Liver Cancer

Research Article

Liver Cancer 2024;13:561–571
DOI: 10.1159/000538301

Received: October 12, 2023
Accepted: March 6, 2024
Published online: March 12, 2024

Risk of Hepatocellular Carcinoma by Steatotic Liver Disease and Its Newly Proposed Subclassification

Byeong Geun Song Aryoung Kim Myung Ji Goh Wonseok Kang
Geum-Youn Gwak Yong-Han Paik Moon Seok Choi Joon Hyeok Lee
Dong Hyun Sinn

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Keywords
Steatotic liver disease · Metabolic dysfunction-associated steatotic liver disease · Nonalcoholic fatty liver disease · Metabolic dysfunction-associated fatty liver disease · Hepatocellular carcinoma

Abstract

Introduction: Steatotic liver disease (SLD) is a new overarching term proposed to replace nonalcoholic fatty liver disease and metabolic dysfunction-associated fatty liver disease. Subclassification includes metabolic dysfunction-associated SLD (MASLD), MASLD with increased alcohol intake (MetALD), and cryptogenic SLD. This study aimed to investigate whether SLD and its subclassification could stratify hepatocellular carcinoma (HCC) risk. ***Methods:*** A cohort of 85,119 adults without viral hepatitis or heavy alcohol intake was analyzed for the risk of HCC according to SLD and its subclassification. The fibrosis-4 (FIB-4) index was used to estimate the degree of liver fibrosis. ***Results:*** During a median follow-up of 11.9 years, HCC was diagnosed in 123 individuals. The incidence rate of HCC per 1,000 person-years was higher in individuals with SLD than in those without SLD (0.197 vs. 0.071, $p < 0.001$), with an adjusted hazard ratio of 2.02 (95% confidence interval: 1.40–2.92). The HCC incidence rate per 1,000 person-years was 0, 0.180, and 0.648 for cryptogenic SLD, MASLD, and MetALD, respectively. When participants with SLD was further stratified by the FIB-4 index, the HCC incidence rate per 1,000 person-years was 0.074 for SLD with FIB-4 < 1.3 and 0.673 for SLD with FIB-4 ≥ 1.3. Of note, HCC risk was substantially high (HCC incidence rate: 1.847 per 1,000 person-years) for MetALD with FIB-4 ≥ 1.3. ***Conclusions:*** HCC risk was different by SLD and its subclassification. The utilization of SLD and its subclassification can aid in stratifying HCC risk and facilitate the identification of individuals requiring interventions to mitigate the risk of HCC.

Introduction

Steatotic liver disease (SLD) and its subcategories are newly proposed overarching terms to replace nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) [1]. The nomenclature of NAFLD has been criticized due to several issues. First, the term "fatty" is perceived by many

karger@karger.com
www.karger.com/lic

Correspondence to:
Dong Hyun Sinn, sinndhn@hanmail.net; dh.sinn@samsung.com

patients as being stigmatizing, thus hindering disease awareness. Second, the NAFLD nomenclature does not fully consider cases where patients have both metabolic and alcohol-related liver disease. In addition, patients with concurrent metabolic risk factors and other chronic liver disease (such as viral or autoimmune) cannot be included under the nomenclature of NAFLD [2]. To address this issue, the new nomenclature of MAFLD has been proposed [3]. The diagnosis of MAFLD required the presence of steatosis in coexistence with stipulated metabolic criteria [4, 5]. Despite being an affirmative nomenclature, its use of "fatty" continued to carry stigma. Also, its permissive approach to alcohol consumption renders it a very different condition from currently known NAFLD in clinical trials and biomarker studies. This raised concerns and highlighted the need to consider the potential impact of such change in definition on existing body of evidence for NAFLD and the development of drugs and biomarkers [6].

In the context of this debate about terminology, an international consensus group has suggested a new nomenclature of SLD and its subcategories, which provides an affirmative non-stigmatizing description of the condition rather than a diagnosis of exclusion [1]. Metabolic dysfunction-associated SLD (MASLD), which will replace NAFLD, encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors. A new category, MASLD with increased alcohol intake (MetALD), describes those with MASLD who consume greater amounts of alcohol [1]. However, the newly suggested nomenclature has not been extensively evaluated for its clinical significance. Hepatocellular carcinoma (HCC) is a main adverse outcome of fatty liver diseases [7]. Thus, the aim of this study was to investigate whether SLD and its subcategories could identify or stratify HCC risk using a large cohort.

Patients and Methods

Study Population

This was a retrospective cohort study of participants (n = 199,375) aged 20 years or older who underwent health screening exams, including abdominal ultrasonography at the Samsung Medical Center Health Promotion Center in Seoul, South Korea, from January 1st 2001 to December 31st 2016. If a participant had multiple health screening exams during the study period, we used data from the first screening exam. Among screened participants, we excluded individuals with current or a history of cancer (n = 3,486), chronic viral hepatitis (n = 5,860), heavy alcohol intake (420 g/week for male, 350 g/week for female) (n = 910), or missing information on alcohol intake (n = 85,632). Although SLD can be diagnosed for people with coexisting chronic liver disease (e.g., chronic viral hepatitis or people with heavy alcohol intake) [1] as HCC risk differs significantly by the presence of coexisting chronic liver disease [8], those with coexisting chronic liver disease were excluded from analysis in this study. Among 106,987 eligible adult participants without malignancy or other chronic liver diseases, 21,868 participants were further excluded with the following exclusion criteria: those with HCC development within 6 months, those with follow-up duration of less than 6 months, and those with missing information for cardiometabolic risk factors. Finally, a total of 85,119 adult participants without malignancy or other chronic liver diseases with information available for cardiometabolic risk factors who had a follow-up duration of at least 6 months were analyzed (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board (IRB) of the Samsung Medical Center approved this study (IRB approval number: 2023-08-021). The requirement for informed consent was waived by the IRB as we only used de-identified data routinely collected during health checkup visits.

Variables

Demographics, past medical history, and amount of alcohol intake were collected through standardized, self-administered questionnaires. Current alcohol intake (g/week) was calculated using frequency of drinking (times/week) and amount of alcohol on each occasion. Height, weight, waist circumference, and blood pressure were measured at the health screening exam. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples for testing aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting glucose, hemoglobin A1c, plasma high-density lipid (HDL) cholesterol, triglyceride, and platelet were collected after 8 h of fasting. The fibrosis-4 (FIB-4) index was calculated as follows: age (years) × AST (IU/L)/platelet count (10^9/L) × $\sqrt{}$ALT [9].

Abdominal ultrasound exams were performed using the LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA), the iU22 xMATRIX (Philips Medical Systems, Cleveland, OH, USA), or Acuson Sequoia 512 machines (Siemens, Issaquah, WA, USA) by experienced radiologists who were unaware of study aims. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head. Hepatic steatosis on ultrasonography was defined based on the standard criteria, which included hepatic parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and brightness of intrahepatic vessel walls or diaphragm [10, 11]. The normal liver was defined as when it showed fine homogeneous isoechoic texture compared to adjacent normal renal cortex.

Definition and Outcome

The diagnosis of SLD was based on hepatic steatosis on ultrasonography. SLD subclassification (MASLD, MetALD, and cryptogenic SLD) were defined as proposed [1]. Cardiometabolic risk factors were defined as follows: (1) BMI ≥23 kg/m^2 or waist circumference >90 cm for males or 80 cm for females [12]; (2) fasting serum glucose ≥100 mg/dL or HbA1c ≥ 5.7% or type 2 diabetes or treatment for type 2 diabetes; (3) blood pressure ≥130/85 mm Hg or antihypertensive drug treatment; (4) plasma triglyceride ≥150 mg/dL or lipid-lowering treatment; (5) plasma HDL cholesterol ≤40 mg/dL for males or ≤50 mg/dL for females or lipid-lowering treatment [1]. Individuals who had hepatic steatosis with at least one of five cardiometabolic risk factors were diagnosed

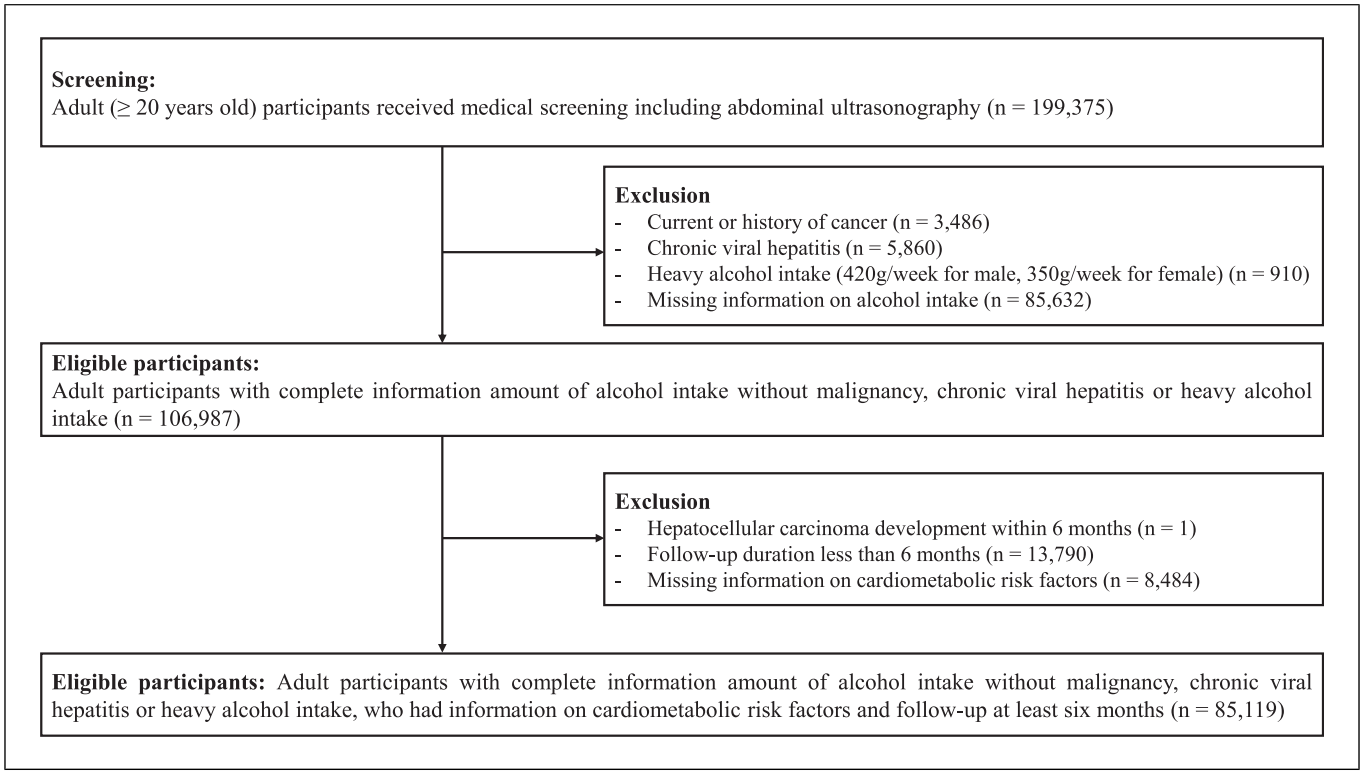

Fig. 1. Patient flow.

as MASLD. Individuals with MASLD who consumed greater amounts of alcohol per week (140–350 g/week for females or 210–420 g/week for males) were diagnosed as MetALD. Those with SLD without metabolic dysregulation or increased alcohol intake were diagnosed as cryptogenic SLD. The FIB-4 index was used to assess the severity of fibrosis and to classify participants with SLD into two groups: high-intermediate (FIB-4 ≥ 1.3) and low-probability (FIB-4 < 1.3) advanced fibrosis [13, 14]. For sensitivity analysis, the Hepatic Steatosis Index (HSI) was used as a biomarker for steatosis and was calculated as follows: HSI = 8 × ALT/AST ratio + BMI + 2 × Diabetes (0 if no, 1 if yes) + 2 × Gender (0 for female, 1 for male). A cutoff value of 36 was used to indicate the presence of hepatic steatosis [15].

The diagnosis of MAFLD was based on the evidence of hepatic steatosis on ultrasonography and meeting one of the three conditions: (1) BMI ≥23 kg/m^2; (2) type 2 diabetes mellitus; (3) the presence of at least two of the seven following metabolic abnormalities variables: a waist circumference of ≥90 cm in men or ≥80 cm in women, a blood pressure of ≥130/85 mm Hg or use of antihypertensive medications, plasma triglycerides of ≥150 mg/dL, plasma HDL cholesterol of <40 mg/dL in men and <50 mg/dL in women or the use of medications for hyperlipidemia, prediabetes (fasting glucose of 100–125 mg/dL or a hemoglobin A1c of 5.7–6.4%), a Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score of ≥2.5, or a plasma high-sensitivity C-reactive protein (hsCRP) of >2 mg/mL [3]. The primary outcome was HCC development during follow-up. The follow-up period was defined as either the time from the index health screening visit to the date of the HCC diagnosis or the last hospital visit (reference date: June 30, 2023), whichever came first. HCC was diagnosed according to regional HCC guidelines [8, 16].

Statistical Analysis

Categorical variables are reported as numbers and percentages. They were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables are reported as median and range. They were compared using the Mann-Whitney U test. Survival curves were calculated using the Kaplan-Meier method. Risks of HCC between groups were compared using the log-rank test. Cox proportional hazards models were used to estimate crude and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for HCC. In a multivariable model, age (continuous variable), sex (male vs. female), the presence of cardiometabolic risk factors (yes vs. no), increased alcohol intake (yes vs. no), and FIB-4 (continuous variable) were adjusted. Cardiometabolic risk factors and increased alcohol intake were not adjusted in the analysis of MASLD, MetALD, or cryptogenic SLD since these factors were required to diagnose MASLD and MetALD. For additional analysis, we stratified individuals according to MASLD and MAFLD definitions and compared the HCC risk between the "MASLD&MAFLD" group and "MASLD without MAFLD" group. As a sensitivity analysis, we used the HSI to define steatosis and categorize individuals according to the definition. All statistical analyses were performed using R version 4.1.2 software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value of <0.05 was considered statistically significant.

Table 1. Baseline characteristics of study subjects

	No SLD (n = 56,059)	SLD (n = 29,060)	p value
Age, years	48.0 (42.0; 54.0)	50.0 (44.0; 57.0)	<0.01
Male, n (%)	25,572 (45.6)	21,053 (72.4)	<0.01
BMI, kg/m^2	22.8 (20.9; 24.5)	25.5 (23.9; 27.2)	<0.01
Cardiometabolic risk factors[a, b]			<0.01
Abdominal obesity, n (%)	26,821 (47.9)	25,150 (86.6)	
High blood glucose, n (%)	10,527 (18.8)	11,584 (39.9)	
High blood pressure, n (%)	10,731 (19.1)	9,744 (33.5)	
High triglyceride, n (%)	9,233 (16.6)	13,625 (47.3)	
Low HDL, n (%)	10,626 (19.0)	9,434 (32.5)	
AST, IU/L	20.0 (17.0; 25.0)	24.0 (20.0; 31.0)	<0.01
ALT, IU/L	18.0 (14.0; 24.0)	29.0 (21.0; 41.0)	<0.01
Fasting glucose, mg/dL	90.0 (84.0; 97.0)	96.0 (89.0; 106.0)	<0.01
HDL, mg/dL	56.0 (47.0; 67.0)	47.0 (41.0; 55.0)	<0.01
Triglyceride, mg/dL	90.0 (66.0; 127.0)	144.0 (104.0; 202.0)	<0.01
Platelet, 10^3/μL	235.0 (203.0; 271.0)	240.0 (208.0; 276.0)	<0.01
FIB-4 index	1.0 (0.7; 1.3)	0.9 (0.7; 1.2)	<0.01
FIB-4 index			<0.01
<1.30	42,711 (76.2)	22,787 (78.4)	
1.30–2.67	12,750 (22.7)	5,947 (20.5)	
≥2.67	598 (1.1)	326 (1.1)	

SLD, steatotic liver disease; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipid cholesterol; FIB-4, fibrosis-4. [a]Cardiometabolic risk factors were defined as follows: abdominal obesity, BMI ≥23 kg/m^2 or waist circumference >90 cm for males or >80 cm for females; high blood glucose, fasting serum glucose ≥100 mg/dL or HbA1c ≥ 5.7% or type 2 diabetes or treatment for type 2 diabetes; high blood pressure, blood pressure ≥130/85 mm Hg or specific antihypertensive drug treatment; high triglyceride, plasmas triglyceride ≥150 or lipid-lowering treatment; low HDL, plasma HDL cholesterol ≤40 mg/dL for males or ≤50 mg/dL for females or lipid-lowering treatment. [b]Thirty-five missing for abdominal obesity, 5 missing for high blood glucose, 23 missing for high blood pressure, 595 missing for high triglyceride, 96 missing for low HDL.

Results

Baseline Characteristics

Among a total of 85,119 individuals, 29,060 (34.1%) had SLD. Of these 29,060 individuals with SLD, 91.7% (26,661 individuals) had MASLD, 5.3% (1,538 individuals) had MetALD, and 2.9% (836 individuals) had cryptogenic SLD. Table 1 shows baseline characteristics of the cohort. Baseline characteristics differed significantly between individuals with SLD and those without SLD. Individuals with SLD were older. They were predominantly males. Those with SLD also had higher aminotransferase levels and poor metabolic profiles (Table 1).

Risk of HCC by SLD

During a median follow-up of 11.9 years (range: 0.6–23.5 years), 123 individuals were newly diagnosed with HCC. The HCC incidence was higher in individuals with SLD than in those without SLD (0.197 vs. 0.071 per 1,000 person-years, p < 0.001). Individuals with SLD showed higher risk of HCC than those without SLD (multivariable adjusted HR: 2.02, 95% CI: 1.40–2.92, Table 2).

Risk of HCC by SLD Subclassification

Among 29,060 individuals with SLD, majority (91.7%) were classified as MASLD. MetALD comprised 5.3%, and cryptogenic SLD comprised 2.9% of participants. The

Table 2. Risk of HCC by SLD and its subclassification

Participants characteristics (or nomenclature)	Subjects, *n*	HCC, *n*	Incidence rate (per 1,000 person-years)	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
SLD							
No SLD	56,059	49	0.071	Reference		Reference	
SLD	29,060	74	0.197	2.64 (1.84–3.80)	<0.001	2.02 (1.40–2.92)[a]	<0.001
SLD subclassification*							
Cryptogenic SLD	836	0	0	N/A		N/A	
MASLD	26,661	63	0.180	2.40 (1.65–3.49)	<0.001	2.03 (1.39–2.95)[b]	<0.001
MetALD	1,538	11	0.648	8.87 (4.61–17.1)	<0.001	5.22 (2.69–10.1)[b]	<0.001

SLD, steatotic liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake. [a]Adjusted for age, sex, the presence of cardiometabolic risk factors, increased alcohol intake (males: 210–420 g/week; females: 140–350 g/week), and FIB-4 index. [b]Adjusted for age, sex, and FIB-4 index. *The analysis excluded 25 individuals who did not fit into any SLD subclassification, characterized as having SLD and increased alcohol intake, but without metabolic syndrome.

HCC incidence per 1,000 person-years was 0 for cryptogenic SLD, 0.180 for MASLD, and 0.648 for MetALD ($p < 0.001$, Table 2; Fig. 2). Compared with individuals without SLD, those with MetALD (adjusted HR: 5.22, 95% CI: 2.69–10.1) and MASLD (adjusted HR: 2.03, 95% CI: 1.39–2.95) showed higher risk of HCC (Table 2). There was no HCC diagnosed in the cryptogenic SLD group during a follow-up of 7,978 person-years.

Sensitivity Analysis

In sensitivity analysis using the HSI, there were 2,423 participants in whom the HSI could not be calculated. A total of 82,696 participants were used in this analysis. The HCC incidence was higher in individuals with SLD than in those without SLD (0.238 vs. 0.059 per 1,000 person-years, $p < 0.001$). Individuals with SLD had a higher HCC risk than those without, with a multivariable adjusted HR of 4.54 (95% CI: 2.99–6.90, $p < 0.001$). The HCC incidence per 1,000 person-years was 0 for cryptogenic SLD, 0.224 for MASLD, and 0.509 for MetALD ($p < 0.001$, online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000538301).

Risk of HCC by SLD Severity

When individuals with SLD were classified using the FIB-4 index, the HCC incidence rate per 1,000 person-years was 0.074 for those with FIB-4 < 1.3 and 0.673 for those with FIB-4 ≥ 1.3 (Table 3; Fig. 3). Compared to individuals without SLD, HCC risk was higher for those with SLD and FIB-4 ≥ 1.3 (adjusted HR: 4.00, 95% CI: 2.65–6.05), while no significant difference was noticed for SLD with FIB-4 < 1.3 (adjusted HR: 0.88, 95% CI: 0.53–1.46) (Table 3). When SLD subclassification was further classified by the FIB-4 index, the proportion of individuals with FIB-4 ≥ 1.3 was 17.5% for those with cryptogenic SLD, 21.0% for those with MASLD, and 33.7% for those with MetALD ($p < 0.001$, Fig. 4). The HCC risk was higher for those with FIB-4 ≥ 1.3 than for those with FIB-4 < 1.3 (Table 3). Of note, the HCC incidence rate was very high for those with MetALD and FIB-4 ≥1.3 (1.847 per 1,000 person-years) with an adjusted HR of 12.4 (95% CI: 6.20–24.9).

Comparison of HCC Risk by MASLD and MAFLD Definition

To define the presence of MAFLD, HOMA-IR and hsCRP values are required in addition to variables used to define MASLD in this study. As individuals with missing values for HOMA-IR or hsCRP had to be excluded further, comparative analysis of HCC risk between MAFLD and MASLD had to be based on a cohort of 62,830 individuals. All individuals with MAFLD were MASLD, while 3,098 out of 21,322 individuals (14.5%) did not qualify for the definition of MAFLD. Additional analysis showed that the "MASLD&MAFLD" group was significantly associated with an increased risk of HCC. However, the "MASLD without MAFLD" group did not show a significant difference in HCC risk compared to the cryptogenic SLD or no SLD group (online suppl. Table S1; Fig. S2).

Discussion

In this study, we found that individuals with SLD had an increased risk of HCC compared to individuals without SLD. When SLD subclassification was assessed, we noticed

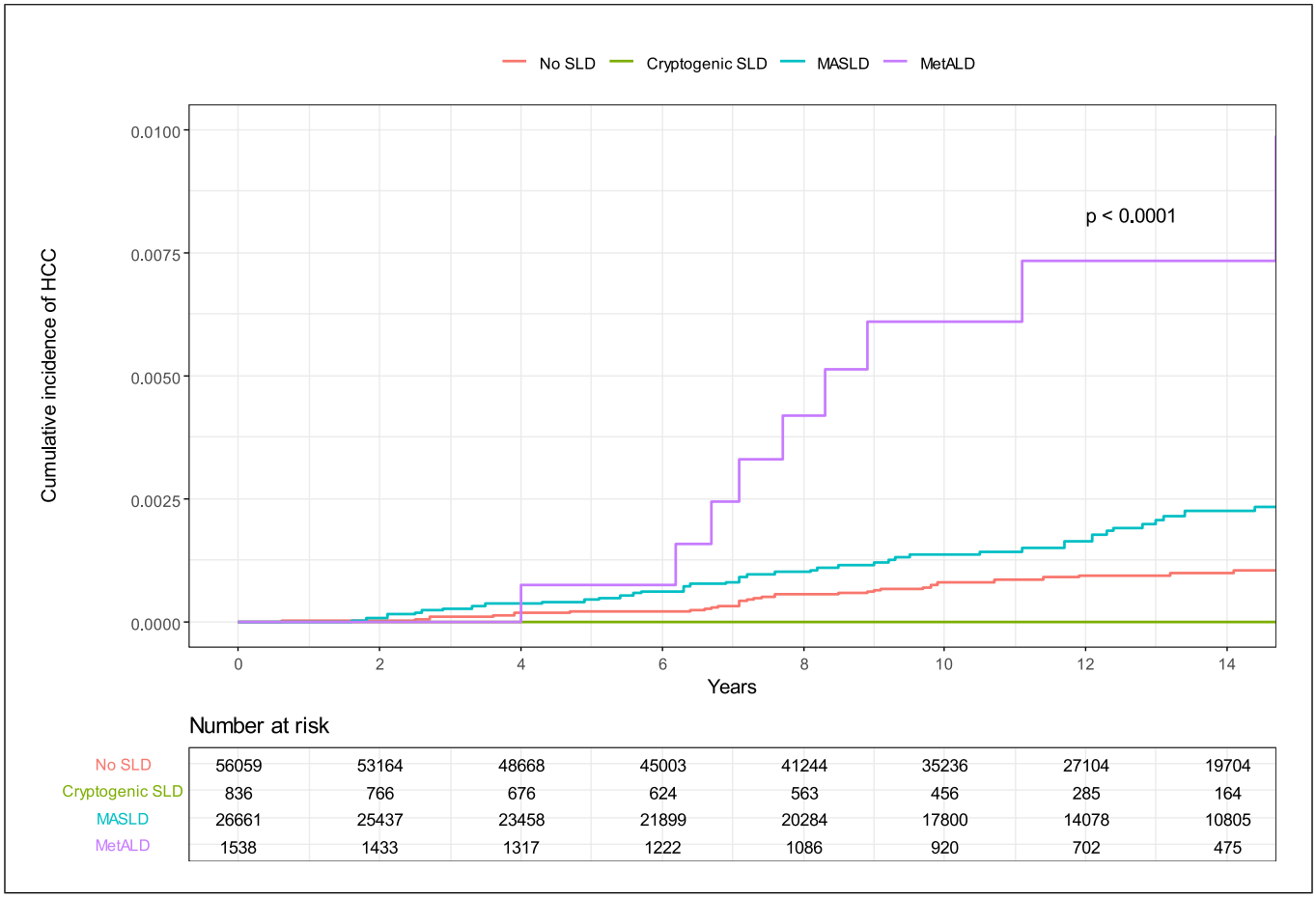

Fig. 2. Risk of HCC according to the presence of SLD and its subclassification. Comparison performed with the log-rank test. HCC, hepatocellular carcinoma; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake. * The analysis excluded 25 individuals who did not fit into any SLD subclassification, characterized as having SLD and increased alcohol intake, but without metabolic syndrome.

that individuals with MASLD and MetALD were at an increased risk of HCC, while the HCC risk was not increased for those with cryptogenic SLD. When SLD and its subclassification were further classified by the severity of fibrosis, increased HCC risk was observed for individuals with intermediate or high likelihood of advanced fibrosis indicated by an increase of the FIB-4 index (≥1.3). Of note, individuals classified as MetALD under newly proposed nomenclature showed a high HCC incidence rate (0.648 for 1,000 person-years), especially when their FIB-4 index was high (≥1.3) (1.847 for 1,000 person-years). This suggests that SLD and its subclassification can risk stratify and capture those at higher risk of HCC development among asymptomatic adults.

The definition of NAFLD does not require metabolic dysfunction for a diagnosis. However, metabolic dysfunction plays a key role in the development and progression of NAFLD and is linked to adverse liver related outcomes [17]. Components of metabolic syndrome, particularly obesity and type 2 diabetes, are independently associated with HCC development. They together contribute to the risk of HCC in those with a noncirrhotic liver [18–20]. Metabolic syndrome itself has also been reported to be associated with an increased risk of HCC in large cohort studies [21, 22]. Compared to NAFLD, MASLD requires metabolic dysfunction. Those without metabolic dysfunction are categorized into cryptogenic SLD. In our study, the risk of HCC in patients with cryptogenic SLD was null, whereas those with MASLD had significantly higher risk for HCC. In a study comparing NAFLD and MAFLD definitions, "NAFLD-only without MAFLD," which would be cryptogenic SLD

Table 3. Risk of HCC by SLD and severity of fibrosis

Participants characteristics (or nomenclature)	Subjects, *n*	HCC, *n*	Incidence rate (per 1,000 person-years)	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
SLD severity							
No SLD	56,059	49	0.071	Reference		Reference	
SLD with FIB-4 <1.3	22,787	22	0.074	0.96 (0.58–1.59)	0.870	0.88 (0.53–1.46)[a]	0.615
SLD with FIB-4 ≥1.3	6,273	52	0.673	9.91 (6.71–14.7)	<0.001	4.00 (2.65–6.05)[a]	<0.001
SLD subclassification severity							
MASLD with FIB-4 <1.3	21,060	21	0.075	0.97 (0.58–1.62)	0.905	0.94 (0.56–1.57)[b]	0.807
MASLD with FIB-4 ≥1.3	5,601	42	0.596	8.79 (5.82–13.3)	<0.001	3.86 (2.50–5.95)[b]	<0.001
MetALD with FIB-4 <1.3	1,020	1	0.086	1.17 (0.16–8.46)	0.877	1.09 (0.15–7.95)[b]	0.932
MetALD with FIB-4 ≥1.3	518	10	1.847	26.4 (13.4–52.2)	<0.001	12.4 (6.20–24.9)[b]	<0.001

SLD, steatotic liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake. [a]Adjusted for age, sex, the presence of cardiometabolic risk factors, and increased alcohol intake (males: 30–60 g/day; females: 20–50 g/day). [b]Adjusted for age and sex.

under the new nomenclature, showed lower rates of advanced fibrosis with equivalent all-cause mortality risk compared to patients without steatosis [23, 24]. In this study, fibrotic burden estimated using the FIB-4 index was higher in MASLD than in cryptogenic SLD. The fibrosis burden is a strong factor associated with HCC risk [25]. In the present study, individuals with an elevated FIB-4 index were also at an increased HCC risk as well. Thus, differentiating between cryptogenic SLD and MASLD within the spectrum of SLD based on the presence of metabolic dysfunction have considerable significance in clinical practice, in terms of HCC risk stratification. However, as cryptogenic SLD had a very small number among individuals with SLD in this study, further research on natural course of cryptogenic SLD in a larger scale are needed to fully understand the natural course of cryptogenic SLD.

Under the NAFLD criteria, people with significant alcohol consumption are excluded from NAFLD diagnosis [26]. Under the MAFLD criteria, people with significant alcohol consumption are classified together with those who do not drink significant amounts of alcohol [4]. However, the natural history may differ according to the amount of alcohol consumption in people with hepatic steatosis [27, 28]. In the newly proposed SLD subclassification, MetALD was proposed for those with MASLD and increased amount of alcohol intake as a new, distinct disease entity [1]. In our study, we noticed that the HCC risk was higher for those with MetALD, especially when the FIB-4 index was elevated. The proportion of individuals with an elevated FIB-4 index (≥1.3) was higher in those with MetALD than in those with MASLD or cryptogenic SLD. This finding supports differentiating between MASLD and MetALD within the spectrum of SLD based on the amount of alcohol intake. Compared to MASLD, MetALD differs only by the amount of alcohol intake. However, those with MetALD showed considerably higher risk of HCC development than those with MASLD. Differentiating people with SLD into MASLD and MetALD has clinical significance in terms of differentiating the risk of HCC.

In this study, we noticed that the HCC risk was elevated for those with SLD and an increased FIB-4 index, while the HCC risk of those with SLD and a low FIB-4 index was not increased. In line with our findings, several studies have shown that the FIB-4 index is a useful indicator for HCC risk among patients with NAFLD [29, 30]. Of note, there was no difference in HCC risk between MASLD and MetALD when the FIB-4 index was low (HCC incidence rate of 0.075 vs. 0.086 per 1,000 person-years). However, there was a substantial difference in HCC risk between MASLD and MetALD when the FIB-4 index was elevated (HCC incidence rate of 0.596 vs. 1.847 per 1,000 person-years). As the number of individuals with MetALD with an elevated FIB-4 index was small (n = 518), our observation needs to be validated by further studies. However, this may indicate that the harmful effect of alcohol consumption may be exponential for SLD with advanced fibrosis. Studies have shown the harmful effect of alcohol on HCC risk in NAFLD [31]. The new nomenclature, MetALD, shows an increased HCC risk, especially when the FIB-4 index is elevated. The amount of alcohol consumed may play an important role in hepatocarcinogenesis among individuals with underlying liver steatosis. Thus, those with MetALD might need active interventions to decrease their HCC

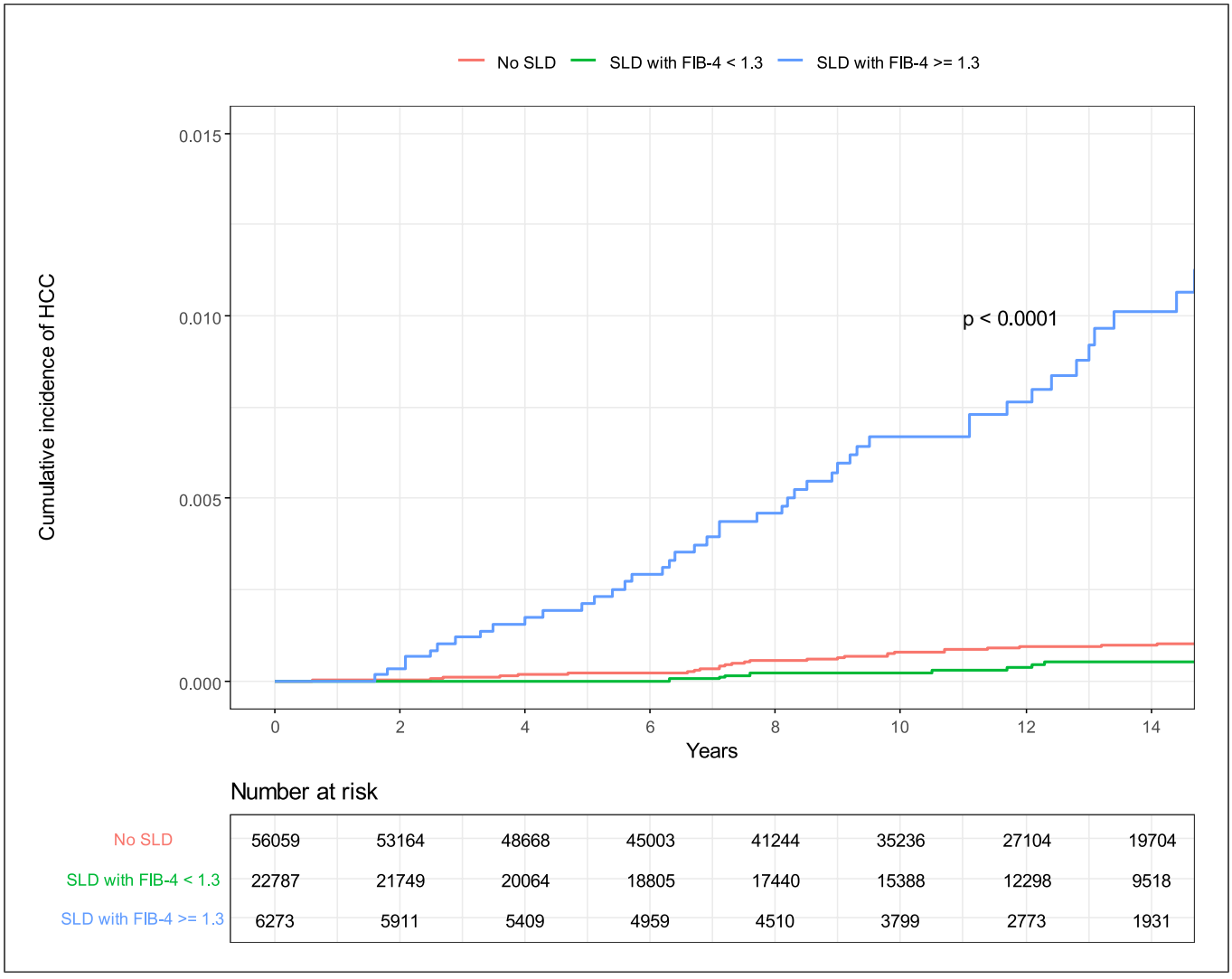

Fig. 3. Risk of HCC according to the severity of SLD. Comparison performed with the log-rank test. HCC, hepatocellular carcinoma; SLD, steatotic liver disease; FIB-4, fibrosis-4.

risk, including interventions to decrease alcohol consumption in this population.

Defining MetALD and assessing the fibrosis burden might also help identify those who could benefit from HCC surveillance. There is a debate about which patients should be targeted for screening as the risk of HCC is low in those with non-cirrhotic NAFLD [32]. The prevalence of SLD is high in the general population. However, the HCC risk is not high enough to perform HCC surveillance for all people with SLD [17, 29, 33]. Risk stratification is mandatory for a tailored approach. In this study, we noticed that SLD subclassification, together with the FIB-4 index, could stratify HCC risk. This might also help identify high-risk individuals who may benefit from regular HCC surveillance. Our study findings suggest that those with MetALD and FIB-4 ≥ 1.3 should be a priority target group to understand risks and benefits of HCC surveillance in SLD. We used an FIB-4 cutoff of 1.3 to categorize individuals into high-intermediate (FIB-4 ≥ 1.3) and low-probability (FIB-4 < 1.3) advanced fibrosis. At the FIB-4 cutoff 2.67, individuals with high probability of advanced fibrosis can be identified. Yet, in this cohort, there were only 319 individuals with FIB-4 > 2.67 (1.13%), limiting stratified analysis. Clinical significance of people with high probability (FIB-4 > 2.67) of advanced fibrosis requires additional studies. Although sample size was small, HCC risk was highest in individuals with FIB-4 > 2.67 (data not shown).

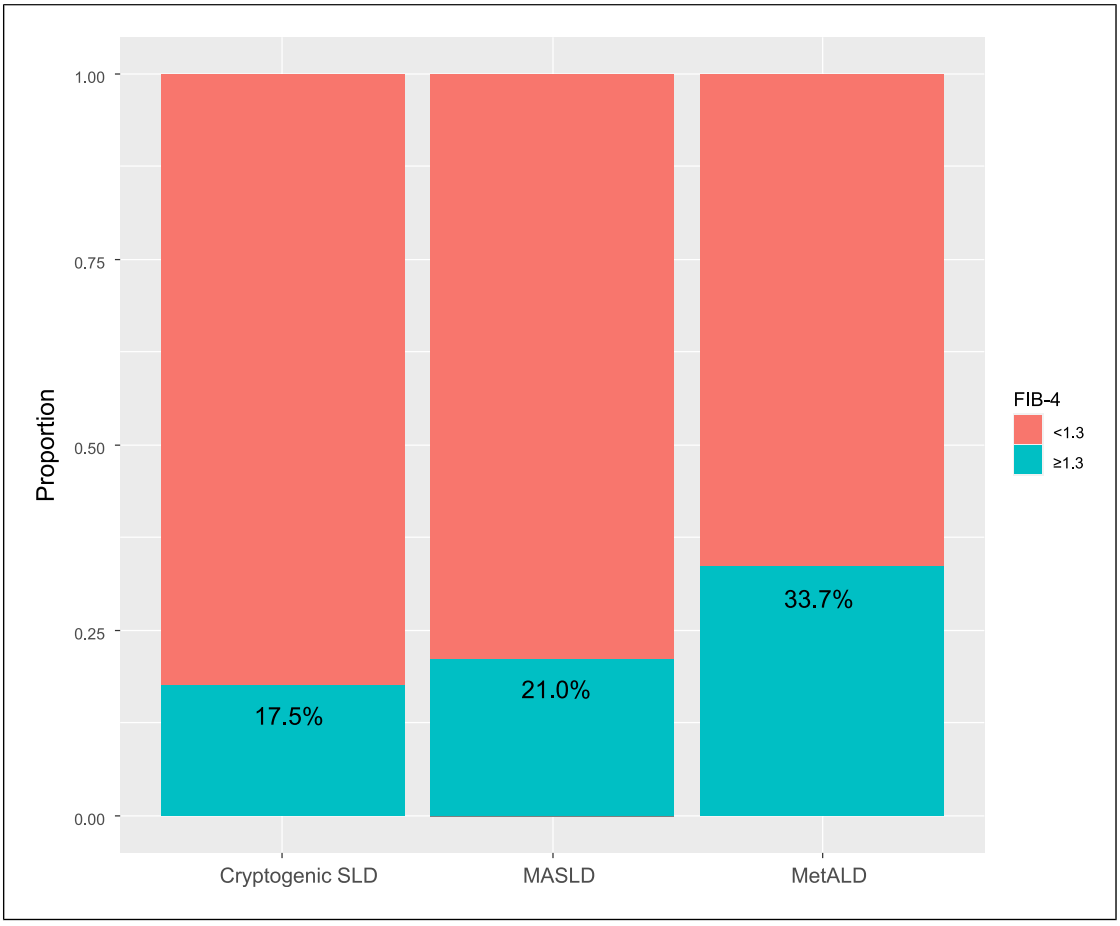

Fig. 4. Proportion of those with advanced fibrosis among individuals with SLD subclassification. SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake; FIB-4, fibrosis-4.

The complex nature of MASLD necessitates a systematic approach, impacting a wide range of health aspects. Hepatic carcinogenesis in this condition is predominantly linked to liver-specific factors like inflammation and fibrosis, whereas cardiovascular morbidities arise from broader metabolic dysfunctions [34, 35]. This highlights the need for research spanning various health outcomes to fully understand the disease's impact.

Our study suggests interplay between alcohol and metabolic alterations in HCC development. Alcohol may exert its carcinogenic effects through metabolic pathways [36]. Also, the presence of metabolic alterations may further enhance the carcinogenic potential of alcohol [37]. Further research is warranted to elucidate the precise molecular pathways driving HCC in this context.

This study has some limitations that should be considered when interpreting its findings. First, hepatic steatosis was defined using ultrasonography, and fibrosis was estimated using the FIB-4 index. Although ultrasonography and FIB-4 index are validated tools for identifying the presence of hepatic steatosis and estimating the fibrosis burden, there might be measurement and classification biases. Nevertheless, we observed that the consistency of our results was confirmed in a sensitivity analysis using a blood-based biomarker to define steatosis. The gold standard to diagnose hepatic steatosis and the degree of fibrosis is histology. Hence, findings of this study need to be evaluated using biopsy-defined cohort. When differentiating MASLD from MetALD, accurate assessment of alcohol intake is needed. In this study, self-reported questionnaires were used for assessing alcohol intake, which might not fully capture the true quantity or patterns of consumption due to potential recall bias or intentional underreporting. While MASLD is an inclusive term encompassing various chronic liver diseases, it is important to note that the Asia-Pacific region exhibits a

high prevalence of viral hepatitis. In our analysis, we excluded individuals with chronic viral hepatitis as information on viral replication status and antiviral therapy was inadequate or missing in large proportion of participants as the cohort was based on a health screening exam. The significance and clinical implications of defining MASLD in individuals with chronic viral hepatitis requires additional study. Lastly, there were also inherent limitations in the definition of metabolic dysfunction itself. When defining metabolic dysfunction, certain levels or cutoff points were used to define the presence or absence of metabolic dysfunction. Yet, there could be biases or artifacts of cutoff levels used in the definition of metabolic health in a given individual [38]. We categorized individuals using baseline characteristics at the index visit. However, SLD status, amounts of alcohol intake, and metabolic dysfunctions were not in a fixed state. They could change over time. In addition, the study cohort was exclusively composed of Asians. Thus, findings of this study might not be applicable to other ethnicity groups. Considering the high prevalence of lean MASLD and the frequent occurrence of minor alleles of PNPLA3 in Asian populations, it is important to acknowledge that these genetic and phenotypic factors might influence the observed association between MASLD and HCC risk [39]. Unfortunately, we lacked information on PNPLA3 in our dataset, and this could not be assessed in this study.

In summary, we observed an increased risk of HCC in individuals with SLD. When HCC risk was assessed using the newly proposed nomenclature, we noticed different risks for those with cryptogenic SLD, MASLD, and MetALD. However, those with cryptogenic SLD did not show an increased risk of HCC. Further risk stratification showed a higher HCC risk for those with a high likelihood of advanced fibrosis, indicated by an elevated FIB-4 index. Individuals classified as MetALD under the new nomenclature showed a particularly high incidence rate of HCC when their FIB-4 index was high. This indicates that SLD and its subclassifications can help identify those at a higher risk of HCC.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of the Samsung Medical Center (IRB approval number: 2023-08-021). Written informed consent has been waived by the Samsung Medical Center IRB Ethics Committee due to the anonymized use of patient data, and an ethical exemption has been granted (IRB approval number: 2023-08-021). The Ethics Committee provided this exemption, acknowledging that the research meets the ethical guidelines and the requirements for exemption from written informed consent. This study has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki and has been approved by the IRB.

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this study to disclose.

Funding Sources

No funding was received.

Author Contributions

Study concept and design, data analysis and interpretation, manuscript draft, and data analysis plan and data management: Byeong Geun Song and Dong Hyun Sinn. Data acquisition: Byeong Geun Song and Aryoung Kim. Critical revision of manuscript: Byeong Geun Song, Myung Ji Goh, Wonseok Kang, Dong Hyun Sinn, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, and Joon Hyeok Lee. Overall study supervision: Dong Hyun Sinn. All the authors participated in the preparation of the manuscript and have seen and approved the final version.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author.

References

1 Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79(6):1542–56. doi: 10.1016/j.jhep.2023.06.003.

2 American Association for the Study of Liver Diseases; Latin American Association for the Study of the Liver; European Association for the Study of the Liver. A call for unity: the path towards a more precise and patient-centric nomenclature for NAFLD. J Hepatol. 2023;79(1):4–5. doi: 10.1016/j.jhep.2023.05.003.

3 Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202–9. doi: 10.1016/j.jhep.2020.03.039.

4 Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158(7):1999–2014.e1. doi: 10.1053/j.gastro.2019.11.312.

5 Gofton C, Upendran Y, Zheng MH, George J. MAFLD: how is it different from NAFLD? Clin Mol Hepatol. 2023;29(Suppl l):S17–31. doi: 10.3350/cmh.2022.0367.
6 Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, et al. From NAFLD to MAFLD: implications of a premature change in terminology. Hepatology. 2021;73(3):1194–8. doi: 10.1002/hep.31420.
7 Daher D, Dahan KSE, Singal AG. Non-alcoholic fatty liver disease-related hepatocellular carcinoma. J Liver Cancer. 2023;23(1):127–42. doi: 10.17998/jlc.2022.12.30.
8 Korean Liver Cancer Association KLCA and National Cancer Center NCC Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. J Liver Cancer. 2023;23(1):1–120. doi: 10.17998/jlc.2022.11.07.
9 Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25. doi: 10.1002/hep.21178.
10 Cengiz M, Senturk S, Cetin B, Bayrak AH, Bilek SU. Sonographic assessment of fatty liver: intraobserver and interobserver variability. Int J Clin Exp Med. 2014;7(12):5453–60.
11 Khov N, Sharma A, Riley TR. Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(22):6821–5. doi: 10.3748/wjg.v20.i22.6821.
12 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23(5):469–80. doi: 10.1111/j.1464-5491.2006.01858.x.
13 Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol. 2019;71(2):371–8. doi: 10.1016/j.jhep.2019.03.033.
14 Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. Gastroenterology. 2023;165(4):1080–8. doi: 10.1053/j.gastro.2023.06.013.
15 Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503–8. doi: 10.1016/j.dld.2009.08.002.
16 Korean Liver Cancer Association KLCA; National Cancer Center NCC, Goyang Korea. 2018 Korean liver cancer association-national cancer center Korea practice guidelines for the management of hepatocellular carcinoma. Korean J Radiol. 2019;20(7):1042–113. doi: 10.3348/kjr.2019.0140.
17 Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. J Hepatol. 2021;75(6):1476–84. doi: 10.1016/j.jhep.2021.08.012.
18 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38. doi: 10.1056/NEJMoa021423.
19 Yang JD, Ahmed F, Mara KC, Addissie BD, Allen AM, Gores GJ, et al. Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease. Hepatology. 2020;71(3):907–16. doi: 10.1002/hep.30858.
20 Norero B, Dufour JF. Should we undertake surveillance for HCC in patients with MAFLD? Ther Adv Endocrinol Metab. 2023;14:20420188231160389. doi: 10.1177/20420188231160389.
21 Borena W, Strohmaier S, Lukanova A, Bjørge T, Lindkvist B, Hallmans G, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. Int J Cancer. 2012;131(1):193–200. doi: 10.1002/ijc.26338.
22 Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology. 2011;54(2):463–71. doi: 10.1002/hep.24397.
23 Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol. 2021;75(6):1284–91. doi: 10.1016/j.jhep.2021.07.035.
24 Nguyen VH, Le MH, Cheung RC, Nguyen MH. Differential clinical characteristics and mortality outcomes in persons with NAFLD and/or MAFLD. Clin Gastroenterol Hepatol. 2021;19(10):2172–81.e6. doi: 10.1016/j.cgh.2021.05.029.
25 Yu JH, Lee HA, Kim SU. Noninvasive imaging biomarkers for liver fibrosis in nonalcoholic fatty liver disease: current and future. Clin Mol Hepatol. 2023;29(Suppl l):S136–49. doi: 10.3350/cmh.2022.0436.
26 Kang SH, Lee HW, Yoo JJ, Cho Y, Kim SU, Lee TH, et al. KASL clinical practice guidelines: management of nonalcoholic fatty liver disease. Clin Mol Hepatol. 2021;27(3):363–401. doi: 10.3350/cmh.2021.0178.
27 Chang Y, Cho YK, Kim Y, Sung E, Ahn J, Jung HS, et al. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: a cohort study. Hepatology. 2019;69(1):64–75. doi: 10.1002/hep.30170.
28 Oh H, Sohn W, Cho YK. The effects of moderate alcohol consumption on non-alcoholic fatty liver disease. Clin Mol Hepatol. 2023;29(Suppl l):S261–7. doi: 10.3350/cmh.2022.0393.
29 Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology. 2018;155(6):1828–37.e2. doi: 10.1053/j.gastro.2018.08.024.
30 Vieira Barbosa J, Milligan S, Frick A, Broestl J, Younossi Z, Afdhal NH, et al. Fibrosis-4 index as an independent predictor of mortality and liver-related outcomes in NAFLD. Hepatol Commun. 2022;6(4):765–79. doi: 10.1002/hep4.1841.
31 Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010;51(6):1972–8. doi: 10.1002/hep.23527.
32 Singal AG, El-Serag HB. Rational HCC screening approaches for patients with NAFLD. J Hepatol. 2022;76(1):195–201. doi: 10.1016/j.jhep.2021.08.028.
33 White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol. 2012;10(12):1342–59.e2. doi: 10.1016/j.cgh.2012.10.001.
34 Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10(6):330–44. doi: 10.1038/nrgastro.2013.41.
35 Margini C, Dufour JF. The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. Liver Int. 2016;36(3):317–24. doi: 10.1111/liv.13031.
36 Rumgay H, Murphy N, Ferrari P, Soerjomataram I. Alcohol and cancer: epidemiology and biological mechanisms. Nutrients. 2021;13(9):3173. doi: 10.3390/nu13093173.
37 Taniai M. Alcohol and hepatocarcinogenesis. Clin Mol Hepatol. 2020;26(4):736–41. doi: 10.3350/cmh.2020.0203.
38 Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, et al. Metabolically-healthy obesity and coronary artery calcification. J Am Coll Cardiol. 2014;63(24):2679–86. doi: 10.1016/j.jacc.2014.03.042.
39 Lin H, Wong GL, Whatling C, Chan AW, Leung HH, Tse CH, et al. Association of genetic variations with NAFLD in lean individuals. Liver Int. 2022;42(1):149–60. doi: 10.1111/liv.15078.