Liver Cancer

Research Article

Liver Cancer 2024;13:426–437
DOI: 10.1159/000535943

Received: November 7, 2023
Accepted: December 19, 2023
Published online: December 22, 2023

Metabolic Dysfunction-Associated Steatotic Liver Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake Increase the Risk of Developing Hepatocellular Carcinoma and Incident or Decompensated Cirrhosis: A Korean Nationwide Study

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Keywords
Alcohol · Fatty liver · Nonalcoholic · Liver neoplasms

Abstract

Introduction: This study aimed to investigate the liver-related outcomes of newly suggested metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD), as well as alcohol-associated liver disease (ALD). ***Methods:*** From a National Health Insurance Service Health Screening Cohort, we included 369,094 participants who underwent health checkups between 2009 and 2010 in South Korea. Steatotic liver disease (SLD) was defined as a fatty liver index ≥60. The risk of primary liver cancer (PLCa), hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA), incident cirrhosis, and decompensated cirrhosis was compared with no SLD. The subdistribution hazard ratio (SHR) was calculated using the Fine-Gray model regarding competing risks. ***Results:*** A total of 3,232 participants (0.9%) developed PLCa during the median follow-up of 3,227,176 person-years: 0.5% with no SLD, 1.1% with MASLD, 1.3% with MetALD, and 1.9% with ALD. Competing risk analysis revealed that compared with no SLD, MASLD (SHR: 1.65; 95% CI: 1.44–1.88), MetALD (SHR: 1.87; 95% CI: 1.52–2.29), and ALD (SHR: 1.86; 95% CI: 1.39–2.49) were associated with an increased risk of PLCa. MASLD (SHR: 1.96; 95% CI: 1.67–2.31), MetALD (SHR: 2.23; 95% CI: 1.75–2.84), and ALD (SHR: 2.34; 95% CI: 1.67–3.29) were associated with a higher risk of HCC. No significant difference was observed in the risk of iCCA. The risk of incident cirrhosis and decompensated cirrhosis increased in the order of no SLD, MASLD,

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MetALD, and ALD. ***Conclusion:*** MASLD, MetALD, and ALD have an increased risk of PLCa, HCC, incident cirrhosis, and decompensated cirrhosis but not iCCA. These findings may serve as a robust ground for the prognostic value of the newly suggested MASLD and MetALD.

Introduction

Although nonalcoholic fatty liver disease has served as an anchor point for clinical practice and trials, substantial concerns have been raised about its use due to the inherent drawbacks of being exclusionary and stigmatizing, prompting a search for new nomenclature [1]. Metabolic dysfunction-associated fatty liver disease was suggested for using positive diagnostic criteria and incorporating metabolic risk factors [2], and studies have reported that metabolic dysfunction-associated fatty liver disease has better prediction performance for various clinical outcomes compared to NAFLD [3–8]. Yet, discarding nonalcoholic steatohepatitis (NASH) and neglecting alcohol consumption challenged its wide application [9–11]. Hence, new nomenclature and definition were sought, and resultingly, metabolic dysfunction-associated steatotic liver disease (MASLD) was recently suggested as an alternative [12, 13].

The new nomenclature proposed steatotic liver disease (SLD) as an umbrella term comprising several subcategories based on the presence of five cardiometabolic risk factors along with other etiologies such as alcohol consumption. SLD patients with cardiometabolic risk factors are further categorized into MASLD and MASLD with increased alcohol intake (MetALD), depending on the amount of alcohol consumption [12, 13]. Those without cardiometabolic risk factors are categorized into cryptogenic SLD or SLD with other specific etiology. Other specific etiologies include alcohol-associated liver disease (ALD), drug-induced liver injury, and monogenic disease. The new nomenclature MetALD has made it possible to recognize previously neglected patients having cardiometabolic risk factors with increased alcohol consumption [12–14].

These new subcategories have presented a new challenge to broaden our knowledge [15]. NAFLD has a strong epidemiological and pathogenic link with metabolic diseases such as obesity, diabetes, and cardiovascular diseases [16]. Since it can progress to NASH, cirrhosis, and hepatocellular carcinoma (HCC), liver-related outcomes are one of the leading causes of death among NAFLD patients [17–19]. In addition, NAFLD is associated with an increased risk of developing intrahepatic cholangiocarcinoma (iCCA) [20]. Nevertheless, little data are available on liver-related outcomes of the newly suggested SLD subtypes.

Thus, this nationwide study aimed to investigate the risk of liver-related outcomes in the newly suggested MASLD and MetALD as well as ALD. The risk of developing primary liver cancer (PLCa) including HCC and iCCA, incident cirrhosis, and decompensated cirrhosis in each subtype of SLD was compared with no SLD.

Methods

Study Population

The participants enrolled in this retrospective national cohort study were derived from the health screening cohort of the Korea National Health Insurance Service (NHIS). The NHIS offers obligatory healthcare insurance, encompassing medical services, for all the citizens of South Korea [21]. This organization gathers personalized information encompassing sociodemographics, anthropometric measurements, health screening records, lifestyle surveys, and treatment details, including hospital attendance and prescribed medications. Alcohol consumption amount was quantified based on the alcohol use disorder identification test questionnaire.

Of the 415,139 individuals aged 47–86 years with no history of cancer who participated in health screening examinations from 2009 to 2010, participants eligible for liver-related outcomes were followed from January 1, 2011, to December 31, 2019. Patients were excluded when they had one of the following: concomitant liver diseases of viral hepatitis, autoimmune hepatitis, toxic hepatitis, hemochromatosis, primary biliary cholangitis, Budd-Chiari syndrome (n = 21,145), a prescription history of hepatic steatosis-inducible drugs such as amiodarone, methotrexate, tamoxifen, valproic acid, and intravenous tetracycline for more than 30 cumulative days (n = 9,330), no available data on alcohol consumption (n = 2,752), no available data on other covariates (n = 9,500), a history of liver transplantation (n = 796), and cryptogenic SLD (n = 2,522). A total of 369,094 participants were included in the final analysis (Fig. 1). This study was approved by the Institutional Review Board of the Seoul Metropolitan Government Boramae Medical Centre (07-2023-5) and followed the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because the NHIS data contain anonymized data that follow the guidelines of the Personal Data Protection Act.

Definitions of Outcomes

The primary outcome was an occurrence of PLCa (10th Revision of the International Classification of Diseases [ICD-10]; C22), encompassing HCC (C220), iCCA (C221), and other liver cancers. Other liver cancers, such as angiosarcoma and hepatic epithelioid hemangioendothelioma, were not included

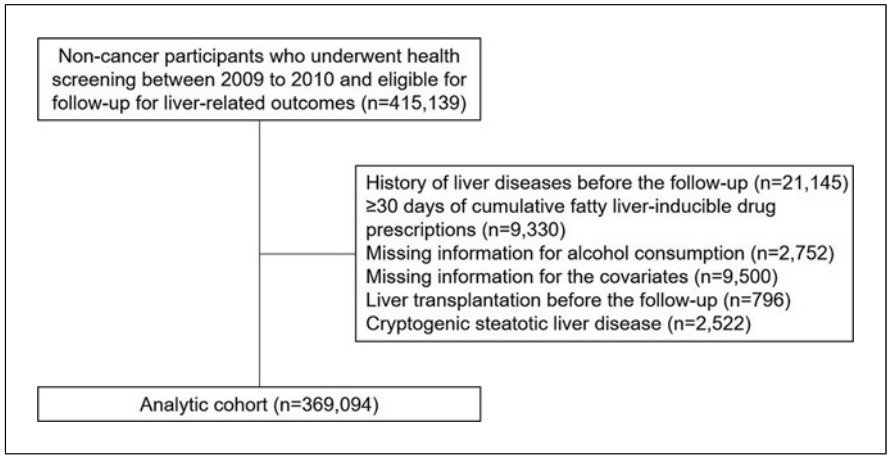

Fig. 1. Flow diagram for selection of study participants. Study participants were derived from the National Health Insurance Service health screening cohort. Of the 415,139 participants without a history of cancer at baseline who were eligible for follow-up investigation, those with a history of concomitant liver diseases, those with missing information for the covariates, those with cryptogenic SLD, those who took steatosis-inducible drugs for at least 30 days, and those who underwent liver transplantation before starting follow-up were excluded.

in the analysis for their rarity. The secondary outcomes were liver cirrhosis and decompensated cirrhosis. Liver cirrhosis was defined with ICD-10 codes of K74, I859, K703, K717, K746, K766, and I982. Decompensated cirrhosis was defined as having hepatic encephalopathy, ascites, variceal bleeding, hepatorenal syndrome, and liver failure. The ICD-10 codes used for decompensated cirrhosis were G934, R18, I850, I983, K767, K704, K720, K721, and K729 for abdominal paracentesis, endoscopic treatment of esophageal or gastric varices, and prescription records for spironolactone, terlipressin, somatostatin, and propranolol. The development of cirrhosis and decompensated cirrhosis was evaluated among participants without any evidence of cirrhosis at baseline. From January 1, 2011, each patient was followed until the earliest instance of PLCa, death, or December 31, 2019, whichever occurred first. During the follow-up for cirrhosis or decompensated cirrhosis, those without cirrhosis at baseline (n = 360,287) were followed until the earliest instance of cirrhosis, PLCa, death, or December 31, 2019, whichever occurred first.

Definitions of SLD Subtypes

Participants having a fatty liver index (FLI) of ≥60 were considered to have SLD. This index is a well recognized and validated noninvasive method for identifying hepatic steatosis. It exhibits an area under the curve of the receiver operating characteristic of 0.844, with positive predictive values of 83.2% and 84.8% for Asian men and women and negative predictive values of 65.3% and 87.4% for Asian men and women [22]. The comprehensive process for assessing the FLI is outlined in previous studies [23].

MASLD was defined as the presence of SLD and at least one of the five cardiometabolic risk factors: body mass index ≥23 kg/m^2 or a high waist circumference (≥90 cm for men and ≥85 cm for women) [24], fasting serum glucose ≥100 mg/dL or type 2 diabetes or a prescription record of antidiabetic medications, blood pressure ≥130/85 mm Hg or a prescription record of antihypertensive medications, triglycerides ≥150 mg/dL or a prescription record of lipid-lowering medications, and a low high-density lipoprotein cholesterol (≤40 mg/dL for men and ≤50 mg/dL for women) [12, 13]. MetALD was defined as the presence of MASLD with moderate alcohol intake (30–60 g/day for men and 20–50 g/day for women). ALD was defined as having SLD with severe alcohol consumption of >60 g/day for men and >50 g/day for women regardless of cardiometabolic risk factors.

Key Variables

The following variables were used for the adjusted analyses: age (continuous, years), sex (men and women), body mass index (continuous, kg/m^2), household income (upper half and lower half), presence of hypertension (yes and no), type 2 diabetes (yes and no), and dyslipidemia (yes and no), smoking (never, former, and current), alcohol consumption (mild, moderate, and severe), moderate-to-vigorous physical activity (0, 1–2, 3–4, and ≥5 times/week), and the Charlson comorbidity index (0, 1, and ≥2). The Charlson comorbidity index was calculated using ICD-10 codes as described previously [25].

Statistical Analysis

For continuous variables, we presented the mean and standard deviation if they followed a normal distribution, or the median and interquartile ranges if they did not. To compare differences between groups, either the independent t test or the Mann-Whitney U test was employed, depending on the distribution of the data. Categorical data were expressed as the number (%), and the differences between groups were determined by the χ^2 test.

To estimate the cause-specific adjusted hazard ratios (aHRs), Cox proportional hazards regression was employed. Cumulative incidence function was used to create the curves illustrating cumulative incidence rates. In the presence of competing risks such as death or liver transplantation, a Fine-Gray model was utilized to determine subdistribution hazard ratios (SHRs), along with their corresponding 95% confidence intervals (CIs). The validity of the proportional hazard assumption was confirmed using the Kolmogorov-type supremum test. The incidence rate was calculated by dividing the number of events by 1,000 person-years (PYs).

We conducted sensitivity analyses, excluding liver-related events within 1, 2, and 3 years from the start of follow-up to

Table 1. Descriptive characteristics of the participants in the National Health Insurance Service Health Screening Cohort across the subtypes of SLD

	No SLD (*n* = 159,206)	MASLD (*n* = 178,596)	MetALD (*n* = 23,546)	ALD (*n* = 7,746)	*p* value
Age, years	57.5 (8.9)	57.6 (8.3)	55.0 (7.0)	56.4 (8.1)	<0.001
Sex, *n* (%)					<0.001
Men	61,477 (38.6)	119,052 (66.7)	22,399 (95.1)	7,566 (97.7)	
Women	97,729 (61.4)	59,544 (33.3)	1,147 (4.9)	180 (2.3)	
Household income[a], *n* (%)					<0.001
Upper half	96,297 (60.5)	117,658 (65.9)	16,351 (69.4)	5,134 (66.3)	
Lower half	62,909 (39.5)	60,938 (34.1)	7,195 (30.6)	2,612 (33.7)	
Body mass index, kg/m^2	22.2 (2.2)	25.5 (2.6)	25.0 (2.6)	24.7 (2.8)	<0.001
Waist circumference, cm	76.4 (6.4)	86.2 (6.7)	86.6 (6.7)	86.6 (7.1)	<0.001
Systolic blood pressure, mm Hg	121.7 (14.9)	127.7 (14.7)	129.8 (14.5)	130.6 (15.3)	<0.001
Diastolic blood pressure, mm Hg	75.3 (9.6)	79.3 (9.7)	81.3 (9.7)	81.4 (9.9)	<0.001
Total cholesterol, mg/dL	196.1 (35.2)	204.6 (38.4)	201.4 (37.3)	198.7 (39.9)	<0.001
HDL cholesterol, mg/dL	57.7 (24.2)	51.9 (27.0)	54.7 (23.6)	57.2 (32.9)	<0.001
Triglycerides, mg/dL	100.5 (50.2)	170.0 (100.0)	190.6 (125.5)	195.1 (135.9)	<0.001
Fasting serum glucose, mg/dL	95.8 (19.9)	104.5 (27.8)	107.8 (29.9)	108.9 (30.9)	<0.001
Alanine aminotransferase, IU/L	18.8 (9.2)	29.3 (20.1)	30.8 (22.4)	32.4 (24.2)	<0.001
Aspartate aminotransferase, IU/L	23.1 (9.7)	27.7 (18.0)	31.5 (23.7)	35.5 (28.1)	<0.001
γ-glutamyl transpeptidase, IU/L	17.8 (7.7)	47.0 (50.3)	83.5 (92.4)	110.7 (130.7)	<0.001
Median (interquartile range)	16 (13–21)	34 (24–51)	56 (37–93)	70 (44–120)	
Alcohol consumption, *n* (%)					<0.001
No	113,637 (71.4)	99,169 (55.5)	0 (0)	0 (0)	
Yes	45,569 (28.6)	79,427 (44.5)	23,546 (100)	7,746 (100)	
Cigarette smoking, *n* (%)					<0.001
Never smoker	120,331 (75.6)	100,589 (56.3)	5,448 (23.1)	1,758 (22.7)	
Past smoker	19,551 (12.3)	41,078 (23.0)	8,014 (34.0)	2,466 (31.8)	
Current smoker	19,324 (12.1)	36,929 (20.7)	10,084 (42.8)	3,522 (45.5)	
MVPA, *n* (%)					<0.001
No	78,445 (49.3)	80,716 (45.2)	9,114 (38.7)	3,641 (47.0)	
1–2 time/week	25,310 (15.9)	31,952 (17.9)	4,379 (18.6)	1,260 (16.3)	
3–4 time/week	21,532 (13.5)	26,492 (14.8)	4,012 (17.0)	953 (12.3)	
≥5 time/week	33,919 (21.3)	39,436 (22.1)	6,041 (25.7)	1,892 (24.4)	
Antihypertensive drugs, *n* (%)	69,704 (43.8)	103,774 (58.1)	12,681 (53.9)	4,174 (53.9)	<0.001
Antidiabetic drugs, *n* (%)	11,153 (7.0)	29,457 (16.5)	3,524 (15.0)	1,230 (15.9)	<0.001
Antidyslipidemic drugs, *n* (%)	32,855 (20.6)	59,177 (33.1)	6,052 (25.7)	1,827 (23.6)	<0.001
Aspirin, *n* (%)	27,852 (17.5)	50,134 (28.1)	5,851 (24.8)	1,924 (24.8)	<0.001
Charlson comorbidity index, *n* (%)					<0.001
0	34,362 (21.6)	34,446 (19.3)	5,770 (24.5)	1,706 (22.0)	
1	49,024 (30.8)	50,016 (28.0)	7,274 (30.9)	2,258 (29.2)	
≥2	75,820 (47.6)	94,134 (52.7)	10,502 (44.6)	3,782 (48.8)	

Continuous data are presented as mean (standard deviation) (normally distributed) or medians (interquartile ranges) (not normally distributed). Categorical data are expressed as the number (%). *p* values were calculated using analysis of variance for continuous variables and the χ^2 test for categorical variables. SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease with increased alcohol intake; ALD, alcohol-associated liver disease; HDL, high-density lipoprotein; MVPA, moderate-to-vigorous physical activity. [a]Proxy for socioeconomic status based on the insurance premium of the National Health Insurance Service.

avoid including participants who might have had liver-related events before the onset of this study. To visually represent the continuous SHRs based on the daily alcohol consumption amount, we used restricted cubic splines. These splines were created using the natural cubic function. All aspects of data collection, data exploration, and statistical analyses were performed using the SAS Enterprise Guide (version 7.3; SAS Institute; Cary, NC, USA). For generating cumulative incidence rate curves, we employed the R Project for Statistical Computing (version 4.3.0; https://www.r-project.org/).

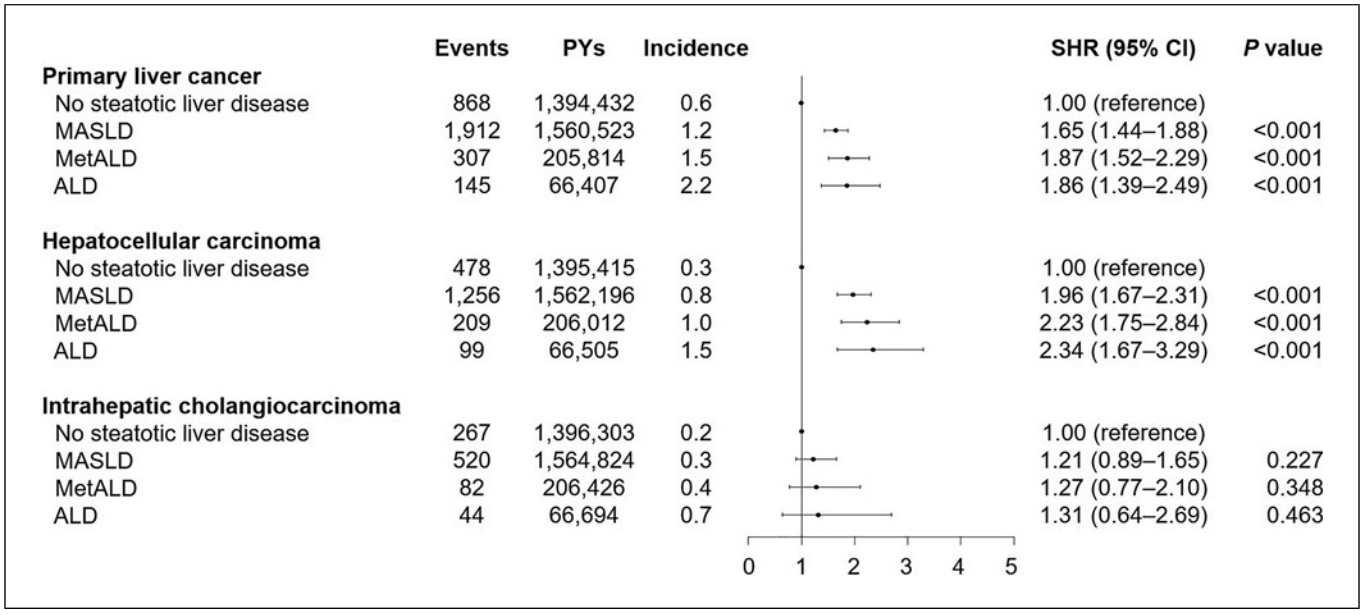

Fig. 2. Association of SLD subtypes with the risk of PLCa. The annual incidence rate per 1,000 PYs of PLCa, HCC, iCCA is presented. SHRs (95% CIs) were calculated using the Fine-Gray model after adjustments for age, sex, body mass index, household income, antihypertensive drugs, antidiabetic drugs, antidyslipidemic drugs, aspirin, smoking, alcohol consumption, moderate-to-vigorous physical activity, and Charlson comorbidity index. Acronyms: PY, person-year; SHR, subdistribution hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease with increased alcohol intake; ALD, alcohol-associated liver disease; NA, non-applicable.

Results

Patient Characteristics

Baseline characteristics are summarized in Table 1 and online supplementary Table S1 (for all online suppl. material, see https://doi.org.com/10.1159/000535943). SLD participants comprised 56.9% (n = 209,888) of the entire cohort, of which 48.4% had MASLD (n = 178,596), 6.4% had MetALD (n = 23,546), and 2.1% had ALD (n = 7,746). Compared with no SLD, the MASLD, MetALD, and ALD groups were more likely to be men (38.6% vs. 66.7% vs. 95.1% vs. 97.7%, respectively). Participants with MASLD, MetALD, and ALD were more likely to take antidiabetic drugs compared to those with no SLD (16.5% vs. 15.0% vs. 15.9% vs. 7.0%, respectively) and antidyslipidemic drugs compared to those with no SLD (33.1% vs. 25.7% vs. 23.6% vs. 20.6%, respectively). Compared to no SLD, MASLD, MetALD, and ALD exhibited higher levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, total cholesterol, and triglycerides.

Development of PLCa across SLD Subtypes

During the follow-up of 3,227,176 PYs, a total of 3,232 participants developed PLCa: 868 (0.5%) with no SLD, 1912 (1.1%) with MASLD, 307 (1.3%) with MetALD, and 145 (1.9%) with ALD (Fig. 2). When stratified by the types of liver cancer, 2,042 participants developed HCC, 913 developed iCCA, and 277 developed other liver cancers.

Risk of PLCa across SLD Subtypes

The annual incidence rate of PLCa was higher in the MASLD (1.2/1,000 PYs), MetALD (1.5/1,000 PYs), and ALD (2.2/1,000 PYs) groups than in no SLD (0.6/1,000 PYs) (Fig. 2). In the unadjusted and multivariate-adjusted analyses, the risk of developing PLCa was higher in MASLD (aHR: 1.27, 95% CI: 1.23–1.31), MetALD (aHR: 1.49, 95% CI: 1.40–1.58), and ALD (aHR: 1.75, 95% CI: 1.62–1.89) than in no SLD (online suppl. Tables S2 and S3). When the reference was switched to either MASLD, MetALD, or ALD, the risk of developing PLCa increased incrementally from MASLD to ALD (online suppl. Tables S2 and S3).

The cumulative incidence rate of PLCa was highest in ALD followed by MetALD, MASLD, and no SLD (p < 0.001 as per Fine-Gray test; Fig. 3a). When death or liver transplantation was treated as a competing risk, MASLD (SHR: 1.87, 95% CI: 1.69–2.09), MetALD (SHR: 2.20, 95% CI: 1.85–2.63), and ALD (SHR: 2.35, 95% CI: 1.79–3.09)

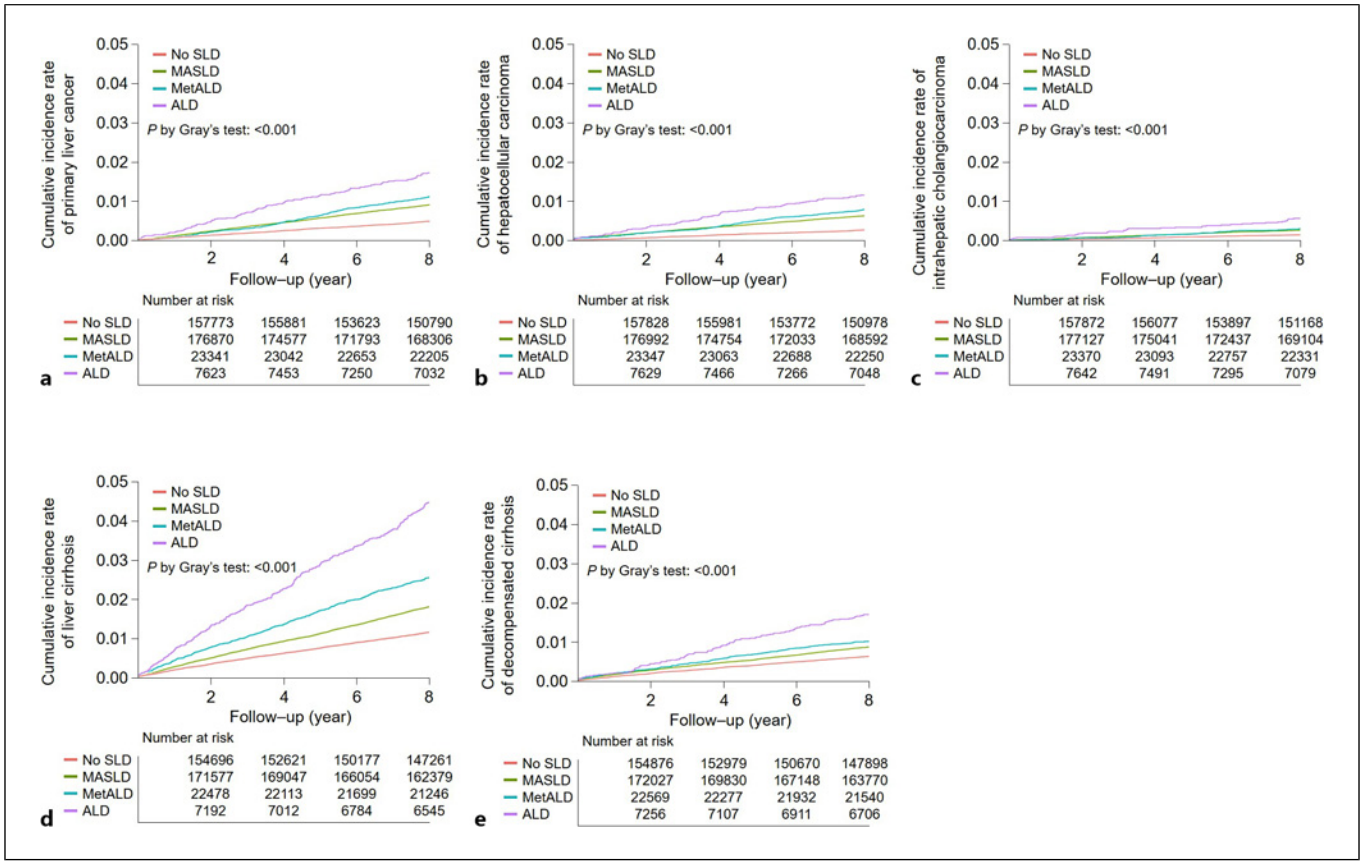

Fig. 3. Cumulative incidence function for liver-related outcomes by the subtypes of SLD. The solid lines show the cumulative incidence rates for PLCa (**a**), HCC (**b**), iCCA (**c**), liver cirrhosis (**d**), and decompensated cirrhosis (**e**). Liver cirrhosis and decompensated cirrhosis were evaluated among participants without any evidence of liver cirrhosis.

had a higher risk of developing PLCa than did no SLD (online suppl. Table S4). After correction for a competing risk and other variables, MASLD (SHR: 1.65, 95% CI: 1.44–1.88), MetALD (SHR: 1.87, 95% CI: 1.52–2.29), and ALD (SHR: 1.86, 95% CI: 1.39–2.49) had a significantly higher risk of PLCa than did no SLD ($p < 0.001$ for trend; Fig. 2 and online suppl. Table S5).

Risk of HCC across SLD Subtypes

The annual incidence rate of HCC was higher in MASLD (0.8/1,000 PYs), MetALD (1.0/1,000 PYs), and ALD (1.5/1,000 PYs) than in no SLD (0.3/1,000 PYs) (Fig. 2). The cumulative incidence rate of HCC was highest in ALD followed by MetALD, MASLD, and no SLD ($p < 0.001$ as per Fine-Gray test; Fig. 3b). When death or liver transplantation was treated as a competing risk, MASLD (SHR: 2.18, 95% CI: 1.91–2.49), MetALD (SHR: 2.62, 95% CI: 2.12–3.24), and ALD (SHR: 2.95, 95% CI: 2.15–4.05) had a higher risk of developing HCC than did no SLD (online suppl. Table S4). When adjusted for a competing risk and other variables, MASLD (SHR: 1.96, 95% CI: 1.67–2.31), MetALD (SHR: 2.23, 95% CI: 1.75–2.84), and ALD (SHR: 2.34, 95% CI: 1.67–3.29) had a higher risk of HCC than did no SLD ($p < 0.001$ for trend; Fig. 2 and online suppl. Table S5).

Risk of iCCA across SLD Subtypes

The annual incidence rate of iCCA was higher in MASLD (0.3/1,000 PYs), MetALD (0.4/1,000 PYs), and ALD (0.7/1,000 PYs) than in no SLD (0.2/1,000 PYs) (Fig. 2). The cumulative incidence rate of iCCA was highest in ALD followed by MetALD, MASLD, and no SLD ($p < 0.001$ as per Fine-Gray test; Fig. 3c). When death or liver transplantation was treated as a competing risk, MASLD (SHR: 1.63, 95% CI: 1.27–2.09) and MetALD (SHR: 1.69, 95% CI: 1.08–2.64) had a higher risk of developing iCCA than did no SLD (online suppl. Table S4). Competing risk analysis after adjustments for death or liver transplantation and other variables showed

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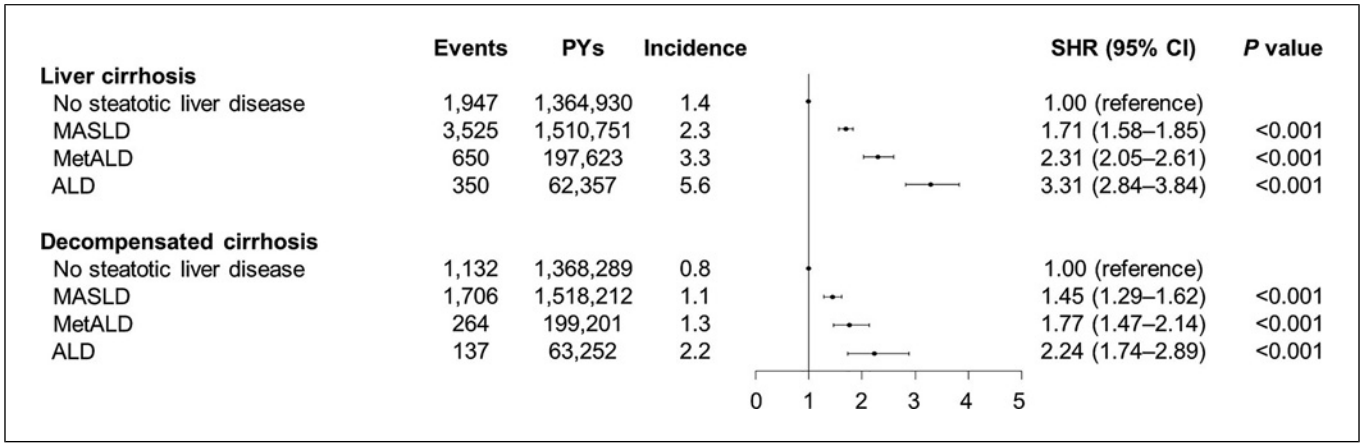

Fig. 4. Association of SLD subtypes with the risk of incident or decompensated cirrhosis among participants without any evidence of liver cirrhosis at baseline. SHRs (95% CIs) were calculated using the Fine-Gray model after adjustments for age, sex, body mass index, household income, antihypertensive drugs, antidiabetic drugs, antidyslipidemic drugs, aspirin, smoking, alcohol consumption, moderate-to-vigorous physical activity, and Charlson comorbidity index. Acronyms: PY, person-year; SHR, subdistribution hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease with increased alcohol intake; ALD, alcohol-associated liver disease.

that the risk of developing iCCA in MASLD (SHR: 1.21, 95% CI: 0.89–1.65), MetALD (SHR: 1.27, 95% CI: 0.77–2.10), and ALD (SHR: 1.31, 95% CI: 0.64–2.69) did not differ significantly from that in no SLD (Fig. 2 and online suppl. Table S5).

Risks of Incident Cirrhosis and Decompensated Cirrhosis across SLD Subtypes

The cumulative incidence rates of cirrhosis ($p < 0.001$ as per Fine-Gray test; Fig. 3d) and decompensated cirrhosis ($p < 0.001$; Fig. 3e) were highest in ALD followed by MetALD, MASLD, and no SLD. When adjusted for a competing risk and other variables, MASLD (SHR: 1.71, 95% CI: 1.58–1.85), MetALD (SHR: 2.31, 95% CI: 2.05–2.61), and ALD (SHR: 3.31, 95% CI: 2.84–3.84) had a higher risk of developing incident cirrhosis than did no SLD ($p < 0.001$ for trend; Fig. 4 and online suppl. Table S5). Compared with no SLD, MASLD (SHR: 1.45, 95% CI: 1.29–1.62), MetALD (SHR: 1.77, 95% CI: 1.47–2.14), and ALD (SHR: 2.24, 95% CI: 1.74–2.89) were at an increased risk of developing decompensated cirrhosis ($p < 0.001$ for trend; Fig. 4 and online suppl. Table S5).

Risk of Liver-Related Outcomes in the New Subcategory of MetALD

In multivariate-adjusted analysis with MASLD as a reference, MetALD had a higher risk of developing PLCa (aHR: 1.17, 95% CI: 1.11–1.24), HCC (aHR: 1.17, 95% CI: 1.11–1.24), iCCA (aHR: 1.17, 95% CI: 1.10–1.24), incident cirrhosis (aHR: 1.21, 95% CI: 1.15–1.27), and decompensated cirrhosis (aHR: 1.17, 95% CI: 1.11–1.24) (online suppl. Table S3). In competing risk analysis with MASLD as a reference, however, the statistical difference between MASLD and MetALD was insignificant in the risk of PLCa (SHR: 1.13, 95% CI: 0.95–1.35, $p = 0.166$), HCC (SHR: 1.13, 95% CI: 0.92–1.39, $p = 0.234$), and iCCA (SHR: 1.05, 95% CI: 0.67–1.65, $p = 0.831$) (online suppl. Table S5). The risk of incident cirrhosis (SHR: 1.35, 95% CI: 1.22–1.50) and decompensated cirrhosis (SHR: 1.22, 95% CI: 1.04–1.45) was significantly higher in MetALD (online suppl. Table S5).

Sensitivity and Subgroup Analyses

Sensitivity analyses considering the latent periods also showed that the risk of developing PLCa and HCC was higher in MASLD, MetALD, and ALD than in no SLD. However, the risk of developing iCCA in each SLD subtype did not differ from that in no SLD. MASLD, MetALD, and ALD were associated with a higher risk of incident cirrhosis and decompensated cirrhosis compared to no SLD (online suppl. Table S6).

When patients without cirrhosis ($n = 360{,}287$) were analyzed separately, MASLD (SHR: 1.49; 95% CI: 1.29–1.72), MetALD (SHR: 1.76; 95% CI: 1.41–2.19), and ALD (SHR: 1.83; 95% CI: 1.33–2.50) were associated with an increased risk of PLCa compared with no SLD (online suppl. Fig. S1). MASLD (SHR: 1.76; 95% CI: 1.46–2.11), MetALD (SHR: 2.15; 95% CI: 1.65–2.81), and ALD (SHR: 2.37; 95% CI: 1.64–3.43) were associated with a higher risk of HCC. No significant difference was observed in the risk of iCCA.

In subgroup analyses, SLD subtypes had significant interactions with sex, smoking status, and antidyslipidemic drugs in the contribution to the risk of HCC. In particular, the opposite trends in the risk of HCC by SLD subtypes (MASLD/MetALD vs. ALD) seemed to be mediated by the interactions between SLD subtypes and smoking status or antidyslipidemic drugs (online suppl. Table S7). Sex and antidiabetic drugs had significant interactions with SLD subtypes in the risk of developing iCCA. Moreover, the opposite trends in the risk of iCCA by SLD subtypes (MASLD/MetALD vs. ALD) seemed to be mediated by the interaction between SLD subtypes and antidiabetic drugs (online suppl. Table S8). Concerning the risk of incident cirrhosis, the impact of the SLD status was more prominent in smokers, participants without obesity, and those taking no antidyslipidemic drugs (online suppl. Table S9). As for the risk of decompensated cirrhosis, the impact of the SLD status was more prominent in smokers rather than in nonsmokers and past smokers (online suppl. Table S10).

Contribution of Alcohol Consumption and Cardiometabolic Risk Factors to the Risk of Liver-Related Outcomes

Restricted cubic splines for the association of alcohol consumption with the risk of liver-related outcomes showed that the risk of developing PLCa, HCC, incident cirrhosis, and decompensated cirrhosis increased as the amount of alcohol consumption increased, while the risk of developing iCCA did not (Fig. 5). When MASLD was further stratified into nonalcohol drinkers and mild alcohol drinkers (<30 g/day for men, <20 g/day for women), mild alcohol drinkers were associated with a decreased risk of HCC (SHR: 0.81; 95% CI: 0.69–0.96; online suppl. Table S11). No significant difference was observed in the risk of cirrhosis (SHR: 1.09; 95% CI: 0.99–1.19) and decompensated cirrhosis (SHR: 1.05; 95% CI: 0.92–1.21). As for the contribution of cardiometabolic risk factors, glucose levels and diabetes had the highest association with the onset of HCC (SHR: 2.06, 95% CI: 1.70–2.50), whereas blood pressure had the highest association with the onset of liver cirrhosis (SHR: 1.79, 95% CI: 1.64–1.95, online suppl. Table S12).

Discussion

This nationwide study investigated the risk of liver-related outcomes among the newly suggested SLD subtypes of MASLD, MetALD, and ALD. The risk of developing PLCa including HCC and iCCA as well as incident cirrhosis and decompensated cirrhosis was compared among the different subtypes of SLD. The current study demonstrated that compared to those with no SLD, all SLD subtypes were at a higher risk of developing PLCa. Notably, this elevated risk of developing PLCa was mainly attributed to the positive association of SLD subtypes with the risk of developing HCC but not iCCA. Compared to no SLD, MASLD, MetALD, and ALD were associated with a higher risk of developing both incident cirrhosis and decompensated cirrhosis. These findings were consistent across unadjusted Cox regression, multivariate-adjusted Cox regression, and competing risk analyses.

NAFLD and its severe form, NASH, are the fastest growing cause of HCC [19, 26], which account for about 75–85% of cases of PLCa [27]. With an overwhelming global prevalence of NAFLD, even a marginal increase in HCC incidence would translate into a significant number of patients affected by HCC. Given that the NAFLD population substantially overlaps with MASLD by about 98% [12, 13], the incidence of MASLD-related HCC is also expected to rise rapidly. Thus, the risk of developing HCC is worth investigating in patients with MASLD. The current study showed that not only MASLD but also MetALD and ALD had an increased risk of developing HCC compared with no SLD. This might be because cardiometabolic risk factors used for diagnosing MASLD and MetALD align with well-established risk factors for HCC, such as diabetes, obesity, insulin resistance, and metabolic syndrome [26]. As for ALD, excessive alcohol consumption per se might be a risk factor for developing HCC [28]. Further studies are warranted to investigate the phenotype of SLD-related HCC, especially among those at a high risk of disease progression.

In the current study, the risk of developing PLCa was higher in MASLD, MetALD, and ALD compared with no SLD. It should be noted that HCC rather than iCCA contributed to the increased risk of PLCa in this study. Although the previous study reported that NAFLD is associated with an increased risk of developing iCCA and the role of tumor necrosis factor-α in cancer progression was suggested as a mechanism behind the association [20], this study found little contribution of MASLD to the development of iCCA after treating death or liver transplantation as a competing risk and adjusting for other variables. MetALD and ALD were not found to be associated with the risk of iCCA, either. The findings should be further validated in other populations involving a larger population of iCCA.

Nonalcoholic fatty liver occasionally can progress to NASH, ultimately leading to cirrhosis and decompensated cirrhosis [29, 30], with worsening the prognosis. An average of 21–26% of NASH patients develop cirrhosis over the 8 years [31]. The number of patients with

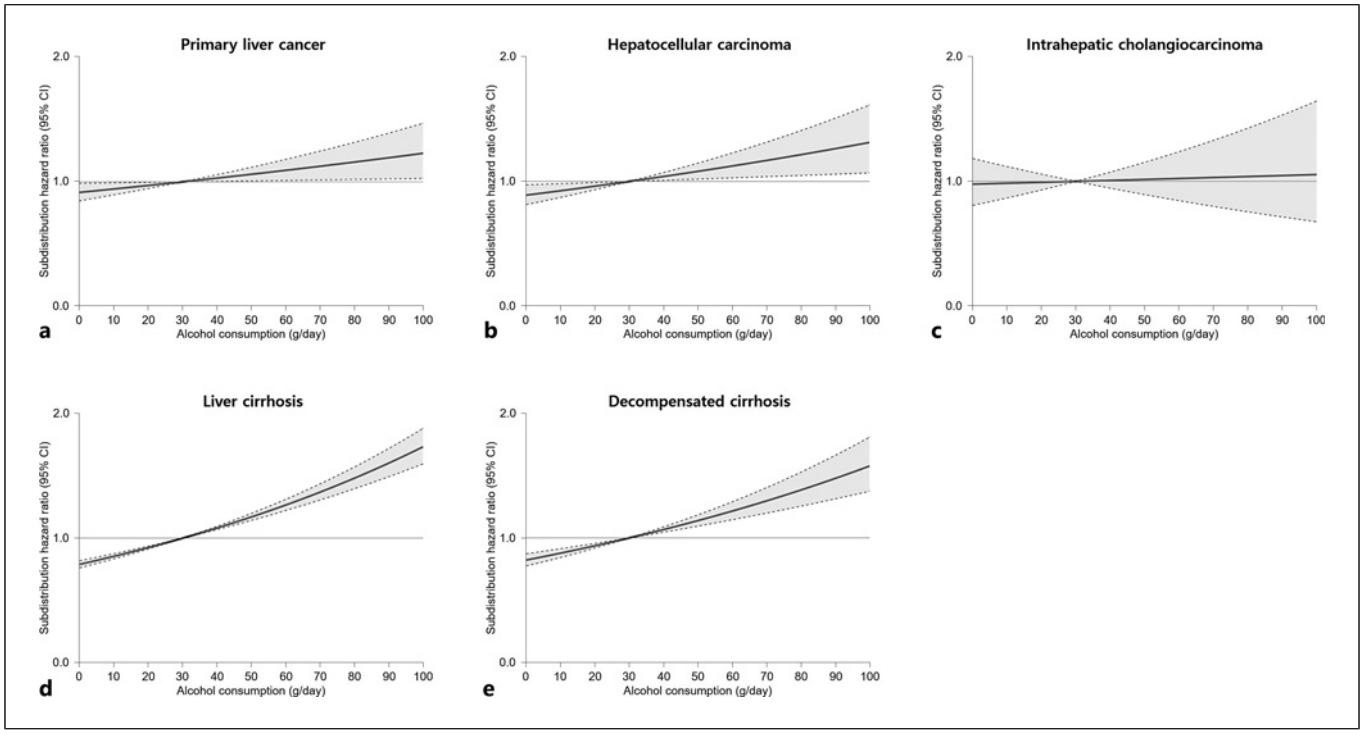

Fig. 5. Restricted cubic splines for the association of alcohol consumption with the risk of liver-related outcomes. SHRs (95% CIs) were calculated using the Fine-Gray model after adjustments for age, sex, body mass index, household income, antihypertensive drugs, antidiabetic drugs, antidyslipidemic drugs, aspirin, smoking, alcohol consumption, moderate-to-vigorous physical activity, and Charlson comorbidity index. Liver cirrhosis and decompensated cirrhosis were evaluated among participants without any evidence of liver cirrhosis. Association of alcohol consumption with PLCa (**a**), HCC (**b**), iCCA (**c**), incident cirrhosis (**d**), and decompensated cirrhosis (**e**).

NASH-related decompensated cirrhosis awaiting liver transplantation has continued to increase, making NASH the second most common indication for liver transplantation in the USA in 2019 [32]. This provides a solid basis for our investigation into cirrhosis and decompensated cirrhosis with the newly suggested SLD subtypes. With metabolic-associated steatohepatitis alternating NASH [12], MASLD would progress to metabolic-associated steatohepatitis and further to cirrhosis or decompensated cirrhosis. In the current study, MASLD was associated with a higher risk of developing cirrhosis and decompensated cirrhosis, bridging the gap between NAFLD and MASLD. ALD and the new subcategory of MetALD were also associated with an even higher risk of cirrhosis and decompensated cirrhosis.

A significant clinical implication of our study lies in the extensive investigation into the risk of liver-related outcomes in the newly suggested subcategory of MetALD. In the current study, participants with MetALD had approximately 87% increased risk of developing PLCa compared to no SLD, while those with MASLD had about 65%. The risk of developing cirrhosis and decompensated cirrhosis in MetALD was significantly higher than that in MASLD. Given that both MASLD and MetALD have one or more cardiometabolic risk factors, it can be interpreted that this increased risk of liver-related outcomes was attributed to the increased amount of alcohol consumption. Thus, for those with MetALD, modifying their drinking behavior or even suggesting abstinence on top of lowering their cardiometabolic burden may be an effective therapeutic option. The current study generated novel evidence for the threats that MetALD patients face, calling for more information on the clinical outcomes of this new category.

Subgroup analyses showed that men and smokers were more affected by the SLD status regarding HCC risk. Men and smokers are known to be associated with a high risk of developing HCC [33, 34]. In addition, the risk of HCC was lower in those with MASLD and MetALD taking antidyslipidemic drugs, which might be explained by a substantial preventive effect of statins against HCC [35, 36]. Participants with MASLD and MetALD who did not take any antidiabetic drugs were more affected by the SLD

status regarding their future risk of iCCA. It can be speculated that antidiabetic drugs might have influenced the development of iCCA. Indeed, metformin was associated with a 60% reduction in iCCA risk among patients with diabetes [37]. The current study observed that the risk of liver-related outcomes increased as the amount of alcohol consumption increased as well. From the therapeutic perspective, correcting cardiometabolic risk factors would be more effective in patients with MASLD, while modifying drinking behavior or abstinence would be more effective in those with MetALD and ALD [38]. A greater preventive effect can be expected for those who were found to be at a higher risk in subgroup analyses.

The current study bears several caveats. First, it was a retrospective study based on the nationwide claim data. Our study utilized the FLI to diagnose SLD since the database lacked radiologic and histologic information. Nevertheless, extensive epidemiological data support the diagnostic performance of FLI for hepatic steatosis, and FLI can serve as a realistic approach for diagnosing SLD under a resource-limited setting since it is reproducible with fair accuracy [22, 23, 39–42]. Although the diagnostic utility of FLI for the new nomenclature of MASLD and SLD classification has not yet been established, several studies using FLI in diagnosing SLD in the absence of histologic and radiologic information were recently published [14, 39]. To overcome inherent limitations, we adopted multiple rigorous strategies, including competing risk, sensitivity, and stratified analyses. Since the database did not provide any radiologic information regarding cirrhosis, the diagnosis of cirrhosis was based on the ICD codes. The potential misclassification bias could not be completely excluded. For thorough diagnosis, the diagnoses of decompensated cirrhosis included treatment codes for cirrhotic complications such as paracentesis and endoscopic variceal ligation. Second, the cohort exclusively consisted of Koreans, which might preclude the generalizability to other ethnic populations. Further studies are required to investigate liver-related outcomes across SLD subtypes among different ethnicities. In addition, patients recruited were from 47 to 86 years old, and the follow-up duration for a certain age group might have been relatively short. To address this challenge, the study performed the analysis considering death or liver transplantation as a competing risk. Third, the study was not able to stratify the risk of liver-related outcomes using noninvasive scores such as Fib-4 index, Fib-3 index, albumin-bilirubin score, and geriatric nutritional risk index since the cohort was void of platelet counts and albumin levels [40, 41]. Future studies for more sophisticated risk prediction of liver-related outcomes in MASLD and MetALD will follow.

In conclusion, MASLD, MetALD, and ALD were associated with a higher risk of developing PLCa than no SLD. While the increased risk of developing HCC was observed in all subtypes of SLD, the risk of developing iCCA in SLD subtypes did not differ from that in no SLD. MASLD, MetALD, and ALD were associated with an increased risk of developing both incident cirrhosis and decompensated cirrhosis, which increment was in consecutive order. Collectively, our findings alert physicians and public health campaigns to advise against any amount of alcohol intake and to reduce cardiometabolic burdens for the prevention of cirrhosis, decompensation, and HCC in individuals with either MASLD, MetALD, or ALD.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the Seoul Metropolitan Government Boramae Medical Centre (07-2023-5) and followed the principles of the Declaration of Helsinki. The requirement for written informed consent was waived because the NHIS data contain anonymized data that follow the guidelines of the Personal Data Protection Act.

Conflict of Interest Statement

The authors have no conflicts to disclose.

Funding Sources

This work was supported by grants from the National Research Foundation of Korea (2022R1F1A1076449 to Gi-Ae Kim, RS-2023-00237783 to Seogsong Jeong, and 2021R1A2C2005820, 2021M3A9E4021818, and RS-2023-00223831 to Won Kim), and the research program funded by the "Korea National Institute of Health" (KNIH) research project (2022ER090202 to Won Kim).

Author Contributions

All authors contributed substantially and in accordance with the guidelines of the International Committee of Medical Journal Editors. Study concept and design: G.-A.K., S.J., and W.K. Acquisition, analysis, or interpretation of data: G.-A.K., S.J., H.J., D.H.L., S.K.J., and W.K. Drafting the work or revising: G.-A.K., S.J., H.J., D.H.L., S.K.J., and W.K. Final approval of the manuscript: G.-A.K., S.J., H.J., D.H.L., S.K.J., and W.K.

Data Availability Statement

Data are available from the National Health Insurance Service (NHIS), which owns the data. Requests for data can be sent to the data owners, NHIS (http://www.nhiss.nhis.or.kr/).

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