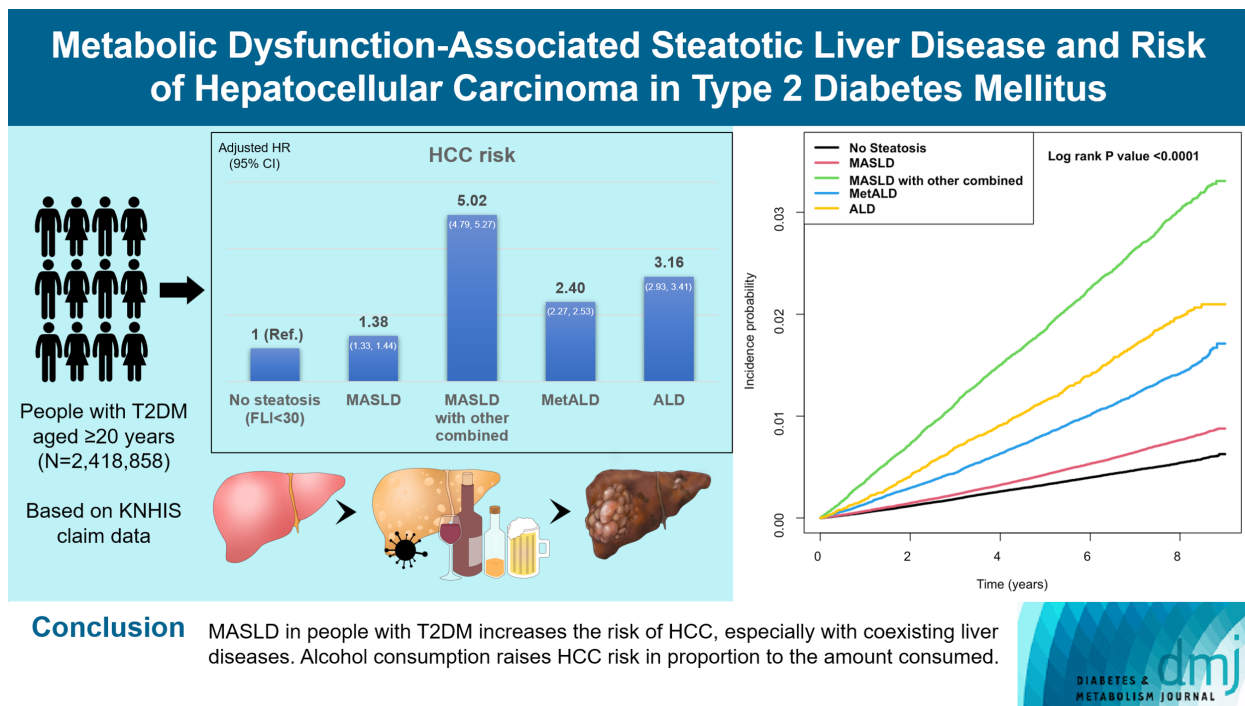


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Highlights

- MASLD increased HCC risk in T2DM, especially with coexisting liver diseases.
- HCC risk increased proportionally with the level of alcohol consumption.
- Managing metabolic risk factors is crucial, particularly in high-risk individuals.

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Metabolic Dysfunction-Associated Steatotic Liver Disease and Risk of Hepatocellular Carcinoma in Type 2 Diabetes Mellitus

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Background: We investigated the incidence rates of hepatocellular carcinoma (HCC) in metabolic dysfunction-associated steatotic liver disease (MASLD) categories, focusing on its association with alcohol consumption in patients with type 2 diabetes mellitus (T2DM).

Methods: This study included 2,418,858 patients with T2DM aged 20 years and older who underwent a health examination between 2009 and 2012. Participants were categorized into five groups according to hepatic steatosis, cardiometabolic risk factors, other liver diseases, and alcohol consumption. Hepatic steatosis was defined as the fatty liver index ≥ 30 . Cox regression analysis was used to analyze the association between steatotic liver disease and development of HCC.

Results: The MASLD group showed a higher risk of HCC development regardless of alcohol consumption or presence of other liver diseases (adjusted hazard ratio [aHR], 1.38; 95% confidence interval [CI], 1.33 to 1.44). The MASLD with other combined group expressed the highest risk (aHR, 5.02; 95% CI, 4.79 to 5.27). In the metabolic dysfunction and alcohol-related steatotic liver disease and alcohol-related liver disease groups, heavy to excessive alcohol consumption increased the risk of HCC development, with a higher risk associated with greater alcohol intake (aHR, 2.40; 95% CI, 2.27 to 2.53 and aHR, 3.16; 95% CI, 2.93 to 3.41). Fine and Gray analysis also exhibited a consistent trend.

Conclusion: MASLD in patients with T2DM was associated with an increased risk of developing HCC, particularly when accompanied by other liver diseases. Moreover, alcohol consumption proportionally increased the risk of HCC with the amount of alcohol consumed.

Keywords: Alcohol drinking; Carcinoma, hepatocellular; Diabetes mellitus; Fatty liver

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is widely recognized as the predominant etiology of chronic liver disease in individ-

uals with type 2 diabetes mellitus (T2DM). Previous studies have identified a bidirectional causal relationship between NAFLD and T2DM as they share similar pathophysiological pathways, with one condition preceding and/or promoting the

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other [1-4]. A new consensus was published on the classification of steatotic liver diseases in 2023 [5]. In particular, the term metabolic dysfunction-associated steatotic liver disease (MASLD) emphasizes the importance of evaluating the distinct components of metabolic syndrome, including alcohol consumption. The risk of MASLD is closely linked to metabolic factors, including obesity, visceral fat, insulin resistance, and dyslipidemia. NAFLD has been associated with a significant burden of adverse liver outcomes, including hepatocellular carcinoma (HCC) [6]. Liver cancer is among the top three cancers worldwide, and HCC is the predominant contributor to the global burden [7]. Approximately 30% of the people in Korea have NAFLD, and its prevalence increases with the rise in T2DM [8,9]. Although previous studies have elucidated the association between NAFLD and T2DM, as well as the risk of HCC [10-12], uncertainty remains in studies investigating the specific risk of HCC development attributable to MASLD in patients with diabetes, particularly regarding differences based on alcohol consumption. Thus, the primary objective of this study was to evaluate the risk of developing HCC in MASLD patients having T2DM using data from a national cohort. Therefore, we aimed to investigate the relationship between MASLD, alcohol consumption, and increased risk of HCC incidence in this high-risk patient population with T2DM.

METHODS

Study population and design

We acquired the relevant data from the Korean National Health Insurance Service (NHIS) database, a comprehensive repository that encompasses the entire Korean population, from January 2009 to December 2018. The entire population of Korea is covered by two healthcare programs: National Health Insurance (NHI) and Medical Aid (MA), with approximately 97% covered by NHI and the remaining 3%, with the lowest income, covered by MA [13].

This government-operated database contains a claims dataset that provides patient demographic information, health check-up records, diagnoses coded according to the International Classification of Disease, 10th revision (ICD-10) codes, and prescriptions. Additionally, the health examination dataset includes responses to questionnaires on health-related behaviors, past and current medical histories, anthropometric measurements, and laboratory test results. For mortality data, we sourced nationwide death certificate records from the Korean

National Statistical Office, which documents the dates and causes of death based on the revised ICD-10 codes. This study was approved by the Institutional Review Board of Samsung Medical Center (approval no. SMC 2024-03-104), Seoul, Republic of Korea, which waived the need for informed consent because all data provided to the researchers were deidentified. All procedures involving human participants were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This study enrolled patients with T2DM aged 20 years and older who underwent a general health examination between 2009 and 2012 ($n=2,746,079$). Among them, 390 under the age of 20 years and 131,147 individuals with missing data were excluded. Additionally, those diagnosed with liver cancer at least once before the index date ($n=70,988$) and those who had undergone liver transplantation ($n=277$) were excluded. Patients who had previously been diagnosed with cancer were excluded ($n=72,292$), as were individuals who died or were diagnosed with HCC within 1 year of screening ($n=52,127$). Consequently, 2,418,858 participants were included in the final analysis.

Measurements and definitions

Height, body weight, and waist circumference (WC) were measured during the health examinations. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared in meters. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². T2DM was defined as a fasting blood glucose ≥ 126 mg/dL, or use of specific medications, or at least one claim using codes E11-14. New-onset diabetes mellitus (DM) was defined as having a fasting blood glucose level of ≥ 126 mg/dL at the time of health screening, with no prior prescription of DM medication before the health check-up. Hypertension (HTN) was identified as a systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or use of antihypertensive medication, or at least one claim using codes I10-11. Dyslipidemia was defined as a total cholesterol level of ≥ 240 mg/dL, or at least one claim per year using the code E78 and at least one claim per year for the prescription of a lipid-lowering agent. Alcohol abuse/misuse, or alcohol-related liver disease (ALD) were defined by the following ICD-10 codes: E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, Q35.4, R78.0, T51.0, T51.8, T51.9, X65, Y15, Y57.3, Y90, Y91, Z50.2, Z71.4, Z71.2, F11-F19. Concomitant liver diseases were also defined by the

following ICD-10 codes: viral hepatitis (B15–B19, B00.8, B25.1), drug-induced (toxic) liver disease (K71), hepatic veno-occlusive disease (I82), liver abscess (K75.0, A06.4), hemochromatosis (E83.1), Wilson's disease (E83.0), alpha-1 anti-trypsin deficiency (E88.0), autoimmune hepatitis (K75.4), biliary cholangitis (K74.3–K74.4), other cholangitis (K83, K83.0), and glycogen storage disease (E74). The Charlson comorbidity index (CCI) is a comorbidity score comprised of 12 conditions. Income was classified based on the quartile (Q) of the study population (Q4: highest; Q1: lowest). Insulin use was defined as having one or more prescriptions of insulin per year and three or more prescriptions in an outpatient setting. Regular exercise was also evaluated through the questionnaire and was defined as meeting any one of the following two criteria: (1) ≥ 3 days/week of vigorous activity (causing extreme shortness of breath) for at least 20 min/day or (2) ≥ 5 days/week of moderate-intensity activity (causing significant shortness of breath) for at least 30 min/day. Alcohol consumption was assessed using questionnaires on participants' drinking behaviors. The participants were asked about their average frequency (days/week) and amount (standard glass). A standard glass sample was calculated as 8 g of pure alcohol. The average amount of alcoholic beverages consumed was converted into pure alcohol (g) consumed per day.

Definition of hepatic steatosis and MASLD

Hepatic steatosis was assessed using the fatty liver index (FLI), which was calculated using the following equation [14]:

$$\left(e^{0.953 \times \log_e(\text{triglycerides [TG]}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{gamma-glutamyl transferase [GGT]}) + 0.053 \times \text{WC} - 15.745} \right) / \left(1 + e^{0.953 \times \log_e(\text{TG}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{WC} - 15.745} \right).$$

MASLD was diagnosed when participants with hepatic steatosis had at least one of the following cardiometabolic risk factors, with FLI ≥ 30 used to define hepatic steatosis [15,16]: (1) BMI ≥ 23 kg/m² or WC ≥ 90 cm in men and ≥ 80 cm in women; (2) fasting blood glucose levels ≥ 100 mg/dL or T2DM or specific drug treatment; (3) blood pressure (BP) $\geq 130/85$ mm Hg or specific medication treatment; (4) TG ≥ 150 mg/dL or specific medication treatment; (5) high-density lipoprotein cholesterol < 40 mg/dL for men and < 50 mg/dL for women or specific medications.

We categorized the patients into five groups as follows: (1) no steatosis group (FLI < 30); (2) MASLD group where mild alcohol consumption was defined as < 30 g/day for men and < 20 g/day for women; (3) MASLD with other combined group, defined as MASLD and a diagnosis of concomitant liver

disease or ALD within 1 year before screening; (4) metabolic dysfunction and alcohol-related steatotic liver disease (Met-ALD) group, defined as heavy alcohol consumption (≥ 30 but < 60 g/day for men and ≥ 20 but < 50 g/day for women) with FLI ≥ 30 and ≥ 1 cardiometabolic risk factor; and (5) ALD group, defined as excessive alcohol consumption (≥ 60 g/day for men and ≥ 50 g/day for women) with FLI ≥ 30 and ≥ 1 cardiometabolic risk factor.

Outcomes

The primary outcome was HCC development. The participants were followed-up from the baseline health examination until the occurrence of the primary outcome event. The period between 2009 and 2012 was designated as the baseline, with the last examination serving as the reference point. The study population was followed-up from baseline until the date of death, onset of HCC, or December 31, 2018, whichever occurred first.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation, and categorical variables were presented as numbers with frequencies (%). Continuous baseline characteristics and categorical baseline variables were compared using one-way analysis of variance (ANOVA) and the chi-squared test, respectively. The incidence of HCC was calculated as the number of incident cases divided by the total duration of follow-up (person-years). Kaplan–Meier curves were used to compare the cumulative incidence of HCC according to the duration of exposure to steatotic liver disease in the five groups, and the significance of differences among the five groups was evaluated using the log-rank test.

We conducted a univariate analysis of risk factors for HCC development providing valuable context for understanding whether these associations with HCC are driven by specific baseline characteristics. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC development. Model 1 is a crude model. Model 2 is adjusted for age and sex. Model 3 was further adjusted for income, smoking status, regular exercise, and CCI scores. Model 4 was additionally adjusted for fasting glucose, DM duration, insulin use, oral hypoglycemic agents (OHA), and CKD. A Fine-Gray competing risk regression model was used to calculate subdistribution HRs and their 95% CIs, accounting for competing risks such as death.

A subgroup analysis was performed to test the association between HCC development and variables. Statistical significance was set at $P < 0.05$, and analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 2,418,858 individuals were categorized into the following five groups: 916,381 (37.9%) in the no steatosis group; 1,177,503 (48.7%) in the MASLD group; 116,426 (4.8%) in the MASLD with other combined group; 158,555 (6.5%) in the MetALD group; and 49,993 (2.1%) in the ALD group. The baseline characteristics of the 2,418,858 participants are presented in Table 1. The median age of the total population was 57 years, and 60.0% were men.

Participants in the ALD group were more likely to be men and current smokers, with a high prevalence of new-onset DM, higher values of SBP, DBP, fasting glucose, eGFR, TG, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and GGT, and lower levels of low-density lipoprotein cholesterol compared to the other groups. Participants in the MASLD with other combined group had the largest WC, and those in the MetALD group were more likely to be current smokers. Among 116,426 individuals in MASLD with other combined group, the most common coexisting disease was ALD diagnosed within 1 year before screening (44.2%), followed by viral hepatitis (41.6%) and drug-induced liver disease (14.9%), while other conditions such as autoimmune, genetic, and bile duct-related liver diseases were less common (Supplementary Table 1).

Risk of HCC development according to alcohol consumption, metabolic risk, and MASLD

Univariate analysis revealed that HCC risk significantly increased with older age, male sex, low income, smoking, regular exercise, higher CCI scores, elevated fasting glucose, longer DM duration, use of insulin or OHA, and CKD, providing valuable context for understanding whether these associations with HCC are driven by specific baseline characteristics (Supplementary Table 2). The cumulative incidence rates for HCC were significantly higher in participants in the MASLD with other combined group, ALD group, MetALD group, and MASLD group compared to those without hepatic steatosis (log-rank $P < 0.0001$) (Fig. 1). After adjustment for age, sex, in-

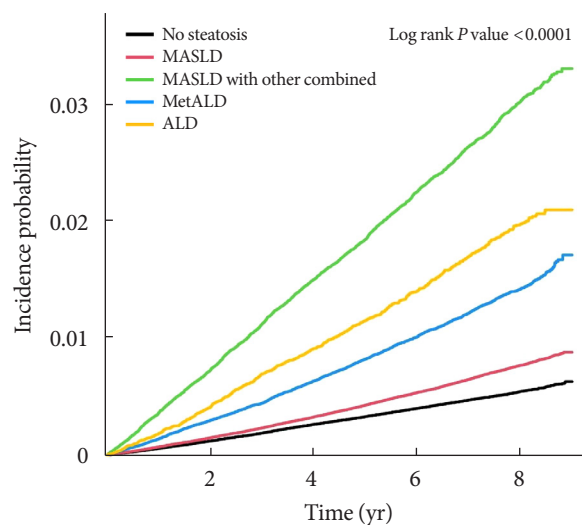


Fig. 1. Cumulative incidence of hepatocellular carcinoma according to the presence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction and alcohol-related steatotic liver disease (MetALD). ALD, alcohol-related liver disease.

come, smoking status, regular exercise, CCI score, fasting glucose, DM duration, insulin use, OHA use, and CKD, the MASLD group showed a higher risk of HCC development compared to those without hepatic steatosis (adjusted hazard ratio [aHR], 1.38; 95% CI, 1.33 to 1.44; Model 4) (Table 2). The MASLD with other combined group expressed the highest risk of HCC (aHR, 5.02; 95% CI, 4.79 to 5.27). In the MetALD and ALD groups, heavy to excessive alcohol consumption increased the risk of HCC development, with a higher risk associated with greater alcohol intake compared to those without hepatic steatosis (aHR, 2.40; 95% CI, 2.27 to 2.53 and aHR, 3.16; 95% CI, 2.93 to 3.41). Fine and Gray analysis also showed a consistent trend.

Subgroup analysis

Subgroup analyses of the HCC incidence stratified by age, sex, income, smoking, regular exercise, CCI score, fasting glucose level, DM duration, insulin use, OHA, and CKD were performed (Supplementary Table 3). In the subgroup analyses, the association between the MASLD category and incident HCC was consistent across the indicated subgroups (P for interaction > 0.05); however, an interaction was noted between age, DM duration, regular exercise, CKD, insulin use, and the number of OHA. Furthermore, an additional analysis was conducted stratifying by follow-up duration (< 5 and ≥ 5 years),

Table 1. Baseline characteristics of the study participants

Characteristic	No steatosis (n=916,381)	MASLD (n=1,177,503)	MASLD with other combined (n=116,426)	MetALD (n=158,555)	ALD (n=49,993)
Age, yr	58.75±12.80	56.64±12.15	57.11±11.02	51.82±10.54	52.16±10.37
Age groups, yr					
<40	66,020 (7.20)	97,847 (8.31)	6,284 (5.40)	18,169 (11.46)	4,982 (9.97)
40–64	529,760 (57.81)	752,520 (63.91)	79,608 (68.38)	121,583 (76.68)	39,028 (78.07)
≥65	320,601 (34.99)	327,136 (27.78)	30,534 (26.23)	18,803 (11.86)	5,983 (11.97)
Sex					
Male	428,408 (46.75)	743,665 (63.16)	81,342 (69.87)	150,638 (95.01)	48,302 (96.62)
Female	487,973 (53.25)	433,838 (36.84)	35,084 (30.13)	7,917 (4.99)	1,691 (3.38)
BMI, kg/m ²	22.71±2.33	26.68±3.11	26.50±3.18	25.96±3.11	25.93±3.29
Waist circumference, cm	78.88±6.40	89.49±7.72	89.71±7.85	89.14±7.45	89.47±8.33
SBP, mm Hg	126.02±15.77	130.82±15.58	129.76±15.26	132.43±15.56	133.13±16.09
DBP, mm Hg	76.61±9.89	80.42±10.17	79.91±9.96	82.59±10.40	82.96±10.58
Fasting glucose, mg/dL	140.60±46.74	147.54±46.99	142.23±46.77	153.62±46.67	157.43±51.00
Total cholesterol, mg/dL	188.24±43.38	203.80±46.18	193.97±47.37	204.09±48.80	203.17±53.33
HDL cholesterol, mg/dL	54.78±27.18	50.16±29.73	50.37±28.29	53.55±33.51	54.36±28.55
LDL cholesterol, mg/dL	112.79±70.56	114.94±86.55	107.29±90.34	106.60±130.96	103.30±132.07
eGFR, mL/min/1.73 m ²	85.09±35.54	84.20±36.23	84.85±37.09	90.20±38.44	91.92±39.70
Triglycerides, mg/dL	100.46 (100.37–100.56)	184.47 (184.30–184.64)	174.15 (173.64–174.67)	206.13 (205.56–206.71)	211.51 (210.41–212.61)
AST, IU/L	22.16 (22.15–22.18)	27.71 (27.69–27.73)	32.02 (31.92–32.11)	32.42 (32.34–32.51)	35.93 (35.75–36.12)
ALT, IU/L	19.72 (19.70–19.74)	30.64 (30.60–30.67)	33.49 (33.37–33.61)	33.55 (33.45–33.65)	35.22 (35.04–35.41)
GGT, IU/L	21.50 (21.48–21.52)	45.38 (45.32–45.44)	57.08 (56.81–57.35)	88.38 (88.05–88.72)	108.69 (107.90–109.50)
Income, lowest Q1	199,528 (21.77)	245,633 (20.86)	25,174 (21.62)	29,479 (18.59)	9,948 (19.90)
Smoking					
None	610,388 (66.61)	632,819 (53.74)	57,162 (49.10)	29,997 (18.92)	9,310 (18.62)
Former	130,300 (14.22)	226,384 (19.23)	25,474 (21.88)	44,754 (28.23)	13,737 (27.48)
Current	175,693 (19.17)	318,300 (27.03)	33,790 (29.02)	83,804 (52.85)	26,946 (53.90)
Drinking ^a					
None	629,236 (68.67)	673,036 (57.16)	64,094 (55.05)	0	0
Mild	243,444 (26.57)	504,467 (42.84)	52,332 (44.95)	0	0
Heavy	35,606 (3.89)	0	0	158,555 (100)	0
Excessive	8,095 (0.88)	0	0	0	49,993 (100)
Regular exercise	202,935 (22.15)	225,120 (19.12)	24,339 (20.91)	33,173 (20.92)	10,513 (21.03)
CKD	107,960 (11.78)	139,843 (11.88)	13,661 (11.73)	8,468 (5.34)	2,446 (4.89)
CCI score, ≥5	142,813 (15.58)	144,540 (12.28)	35,064 (30.12)	11,998 (7.57)	4,536 (9.07)
DM duration					
New onset	331,782 (36.21)	491,420 (41.73)	30,306 (26.03)	86,681 (54.67)	25,668 (51.34)
<5 years	264,986 (28.92)	380,081 (32.28)	50,864 (43.69)	43,178 (27.23)	14,145 (28.29)
≥5 years	319,613 (34.88)	306,002 (25.99)	35,256 (30.28)	28,696 (18.10)	10,180 (20.36)
OHA, ≥3	145,123 (15.84)	158,259 (13.44)	22,066 (18.95)	15,695 (9.90)	5,871 (11.74)
Insulin ^b	89,007 (9.71)	81,070 (6.88)	13,443 (11.55)	6,340 (4.00)	2,498 (5.00)

Values are presented as mean±standard deviation, number (%), or geometric mean (95% confidence interval).

MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; ALD, alcohol-related liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Q, quartile; CKD, chronic kidney disease; CCI, Charlson comorbidity index; DM, diabetes mellitus; OHA, oral hypoglycemic agent.

^aAlcohol consumption: (1) None, (2) Mild (<30 g/day for men, <20 g/day for women), (3) Heavy (30≤ men <60 g/day, 20≤ women <50 g/day), (4) Excessive ≥60 g/day for men, ≥50 g/day for women), ^bInsulin use: A total of three or more prescriptions of insulin in an outpatient setting and at least one prescription of insulin per year.

Table 2. Hazard ratios and subdistribution hazard ratios for hepatocellular carcinoma development according to the group

Variable	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	HR (95% CI)				Model 4+ competing risk ^a
					Model 1	Model 2	Model 3	Model 4	
No steatosis	916,381	4,252	6,299,200.4	0.6750	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
MASLD	1,177,503	7,642	8,168,274.6	0.9356	1.39 (1.34–1.44)	1.36 (1.30–1.41)	1.36 (1.31–1.41)	1.38 (1.33–1.44)	1.41 (1.36–1.46)
MASLD with other combined	116,426	3,021	793,090.5	3.8092	5.65 (5.39–5.92)	5.15 (4.91–5.39)	4.96 (4.73–5.20)	5.02 (4.79–5.27)	5.13 (4.89–5.39)
MetALD	158,555	1,928	1,091,556.5	1.7663	2.62 (2.48–2.77)	2.43 (2.30–2.57)	2.35 (2.22–2.49)	2.40 (2.27–2.53)	2.41 (2.29–2.56)
ALD	49,993	830	341,529.3	2.4303	3.61 (3.35–3.88)	3.28 (3.04–3.54)	3.15 (2.92–3.40)	3.16 (2.93–3.41)	3.17 (2.93–3.42)
P value					<0.001	<0.001	<0.001	<0.001	<0.001

The results were obtained using Cox proportional hazards analysis. Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for income, smoking, regular exercise, and Charlson comorbidity index score; Model 4: adjusted for fasting glucose, diabetes mellitus duration, insulin use, oral hypoglycemic agent, and chronic kidney disease. Model 4+competing risk: Fine-Gray competing risk model adjusted for the same variables as model 4, accounting for death as a competing risk.

HR, hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; ALD, alcohol-related liver disease.

^aResults are presented as subdistribution HR with 95% CI.

Table 3. Hazard ratios and subdistribution hazard ratios for hepatocellular carcinoma development according to the degree of fatty liver index group (FLI <30, 30 ≤ FLI <60, FLI ≥60) and alcohol consumption

Variable	Drinking ^a	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	HR (95% CI)				Model 4+ competing risk ^b
						Model 1	Model 2	Model 3	Model 4	
FLI <30	None	629,236	2,679	4,312,991.9	0.6212	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	243,444	1,240	1,687,803.7	0.7347	1.18 (1.11–1.27)	1.04 (0.97–1.11)	1.03 (0.96–1.11)	1.04 (0.97–1.12)	1.06 (0.99–1.14)
	Heavy	35,606	246	243,522.9	1.0102	1.63 (1.43–1.86)	1.40 (1.23–1.60)	1.33 (1.17–1.52)	1.35 (1.18–1.54)	1.36 (1.19–1.55)
	Excessive	8,095	87	54,881.9	1.5852	2.56 (2.06–3.16)	2.04 (1.65–2.53)	1.92 (1.55–2.38)	1.91 (1.54–2.37)	1.88 (1.52–2.33)
30 ≤ FLI <60	None	462,908	3,183	3,210,748.1	0.9914	1.59 (1.51–1.68)	1.49 (1.42–1.57)	1.49 (1.42–1.57)	1.51 (1.44–1.60)	1.55 (1.48–1.64)
	Mild	271,877	2,092	1,891,234.1	1.1062	1.78 (1.68–1.89)	1.47 (1.39–1.56)	1.46 (1.37–1.55)	1.51 (1.42–1.60)	1.55 (1.45–1.65)
	Heavy	59,461	619	409,470.4	1.5117	2.44 (2.23–2.66)	2.01 (1.84–2.20)	1.94 (1.78–2.13)	1.99 (1.82–2.18)	2.04 (1.87–2.23)
	Excessive	15,912	205	108,674.4	1.8864	3.04 (2.64–3.50)	2.44 (2.11–2.81)	2.32 (2.01–2.68)	2.34 (2.02–2.70)	2.35 (2.04–2.71)
FLI ≥60	None	274,222	2,537	1,892,304.0	1.3407	2.16 (2.04–2.28)	2.22 (2.10–2.34)	2.22 (2.10–2.34)	2.27 (2.15–2.40)	2.32 (2.20–2.45)
	Mild	284,922	2,851	1,967,078.8	1.4494	2.34 (2.22–2.46)	2.27 (2.14–2.40)	2.23 (2.10–2.36)	2.32 (2.19–2.46)	2.38 (2.25–2.53)
	Heavy	99,094	1,309	682,086.1	1.9191	3.09 (2.90–3.32)	2.95 (2.76–3.17)	2.86 (2.67–3.07)	2.97 (2.77–3.19)	3.01 (2.80–3.23)
	Excessive	34,081	625	232,854.9	2.6841	4.33 (3.97–4.72)	4.02 (3.67–4.39)	3.87 (3.54–4.24)	3.95 (3.61–4.33)	4.00 (3.65–4.38)
P value						<0.001	<0.001	<0.001	<0.001	<0.001

The results were obtained using Cox proportional hazards analysis. Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for income, smoking, regular exercise, and Charlson comorbidity index score; Model 4: adjusted for fasting glucose, diabetes mellitus duration, insulin use, oral hypoglycemic agent, and chronic kidney disease. Model 4+competing risk: Fine-Gray competing risk model adjusted for the same variables as model 4, accounting for death as a competing risk.

FLI, fatty liver disease; HR, hazard ratio; CI, confidence interval.

^aAlcohol consumption: (1) None, (2) Mild (<30 g/day for men, <20 g/day for women), (3) Heavy (30 ≤ men <60 g/day, 20 ≤ women <50 g/day), (4) Excessive (≥60 g/day for men, ≥50 g/day for women), ^bResults are presented as subdistribution HR with 95% CI.

and the HRs for HCC risk remained consistent with the main findings, further supporting the robustness of the results (Supplementary Table 4). Individuals with MASLD and viral hepatitis, the risk of HCC was significantly higher (aHR, 8.60; 95% CI, 8.15 to 9.09) compared to MASLD without viral hepatitis

(aHR, 2.92; 95% CI, 2.73 to 3.12) (data not shown).

Risk of HCC development according to the degree of hepatic steatosis in the alcohol consumption group

We further stratified the participants according to the degree

of hepatic steatosis using FLI categories and alcohol consumption (none, mild, heavy, and excessive drinking). In Table 3, compared with the group with $FLI < 30$ or $30 \leq FLI < 60$, the group with $FLI \geq 60$ showed increased aHRs of HCC development. Moreover, as alcohol consumption increased from mild to heavy and then to excessive levels, the risk further increased accordingly. There was also a consistent trend in the Fine and Gray analysis.

Sensitivity analysis was performed by excluding individuals diagnosed with ALD or concomitant liver disease (Supplementary Table 5). The analysis consistently demonstrated an increased risk of high alcohol consumption and FLI, suggesting a robust association across different degrees of hepatic steatosis and alcohol consumption.

DISCUSSION

This nationwide population-based retrospective study, which included 2,418,858 individuals, showed that MASLD in patients with T2DM was associated with an increased risk of HCC development, particularly when accompanied by other liver diseases. Moreover, alcohol consumption further increased the risk of HCC with the amount of alcohol consumed.

In a meta-analysis of 49,419 patients with T2DM from 20 countries, the incidence of NAFLD was found to be 55.5% [17]. Patients with diabetes and NAFLD have a three-fold higher risk of HCC than those without diabetes [18]. Using dynamic Markov modeling, the prevalence of HCC related to NAFLD was estimated to increase across eight countries, ranging from 47% in Japan to 130% in the United States [19]. HCC incidence trends worldwide have shifted toward ALD or MASLD over time, with MASLD being considered a particularly important risk factor in Asia [20]. The results of our study indicate that the increased incidence of HCC in T2DM patients with MASLD is pertinent to the current situation. In 2019, alcohol consumption was the third leading cause of cirrhosis in liver cancer, contributing to 19% of deaths [21]. In a population-based study using liver biopsies, the incidence of alcohol-associated HCC was reported to be 5% after 10 years, whereas a meta-analysis found that the cumulative risk was 9% after the same period [22,23]. In a previous study, the risk of HCC associated with alcohol consumption was increased across all glycemic states, from mild to heavy, with the highest increase observed in the diabetes group [24]. These findings are consistent with those of the current study; therefore, HCC

surveillance is warranted in patients with high alcohol intake and diabetes. Alcohol intake was positively associated with HCC risk in men, those aged ≥ 60 years, and those with abnormal ALT levels, showing a dose-response relationship in a prospective cohort study [25]. In our study, we observed an increased risk of HCC development in the MASLD, MetALD, and ALD groups corresponding to increasing levels of alcohol consumption. In particular, heavy to excessive alcohol intake was associated with a substantially higher risk of HCC development in these groups (aHR, 2.40; 95% CI, 2.27 to 2.53 and aHR, 3.16; 95% CI, 2.93 to 3.41). Additionally, findings from a systematic review suggested that even mild alcohol consumption was associated with a higher risk of liver cancer [26]. Furthermore, abstaining from alcohol may necessitate a 23-year washout period for a reduction in HCC risk comparable to that of never drinkers [27]. Clinicians often encounter patients who continue drinking alcohol despite having other liver diseases or cardiometabolic risk factors and taking multiple medications. However, current evidence suggests that alcohol cessation is necessary for individuals with these comorbidities, as it could improve liver function and reduce disease progression.

In our study, the MASLD with other combined group had the highest risk of HCC (aHR, 5.02; 95% CI, 4.79 to 5.27), particularly among individuals with MASLD and coexisting viral hepatitis (aHR, 8.60; 95% CI, 8.15 to 9.09). This is consistent with a previous study in which the lack of hepatitis C virus eradication and alcohol intake increased the risk of HCC three-fold (HR, 3.43; 95% CI, 1.49 to 7.92; $P=0.004$) [28]. In addition, Lee et al. [29] demonstrated that chronic viral hepatitis B or C significantly outweighs MASLD in terms of the associated risk of cirrhosis and HCC. In their cohort, the risk of HCC was substantially elevated in patients with both chronic viral hepatitis and MASLD. Mild alcohol consumption combined with other liver diseases further increases this risk. Given the significant mortality rates associated with HCC, identification of susceptible individuals is critical for public health. Although genetic susceptibility and environmental factors play important roles in the development of progressive liver disease and its complications [30], they are often uncontrollable. However, in the absence of treatment for MASLD, interventions targeting modifiable comorbidities and behavioral modifications are essential to mitigate these risks [31]. One study found that the risk of HCC increases with increasing components of the metabolic syndrome [32]. Obesity was also found to be a significant independent risk factor for HCC [33]. The Look

Action for Health in Diabetes (Look AHEAD) study found that the implementation of lifestyle changes resulted in an average weight reduction of 8%, which correlated with a significant decrease in liver fat [34]. In our study, elevated fasting glucose levels and BP were observed in the ALD group. In one study, the presence of HTN (odds ratio [OR], 1.33; 95% CI, 1.04 to 1.71) or DM was associated with a higher risk of HCC (OR, 2.64; 95% CI, 1.87 to 3.73) [35]. In a previous study, the mechanism linking HTN to the incidence of HCC remained unknown; however, an association with tyrosine kinase activation was suggested [36]. Individuals with MASLD and diabetes require early identification and intervention, including strategies to facilitate weight loss, promote increased physical activity, and maintain alcohol abstinence. Controlling metabolic risk factors, especially in high-risk individuals, is crucial, emphasizing the need for heightened vigilance.

The strength of this study is its nationwide population-based analysis with extensive long-term follow-up. In addition, we demonstrated a consistent and robust association by multivariate adjustment for several variables, performing subgroup analyses based on important clinical variables and additional analyses of hepatic steatosis and alcohol consumption, Fine and Gray analysis to account for competing risks, along with sensitivity analyses excluding individuals diagnosed with ALD or concomitant liver disease. This study represents the first exploration of the relationship between the newly revised term, MASLD, MetALD, and ALD groups corresponding to increasing levels of alcohol consumption and their association with incidence of HCC in patients with T2DM.

This study had several limitations. First, hepatic steatosis was defined using FLI rather than imaging or histology. Although a liver biopsy is considered the gold standard for diagnosing hepatic steatosis, its invasive and costly characteristics limit its feasibility for a nationwide study population. FLI has been well validated in previous studies for its ability to accurately predict the presence of steatosis >5%, with an area under ROC curve (AUROC) of 0.83, affirming its utility in identifying hepatic steatosis for clinical purposes [37-39]. In addition, the study included only Korean participants; therefore, carefully considering our findings with regards to different populations is important. Although our study benefited from the use of a large database, the use of self-reported questionnaires has the potential to introduce recall bias, which may have affected our findings. Moreover, changes in alcohol consumption patterns or shifts in steatotic liver disease groups over time could impact

the risk of HCC. Lastly, although the median follow-up duration of 7.16 years may limit the assessment of long-term HCC risk, our additional analyses confirmed consistency with the main findings. Nevertheless, further studies with extended follow-up periods are warranted.

In conclusion, the presence of MASLD in patients with T2DM demonstrated a notable association with HCC and the elevated risk of its development, particularly when concurrent with other liver diseases. Furthermore, alcohol consumption was found to exacerbate this risk, with a proportional increase observed in correlation with the amount of alcohol consumed.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2024.0641>.

CONFLICTS OF INTEREST

Sang-Man Jin has been an associate editor of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design: G.K., K.H., J.H.K.

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Supplementary Table 1. Prevalence of coexisting liver diseases in the MASLD with other combined group

Variable	MASLD with other combined (n=116,426)
Alcohol abuse/misuse, or ALD	51,414 (44.16)
Drug-induced liver disease	17,372 (14.92)
Viral hepatitis	48,455 (41.62)
Hepatic veno-occlusive disease	4,943 (4.25)
Liver abscess	445 (0.38)
Hemochromatosis	30 (0.03)
Wilson's disease	47 (0.04)
Alpha-1 antitrypsin deficiency	771 (0.66)
Autoimmune hepatitis	239 (0.21)
Primary biliary cholangitis	130 (0.11)
Other cholangitis	3,163 (2.72)
Glycogen storage disease	218 (0.19)

Values are presented as number (%).

MASLD, metabolic dysfunction-associated steatotic liver disease; ALD, alcohol-related liver disease.

Supplementary Table 2. Univariate analysis of risk factors for hepatocellular carcinoma development

	Univariate HR (95% CI)	<i>P</i> value
Age, yr	1.04 (1.04–1.04)	<0.001
Sex		<0.001
Male	2.83 (2.73–2.94)	
Female	1 (Ref)	
Income		0.006
Q2–Q4	1 (Ref)	
MA, Q1	1.05 (1.01–1.09)	
Smoking		<0.001
Never	1 (Ref)	
Former	1.72 (1.65–1.78)	
Current	1.78 (1.72–1.84)	
Regular exercise		<0.001
No	1 (Ref)	
Yes	1.08 (1.04–1.12)	
CCI score	1.16 (1.15–1.17)	<0.001
Fasting glucose, /1 SD	1.05 (1.03–1.06)	<0.001
DM duration		
New onset	1 (Ref)	<0.001
<5 years	1.37 (1.32–1.42)	
≥5 years	1.67 (1.61–1.74)	
Insulin		<0.001
No	1 (Ref)	
Yes	1.59 (1.52–1.67)	
OHA		<0.001
No	1 (Ref)	
Yes	1.41 (1.35–1.46)	
CKD		0.045
No	1 (Ref)	
Yes	1.05 (1.00–1.10)	

HR, hazard ratio; CI, confidence interval; Q, quartile; MA, Medical Aid; CCI, Charlson comorbidity index; SD, standard deviation; DM, diabetes mellitus; OHA, oral hypoglycemic agent; CKD, chronic kidney disease.

Supplementary Table 3. Subgroup analysis of hazard ratio for hepatocellular carcinoma development according to the group

Variable	Group	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	aHR (95% CI)	P for interaction
Age, yr							<0.001
<65	No steatosis	595,780	2,214	4,192,710.6	0.5281	1 (Ref)	
	MASLD	850,367	4,045	5,962,428.6	0.6784	1.14 (1.09–1.21)	
	MASLD with other combined	85,892	2,028	592,247.0	3.4243	4.97 (4.68–5.28)	
	MetALD	139,752	1,362	967,337.4	1.4080	2.01 (1.87–2.15)	
	ALD	44,010	611	302,827.1	2.0177	2.73 (2.49–2.99)	
≥65	No steatosis	320,601	2,038	2,106,489.8	0.9675	1 (Ref)	
	MASLD	327,136	3,597	2,205,845.9	1.6307	1.69 (1.60–1.78)	
	MASLD with other combined	30,534	993	200,843.5	4.9442	4.62 (4.28–4.99)	
	MetALD	18,803	566	124,219.1	4.5565	3.13 (2.85–3.44)	
	ALD	5,983	219	38,702.3	5.6586	3.81 (3.32–4.39)	
Sex							0.159
Male	No steatosis	428,408	3,025	2,908,070.1	1.0402	1 (Ref)	
	MASLD	743,665	6,004	5,131,680.6	1.1700	1.35 (1.30–1.41)	
	MASLD with other combined	81,342	2,523	550,494.8	4.5832	4.91 (4.65–5.18)	
	MetALD	150,638	1,889	1,037,435.9	1.8208	2.35 (2.21–2.49)	
	ALD	48,302	819	330,116.2	2.4809	3.10 (2.87–3.35)	
Female	No steatosis	487,973	1,227	3,391,130.3	0.3618	1 (Ref)	
	MASLD	433,838	1,638	3,036,594.0	0.5394	1.46 (1.35–1.57)	
	MASLD with other combined	35,084	498	242,595.7	2.0528	5.41 (4.88–6.01)	
	MetALD	7,917	39	54,120.7	0.7206	3.16 (2.30–4.35)	
	ALD	1,691	11	11,413.1	0.9638	4.01 (2.21–7.25)	
BMI, kg/m ²							0.076
<25	No steatosis	766,842	3,721	5,246,886.4	0.7092	1 (Ref)	
	MASLD	346,594	2,849	2,384,163.7	1.1950	1.48 (1.41–1.56)	
	MASLD with other combined	36,988	1,243	245,375.4	5.0657	5.58 (5.23–5.96)	
	MetALD	61,291	951	417,153.1	2.2797	2.69 (2.50–2.90)	
	ALD	19,682	422	131,893.7	3.1996	3.56 (3.22–3.94)	
≥25	No steatosis	149,539	531	1,052,314.0	0.5046	1 (Ref)	
	MASLD	830,909	4,793	5,784,110.8	0.8287	1.44 (1.32–1.58)	
	MASLD with other combined	79,438	1,778	547,715.1	3.2462	5.08 (4.61–5.61)	
	MetALD	97,264	977	674,403.4	1.4487	2.36 (2.11–2.62)	
	ALD	30,311	408	209,635.7	1.9462	3.08 (2.70–3.51)	
Fasting glucose, mg/dL							0.210
<140	No steatosis	580,436	2,599	3,981,099.2	0.6528	1 (Ref)	
	MASLD	655,499	4,177	4,531,096.7	0.9219	1.39 (1.33–1.46)	
	MASLD with other combined	70,330	1,791	478,581.8	3.7423	5.11 (4.80–5.43)	
	MetALD	79,358	890	543,125.4	1.6387	2.32 (2.15–2.51)	
	ALD	23,530	374	159,819.5	2.3401	3.21 (2.87–3.58)	

(Continued to the next page)

Supplementary Table 3. Continued

Variable	Group	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	aHR (95% CI)	P for interaction
140–199	No steatosis	258,384	1,235	1,788,523.5	0.6905	1 (Ref)	<0.001
	MASLD	395,811	2,550	2,760,275.4	0.9238	1.35 (1.26–1.44)	
	MASLD with other combined	35,421	893	242,790.9	3.6781	4.74 (4.35–5.17)	
	MetALD	59,373	717	411,169.4	1.7438	2.31 (2.10–2.53)	
	ALD	18,988	316	130,469.9	2.4220	3.07 (2.71–3.47)	
≥ 200	No Steatosis	77,561	418	529,577.8	0.7893	1 (Ref)	
	MASLD	126,193	915	876,902.5	1.0435	1.42 (1.26–1.59)	
	MASLD with other combined	10,675	337	71,717.7	4.6990	5.34 (4.62–6.17)	
	MetALD	19,824	321	137,261.7	2.3386	2.87 (2.48–3.33)	
	ALD	7,475	140	51,240.0	2.7322	3.21 (2.65–3.89)	
DM duration, yr							<0.001
New onset	No steatosis	331,782	1,184	2,248,326.6	0.5266	1 (Ref)	
	MASLD	491,420	2,367	3,356,157.9	0.7053	1.25 (1.17–1.34)	
	MASLD with other combined	30,306	710	203,215.1	3.4938	5.53 (5.04–6.07)	
	MetALD	86,681	778	590,351.2	1.3179	2.13 (1.94–2.33)	
	ALD	25,668	317	174,033.6	1.8215	2.83 (2.50–3.21)	
<5	No Steatosis	264,986	1,270	1,848,108.4	0.6872	1 (Ref)	
	MASLD	380,081	2,468	2,684,891.5	0.9192	1.29 (1.21–1.38)	
	MASLD with other combined	50,864	1,203	351,250.7	3.4249	4.55 (4.20–4.93)	
	MetALD	43,178	585	303,024.8	1.9305	2.30 (2.08–2.54)	
	ALD	14,145	276	97,918.7	2.8187	3.26 (2.86–3.72)	
≥5	No Steatosis	319,613	1,798	2,202,765.4	0.8163	1 (Ref)	
	MASLD	306,002	2,807	2,127,225.2	1.3196	1.56 (1.47–1.65)	
	MASLD with other combined	35,256	1,108	238,624.7	4.6433	5.08 (4.71–5.48)	
	MetALD	28,696	565	198,180.6	2.8509	2.79 (2.54–3.07)	
	ALD	10,180	237	69,577.0	3.4063	3.30 (2.88–3.78)	
Regular exercise							0.001
No	No steatosis	713,446	3,276	4,872,162.2	0.6724	1 (Ref)	
	MASLD	952,383	5,931	6,586,550.8	0.9005	1.34 (1.28–1.40)	
	MASLD with other combined	92,087	2,409	624,924.5	3.8549	5.08 (4.82–5.36)	
	MetALD	125,382	1,492	860,569.0	1.7337	2.36 (2.21–2.51)	
	ALD	39,480	641	268,795.5	2.3847	3.09 (2.84–3.37)	
Yes	No steatosis	202,935	976	1,427,038.2	0.6839	1 (Ref)	
	MASLD	225,120	1,711	1,581,723.8	1.0817	1.53 (1.42–1.66)	
	MASLD with other combined	24,339	612	168,166.0	3.6393	4.77 (4.31–5.28)	
	MetALD	33,173	436	230,987.5	1.8876	2.51 (2.24–2.82)	
	ALD	10,513	189	72,733.9	2.5985	3.39 (2.90–3.96)	

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Supplementary Table 3. Continued

Variable	Group	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	aHR (95% CI)	P for interaction
CKD							<0.001
No	No steatosis	808,421	3,780	5,589,792.1	0.6762	1 (Ref)	
	MASLD	1,037,660	6,584	7,222,623.7	0.9116	1.35 (1.30–1.41)	
	MASLD with other combined	102,765	2,716	702,853.2	3.8643	5.08 (4.83–5.35)	
	MetALD	150,087	1,804	1,032,938.6	1.7465	2.37 (2.23–2.51)	
	ALD	47,547	776	325,126.1	2.3868	3.09 (2.85–3.34)	
Yes (eGFR <60 mL/min/1.73 m ²)							
	No steatosis	107,960	472	709,408.3	0.6653	1 (Ref)	
	MASLD	139,843	1,058	945,650.8	1.1188	1.62 (1.45–1.80)	
	MASLD with other combined	13,661	305	90,237.3	3.3800	4.52 (3.91–5.22)	
	MetALD	8,468	124	58,617.9	2.1154	2.68 (2.19–3.26)	
	ALD	2,446	54	16,403.2	3.2920	4.13 (3.12–5.48)	
Income							0.127
Q2–4	No steatosis	716,853	3,345	4,940,726.2	0.6770	1 (Ref)	
	MASLD	931,870	5,959	6,479,853.5	0.9196	1.38 (1.32–1.44)	
	MASLD with other combined	91,252	2,341	625,838.9	3.7406	4.99 (4.73–5.26)	
	MetALD	129,076	1,507	891,217.2	1.6910	2.35 (2.21–2.50)	
	ALD	40,045	683	274,516.5	2.4880	3.28 (3.01–3.56)	
Lowest Q1, MA	No steatosis	199,528	907	1,358,474.2	0.6677	1 (Ref)	
	MASLD	245,633	1,683	1,688,421.1	0.9968	1.39 (1.28–1.51)	
	MASLD with other combined	25,174	680	167,251.5	4.0657	5.14 (4.65–5.68)	
	MetALD	29,479	421	200,339.3	2.1014	2.56 (2.28–2.88)	
	ALD	9,948	147	67,012.8	2.1936	2.70 (2.26–3.22)	
Insulin							0.043
No	No steatosis	827,374	3,622	5,709,913.1	0.6343	1 (Ref)	
	MASLD	1,096,433	6,899	7,624,555.8	0.9048	1.40 (1.35–1.46)	
	MASLD with other combined	102,983	2,554	706,765.0	3.6137	5.09 (4.83–5.35)	
	MetALD	152,215	1,775	1,048,953.9	1.6922	2.39 (2.25–2.53)	
	ALD	47,495	763	325,269.6	2.3458	3.19 (2.95–3.46)	
Yes	No steatosis	89,007	630	589,287.3	1.0691	1 (Ref)	
	MASLD	81,070	743	543,718.8	1.3665	1.23 (1.10–1.37)	
	MASLD with other combined	13,443	467	86,325.5	5.4098	4.67 (4.14–5.27)	
	MetALD	6,340	153	42,602.6	3.5913	2.66 (2.23–3.18)	
	ALD	2,498	67	16,259.7	4.1206	2.96 (2.30–3.81)	
Number of OHA							<0.001
No	No steatosis	349,670	1,318	2,364,760.0	0.5574	1 (Ref)	
	MASLD	502,904	2,493	3,430,674.6	0.7267	1.24 (1.16–1.33)	
	MASLD with other combined	32,227	802	215,000.5	3.7302	5.58 (5.11–6.09)	
	MetALD	87,628	801	596,582.6	1.3427	2.10 (1.92–2.30)	
	ALD	25,991	327	176,147.7	1.8564	2.80 (2.48–3.16)	

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Supplementary Table 3. Continued

Variable	Group	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	aHR (95% CI)	P for interaction
1–2	No steatosis	421,588	2,073	2,925,202.5	0.7087	1 (Ref)	
	MASLD	516,340	3,690	3,625,580.7	1.0178	1.41 (1.34–1.49)	
	MASLD with other combined	62,133	1,579	426,873.5	3.6990	4.90 (4.59–5.24)	
	MetALD	55,232	835	385,378.7	2.1667	2.56 (2.36–2.78)	
	ALD	18,131	378	124,918.3	3.0260	3.52 (3.15–3.93)	
≥3	No steatosis	145,123	861	1,009,237.8	0.8531	1 (Ref)	
	MASLD	158,259	1,459	1,112,019.2	1.3120	1.56 (1.44–1.70)	
	MASLD with other combined	22,066	640	151,216.4	4.2324	4.76 (4.29–5.27)	
	MetALD	15,695	292	109,595.2	2.6644	2.65 (2.32–3.03)	
	ALD	5871	125	40,463.4	3.0892	2.98 (2.47–3.60)	

Results were obtained using Cox proportional hazards analysis.

aHR, adjusted hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; ALD, alcohol-related liver disease; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Q, quartile; MA, Medical Aid; OHA, oral hypoglycemic agent.

Supplementary Table 4. Hazard ratios for hepatocellular carcinoma risk stratified by follow-up duration (<5 years vs. ≥5 years)

Variable	Number	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	HR (95% CI)			
					Model 1	Model 2	Model 3	Model 4
<5 years								
No steatosis	916,381	2,906	4,457,594.7	0.6519	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
MASLD	1,177,503	4,900	5,762,983.2	0.8503	1.30 (1.24–1.36)	1.27 (1.21–1.33)	1.27 (1.22–1.33)	1.30 (1.24–1.36)
MASLD with other combined	116,426	2,082	559,429.4	3.7217	5.69 (5.38–6.02)	5.19 (4.90–5.49)	4.99 (4.71–5.29)	5.04 (4.76–5.34)
MetALD	158,555	1,280	774,074.8	1.6536	2.51 (2.35–2.68)	2.33 (2.18–2.49)	2.25 (2.10–2.41)	2.30 (2.15–2.46)
ALD	49,993	558	241,827.1	2.3074	3.51 (3.21–3.84)	3.18 (2.90–3.49)	3.06 (2.79–3.36)	3.07 (2.80–3.37)
<i>P</i> value					<0.001	<0.001	<0.001	<0.001
≥5 years								
No steatosis	858,600	1,346	1,857,355.5	0.7247	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
MASLD	1,120,541	2,742	2,404,405.6	1.1404	1.57 (1.47–1.68)	1.53 (1.43–1.63)	1.52 (1.43–1.63)	1.55 (1.45–1.65)
MASLD with other combined	107,013	939	232,068.1	4.0462	5.58 (5.14–6.07)	5.09 (4.68–5.54)	4.97 (4.56–5.41)	5.01 (4.60–5.46)
MetALD	150,891	648	314,175.9	2.0625	2.85 (2.59–3.13)	2.64 (2.39–2.91)	2.53 (2.30–2.79)	2.57 (2.34–2.84)
ALD	46,698	272	98,398.2	2.7643	3.82 (3.35–4.35)	3.46 (3.03–3.95)	3.31 (2.90–3.78)	3.32 (2.91–3.79)
<i>P</i> value					<0.001	<0.001	<0.001	<0.001

The results were obtained using Cox proportional hazards analysis. Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for income, smoking, regular exercise, and Charlson comorbidity index score; Model 4: adjusted for fasting glucose, diabetes mellitus duration, insulin use, oral hypoglycemic agent, and chronic kidney disease.

HR, hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; ALD, alcohol-related liver disease.

Supplementary Table 5. Hazard ratios for hepatocellular carcinoma development according to the degree of fatty liver index group (FLI <30, 30 ≤ FLI <60, FLI ≥60) and alcohol consumption after excluding individuals who diagnosed alcohol-related liver disease and concomitant liver disease

Variable	Drinking ^a	No. of patients	Event	Duration, person-yr	Incidence rate, /1,000 person-yr	HR (95% CI)			
						Model 1	Model 2	Model 3	Model 4
FLI <30	None	582,167	1,812	3998408.1	0.4532	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	226,324	914	1571325.2	0.5817	1.28 (1.19–1.39)	1.20 (1.11–1.31)	1.18 (1.08–1.28)	1.19 (1.10–1.29)
	Heavy	32,239	179	221292.8	0.8089	1.79 (1.53–2.09)	1.66 (1.42–1.94)	1.56 (1.33–1.82)	1.57 (1.34–1.83)
	Excessive	7,061	61	48146.4	1.2670	2.80 (2.17–3.62)	2.42 (1.88–3.13)	2.25 (1.74–2.91)	2.24 (1.73–2.89)
30 ≤ FLI <60	None	424,521	2,195	2950102.4	0.7440	1.64 (1.54–1.75)	1.55 (1.46–1.65)	1.55 (1.46–1.65)	1.57 (1.48–1.67)
	Mild	248,675	1,557	1732014.2	0.8990	1.98 (1.85–2.12)	1.77 (1.65–1.90)	1.73 (1.61–1.85)	1.77 (1.65–1.90)
	Heavy	53,005	445	366083.8	1.2156	2.69 (2.42–2.98)	2.42 (2.18–2.69)	2.30 (2.07–2.56)	2.34 (2.12–2.61)
	Excessive	13,563	133	93226.1	1.4266	3.15 (2.64–3.76)	2.76 (2.31–3.30)	2.60 (2.17–3.10)	2.60 (2.18–3.11)
FLI ≥60	None	248,515	1,831	1718001.4	1.0658	2.35 (2.20–2.51)	2.50 (2.34–2.67)	2.51 (2.35–2.68)	2.55 (2.39–2.73)
	Mild	255,792	2,059	1768156.6	1.1645	2.58 (2.42–2.74)	2.76 (2.58–2.96)	2.68 (2.50–2.87)	2.78 (2.59–2.97)
	Heavy	86,474	919	596435.7	1.5408	3.41 (3.15–3.69)	3.64 (3.35–3.96)	3.48 (3.20–3.78)	3.58 (3.29–3.90)
	Excessive	28,510	412	195916.0	2.1029	4.65 (4.18–5.18)	4.84 (4.34–5.41)	4.62 (4.13–5.16)	4.68 (4.19–5.23)
P value						<0.001	<0.001	<0.001	<0.001

The results were obtained using Cox proportional hazards analysis. Model 1: unadjusted model; Model 2: adjusted for age and sex; Model 3: adjusted for income, smoking, regular exercise, and Charlson comorbidity index score; Model 4: adjusted fasting glucose, diabetes mellitus duration, insulin use, oral hypoglycemic agent, and chronic kidney disease.

FLI, fatty liver disease; HR, hazard ratio; CI, confidence interval.

^aAlcohol consumption: (1) None, (2) Mild (<30 g/day for men, <20 g/day for women), (3) Heavy (30 ≤ men <60 g/day, 20 ≤ women <50 g/day), (4) Excessive (≥60 g/day for men, ≥50 g/day for women).