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) and quantifiable serum HCV RNA level (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, lower limit of quantification of 15 IU/ml) for ≥ 6 months.

Patients with MASLD were diagnosed based on the presence of SLD with a controlled attenuation parameter (CAP) of ≥ 248 dB/m, determined by vibration-controlled transient elastography (VCTE) (FibroScan[®], Echosens, Paris, France) in conjunction with at least one of the five adult cardiometabolic risk factors (CMRFs), including (1) BMI ≥ 23 kg/m² or waist circumference of >90 cm for males and >80 cm for females; (2) fasting serum glucose ≥ 100 mg/dl, glycosylated hemoglobin (HbA1c) $\geq 5.7\%$, a diagnosis of T2D, or treatment for T2D; (3) blood pressure $\geq 130/85$ mmHg or under specific drug treatment for hypertension (HTN); (4) plasma triglyceride ≥ 150 mg/dl or under lipid-lowering treatment; (5) plasma high-density lipoprotein-cholesterol (HDL-C) ≤ 40 mg/dl for males and ≤ 50 mg/dl for females or under lipid-lowering agent.^{4,21}

Exclusion criteria included failure to achieve SVR12, unreliable liver stiffness measurements (LSMs), defined as <10 valid measurements, a successful rate of measurement of $<60\%$, or an IQR of $>30\%$ of the median value of LSM with VCTE, unreliable CAP, defined as <10 valid measurements, a successful

rate of measurement of $<60\%$, or an IQR of >40 dB/m with VCTE, decompensated cirrhosis, active or a history of HCC, organ transplantation, increased alcohol consumption (≥ 140 g/week for females and ≥ 210 g/week for males), HBV coinfection defined as presence of hepatitis B surface antigen (HBsAg) (Abbott Architect HBsAg qualitative assay, Abbott Laboratories, Abbott Park, Illinois, USA), HIV coinfection defined as presence of anti-HIV (Abbott Architect HIV Ag/Ab Combo, Abbott Laboratories, Abbott Park, Illinois, USA), lack of post-SVR12 follow-up for at least 6 months, or declining or being unable to provide written informed consent.^{4,22,23} Patients who were diagnosed with SLD with a CAP ≥ 248 dB/m using VCTE but who lacked any CMRF were categorized in the non-MASLD group. The study was conducted in accordance with ethical principles, with approval from the Research Ethics Committee of each participating center, and adhered to the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

Study design

To analyze the risk of *de novo* HCC among patients achieving SVR12, we set the date of SVR12 for the baseline time point (time zero). Baseline patient demographic data, including age, sex, blood pressure, weekly alcohol consumption, BMI, waist circumference, and history of HCC or organ transplantation, were assessed. All patients underwent testing at the SVR12 time point for hemogram, international normalized ratio (INR), serum albumin, total bilirubin, alanine aminotransferase (ALT) (the upper limit of normal (ULN): 30 U/L for males and 19 U/L for females), fasting glucose, HbA1c, triglyceride, HDL-C, and alpha-fetoprotein (AFP) levels were also measured. Moreover, we collected pre-treatment data for anti-HCV, serum HCV RNA, HCV genotype (Roche Cobas HCV GT, Roche Diagnostics GmbH, Mannheim, Germany, or Abbott RealTime HCV Genotype II, Abbott Laboratories, Abbott Park, Illinois, USA), HBsAg, hepatitis B surface antibody (anti-HBs) (Abbott Architect anti-HBs qualitative assay, Abbott Laboratories, Abbott Park, Illinois, USA), hepatitis B core antibody (anti-HBc) (Abbott Architect anti-HBc qualitative assay, Abbott Laboratories, Abbott Park, Illinois, USA), and anti-HIV.²⁴ The LSM and CAP were performed at the SVR12 time point using VCTE equipped with an M probe for patients with BMI levels <30 kg/m² and an XL probe for patients with BMI levels ≥ 30 kg/m². The albumin-bilirubin (ALBI) grade was calculated based on laboratory parameters.²⁵

All patients underwent abdominal ultrasonography and serum AFP testing for HCC surveillance at semiannual intervals from the SVR12 time point to the last visit. The diagnosis of HCC was confirmed using various diagnostic methods such as contrast-enhanced CT, MRI, hepatic angiography, or histology when appropriate.²⁶

Statistical analysis

The study utilized the R statistical software (version 4.1.1) for the statistical analyses. Patient characteristics were presented as median (IQR) for continuous variables and n (%) for categorical variables. We employed Mann-Whitney *U* and chi-square tests to compare patient characteristics between individuals with and without MASLD. The primary endpoint was the development of *de novo* HCC. All patients were followed up

until the presentation of HCC or their last visit if HCC did not develop. The length of post-SVR12 follow-up was reported as the median years with a range. The proportion of patients with HCC development beyond SVR12 was expressed as a number and percentage. HCC incidence rate was calculated as the number of patients with HCC development per 100 person-years of follow-up (PYFU), along with a 95% CI.

We analyzed the cumulative incidences of HCC with 95% CIs using the Kaplan-Meier methods and compared them using the log-rank test. Univariable Cox proportional hazards model was employed to assess the relationship between factors of interest and HCC. The results were reported as crude hazard ratios (cHRs) with 95% CIs. We built various multivariable Cox proportional hazards models, targeting MASLD, SLD, CMRFs, and conventional risk factors, respectively, to assess effects of various covariates on the development of *de novo* HCC. The results were reported as adjusted HRs (aHRs) with 95% CIs. Additionally, we performed sensitivity analyses using the Fine-Gray subdistribution hazards model, taking deaths as the competing risk, which were reported as subdistribution HRs (sHRs) with 95% CIs.^{27,28} To clarify the contribution of MASLD and CMRFs to HCC development, mediation analyses using the time-to-event outcomes with bootstrap resampling for 5,000 times were conducted, assuming CMRFs as the independent variables, MASLD as the mediator, and HCC as the dependent variable, and assuming MASLD as the independent variables, CMRFs as the mediator, and HCC as the dependent variable, respectively.²⁹ Results were reported as average causal mediation effect (ACME), average direct effect (ADE), total effect, and proportion mediated with 95% CI, respectively. The proportion mediated was calculated by dividing the ACME divided by the total effect. The units of ACME, ACE and total effect represent the log-hazard ratios of the outcome due to the effect of exposure that was mediated by the mediator, the effect of exposure independent of the mediator, and the sum of ACME and ADE, respectively. Values of proportion mediated of 0, between 0 and 1, and 1 indicate no mediation, partial mediation, and complete mediation, respectively. Values of proportion mediated of >1 and <0 indicate the opposite direction of the direct and indirect effects, which result from complex and potential suppression relationships among independent variables, mediators and dependent variables. All statistical analyses were two-tailed, and statistical significance was defined as a *p* value less than 0.05.

Results

Patient characteristics

Of the initial group of 2,289 patients who received IFN-free DAAs for HCV infection, 79 were excluded from the study due to a lack of SVR12. An additional 612 patients were excluded for various reasons, including decompensated cirrhosis (*n* = 47), active or a history of HCC (*n* = 69), organ transplantation (*n* = 52), increased alcohol intake (*n* = 29), HBV coinfection (*n* = 163), HIV coinfection (*n* = 205), lack of reliable LSM or CAP (*n* = 12), a post-SVR12 follow-up period of <6 months (*n* = 12), and patients who declined or were unable to provide written informed consent (*n* = 23). Among the 685 patients diagnosed with SLD, 679 (99.1%) presented with MASLD, leaving the remaining six patients with SLD but lacking any CMRF, categorized into the non-MASLD group. The final

eligible study population consisted of 1,598 patients, including 679 with MASLD and 919 without MASLD (Fig. 1).

In the baseline characteristics, the median age was 57 years, with 849 (53.1%) patients being male. A small percentage of patients had an ALT quotient of ≥ 2 (4.8%) and an AFP level >10 ng/ml (3.6%). A significant proportion of patients had MASLD (42.5%). The median LSM was 6.1 kPa and 310 (19.4%) had a LSM ≥ 9.5 kPa at the SVR12 time point. The ALBI grade classification showed that most patients were categorized as grade 1 (94.8%), with smaller proportions categorized as grade 2 (4.7%) and grade 3 (0.5%) (Table 1). The median (IQR) duration of post-SVR12 follow-up was 5.0 (2.5 to 6.5) years. A total of 107 patients (6.7%) developed *de novo* HCC during the 7,405 PYFU period, with an HCC incidence rate of 1.44 per 100 PYFU (95% CI 1.19 to 1.74).

Compared to patients without MASLD, those with MASLD exhibited a significantly higher median level of LSM, CAP, BMI, waist circumference, ALT, fasting glucose, HbA1c, TG and AFP levels. Additionally, these patients had a significantly lower median level of platelet count and HDL-C levels. Patients with MASLD were more likely to be males and have T2D, dyslipidemia, HTN, metformin and statin use for T2D and dyslipidemia, high BMI distribution, waist circumference, LSM ≥ 9.5 kPa, ALT $\geq 2 \times$ ULN, and AFP >10 ng/ml (Table 1). Among 679 patients with MASLD, 230 (33.9%), 245 (36.1%), 274 (40.4%), and 638 (94.0%) had T2D, dyslipidemia, HTN, and a BMI ≥ 23 kg/m².

Risk of *de novo* HCC in patients achieving SVR12

During the study period, 215 (31.7%) out of the 679 patients with MASLD and 302 (32.9%) out of the 919 patients without MASLD were lost to follow-up (*p* = 0.63), including 29 (4.3%) and 49 (5.3%) due to death (*p* = 0.35).

Among 679 patients with MASLD, 74 (10.9%) developed HCC, while in 919 patients without MASLD, 33 (3.6%) developed HCC. This marked a substantial difference in HCC incidence, with rates of 2.41 per 100 PYFU (95% CI 1.91 to 3.03) for patients with MASLD and 0.76 per 100 PYFU (95% CI 0.54 to 1.07) for patients without MASLD. The cumulative incidence rate of HCC in patients with MASLD was significantly higher than in patients without MASLD, as confirmed by the log-rank test (*p* <0.001) (Fig. 2). Patients with MASLD had a 5-year cumulative risk of 10.4% (95% CI 7.7 to 13.0), compared to 3.5% (95% CI 2.2 to 4.8) for those without MASLD.

In the univariable Cox proportional hazards model, MASLD (cHR 3.12; 95% CI 2.07 to 4.70, *p* <0.001), SLD (cHR 3.09; 95% CI 2.05 to 4.66, *p* <0.001), T2D (cHR 2.76; 95% CI 1.89 to 4.07, *p* <0.001), HTN (cHR 1.50; 95% CI 1.02 to 2.20, *p* = 0.041), waist circumference per cm increase (cHR 1.04; 95% CI 1.02 to 1.06, *p* <0.001), age per year increase (cHR 1.07; 95% CI 1.05 to 1.09, *p* <0.001), male sex (cHR 1.94; 95% CI 1.30 to 2.89, *p* <0.001), LSM per kPa increase (cHR 1.07; 95% CI 1.05 to 1.08, *p* <0.001), ALBI grade (cHR 4.40; 95% CI 2.62 to 7.41, *p* <0.001 for grade 2 vs. grade 1), platelet count per $10 \times 10^9/L$ increase (cHR 0.85; 95% CI 0.82 to 0.89, *p* <0.001), ALT $\geq 2 \times$ ULN (cHR 2.10; 95% CI 1.09 to 4.02, *p* = 0.026), and AFP >10 ng/ml (cHR 6.63; 95% CI 3.99 to 11.02, *p* <0.001) were significantly associated with HCC development (Table 2). Dyslipidemia (cHR 0.93; 95% CI 0.61 to 1.42, *p* = 0.73), BMI (cHR 1.05; 95% CI 0.99 to 1.10, *p* = 0.07), ALBI grade (cHR 3.81; 95% CI 0.53 to 27.42, *p* = 0.18 for grade 3 vs. grade 1), HCV RNA at a cut-off

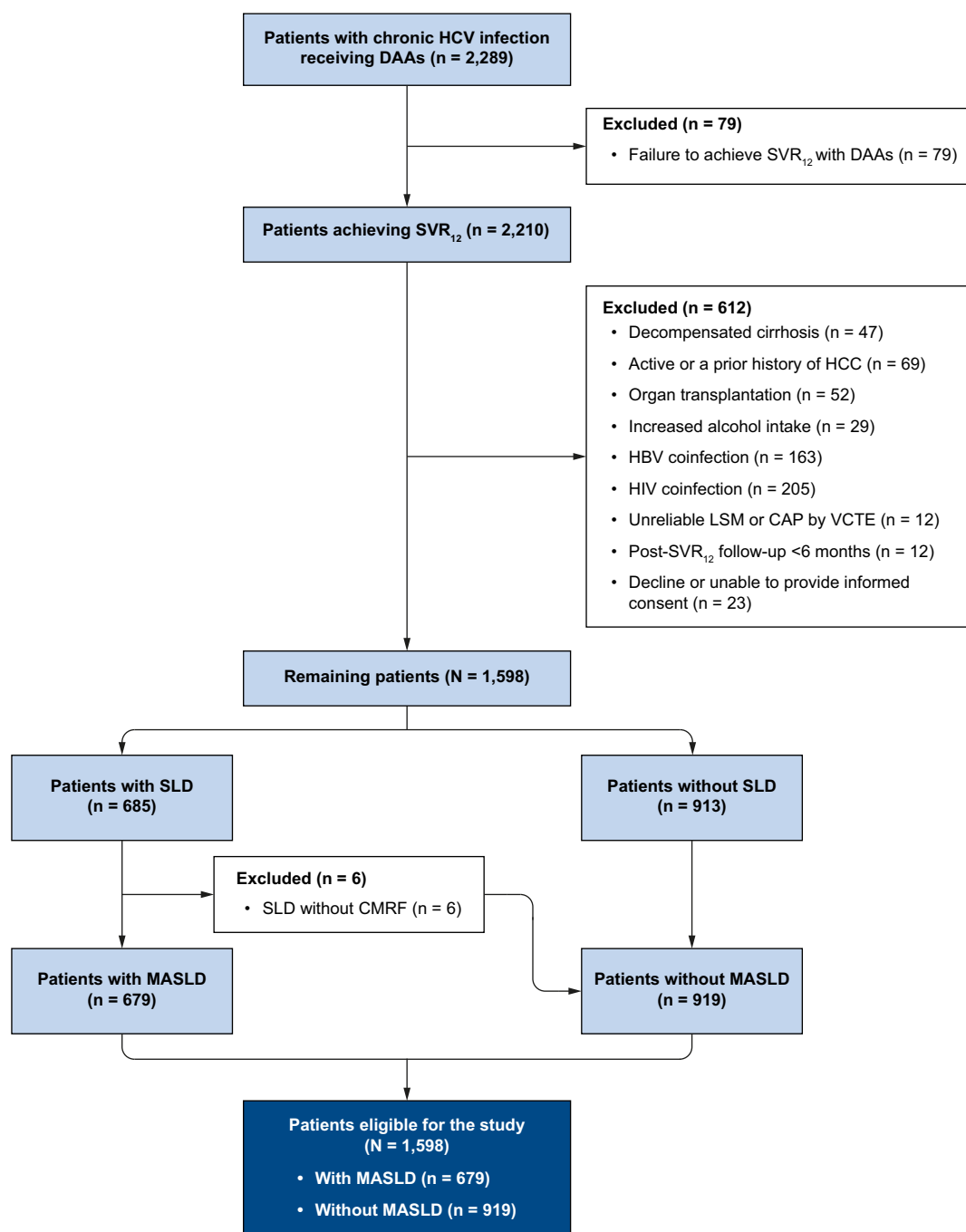


Fig. 1. Study flowchart. CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver disease; SVR12, sustained virologic response at off-treatment week 12; VCTE, vibration-controlled transient elastography.

value of 2,000,000 IU/ml (cHR 0.86; 95% CI 0.58 to 1.31, $p = 0.50$), HCV genotype 1 (cHR 1.35; 95% CI 0.91 to 2.00, $p = 0.13$), and anti-HBc positivity (cHR 1.10; 95% CI 0.68 to 1.79, $p = 0.70$) were not associated with HCC development.

Cox proportional hazards model 1 identified MASLD (aHR 2.61; 95% CI 1.56 to 4.36, $p < 0.001$), age per year increase (aHR 1.05; 95% CI 1.03 to 1.08, $p < 0.001$), males (aHR 3.03; 95% CI 1.89 to 4.88, $p < 0.001$), LSM per kPa increase (aHR 1.04; 95% CI 1.02 to 1.06, $p < 0.001$), platelet count per $10 \times 10^9/L$ increase (aHR 0.92; 95% CI 0.88 to 0.96, $p < 0.001$), and AFP >10 ng/ml (aHR 3.22; 95% CI 1.70 to 6.09, $p < 0.001$) as independently associated with HCC development. Cox proportional hazards model 2 identified SLD (aHR 2.56; 95% CI 1.54 to 4.27, $p < 0.001$), age per year increase (aHR 1.05; 95% CI 1.03 to 1.07, $p < 0.001$), male sex (aHR 3.04; 95% CI 1.89 to 4.89, $p < 0.001$), LSM per kPa increase (aHR 1.04; 95% CI 1.02 to 1.06, $p < 0.001$), platelet count per $10 \times 10^9/L$ increase (aHR 0.92; 95% CI 0.88 to 0.96, $p < 0.001$), and AFP >10 ng/ml (aHR 3.22; 95% CI 1.70 to 6.09, $p < 0.001$) as independently associated with HCC development.

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Table 1. Baseline characteristics.

Characteristics*	Entire population (N = 1,598)	Patient with MASLD (n = 679)	Patient without MASLD (n = 919)	p value†
Duration of post-SVR12 follow-up, year	5.0 (2.5, 6.5)	4.5 (2.0, 6.5)	5.0 (2.5, 6.5)	0.28
Age, year	57 (49, 64)	57 (49, 64)	57 (48, 65)	0.45
Age >50 years, n (%)	1,131 (70.8)	487 (71.7)	644 (70.1)	0.50
Male, n (%)	849 (53.1)	402 (59.2)	447 (48.6)	<0.001
T2D, n (%)	333 (20.8)	230 (33.9)	103 (11.2)	<0.001
Dyslipidemia, n (%)	456 (28.5)	245 (36.1)	211 (23.0)	<0.001
HTN, n (%)	488 (30.5)	274 (40.4)	214 (23.3)	<0.001
Drug therapy, n (%)				
Metformin	222 (13.9)	183 (27.0)	39 (4.2)	<0.001
Statins	141 (8.8)	81 (11.9)	60 (6.5)	<0.001
BMI, kg/m ²	24.5 (22.2, 26.9)	26.9 (25.0, 28.9)	22.7 (20.9, 24.6)	<0.001
BMI, n (%)				<0.001
Underweight (<18.5 kg/m ²)	42 (2.6)	1 (0.1)	41 (4.5)	
Normal weight (18.5 to 22.9 kg/m ²)	499 (31.2)	40 (5.9)	459 (49.9)	
Overweight (23.0 to 24.9 kg/m ²)	367 (23.0)	127 (18.7)	240 (26.1)	
Obese (≥25 kg/m ²)	690 (43.2)	511 (75.3)	179 (18.5)	
Waist circumference, cm	88 (81, 94)	93 (88, 99)	84 (78, 89)	<0.001
Waist circumference > ULN, n (%)‡	929 (58.1)	551 (81.1)	378 (41.1)	<0.001
CMRF, n (%)§				
BMI or waist circumference	1,184 (74.1)	638 (94.0)	546 (59.4)	<0.001
Glycemic criteria	729 (45.6)	399 (58.8)	330 (35.9)	<0.001
HTN	488 (30.5)	274 (40.4)	214 (23.3)	<0.001
Triglyceride	344 (21.5)	186 (27.4)	158 (17.2)	<0.001
HDL-C	299 (18.7)	172 (25.3)	127 (13.8)	<0.001
CAP, dB/m¶	240 (212, 270)	276 (259, 296)	218 (200, 235)	<0.001
LSM, kPa¶	6.1 (4.7, 8.3)	6.7 (5.3, 10.0)	5.8 (4.4, 7.6)	<0.001
LSM ≥9.5 kPa, n (%)¶	310 (19.4)	171 (25.9)	139 (15.1)	<0.001
HBsAg-negative and anti-HBc positivity, n (%)	1,280 (80.1)	553 (81.4)	727 (79.1)	0.26
ALBI grade, n (%)				0.93
Grade 1	1,515 (94.8)	643 (94.7)	872 (94.9)	
Grade 2	75 (4.7)	33 (4.9)	42 (4.6)	
Grade 3	8 (0.5)	3 (0.4)	5 (0.5)	
HCV RNA >2,000,000 IU/ml, n (%)	574 (35.9)	247 (36.4)	327 (35.6)	0.75
HCV genotype 1, n (%)	899 (56.3)	382 (56.3)	517 (56.3)	0.99
Platelet count, 10 ⁹ /L	184 (142, 223)	179 (139, 220)	188 (144, 225)	0.017
INR	1.00 (0.96, 1.03)	1.00 (0.96, 1.03)	1.00 (0.96, 1.03)	0.37
Albumin, g/dl	4.5 (4.3, 4.7)	4.5 (4.3, 4.7)	4.5 (4.3, 4.7)	0.87
Total bilirubin, mg/dl	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.7 (0.6, 1.0)	0.005
ALT, U/L	17 (13, 25)	20 (15, 29)	15 (12, 22)	<0.001
ALT ≥2x ULN, n (%)#	77 (4.8)	52 (7.7)	25 (2.7)	<0.001
Fasting glucose, mg/dl	97 (89, 109)	101 (92, 116)	94 (87, 104)	<0.001
HbA1c, %	5.6 (5.3, 6.0)	5.7 (5.4, 6.3)	5.5 (5.2, 5.8)	<0.001
Triglyceride, mg/dl	102 (76, 141)	113 (85, 153)	70 (94, 128)	<0.001
HDL-C, mg/dl	46 (39, 56)	43 (37, 52)	48 (41, 59)	<0.001
AFP, ng/ml	3.06 (2.18, 4.54)	3.33 (2.36, 5.02)	2.88 (2.07, 4.03)	<0.001
AFP >10 ng/ml, n (%)	58 (3.6)	33 (4.9)	25 (2.7)	0.030

AFP, alpha-fetoprotein; ALBI grade, albumin-bilirubin grade; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein-cholesterol; HTN, hypertension; INR, international normalized ratio; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; SVR12, sustained virologic response at off-treatment week 12; T2D, type 2 diabetes; ULN, upper limit of normal.

*Data are shown in median (IQR) unless otherwise indicated.

†Comparison of groups using Mann-Whitney *U* test for continuous variables and chi-square tests for categorical variables for patient with and without MASLD.

‡The ULN for waist circumference is 90 cm for males and 80 cm for females.

§Including BMI ≥23 kg/m² or waist circumference of >90 cm for males and >80 cm for females; fasting serum glucose ≥100 mg/dl, HbA1c ≥5.7%, a diagnosis of T2D, or treatment for T2D; blood pressure ≥130/85 mmHg or under specific drug treatment for HTN; plasma triglyceride ≥150 mg/dl or under lipid-lowering treatment; plasma HDL-C ≤40 mg/dl for males and ≤50 mg/dl for females or under lipid-lowering agent.

¶Assessed by vibration-controlled transient elastography.

#The ULN for ALT is 30 U/L for males and 19 U/L for females.

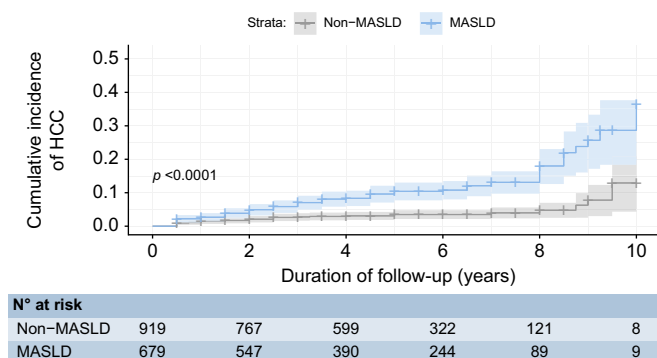


Fig. 2. Cumulative incidences of HCC in patients with and without MASLD. The cumulative incidence of HCC among patients with MASLD was significantly higher than that among patients without MASLD (log-rank tests, $p < 0.001$). HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

3.23; 95% CI 1.71 to 6.11, $p < 0.001$) as independently associated with HCC development (Table 2). Cox proportional model 3 identified MASLD (aHR 2.07; 95% CI 1.36 to 3.16, $p < 0.001$), age per year increase (aHR 1.05; 95% CI 1.03 to 1.08, $p < 0.001$), male sex (aHR 2.73; 95% CI 1.79 to 4.16, $p < 0.001$), LSM per kPa increase (aHR 1.04; 95% CI 1.02 to 1.06, $p < 0.001$), platelet count per $10 \times 10^9/L$ increase (aHR 0.91; 95% CI 0.88 to 0.95, $p < 0.001$), and AFP >10 ng/ml (aHR 3.25; 95% CI 1.80 to 5.86, $p < 0.001$) as independently associated with HCC development (Table 2).

In Cox proportional hazards model 4, T2D (aHR 1.46; 95% CI 0.95 to 2.24, $p = 0.09$), dyslipidemia (aHR 1.21; 95% CI 0.77 to 1.91, $p = 0.42$), HTN (aHR 1.05; 95% CI 0.68 to 1.61, $p = 0.83$), waist circumference (aHR 1.00; 95% CI 0.97 to 1.04, $p = 0.99$), and BMI (aHR 0.99; 95% CI 0.90 to 1.08, $p = 0.76$) were not associated with HCC development after adjusting for age, sex, LSM, ALBI grade, HCV RNA level, HCV genotype, platelet count, ALT level, anti-HBc, and AFP level. Additionally, Cox proportional hazards model 5 identified MASLD (aHR 1.96; 95% CI 1.27 to 3.02, $p = 0.002$), but not T2D (aHR 1.28; 95% CI 0.84 to 1.95, $p = 0.24$), as being associated with HCC development (Table S1).

Mediation analysis of the effect of MASLD on CMRFs for *de novo* HCC

The ACMEs of MASLD on T2D, dyslipidemia, HTN, waist circumference, and BMI for HCC were 0.0265 (95% CI 0.0136 to 0.0400, $p < 2e-16$), 0.0144 (95% CI 0.0059 to 0.0200, $p < 2e-16$), 0.0127 (95% CI 0.0079 to 0.0200, $p < 2e-16$), 0.0014 (95% CI: 0.0008 to 0.0021, $p < 2e-16$), and 0.0062 (95% CI 0.0035 to 0.0091, $p < 2e-16$), respectively. The ADEs of T2D, dyslipidemia, HTN, waist circumference, and BMI for HCC were 0.0504 (0.0148 to 0.0900), $p = 0.0048$), -0.0159 (-0.0420 to 0.0100), $p = 0.24$), 0.0162 (-0.0113 to 0.0400), $p = 0.25$), 0.0006 (-0.0014 to 0.0027), $p = 0.34$), and -0.0151 (-0.0163 to 0.0021), $p = 0.16$), respectively. After adjusting for age, sex, LSM, platelet count and AFP, the ACMEs of MASLD on T2D, dyslipidemia, HTN, waist circumference, and BMI for HCC were 0.0144 (95% CI 0.0063 to 0.0200, $p < 2e-16$), 0.0084 (95% CI 0.0037 to 0.0100, $p < 2e-16$), 0.0096 (95% CI 0.0044 to 0.0200), $p < 2e-16$), 0.0016 (95% CI: 0.0009 to 0.0023, $p < 2e-16$), and

0.0059 (95% CI 0.0031 to 0.0100, $p < 2e-16$), respectively (Table 3).

Mediation analysis of the effect of CMRFs on MASLD for *de novo* HCC

The ACMEs of T2D, dyslipidemia, HTN, waist circumference, and BMI on MASLD for HCC were 0.0042 (95% CI -0.0038 to 0.0100, $p = 0.34$), 0.0008 (95% CI -0.0031 to 0.00100, $p = 0.69$), 0.0002 (95% CI -0.0046 to 0.0100), $p = 0.91$), 0.0001 (95% CI: -0.0211 to 0.0200, $p = 0.98$), and -0.0206 (95% CI -0.0522 to 0.0100, $p = 0.14$), respectively. The ADEs of MASLD when mediated by T2D, dyslipidemia, HTN, waist circumference, and BMI for HCC were 0.0617 (0.0352 to 0.0900), $p < 2e-16$), 0.0752 (0.0475 to 0.1000), $p < 2e-16$), 0.0703 (0.0447 to 0.1000), $p < 2e-16$), 0.0663 (0.0386 to 0.0900), $p < 2e-16$), and 0.0935 (0.0590 to 0.1300), $p < 2e-16$), respectively. After adjusting for age, sex, LSM, platelet count and AFP, the ACMEs of T2D, dyslipidemia, HTN, waist circumference, and BMI on MASLD for HCC were 0.0042 (95% CI -0.0038 to 0.0100, $p = 0.34$), 0.0008 (95% CI -0.0031 to 0.0100, $p = 0.69$), 0.0002 (95% CI -0.0046 to 0.0100), $p = 0.91$), 0.0001 (95% CI: -0.0211 to 0.0200, $p = 0.98$), and -0.0206 (95% CI -0.0522 to 0.0100, $p = 0.14$), respectively (Table 4).

Sensitivity analysis using the Fine-Gray subdistribution hazards model

We set 78 patients who died during the study period as the competing risk. In Fine-Gray subdistribution hazards model 1, MASLD (sHR 2.61; 95% CI 1.55 to 4.38, $p < 0.001$), age per year increase (sHR 1.05; 95% CI 1.03 to 1.07, $p < 0.001$), male sex (sHR 3.03; 95% CI 1.87 to 4.94, $p < 0.001$), LSM per kPa increase (sHR 1.04; 95% CI 1.02 to 1.05, $p < 0.001$), platelet count per $10 \times 10^9/L$ increase (sHR 0.92; 95% CI 0.87 to 0.96, $p < 0.001$), and AFP >10 ng/ml (sHR 3.22; 95% CI 1.53 to 6.78, $p < 0.001$) were associated with HCC development. After excluding T2D, dyslipidemia, HTN, waist circumference, and BMI, the Fine-Gray subdistribution hazards model 2 revealed that in addition to age per year increase (sHR 1.05; 95% CI 1.03 to 1.07, $p < 0.001$), male sex (sHR 2.72; 95% CI 1.80 to 4.12, $p < 0.001$), LSM per kPa increase (sHR 1.04; 95% CI 1.02 to 1.05, $p < 0.001$), platelet count per $10 \times 10^9/L$ increase (sHR 0.91; 95% CI 0.87 to 0.96, $p < 0.001$), and AFP >10 ng/ml (sHR 3.17; 95% CI 1.61 to 6.27, $p < 0.001$), MASLD was associated with HCC development (sHR 2.07; 95% CI 1.34 to 3.19, $p < 0.001$) (Table 5).

Discussion

While DAAs have proven highly effective in eradicating HCV in the majority of cases, various residual risks, such as incomplete hepatic fibrosis remodeling, concomitant hepatotoxic injuries, and pre-neoplastic genetic and epigenetic changes, may still lead to HCC development.^{30–33} The prevalence of MASLD, which often involves concurrent MS components like T2D, dyslipidemia, HTN and obesity, is noteworthy, with global figures around 25% to 30% in adults without viral hepatitis.^{34,35} The existing body of evidence consistently indicates that HCV is a significant contributor to the increased prevalence of MASLD when compared to the general population.^{4,5,36,37} It is worth noting that the impact of achieving SVR12 on the

Table 2. Univariable and multivariable Cox proportional hazards models for factors associated with HCC.

Parameter	No HCC (n = 1,491)	HCC (n = 107)	Univariable analysis		Multivariable analysis*					
			cHR (95% CI)	p value	Model 1 [†]		Model 2 [‡]		Model 3 [§]	
					aHR (95% CI)	p value	aHR (95% CI)	p value	aHR (95% CI)	p value
MASLD										
Present	605 (40.6)	74 (69.2)	3.12 (2.07, 4.70)	<0.001	2.61 (1.56, 4.36)	<0.001	-	-	2.07 (1.36, 3.16)	<0.001
Absent	886 (59.4)	33 (30.8)	Ref		Ref				Ref	
SLD										
Present	611 (41.0)	74 (69.2)	3.09 (2.05, 4.66)	<0.001	-	-	2.56 (1.54, 4.27)	<0.001	-	-
Absent	880 (59.0)	33 (30.8)	Ref				Ref			
T2D										
Presence	291 (19.5)	42 (39.3)	2.76 (1.89, 4.07)	<0.001	1.27 (0.82, 1.95)	0.28	1.27 (0.83, 1.96)	0.27	-	-
Absence	1,200 (80.5)	65 (60.7)	Ref		Ref		Ref			
Dyslipidemia										
Presence	427 (28.6)	29 (27.1)	0.93 (0.61, 1.42)	0.73	1.12 (0.71, 1.77)	0.64	1.12 (0.71, 1.77)	0.63	-	-
Absence	1,064 (71.4)	78 (72.9)	Ref		Ref		Ref			
HTN										
Presence	445 (29.8)	43 (40.2)	1.50 (1.02, 2.20)	0.041	0.92 (0.60, 1.43)	0.72	0.93 (0.60, 1.44)	0.74	-	-
Absence	1,046 (70.2)	64 (59.8)	Ref		Ref		Ref			
Waist circumference, per cm increase	-	-	1.04 (1.02, 1.06)	<0.001	1.00 (0.97, 1.04)	0.98	1.00 (0.97, 1.04)	0.99	-	-
BMI, per kg/m ² increase	-	-	1.05 (0.99-1.10)	0.07	0.93 (0.84, 1.02)	0.11	0.93 (0.84, 1.02)	0.12	-	-
Age, per year increase	-	-	1.07 (1.05, 1.09)	<0.001	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001
Sex										
Male	778 (52.2)	71 (66.4)	1.94 (1.30, 2.89)	0.001	3.03 (1.89, 4.88)	<0.001	3.04 (1.89, 4.89)	<0.001	2.73 (1.79, 4.16)	<0.001
Female	713 (47.8)	36 (33.6)	Ref		Ref		Ref		Ref	
LSM, per kPa increase	-	-	1.07 (1.05, 1.08)	<0.001	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001
ALBI grade										
Grade 3	7 (0.5)	1 (0.9)	3.81 (0.53, 27.42)	0.18	0.85 (0.10, 6.93)	0.88	0.85 (0.11, 6.96)	0.88	0.84 (0.11, 6.54)	0.87
Grade 2	58 (3.9)	17 (15.9)	4.40 (2.62, 7.41)	<0.001	1.34 (0.72, 2.72)	0.33	1.40 (0.72, 2.73)	0.33	1.32 (0.69, 2.53)	0.40
Grade 1	1,246 (95.6)	89 (83.2)	Ref		Ref		Ref		Ref	
HCV RNA										
>2,000,000 IU/ml	541 (36.3)	33 (30.8)	0.86 (0.58, 1.31)	0.50	1.00 (0.66, 1.53)	0.99	1.00 (0.66, 1.63)	0.99	0.99 (0.65, 1.51)	0.97
≤2,000,000 IU/ml	950 (63.7)	74 (69.2)	Ref		Ref		Ref		Ref	
HCV genotype 1										
Yes	833 (55.9)	66 (61.7)	1.35 (0.91, 2.00)	0.13	1.13 (0.75, 1.70)	0.57	1.13 (0.75, 1.70)	0.56	1.15 (0.77, 1.72)	0.50
No	658 (44.1)	41 (38.3)	Ref		Ref		Ref		Ref	
Platelet count, per 10 ⁹ /L increase	-	-	0.85 (0.82, 0.89)	<0.001	0.92 (0.88, 0.96)	<0.001	0.92 (0.88, 0.96)	<0.001	0.91 (0.88, 0.95)	<0.001
ALT ≥2x ULN										
Yes	67 (4.5)	10 (9.3)	2.10 (1.09, 4.02)	0.026	0.78 (0.36, 1.68)	0.52	0.78 (0.36, 1.68)	0.53	0.90 (0.43, 1.85)	0.77
No	1,424 (95.5)	97 (90.7)	Ref		Ref		Ref		Ref	
Anti-HBc positivity										
Yes	1,193 (80.0)	87 (81.3)	1.10 (0.68, 1.79)	0.70	0.84 (0.51, 1.37)	0.47	0.84 (0.51, 1.37)	0.48	0.85 (0.52, 1.39)	0.52
No	298 (20.0)	20 (18.7)	Ref		Ref		Ref		Ref	
AFP, ng/ml										
>10	40 (2.7)	18 (16.8)	6.63 (3.99, 11.02)	<0.001	3.22 (1.70, 6.09)	<0.001	3.23 (1.71, 6.11)	<0.001	3.25 (1.80, 5.86)	<0.001
≤10	1,451 (97.3)	89 (83.2)	Ref		Ref		Ref		Ref	

AFP, alpha-fetoprotein; aHR, adjusted hazard ratio; ALBI grade, albumin-bilirubin grade; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; cHR, crude hazard ratio; HCC, hepatocellular carcinoma; HTN, hypertension; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver disease; T2D, type 2 diabetes; ULN, upper limit of normal.

*Covariates identified in the univariable Cox proportional hazards model were selectively included the multivariable Cox proportional hazards models.

[†]Model 1: including all covariates except for SLD.

[‡]Model 2: including all covariates except for MASLD.

[§]Model 3: including MASLD, age, sex, LSM, ALBI grade, HCV RNA, HCV genotype, platelet count, ALT level, anti-HBc, and AFP.

Table 3. Mediation analysis with bootstrapping to assess the mediation effect of MASLD on CMRFs for HCC.

Independent factors	Mediation effect (univariable model)*							
	ACME (95% CI)	ADE (95% CI)	Total effect (95 % CI)	Proportion mediated (95% CI)	p value [†]	p value [‡]	p value [§]	p value [¶]
T2D	0.0265 (0.0136, 0.0400)	0.0504 (0.0148, 0.0900)	0.0769 (0.0379, 0.1100)	0.3448 (0.1657, 0.6400)	<2e-16	0.0048	<2e-16	<2e-16
Dyslipidemia	0.0144 (0.0059, 0.0200)	-0.0159 (-0.0420, 0.0100)	-0.0015 (-0.0309, 0.0200)	-9.4733 (-12.3592, 11.6600)	<2e-16	0.24	0.71	0.71
HTN	0.0127 (0.0079, 0.0200)	0.0162 (-0.0113, 0.0400)	0.0289 (0.0017, 0.0600)	0.4392 (0.1787, 2.2300)	<2e-16	0.25	0.037	0.037
Waist circumference, cm	0.0014 (0.0008, 0.0021)	0.0006 (-0.0014, 0.0027)	0.0020 (0.0011, 0.0027)	0.7042 (0.2855, 1.1130)	<2e-16	0.34	0.0003	0.0003
BMI, kg/m ²	0.0062 (0.0035, 0.0091)	-0.0151 (-0.0163, 0.0021)	-0.0089 (-0.0239, 0.0071)	2.4300 (-0.1430, 19.5900)	<2e-16	0.16	0.07	0.07
Independent factors	Mediation effect (multivariable model)*, #							
	ACME (95% CI)	ADE (95% CI)	Total effect (95 % CI)	Proportion mediated (95% CI)	p value [†]	p value [‡]	p value [§]	p value [¶]
T2D	0.0144 (0.0063, 0.0200)	0.0187 (-0.0203, 0.0600)	0.0331 (-0.0044, 0.0700)	0.4340 (-1.7971, 3.6800)	<2e-16	0.36	0.08	0.08
Dyslipidemia	0.0084 (0.0037, 0.0100)	0.0020 (-0.0230, 0.0300)	0.0104 (-0.0140, 0.0400)	0.8068 (-6.7325, 8.7600)	<2e-16	0.89	0.43	0.43
HTN	0.0096 (0.0044, 0.0200)	-0.0013 (-0.0295, 0.0300)	0.0083 (-0.0203, 0.0400)	1.1501 (-8.5995, 8.9100)	<2e-16	0.95	0.58	0.58
Waist circumference, cm	0.0016 (0.0009, 0.0023)	-0.0014 (-0.0031, 0.0004)	0.0002 (-0.0012, 0.0016)	6.8200 (-33.9000, 32.9000)	<2e-16	0.09	0.73	0.73
BMI, kg/m ²	0.0059 (0.0031, 0.0100)	-0.0060 (-0.0137, 0.0023)	-0.0002 (-0.0037, 0.0031)	0.7115 (0.3673, 1.6700)	<2e-16	0.17	0.98	0.98

ACME, average causal mediation effect; ADE, average direct effect; CMRF, cardiometabolic risk factor; HCC, hepatocellular carcinoma; HTN, hypertension; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

*The β coefficients for ACME, ADE, and total effect were analyzed using the Cox proportional hazards models.

[†]Statistical significance for the indirect (mediation) effect.

[‡]Statistical significance for the direct effect.

[§]Statistical significance for the total effect.

[¶]Statistical significance for the proportion mediated.

#Adjusted for age, sex, liver stiffness measurement, platelet count, and alpha-fetoprotein.

Table 4. Mediation analysis with bootstrapping to assess the mediation effect of CMRFs on MASLD for HCC.

Mediators	Mediation effect (univariable model)*							
	ACME (95% CI)	ADE (95% CI)	Total effect (95 % CI)	Proportion mediated (95% CI)	p value [†]	p value [‡]	p value [§]	p value [¶]
T2D	0.0112 (0.0033, 0.0200)	0.0617 (0.0352, 0.0900)	0.0729 (0.0473, 0.1000)	0.1542 (0.0455, 0.3100)	0.004	<2e-16	<2e-16	0.004
Dyslipidemia	-0.0024 (-0.0063, 0.0013)	0.0752 (0.0475, 0.1000)	0.0728 (0.0464, 0.1000)	-0.0323 (-0.0924, 0.0200)	0.24	<2e-16	<2e-16	0.24
HTN	0.0025 (-0.0017, 0.0100)	0.0703 (0.0447, 0.1000)	0.0728 (0.0475, 0.1000)	0.0344 (-0.0247, 0.1200)	0.25	<2e-16	<2e-16	0.25
Waist circumference, cm	0.0068 (-0.0081, 0.0200)	0.0663 (0.0386, 0.0900)	0.0731 (0.0476, 0.1000)	0.0929 (-0.1139, 0.2900)	0.35	<2e-16	<2e-16	0.35
BMI, kg/m ²	-0.0213 (-0.0488, 0.0063)	0.0935 (0.0590, 0.1300)	0.0722 (0.0465, 0.1000)	-0.2947 (-0.7494, 0.0300)	0.07	<2e-16	<2e-16	0.07
Mediators	Mediation effect (multivariable model)*, #							
	ACME (95% CI)	ADE (95% CI)	Total effect (95 % CI)	Proportion mediated (95% CI)	p value [†]	p value [‡]	p value [§]	p value [¶]
T2D	0.0042 (-0.0038, 0.0100)	0.0682 (0.0381, 0.1000)	0.0724 (0.0418, 0.1000)	0.0585 (-0.0585, 0.1800)	0.34	<2e-16	<2e-16	0.34
Dyslipidemia	0.0008 (-0.0031, 0.0100)	0.0683 (0.0394, 0.1000)	0.0692 (0.0402, 0.1000)	-0.0058 (-0.0475, 0.0800)	0.69	<2e-16	<2e-16	0.69
HTN	0.0002 (-0.0046, 0.0100)	0.0683 (0.0391, 0.1000)	0.0685 (0.0387, 0.1000)	0.0030 (-0.0746, 0.0800)	0.91	<2e-16	<2e-16	0.91
Waist circumference, cm	0.0001 (-0.0211, 0.0200)	0.0683 (0.0383, 0.1000)	0.0684 (0.0320, 0.1100)	-0.0185 (-0.5070, 0.2500)	0.98	<2e-16	<2e-16	0.98
BMI, kg/m ²	-0.0206 (-0.0522, 0.0100)	0.0676 (0.0385, 0.1000)	0.0471 (0.0169, 0.0800)	-0.4373 (-2.3289, 0.1200)	0.14	<2e-16	<2e-16	0.14

ACME, average causal mediation effect; ADE, average direct effect; CMRF, cardiometabolic risk factor; HCC, hepatocellular carcinoma; HTN, hypertension; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

*The β coefficients for ACME, ADE, and total effect were analyzed using the Cox proportional hazards models.

[†]Statistical significance for the indirect (mediation) effect.

[‡]Statistical significance for the direct effect.

[§]Statistical significance for the total effect.

[¶]Statistical significance for the proportion mediated.

#Adjusted for age, sex, liver stiffness measurement, platelet count, and alpha-fetoprotein.

Table 5. Fine-Gray subdistribution hazards model for factors associated with HCC.

Parameter	Multivariable analysis*			
	Model 1 [†]		Model 2 [‡]	
	sHR (95% CI)	p value	sHR (95% CI)	p value
MASLD				
Present	2.61 (1.55, 4.38)	<0.001	2.07 (1.34, 3.19)	<0.001
Absent	Ref			
T2D				
Present	1.27 (0.79, 2.05)	0.33	-	-
Absent	Ref			
Dyslipidemia				
Present	1.12 (0.70, 1.78)	0.65	-	-
Absent	Ref			
HTN				
Present	0.92 (0.60, 1.42)	0.72	-	-
Absent	Ref			
Waist circumference, per cm increase	1.00 (0.96, 1.04)	0.98	-	-
BMI, per kg/m ² increase	0.93 (0.83, 1.03)	0.15	-	-
Age, per year increase	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001
Sex				
Male	3.03 (1.87, 4.94)	<0.001	2.72 (1.80, 4.12)	<0.001
Female	Ref		Ref	
LSM, per kPa increase	1.04 (1.02, 1.05)	<0.001	1.04 (1.02, 1.05)	<0.001
ALBI grade				
Grade 3	0.85 (0.08, 9.18)	0.89	0.84 (0.08, 8.43)	0.88
Grade 2	1.40 (0.71, 2.76)	0.34	1.32 (0.70, 2.51)	0.39
Grade 1	Ref		Ref	
HCV RNA				
>2,000,000 IU/ml	1.00 (0.66, 1.52)	0.99	0.99 (0.65, 1.50)	0.96
≤2,000,000 IU/ml	Ref		Ref	
HCV genotype 1				
Yes	1.13 (0.76, 1.67)	0.55	1.15 (0.78, 1.70)	0.49
No	Ref		Ref	
Platelet count, per 10 ⁹ /L increase	0.92 (0.87, 0.96)	<0.001	0.91 (0.87, 0.96)	<0.001
ALT ≥2x ULN				
Yes	0.78 (0.31, 1.97)	0.60	0.89 (0.38, 2.06)	0.78
No	Ref		Ref	
Anti-HBc positivity				
Yes	0.84 (0.52, 1.35)	0.46	0.85 (0.53, 1.38)	0.51
No	Ref		Ref	
AFP, ng/ml				
>10	3.22 (1.53, 6.78)	<0.001	3.17 (1.61, 6.27)	<0.001
≤10	Ref		Ref	

AFP, alpha-fetoprotein; ALBI grade, albumin-bilirubin grade; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; HCC, hepatocellular carcinoma; HTN, hypertension; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; sHR, subdistribution hazard ratio; SLD, steatotic liver disease; T2D, type 2 diabetes; ULN, upper limit of normal.

*Covariates were selectively included the multivariable Fine-Gray subdistribution hazards models.

[†]Model 1: including all covariates except for SLD.

[‡]Model 2: including MASLD, age, sex, LSM, ALBI grade, HCV RNA, HCV genotype, platelet count, ALT level, anti-HBc, and AFP.

changing prevalence of MASLD, as assessed by CAP, in patients receiving DAAs for HCV, is conflicting in the current literature.^{38–43} Furthermore, it is crucial to investigate the role of MASLD, including its contributing etiologies, in the development of post-SVR12 HCC for patients with HCV in the era of DAAs.

The findings from our study revealed that the prevalence of MASLD remained notably high (42.7%) among East Asian patients.⁴⁰ Not surprisingly, compared to patients without MASLD, those with MASLD exhibited a higher proportion of MS, more severe LSM and CAP, and higher ALT and AFP levels. The lower median level of HDL-C in our patients with MASLD suggested that more were likely using lipid-lowering agents to manage dyslipidemia, in contrast to their non-MASLD counterparts.

In our study, focusing on the presence of MASLD among patients achieving SVR12 for HCV, we observed that the incidence and cumulative incidence rates of *de novo* HCC were significantly higher in this group than in those without MASLD. Notably, the incidence rates of HCC in our patients tended to be higher than the reported HCC risk for individuals without HCV infection, regardless of the presence (2.41 vs. 2.10 per 100 PYFU) or absence (0.76 vs. 0.20 per 100 PYFU) of MASLD.⁴⁴ This increase in HCC risk is likely due to the existence of HCV-induced pre-neoplastic genetic and epigenetic changes or suboptimal fibrosis regression, despite successful HCV eradication with DAAs.

Consistent with prior research, we reaffirmed that in the univariable Cox proportional hazards model, the presence of SLD or CMRFs such as T2D, HTN, higher waist circumference,

older age, male sex, higher LSM, more advanced ALBI grade, lower platelet count, higher levels of ALT, and higher AFP levels were predictors of HCC development beyond SVR12.^{17,18,25,45–50} To delineate the contribution of MASLD and CMRFs to HCC development, we included MASLD, various CMRFs, and other known risk factors in multivariable models. The results demonstrated that the presence of MASLD outweighed all CMRFs in its association with HCC. Additionally, we built another multivariable model including SLD and CMRFs, confirming that presence of SLD, rather than CMRFs, primarily contributed to the development of HCC. Intriguingly, results from the two models yielded similar risk estimates, largely due to 99.1% concordance between our patients with a diagnosis of SLD and MASLD. This finding aligns with a recent report from the TARGET cohort, which demonstrated a 99% overlap of non-alcoholic fatty liver disease (NAFLD) and MASLD among those without HCV.⁵¹ Because MASLD showed high collinearity with CMRFs, we included MASLD and covariates other than CMRFs, which did not show collinearity with MASLD, in a multivariable model. In addition to age, sex, LSM, platelet count, and AFP, the presence of MASLD at the SVR12 time point was associated with an approximately two-fold increased risk of *de novo* HCC development. Conversely, we examined the effects of CMRFs in multivariable Cox proportional hazards models by excluding MASLD or SLD, demonstrating that none of these CMRFs showed a significant association with HCC when conventional covariates were taken into consideration. Given its significant role, the new MASLD nomenclature may replace SLD, NAFLD, or CMRFs in predicting the risk of post-SVR12 HCC development for HCV.

To elucidate the complex mediation between MASLD and CMRFs, we performed mediation analyses using CMRFs as the independent covariates and MASLD as the mediator, and vice versa, for HCC development. Results from our mediation analyses demonstrated strong mediation effects of MASLD on various CMRFs for HCC development after adjusting for age, sex, LSM, platelet count, and AFP. In contrast, CMRFs did not play an important role in mediating the effect of MASLD on HCC development.

While meta-analyses have indicated a three to four-fold higher risk of HCC in untreated HCV patients with MASLD compared to those without MASLD, our data found that the time-dependent risk of HCC decreased to approximately two-fold in patients with MASLD after HCV eradication.^{12,13,17,50} This suggests that the concurrent presence of active HCV and MASLD may potentiate the effect of hepatocarcinogenesis,

which may be ameliorated by the successful eradication of HCV with DAAs.⁵²

To correctly estimate the marginal probability of HCC in the presence of deaths, which were the major competing risk during the post-SVR12 follow-up, we performed sensitivity analysis using the Fine-Gray subdistribution hazards models to confirm the risk estimates performed in the multivariable Cox proportional hazards models. The sHRs of variables significantly associated with HCC development were consistent with the results shown in the Cox regression models, indicating that deaths did not significantly affect the risk estimates in our cohort.

This study has several notable strengths, including the enrollment of a substantial number of East Asian patients with HCV who achieved SVR12 with DAAs, utilization of a well-defined cut-off value of CAP to discern SLD, comprehensive assessment of various parameters to ensure outcome estimation, and application of mediation analysis to quantify the extent of transmittance of MASLD from CMRFs to HCC development, as well as competing risk analysis to correctly evaluate the effects of deaths on risk estimates. Nevertheless, there are certain limitations to consider. Firstly, the study population exclusively comprised East Asians, emphasizing the importance of external validation to confirm our findings, especially in non-East Asian populations. Secondly, the relatively small number of patients classified as ALBI grade 3 indicates the need for larger cohorts to substantiate the risk of HCC in these subgroups. Lastly, the lack of DCP (des-gamma carboxyprothrombin) or GALAD (gender, age, AFP-L3, AFP, and DCP) score from our prediction models may warrant consideration in future studies.^{53,54}

In summary, our study has provided important insights into the risk factors for *de novo* HCC development following the achievement of SVR12 with DAAs in patients with HCV. We found that, along with factors such as age, sex, LSM, BMI, platelet count, and AFP levels, patients with MASLD following the HCV eradication still faced approximately a two-fold increased risk of time-dependent *de novo* HCC. Additionally, we also confirmed that MASLD played a crucial role in positively mediating the effects of all CMRFs on HCC development. These findings underscore the critical importance of well-controlled CMRFs through pharmacological interventions and proactive lifestyle modifications to mitigate the effect of MASLD on post-SVR12 HCC development.^{55–57} They also highlight the need for vigilant HCC surveillance in patients with MASLD to ensure long-term favorable outcomes following HCV eradication.

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Abbreviations

ACME, average causal mediation effect; ADE, average direct effect; AFP, alpha-fetoprotein; aHR, adjusted hazard ratio; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CAP, controlled attenuation parameter; cHR, crude hazard ratio; CMRF, cardiometabolic risk factor; DAA, direct-acting antiviral; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein-cholesterol; HTN, hypertension; IFN, interferon; INR, international normalized ratio; LLOQ, lower limit of quantification; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MS, metabolic syndrome; PYFU, person-years of follow-up; sHR, subdistribution hazard ratio; SLD, steatotic liver disease; SVR12, sustained virologic response at off-treatment week 12; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography; ULN, upper limit of normal.

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Conflicts of interest

All authors declare no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: CH Liu, JH Kao. Data curation: CH Liu. Formal analysis: CH Liu. Investigation: CH Liu, PN Cheng, YJ Fang, CY Chen, WY Kao, CL Lin, SS Yang, YL Shih, YP Chang, SC Huang, TH Su, TC Tseng, CJ Liu, PJ Chen, JH Kao. Methodology: CH Liu, JH Kao. Project administration: CH Liu, JH Kao. Resources: CH Liu, PN Cheng, YJ Fang, CY Chen, WY Kao, CL Lin, SS Yang, YL Shih, YP Chang, SC Huang, TH Su, TC Tseng, CJ Liu, PJ Chen, JH Kao. Software: CH Liu. Supervision: CH Liu. Validation: CH Liu. Visualization: CH Liu. Writing – original draft: CH Liu, JH Kao. Writing – review & editing: CH Liu, PN Cheng, YJ Fang, CY Chen, WY Kao, CL Lin, SS Yang, YL Shih, YP Chang, SC Huang, TH Su, TC Tseng, CJ Liu, PJ Chen, JH Kao.

Data availability statement

Data are available upon reasonable request to the corresponding author.

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Supplementary data

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