Metabolic dysfunction-associated fatty liver disease and the risk of hepatocellular carcinoma

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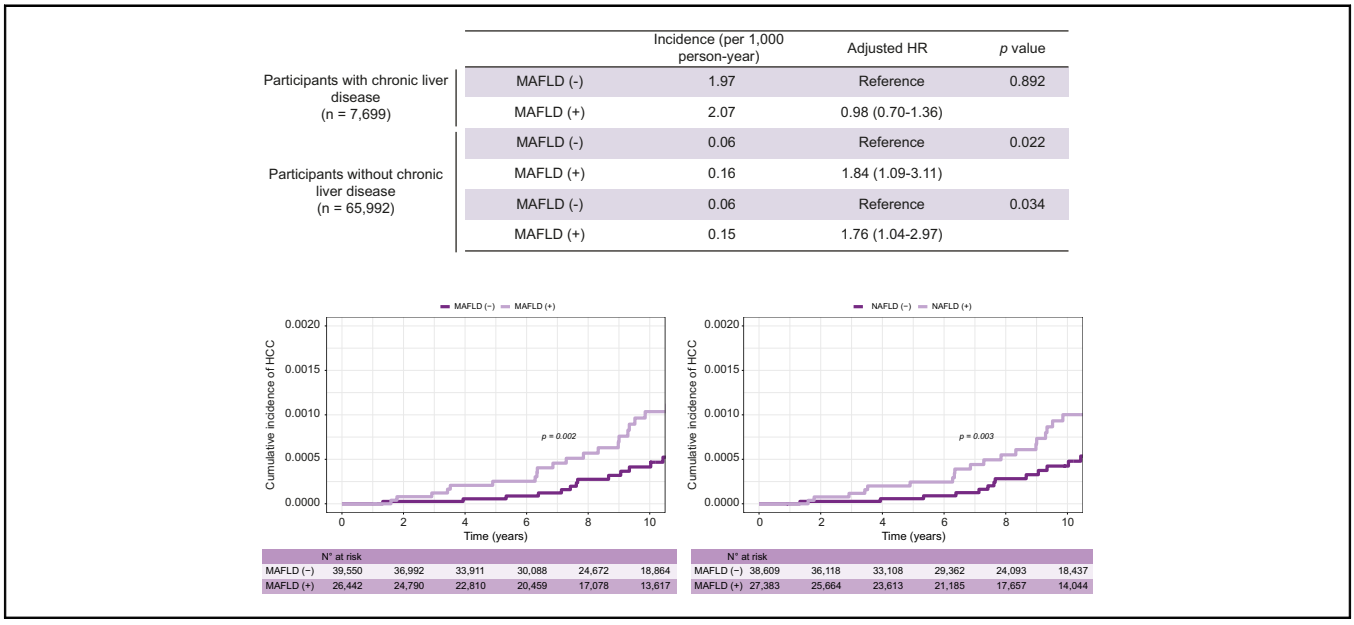
Graphical abstract



Highlights

- In patients with other chronic liver diseases, the presence of MAFLD is not independently associated with an increased risk of HCC.
- For those without other chronic liver diseases, MAFLD largely overlaps with NAFLD.
- Both MAFLD and NAFLD are associated with an increased risk of HCC for individuals without other chronic liver diseases.

Impact and Implications

This study investigated the usefulness of newly proposed nomenclature, metabolic dysfunction-associated fatty liver disease (MAFLD), over non-alcoholic fatty liver disease (NAFLD), in terms of predicting hepatocellular carcinoma. In patients with other chronic liver diseases, the presence of MAFLD is not independently associated with an increased risk of HCC. However, for those without chronic liver disease, MAFLD largely overlaps with NAFLD and is associated with an increased risk of HCC.

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Research article

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Metabolic dysfunction-associated fatty liver disease and the risk of hepatocellular carcinoma

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Background & Aims: The metabolic dysfunction-associated fatty liver disease (MAFLD) is a new inclusive term proposed to replace non-alcoholic fatty liver disease (NAFLD). We analysed whether hepatocellular carcinoma (HCC) risk differs by MAFLD or NAFLD status in a large sample of asymptomatic adults.
Methods: A cohort comprising 73,691 adults were followed up for the development of HCC. NAFLD was diagnosed among participants without other liver diseases (n = 65,992).
Results: Participants with MAFLD showed higher incidence of HCC than those without MAFLD (0.37 and 0.24 per 1,000 person-years, respectively; $p = 0.006$). However, MAFLD was not an independent factor associated with HCC in multivariable adjusted analysis (hazard ratio [HR] 1.21; 95% CI 0.92–1.60). When stratified according to presence of other liver diseases, MAFLD was not associated with HCC in participants with other liver diseases. In participants without other liver diseases, both MAFLD (adjusted HR 1.84; 95% CI 1.09–3.11) and NAFLD (adjusted HR 1.71; 95% CI 1.01–2.90) were independent factors associated with HCC. When stratified according to NAFLD and MAFLD status, there was no HCC development among participants with NAFLD only during 8,936 person-years of follow-up, but this NAFLD-only group comprised 3.4%, and the majority of participants with hepatic steatosis fulfilled both NAFLD and MAFLD criteria.
Conclusions: In patients with other chronic liver diseases, the presence of MAFLD is not independently associated with an increased risk of HCC. For those without other chronic liver diseases, MAFLD largely overlaps with NAFLD and is associated with an increased risk of HCC.
Impact and Implications: This study investigated the usefulness of newly proposed nomenclature, metabolic dysfunction-associated fatty liver disease (MAFLD), over non-alcoholic fatty liver disease (NAFLD), in terms of predicting hepatocellular carcinoma. In patients with other chronic liver diseases, the presence of MAFLD is not independently associated with an increased risk of HCC. However, for those without chronic liver disease, MAFLD largely overlaps with NAFLD and is associated with an increased risk of HCC.

Introduction

A new concept of metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed to replace that of non-alcoholic fatty liver disease (NAFLD).[1,2] The major changes are: including individuals with significant alcohol intake or chronic viral hepatitis in the MAFLD criteria who have been excluded in the NAFLD criteria, and excluding individuals with fatty liver without metabolic abnormality who have been included in the NAFLD criteria.[1,2] The proposed change in nomenclature has brought huge controversies.[2–5] It has been suggested that MAFLD is a more suitable definition for fatty liver disease than NAFLD, although others do not agree.[2–5]

Fatty liver disease is associated with an increased risk of adverse outcomes, including overall mortality, cardiovascular morbidity and mortality, and liver-related morbidity and mortality.[6,7] Hepatocellular carcinoma (HCC) development is a major adverse outcome in patients with fatty liver disease.[8] NAFLD is associated with an increased risk of HCC[9,10] and is the fastest growing cause of HCC.[11,12] Metabolic dysfunction, obesity, and diabetes are risk factors for HCC in NAFLD.[13–19] Concurrent fatty liver in patients with chronic viral hepatitis has been reported to be associated with an increased risk of HCC.[20,21] These studies suggest that MAFLD might be better than NAFLD in stratifying HCC risk, as MAFLD can be diagnosed in individuals with other chronic liver diseases (chronic viral hepatitis and significant alcohol intake), and identify those with metabolic dysfunction among patients with NAFLD who might be at higher risk of HCC compared with those without liver disease. However, to our best

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knowledge, there is no large-size cohort study that assessed the usefulness of the MAFLD criteria in stratifying HCC risk. In this study, we investigated whether the MAFLD criteria can identify those at higher risk of HCC, in a large sample of asymptomatic adults, with and without other chronic liver diseases. In addition, we also assessed whether MAFLD is better than NAFLD in identifying HCC risk among participants without other chronic liver diseases.

Patients and methods

Study population and study design

We conducted a retrospective cohort study of participants aged 19 years or older who underwent a health screening exam, including ultrasonography, at the Samsung Medical Center Health Promotion Center in Seoul, South Korea, from 1 January 2001 to 31 December 2016 (n = 136,213). As our study aimed to analyse the association between MAFLD and the incidence of HCC, we excluded participants with a history of malignancy, including HCC (n = 4,217), to identify participants without malignancy at baseline (n = 131,996). We also excluded participants with HCC development within 6 months (n = 15), participants with less than 6 months of follow-up (n = 12,679), participants with missing variables for HBV and HCV or amount of alcohol intake (n = 39,666), and participants with missing variables required to assess MAFLD status (n = 41,335, which includes missing information regarding BMI, diabetes mellitus [DM], waist circumference, blood pressure, plasma triglycerides, plasma high-density lipid [HDL]-cholesterol, fasting glucose, haemoglobin A_{1c}, the homoeostatic model assessment for insulin resistance (HOMA-IR) score, and plasma high-sensitivity C-reactive protein [hs-CRP]). Because some participants met more than one exclusion criteria, the final analysable sample size was 73,691.

The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the Samsung Medical Center approved this study and waived the requirement for informed consent as we only used de-identified data that were routinely collected during health check-up visits (institutional review board number 2022-08-069).

Data collection and study variables

Demographic characteristics, past medical history, alcohol intake, and smoking status were collected through standardised, self-reported questionnaires. Alcohol intake was categorised into none, moderate, and significant drinking (≥30 g/day in men and ≥20 g/day in women). Smoking status was categorised into none, past, and current. Height, weight, and waist circumference were measured by trained nurses, and the BMI was calculated as weight in kilograms divided by height in meters squared and was classified according to Asian-specific criteria[22] (underweight: BMI <18.5 kg/m^2; normal weight: BMI 18.5–22.9 kg/m^2; overweight: BMI of 23–24.9 kg/m^2; and obese: BMI ≥25 kg/m^2). Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the current use of antihypertensive medications.[23,24] DM was defined as a fasting serum glucose of ≥126 mg/dl or a haemoglobin A_{1c} of ≥6.5%, or a self-reported use of insulin or antidiabetic medications.[25] Blood samples, for the testing of aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, fasting glucose, haemoglobin A_{1c}, triglyceride, HDL-cholesterol, and hs-CRP and insulin, were collected after 8 h of fasting. The fibrosis-4 (FIB-4) score was calculated as follows: age (years) × AST (IU/L)/platelet count (10^9/L) × $\sqrt{}$ALT.

Abdominal ultrasound exams were performed using the LogiQ E9 (GE Healthcare, Milwaukee, WI, USA), the iU22 xMatrix (Philips Medical Systems, Cleveland, OH, USA), or the ACUSON Sequoia 512 machines (Siemens, Issaquah, WA, USA) by experienced radiologists who were unaware of the study aims. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head. An ultrasound diagnosis of fatty liver was made based on standard criteria, which include parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls.[26]

Definitions of exposures and endpoints

The diagnosis of MAFLD was based on the evidence of hepatic steatosis on ultrasonography and meeting one of the following three conditions: (1) BMI ≥23 kg/m^2; (2) DM; and (3) the presence of at least two of the seven metabolic abnormality variables: a waist circumference of ≥90 cm in men or ≥80 cm in women, a blood pressure of ≥130/85 mmHg 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 hyperlipidaemia, prediabetes (fasting glucose of 100–125 mg/dl or a haemoglobin A_{1c} of 5.7 to 6.4%), a HOMA-IR score of ≥2.5, or a plasma hs-CRP of >2 mg/ml.[1] We also defined NAFLD based on the evidence of hepatic steatosis on ultrasonography in the absence of significant alcohol intake (≥30 g/day in men and ≥20 g/day in women) and HBV or HCV infection.[27,28] Participants were categorised into those having HBV, HCV, and/or significant alcohol intake (other chronic liver diseases) or not.

The primary outcome was HCC development during follow-up examinations. The follow-up period was defined as either the time from the initial index health screening visit to the date of the diagnosis of HCC or the last health screening visit that included abdominal ultrasonography (reference date: 31 May 2022), whichever came first. HCC was diagnosed according to regional HCC guidelines.[29]

Statistical analysis

Categorical variables are reported as numbers as a percentage and compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables are reported as median and range or mean ± SD and compared using the Student *t* test or the Mann–Whitney *U* test. Survival curves were calculated using the Kaplan–Meier method. The risk of HCC was compared between participants with and without MAFLD and participants with and without NAFLD, using the log-rank test. Cox proportional hazards models were used to estimate crude and multivariable-adjusted hazard ratios (HRs) with 95% CIs for HCC. In a multivariable-adjusted model, sex (male *vs.* female), FIB-4 (continuous variable), smoking status (none, past, and current), and other chronic liver diseases (yes *vs.* no) were all adjusted. Age was not included in the multivariable-adjusted model because the FIB-4 formula included age. To compare HCC risk between groups, NAFLD was assessed only in participants without other chronic liver diseases (HBV, HCV, or significant alcohol intake). Statistical analysis was performed using R version 4.1.2 software (R Foundation for Statistical Computing,

Table 1. Baseline characteristics.

	No MAFLD (n = 43,715)	MAFLD (n = 29,976)	*p* value
Age, mean ± SD	48.4 ± 10.6	50.7 ± 9.7	<0.001
Sex, male (%)	18,184 (41.6%)	21,277 (71.0%)	<0.001
Chronic liver disease, n (%)			
Significant alcohol intake	1,933 (4.4%)	2,219 (7.4%)	<0.001
HBV	1,957 (4.5%)	1,175 (3.9%)	<0.001
HCV	374 (0.9%)	267 (0.9%)	0.642
Smoking, n (%)			<0.001
None	29,758 (68.1%)	15,037 (50.2%)	
Past	7,373 (16.9%)	7,534 (25.1%)	
Current	6,584 (15.1%)	7,405 (24.7%)	
BMI, n (%)			<0.001
Underweight	2,692 (6.2%)	15 (0.1%)	
Normal	24,653 (56.5%)	2,787 (9.3%)	
Overweight	10,720 (24.6%)	7,818 (26.1%)	
Obese	5,592 (12.8%)	19,348 (64.6%)	
Hypertension, n (%)	6,911 (15.8%)	9,986 (33.3%)	<0.001
Diabetes, n (%)	1,495 (3.4%)	4,764 (15.9%)	<0.001
ALT (IU/ml), median (range)	17.0 (13.0-23.0)	30.0 (22.0-42.0)	<0.001
FIB-4			<0.001
<1.45, n (%)	34,932 (79.9%)	25,038 (83.5%)	
≥1.45, n (%)	8,783 (20.1%)	4,938 (16.5%)	
Liver cirrhosis on ultrasonography	24 (0.05%)	7 (0.02%)	0.062

Levels of significance: p <0.05 (Chi-square test or Fisher's exact test for categorical variables and the Student t test or Mann–Whitney U test for continuous variables).
ALT, alanine aminotransferase; FIB-4, fibrosis-4; MAFLD, metabolic dysfunction-associated fatty liver disease.

Vienna, Austria). A two-tailed p value of <0.05 was statistically significant.

Results

Baseline characteristics of the cohort

Baseline characteristics of the cohort are summarised in Table 1. The baseline characteristics differed significantly between participants with and without MAFLD. Participants with MAFLD were older and predominantly male. Significant alcohol intake, past or current smoking, obesity, hypertension, and diabetes were more common in participants with MAFLD. ALT levels were higher in participants with MAFLD, but those with a high FIB-4 index (≥1.45) were more common in participants without MAFLD. Other chronic liver diseases (HBV, HCV, or significant alcohol intake) were observed in 11.8% of participants with MAFLD and in 9.5% of participants without MAFLD (Fig. 1).

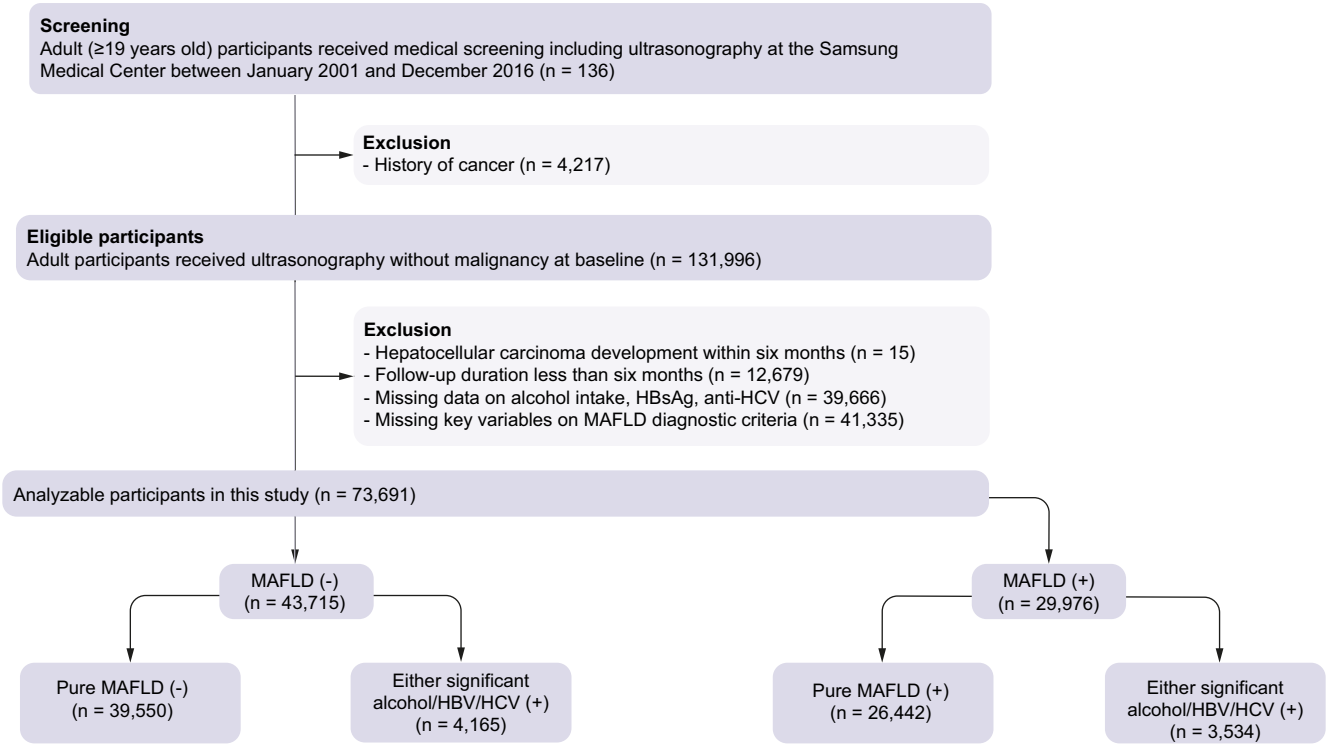

Fig. 1. Patient flow. MAFLD, metabolic dysfunction-associated fatty liver disease.

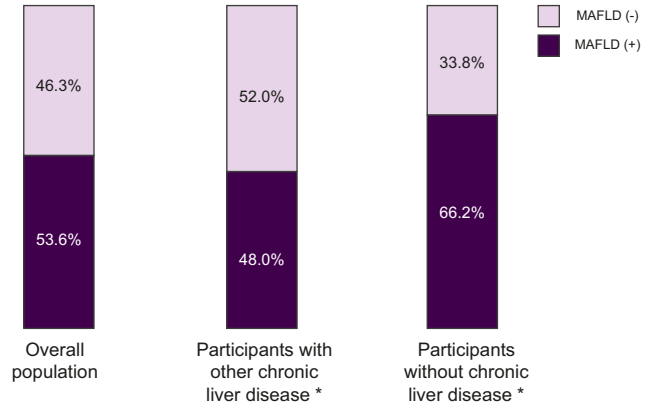

Fig. 2. Proportion of MAFLD among participants who developed HCC in overall participants, and participants with and without other chronic liver diseases. Chronic liver disease: chronic hepatitis B, chronic hepatitis C, or significant amount of alcohol intake. HCC, hepatocellular carcinoma; MAFLD, metabolic dysfunction-associated fatty liver disease.

Risk of HCC by MAFLD

During a median follow-up period of 9.9 years (range 0.5–21.5 years), 220 participants were newly diagnosed with HCC. Among 220 patients with HCC, 53.6% (118 patients) had MAFLD at baseline, whereas 46.4% (102 patients) had no MAFLD at baseline (Fig. 2). The HCC incidence was higher for participants with MAFLD than for those without MAFLD (0.37 and 0.24 per 1,000 person-years, respectively; p = 0.006; Fig. 3A). However, there was an overlap in the HCC incidence curve between the two groups (Fig. 3A), and HCC risk was not different between participants with and without MAFLD in adjusted models (Table 2).

Risk of HCC by MAFLD, stratified by the presence of other chronic liver diseases

The comparisons of baseline characteristics of four groups, stratified by the presence of MAFLD and other chronic liver disease, are shown in Table S1. Participants with other chronic liver diseases had a higher incidence of HCC than those without (2.02 and 0.10 per 1,000 person-years, respectively; p <0.001). Among participants with other chronic liver diseases who

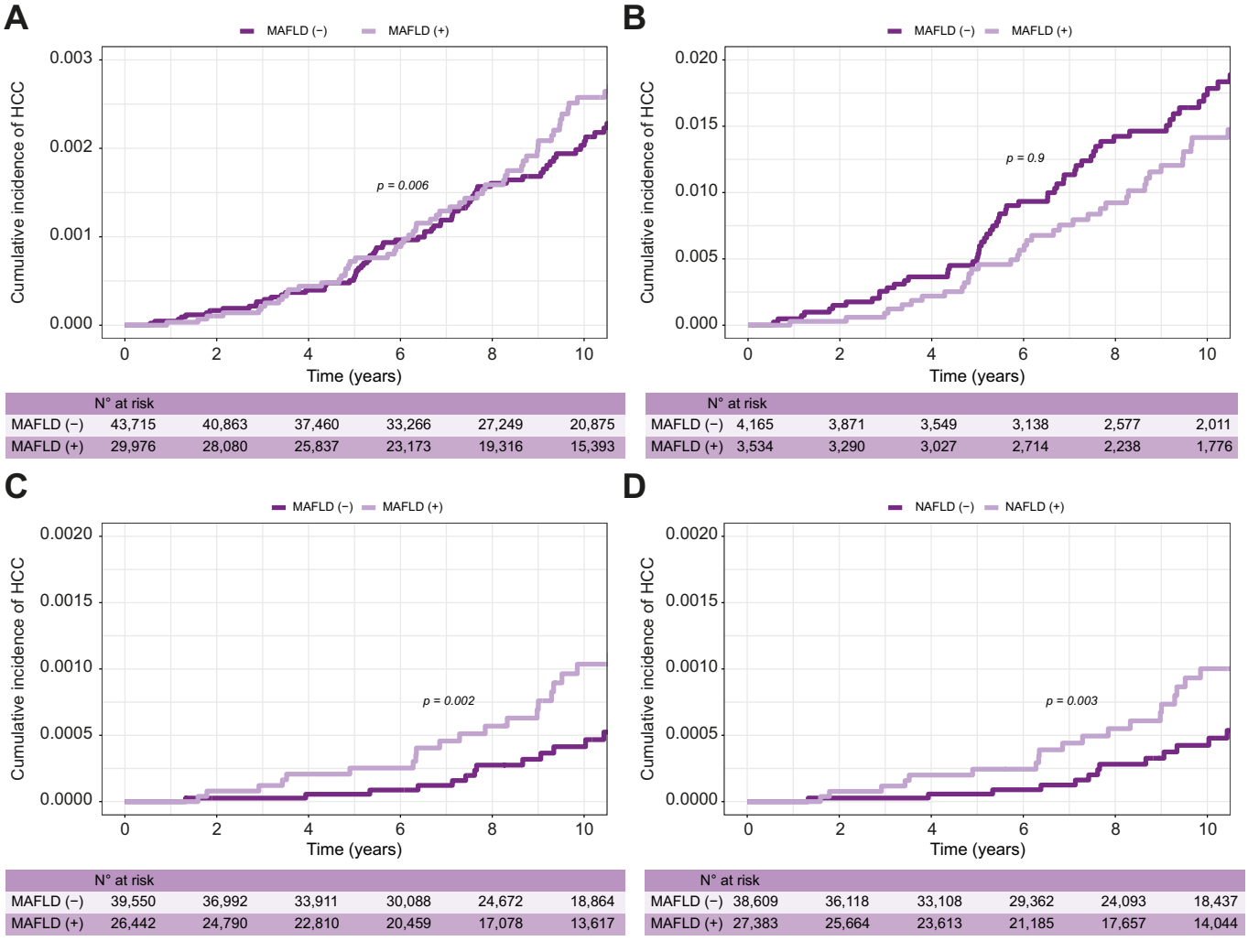

Fig. 3. Cumulative incidence of HCC according to MAFLD or NAFLD. (A) Cumulative incidence of HCC according to MAFLD in the overall cohort (N = 73,691). Level of significance: p = 0.006 (log-rank test). (B) Cumulative incidence of HCC according to MAFLD in participants with other chronic liver diseases (n = 7,699). Level of significance: p = 0.9 (log-rank test). (C) Cumulative incidence of HCC according to MAFLD in participants without other chronic liver diseases (n = 65,992). Level of significance: p = 0.002 (log-rank test). (D) Cumulative incidence of HCC according to NAFLD in participants without other chronic liver diseases (n = 65,992). Level of significance: p = 0.003 (log-rank test). HCC, hepatocellular carcinoma; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

Table 2. Risk of HCC by MAFLD.

	Person-years	No. of HCC	Incidence (per 1,000 person-years)	Crude		Multivariable-adjusted[†]	
				Hazard ratio	*p* value	Hazard ratio	*p* value
Overall population (N = 73,691)							
MAFLD (−) (n = 43,715)	433,021	102	0.24	Reference	0.006	Reference	0.179
MAFLD (+) (n = 29,976)	315,349	118	0.37	1.45 (1.11–1.90)		1.21 (0.92–1.60)	
Participants with other chronic liver diseases[*] (n = 7,699)							
MAFLD (−) (n = 4,165)	40,160	79	1.97	Reference	0.901	Reference	0.892
MAFLD (+) (n = 3,534)	35,242	73	2.07	1.02 (0.74–1.40)		0.98 (0.70–1.36)	
Participants without other chronic liver diseases[*] (n = 65,992)							
MAFLD (−) (n = 39,550)	384,096	22	0.06	Reference	0.002	Reference	0.022
MAFLD (+) (n = 26,442)	275,346	43	0.16	2.27 (1.35–3.81)		1.84 (1.09–3.11)	

Levels of significance: p <0.05 (univariable and multivariable Cox proportional hazards model).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; MAFLD, metabolic dysfunction-associated fatty liver disease.
[*] Chronic liver disease: chronic hepatitis B, chronic hepatitis C, or significant alcohol intake.
[†] Adjusted for sex (male and female), FIB-4 (continuous variable), smoking status (never, past, and current), and other chronic liver diseases (yes and no). Age was not used because the FIB-4 formula (*i.e.* Age (years) × AST (IU/L)/platelet count (10^9/L) × √ALT) includes age.

Table 3. Risk of HCC by MAFLD and NAFLD among participants without other chronic liver diseases[*] (n = 65,992).

Group	Person-years	No. of HCC	Incidence (per 1,000 person-years)	Crude		Multivariable-adjusted[†]	
				Hazard ratio	*p* value	Hazard ratio	*p* value
NAFLD (−) (n = 38,609)	375,159	22	0.06	Reference	0.004	Reference	0.034
NAFLD (+) (n = 27,383)	284,282	43	0.15	2.16 (1.29–3.63)		1.76 (1.04–2.97)	
Neither NAFLD nor MAFLD (n = 38,609)	375,159	22	0.06	Reference	0.003	Reference	0.026
NAFLD only (n = 941)	8,936	0	0	n.a.		n.a.	
MAFLD only (n = 0)	0	0	0	n.a.		n.a.	
Both NAFLD and MAFLD (n = 26,442)	275,346	43	0.16	2.22 (1.32–3.73)		1.80 (1.07–3.02)	

Levels of significance: p <0.05 (univariable and multivariable Cox proportional hazards model).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; MAFLD, metabolic dysfunction-associated fatty liver disease; NA, nonapplicable; NAFLD, non-alcoholic fatty liver disease.
[*] Chronic liver disease: chronic hepatitis B, chronic hepatitis C, or significant amount of alcohol intake.
[†] Adjusted for sex (male and female), FIB-4 (continuous variable), and smoking status (never, past, and current). Age was not used because the FIB-4 formula (*i.e.* Age (years) × AST (IU/L)/platelet count (10^9/L) × √ALT) includes age.

developed HCC, 48.0% (73 patients) had MAFLD at the baseline, whereas 52.0% (79 patients) had no MAFLD at baseline (Fig. 2). In this group, the presence of MAFLD did not increase the risk of HCC (Fig. 3B), and HCC risk was not different between participants with and without MAFLD (Table 2). On the contrary, among those without other chronic liver diseases who developed HCC, 66.2% had MAFLD at baseline (Fig. 2). MAFLD was a significant factor for the development of HCC in both unadjusted and adjusted models (Fig. 3C and Table 2). When participants were grouped into single aetiology and dual aetiology with MAFLD, those with dual aetiology had higher risk of HCC than those with single aetiology without MAFLD, regardless of underlying liver disease (Table S2).

Risk of HCC by NAFLD or MAFLD criteria among participants without other chronic liver diseases

Among participants without other chronic liver diseases, 27,383 had NAFLD. The HCC incidence rate was higher for those with NAFLD than for those without NAFLD (Fig. 3D). In addition, the presence of NAFLD was a significant factor for HCC (Table 3). When participants were classified into neither NAFLD nor MAFLD, MAFLD-only, NAFLD-only, and both MAFLD and NAFLD groups, it was found that the NAFLD-only group consisted of 3.4%. In the NAFLD-only group, HCC did not develop during a follow-up period of 8,936 person-years. The incidence of HCC was higher for participants with both MAFLD and NAFLD than for participants with neither NAFLD nor MAFLD (0.16 and 0.06 per 1,000 person-years, respectively; Table 3).

Discussion

In this large cohort study, we found that MAFLD is associated with an increased risk of HCC in participants without other chronic liver diseases (HBV, HCV, or significant alcohol intake). However, MAFLD does not seem to independently increase the HCC risk for those with other chronic liver diseases. When participants without other chronic liver diseases were stratified according to MAFLD and NAFLD criteria, the incidence of HCC was *null* during follow up among participants within the NAFLD-only group. However, the NAFLD-only group comprised only a minority (3.4%), and the majority (96.6%) qualified both NAFLD and MAFLD criteria.

One major difference between MAFLD and NAFLD criteria is including participants with other chronic liver diseases in the MAFLD criteria who were excluded in the NAFLD criteria. In this population (participants with other chronic liver diseases), only MAFLD can be diagnosed. Notably, MAFLD does not seem to independently increase the HCC risk in participants with other chronic liver diseases. Several conflicting results have been reported regarding the impact of hepatic steatosis on HCC risk in participants with other chronic liver diseases. Some studies have reported fatty liver increases HCC risk in patients with chronic HBV infection.[20,21,30] However, other studies have failed to demonstrate such associations.[31,32] A recent study reported that biopsy-proven fatty liver was associated with an increased risk of HCC in patients with chronic hepatitis B; however, this significance disappeared in multivariable analysis.[30] In some studies, fatty liver was significantly associated with a lower HCC

risk,[32,33] which was partly explained by the burn-out of hepatic steatosis during fibrosis progression.[33] Advanced liver fibrosis is a strong risk factor for HCC development,[10,34] and it is well known that steatosis disappears in more advanced cirrhosis.[35] In this study, participants with other chronic liver diseases comprised a heterogeneous population (including viral hepatitis and/or heavy alcohol intake) with different degrees of liver fibrosis. In addition, strong modifying risk factors for HCC (*e.g.* antiviral treatment for viral hepatitis) had not been controlled. Thus, it is plausible that the other concomitant liver disease itself played an important role in terms of HCC occurrence. This may explain why MAFLD was not associated with HCC risk in this cohort, and there is the possibility that MAFLD might be a risk factor for HCC in some subgroup of participants with other chronic liver diseases. Although HCC occurrence was not great enough to draw statistical significance, patients with both chronic liver disease and MAFLD had higher incidence of HCC compared with those with chronic liver disease but without MAFLD, regardless of underlying liver disease. Nevertheless, in general, MAFLD might not be a strong risk factor associated with HCC in participants with other chronic liver diseases. This study finding indicates that there is no added benefit of diagnosing MAFLD in participants with other chronic liver diseases in terms of HCC risk.

The other difference between MAFLD and NAFLD is excluding participants with fatty liver without metabolic abnormality in MAFLD criteria, who have been included in the NAFLD criteria.[1,2] In participants without other chronic liver diseases, in whom both NAFLD and MAFLD could be assessed, both NAFLD and MAFLD were associated with HCC risk. Of note, HCC development was *null* among the NAFLD-only group. This suggest that MAFLD might be better than NAFLD in terms of HCC risk, by excluding those with very low risk of HCC among patients with fatty liver and other chronic liver diseases. As diagnosis of MAFLD requires the presence of obesity, DM, and metabolic abnormalities that play an important role in the development of HCC,[17,36,37] it is reasonable to assume MAFLD might be better to capture those with higher risk of HCC than NAFLD criteria. However, the proportion of participants with NAFLD only (not meeting MAFLD criteria) was very small, and there was substantial overlap, largely the same, between MAFLD and NAFLD, as NAFLD is largely explained by metabolic risk factors. In addition, compared with the NAFLD criteria, the MAFLD criteria are more complex to use and requires additional costs to evaluate HOMA-IR and hs-CRP status to rule in or rule out the presence of metabolic abnormality. Although cost-effectiveness analysis is lacking, simple-to-use NAFLD criteria might be more relevant than MAFLD criteria for participants without other chronic liver diseases in clinical practice.[38,39] This study finding indicates that there can be added benefit of diagnosing MAFLD in participants without other liver diseases, but the benefit seems to be very small and may not be clinically relevant.

The small group of NAFLD only comprises a very small percentage, and there was no HCC incidence in this cohort. This group represents a specific population of which we understand very little in terms of pathophysiology.[40] The so-called 'lean NAFLD' or 'non-obese NAFLD' probably composed most of this group. The HCC risk is reported to be lower in those with non-obese NAFLD than in those with obese NAFLD.[41] Although the number of patients was too small to analyse, the absence of HCC incidence in this cohort in our study is reassuring but needs further confirmation with a larger study. This study has some limitations. We lacked information regarding some important factors that are associated with HCC development, such as HBV DNA levels and any previous antiviral treatment for HBV or HCV infections.[42] Residual confounding may exist. The study design was retrospective, and many participants had to be excluded as they lacked information regarding HOMA-IR or hs-CRP values, which may have acted as selection bias. Advanced fibrosis is a strong risk factor for HCC development, and the gold standard to assess liver fibrosis is through liver biopsy. We evaluated the fibrosis burden by using a FIB-4 index but lacked histological information. Finally, the study participants came from a sample of Korean participants undergoing health check-ups and might not be applicable to the entire population and other ethnic populations. The strength of this study is in the large numbers of fatty liver cases diagnosed by ultrasonography, the long patient follow-up period, and the relevant number of HCC outcomes.

In summary, for patients with dual-aetiology liver disease with MAFLD and other chronic liver diseases, the presence of MAFLD is not independently associated with an increased risk of HCC. However, for those without other chronic liver diseases, MAFLD largely overlaps with NAFLD and is associated with an increased risk of HCC.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HDL, high-density lipid; HOMA-IR, homoeostatic model assessment for insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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

Authors' contributions

Study concept and design: BGS, DHS. Data acquisition: BGS, SCC, MJG, WK, DHS, G-YG, Y-HP, MSC, JHL, SWP. Data analysis and interpretation: BGS, DHS. Manuscript draft: BGS, DHS. Data analysis plan and data management: BGS, DHS. Critical revision of manuscript: BGS, MJG, WK, DHS, G-YG, Y-HP, MSC, JHL, SWP. Overall study supervision: DHS. Participated in the preparation of the manuscript and have seen and approved the final version: all authors.

Data availability statement

Data are available upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100810.

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Author names in bold designate shared co-first authorship.

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