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Original Article

Fibrotic Burden in the Liver Differs Across Metabolic Dysfunction-Associated Fatty Liver Disease Subtypes

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Background/Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is categorized into three subtypes: overweight/obese (OW), lean/normal weight with metabolic abnormalities, and diabetes mellitus (DM). We investigated whether fibrotic burden in liver differs across subtypes of MAFLD patients.

Methods: This cross-sectional multicenter study was done in cohorts of subjects who underwent a comprehensive medical health checkup between January 2014 and December 2020. A total of 42,651 patients with ultrasound-diagnosed fatty liver were included. Patients were classified as no MAFLD, OW-MAFLD, lean-MAFLD, and DM-MAFLD. Advanced liver fibrosis was defined based on the nonalcoholic fatty liver disease fibrosis score (NFS) or fibrosis-4 (FIB-4) index.

Results: The mean age of the patients was 50.0 years, and 74.1% were male. The proportion of patients with NFS-defined advanced liver fibrosis was the highest in DM-MAFLD (6.6%), followed by OW-MAFLD (2.0%), lean-MAFLD (1.3%), and no MAFLD (0.2%). The proportion of patients with FIB-4-defined advanced liver fibrosis was the highest in DM-MAFLD (8.6%), followed by lean-MAFLD (3.9%), OW-MAFLD (3.0%), and no MAFLD (2.0%). With the no MAFLD group as reference, the adjusted odds ratios (95% confidence intervals) for NFS-defined advanced liver fibrosis were 4.46 (2.09 to 9.51), 2.81 (1.12 to 6.39), and 9.52 (4.46 to 20.36) in OW-MAFLD, lean-MAFLD, and DM-MAFLD, respectively, and the adjusted odds ratios for FIB-4-defined advanced liver fibrosis were 1.03 (0.78 to 1.36), 1.14 (0.82 to 1.57), and 1.97 (1.48 to 2.62) in OW-MAFLD, lean-MAFLD, and DM-MAFLD.

Conclusions: Fibrotic burden in the liver differs across MAFLD subtypes. Optimized surveillance strategies and therapeutic options might be needed for different MAFLD subtypes. **(Gut Liver 2023;17:610-619)**

Key Words: Metabolic dysfunction-associated fatty liver disease; Non-alcoholic fatty liver disease; Liver fibrosis; Subtype

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease affecting 25% of the global population.[1-3] Unhealthy lifestyle practices such as excess calorie intake, sedentary behavior, and low levels of physical activity have led to a rapid increase in the prevalence of NAFLD, which is a major burden on healthcare outcomes.[4,5] Despite such a rapid increase in its prevalence, there is no approved specific therapy for NAFLD. NAFLD has exclusion criteria such as significant alcohol use and other liver diseases, but its coexisting diseases and primary drivers are heterogeneous, which may hinder the discovery of an effective treatment.[6,7]

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a recently proposed new diagnosis by an in-

ternational expert panel, and it is defined from "positive criteria" for the presence of metabolic abnormalities in fatty liver disease (FLD), regardless of the causes.[8] While NAFLD may include "metabolically healthy" patients, MAFLD only includes patients with metabolic dysfunction such as overweight, diabetes mellitus (DM), or metabolic syndrome. Therefore, MAFLD may better reflect the nature of diseases associated with metabolic abnormalities. It has already been shown that high-risk populations are better predicted by "MAFLD" than by "NAFLD."[7,9-12]

Liver fibrosis is one of the most important risk factors in patients with chronic liver disease.[13,14] In patients with NAFLD, the presence of advanced liver fibrosis is a powerful predictor of liver-related complications, such as decompensation or hepatocellular carcinoma (HCC), and is also associated with cardiovascular disease (CVD)-the leading cause of death in NAFLD.[15-18] Several studies have reported that advanced liver fibrosis occurs more commonly in MAFLD than in NAFLD.[9,11] In addition, a recent study showed that advanced liver fibrosis increases CVD risk in patients with MAFLD.[19] Although MAFLD is a concept proposed with the expectation that it may have homogeneity by sharing the characteristic of metabolic dysfunction, it has three subtypes: overweight/obese (OW), lean/normal weight, and DM.[8] However, differences in fibrotic burden among MAFLD subtypes are not well known, and these differences may have potentially different prognostic values across MAFLD subtypes.

Thus, in this study, we investigated whether fibrotic burden in liver differs across MAFLD subtypes.

MATERIALS AND METHODS

1. Study population

This cross-sectional study was based on cohorts from three academic institutions in South Korea, including Severance Hospital, Ewha Womans University Seoul and Mokdong Hospitals, and Ajou University Hospital. Data from subjects who underwent comprehensive medical health checkups, from January 2014 to December 2020, were used (Fig. 1, Supplementary Table 1). Among the 58,727 patients with ultrasound-diagnosed FLD, patients were excluded based on the following criteria: (1) insufficient laboratory test results regarding aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and platelet count; (2) insufficient anthropometric measurements, including body mass index (BMI) and waist circumference; and (3) age <19 years. Finally, 42,651 patients were included in the study.

The study protocol was performed in accordance with the principles of the Declaration of Helsinki, and this study was approved by the Institutional Review Boards of Yonsei University Health System, Seoul, Korea (IRB number: 4-2021-0165), Ewha Womans University Medical Center, Seoul, Korea (IRB number: 2021-09-024), and Ajou University Hospital, Suwon, Korea (IRB number: AJIRB-MED-MDB-21-616). As the current study had a retrospective design, the requirement for written informed consent was waived.

2. Definition of MAFLD

Definitions of metabolic dysfunction and MAFLD are described in Supplementary Table 2. Abdominal ultraso-

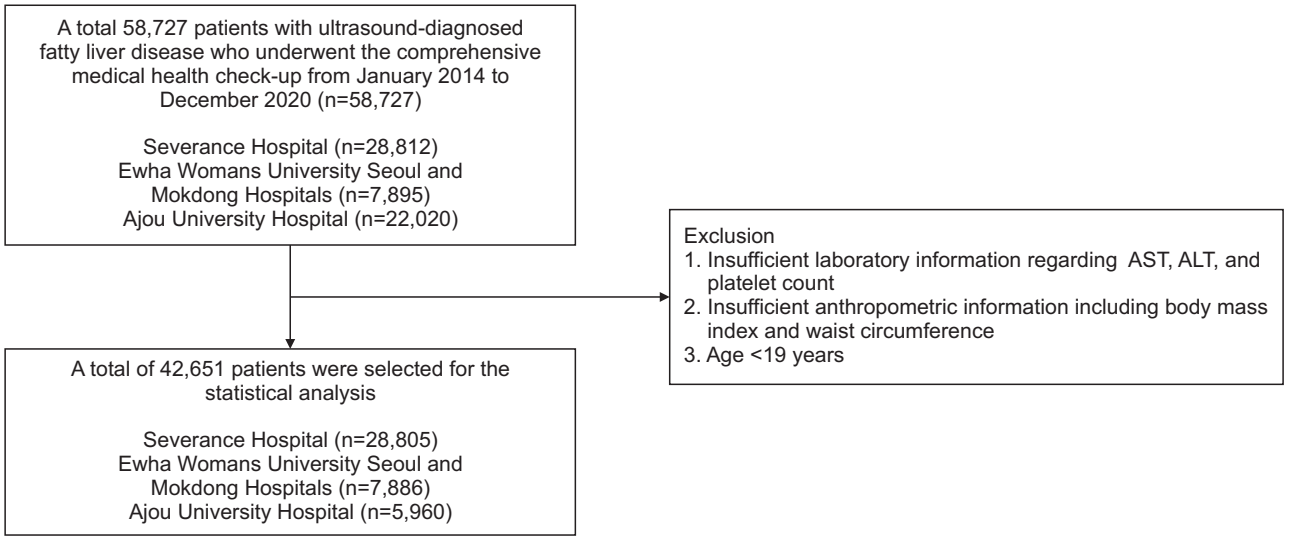

Fig. 1. Flowchart displaying the selection process for the study participants.
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

nography was performed by experienced radiologists. Hepatic steatosis was defined by liver-to-kidney contrast, parenchymal brightness, deep beam attenuation, and bright vessel walls on ultrasonography scans.[20]

MAFLD was defined as the presence of ultrasound-based hepatic steatosis, with the patient displaying one or more of the following criteria: (1) being OW (BMI ≥23 kg/m^2); (2) presence of more than two metabolic risk abnormalities despite normal weight (BMI <23 kg/m^2); and (3) DM. From these criteria, four subtypes were defined: (1) FLD without MAFLD ("no MAFLD"); (2) OW-MAFLD without DM ("OW-MAFLD"); (3) lean/normal-weight MAFLD with more than two metabolic risk abnormalities but without DM ("lean-MAFLD"); and (4) MAFLD with DM ("DM-MAFLD").

3. Assessment of fibrotic burden in liver

Fibrotic burden in liver was assessed using the NAFLD fibrosis score (NFS) and fibrosis-4 (FIB-4) index (Supplementary Table 2). According to a previous study, the cutoff value for advanced liver fibrosis using NFS was >0.676 in patients <65 years of age and >0.12 in patients ≥65 years of age.[21] The cutoff value for advanced liver fibrosis using FIB-4 was set at >2.67 in patients <65 years of age and >2.0 in patients ≥65 years of age.[21]

4. Definition of co-variates

Co-variates were defined according to the Korean clinical guidelines (Supplementary Table 2). OW was defined as BMI ≥23 kg/m^2.[22] DM was defined as fasting blood glucose level ≥126 mg/dL, hemoglobin A1c (HbA1c) level ≥6.5%, or the use of specific drug treatments.[23] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or the use of specific drug treatments.[24] Dyslipidemia was defined as one or more of the following: (1) total cholesterol level ≥240 mg/dL, (2) triglyceride level ≥200 mg/dL, (3) high-density lipoprotein-cholesterol level <40 mg/dL, and (4) low-density lipoprotein-cholesterol level ≥160 mg/dL, or the use of specific drug treatments.[25]

5. Statistical analysis

Data are presented as mean±standard deviation or number (%). The one-way analysis of variance was performed to compare continuous variables, followed by *post hoc* analyses using the Tukey method. Chi-square tests were performed to compare categorical variables.

Univariate and multivariate logistic regression analyses were performed to determine the risk factors for NFS- or FIB-4-defined advanced liver fibrosis in patients with FLD. Various adjusted models for predicting advanced liver fibrosis were then tested according to MAFLD subtypes, after adjusting for potential confounding factors in an incremental manner. Confounding factors were selected if variables were statistically significant in multivariate logistic regression tests.

The models were as follows: model 1, unadjusted; model 2, age (cutoff: 50 years) and sex; model 3, age (cutoff: 50 years), sex, central obesity, and viral hepatitis; model 4, age (cutoff: 50 years), sex, central obesity, and viral hepatitis, and hypertension.

Three sensitivity analyses were performed. First, using a single cutoff value regardless of age (>0.676 for NFS, >3.25 for FIB-4), the risk of advanced liver fibrosis was evaluated. Second, since a significant number of patients with DM-MAFLD were OW, the risk of advanced liver fibrosis in non-obese DM was reassessed to evaluate the effect of DM on fibrotic burden. Patients with non-obese DM-MAFLD was defined as MAFLD with DM and BMI <23 kg/m^2. Third, advanced liver fibrosis was evaluated by the FibroScan-AST (FAST) score in 5,017 patients who underwent transient elastography. FAST score was calculated according to a previous study (Supplementary Table 2).[26]

A $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

Baseline characteristics of the participants are presented in Table 1. The study included 42,651 patients with FLD (mean age 50 years; 74.1% male). Among those with FLD, the number of patients with no MAFLD, OW-MAFLD, lean-MAFLD, and DM-MAFLD were 3,037 (7.1%), 30,078 (70.5%), 2,631 (6.0%), and 6,905 (16.2%), respectively.

Patients with no MAFLD were more likely to: be younger; be female; have lower BMI and waist circumference; have lower blood pressure; present with hypertension, dyslipidemia, and central obesity, less frequently; present with lower levels of AST, ALT, gamma-glutamyl transferase, triglyceride, fasting blood glucose, high-sensitivity C-reactive protein, and HbA1c; and have higher levels of high-density lipoprotein-cholesterol than patients with other MAFLD subtypes (all $p<0.05$). Patients with DM-MAFLD were more likely to: be older; present with hypertension and dyslipidemia more frequently; have a lower platelet count; have lower levels of total cholesterol, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol, and have higher levels of AST, ALT, gamma-glutamyl transferase, triglyceride, fasting glucose, high-sensitivity

Table 1. Baseline Characteristics

Variable	All patients (n=42,651)	No MAFLD (n=3,037)	MAFLD (n=39,614)			p-value
			OW-MAFLD (n=30,078)	Lean-MAFLD (n=2,631)	DM-MAFLD (n=6,905)	
Demographic variable						
Age, yr	50.0±10.7	47.4±9.8	48.9±10.6‡	52.6±10.0‡,§	55.4±9.8‡,§,‖	<0.001
Male sex	31,593 (74.1)	1,693 (55.7)	23,219 (77.2)	1,502 (57.1)	5,179 (75.0)	<0.001
Body mass index, kg/m^2	26.0±3.2	21.6±1.1	26.7±2.7‡	22.0±0.9‡,§	26.5±3.4‡,§,‖	<0.001
Overweight or obese*	36,074 (84.6)	0	30,078 (100)	0	5,996 (86.8)	<0.001
Waist circumference, cm	89.0±9.1	77.3±5.7	90.6±8.1‡	79.6±5.4‡,§	90.8±9.4‡,‖	<0.001
Systolic blood pressure, mm Hg	124.2±13.8	114.1±11.6	124.7±13.4‡	123.1±13.9‡,§	127.0±14.4‡,§,‖	<0.001
Diastolic blood pressure, mm Hg	80.4±10.7	72.7±9.0	81.0±10.6‡	79.5±10.7‡,§	81.6±10.5‡,§,‖	<0.001
DM	6,905 (16.2)	0	0	0	6,905 (100)	<0.001
Hypertension	16,239 (38.1)	213 (7.0)	11,149 (37.1)	901 (34.2)	3,976 (57.6)	<0.001
Dyslipidemia	22,708 (53.2)	701 (23.1)	16,039 (53.3)	1,597 (60.7)	4,371 (63.3)	<0.001
Central obesity†	23,669 (55.5)	106 (3.5)	18,843 (62.6)	411 (15.6)	4,309 (62.4)	<0.001
Laboratory variable						
Platelet, 10^9/L	246.2±54.9	247.4±53.9	247.0±54.2	251.6±55.4‡,§	240.1±57.5‡,§,‖	<0.001
Aspartate aminotransferase, IU/L	30.8±17.0	26.0±12.8	30.4±15.3‡	28.5±22.3‡,§	35.5±21.4‡,§,‖	<0.001
Alanine aminotransferase, IU/L	36.6±26.3	25.2±16.0	37.2±26.5‡	28.7±18.8‡,§	42.0±29.5‡,§,‖	<0.001
Albumin, g/dL	4.6±0.3	4.5±0.3	4.6±0.3‡	4.6±0.3	4.6±0.3‡,§,‖	<0.001
Gamma-glutamyl transferase, mg/dL	44.4±50.4	28.0±35.8	43.9±43.1‡	41.3±81.5‡	54.9±65.3‡,§,‖	<0.001
Total cholesterol, mg/dL	201.6±38.6	202.5±33.7	204.8±37.1‡	206.7±37.2‡	184.9±43.4‡,§,‖	<0.001
Triglyceride, mg/dL	155.9±99.7	98.8±43.9	158.1±97.9‡	161.1±91.9‡	169.4±118.0‡,§,‖	<0.001
HDL-cholesterol, mg/dL	49.9±11.3	58.7±13.4	49.4±10.7‡	51.6±12.5‡,§	47.8±10.7‡,§,‖	<0.001
LDL-cholesterol, mg/dL	125.1±34.7	124.2±30.8	128.4±33.6‡	126.8±33.7‡	110.5±37.5‡,§,‖	<0.001
Fasting blood glucose, mg/dL	104.9±22.7	93.0±7.6	98.7±9.2‡	99.9±9.0‡,§	139.2±36.6‡,§,‖	<0.001
hs-CRP, mg/L	1.5±3.8	0.6±1.0	1.6±3.7‡	1.5±3.8‡	1.9±5.0‡,§,‖	<0.001
Hemoglobin A1c, %	5.8±0.8	5.3±0.3	5.5±0.3‡	5.6±0.3‡,§	7.1±1.2‡,§,‖	<0.001
HBsAg positivity	1,088 (2.6)	75 (2.5)	788 (2.6)	65 (2.5)	160 (2.3)	0.524
HCV antibody positivity	133 (0.3)	15 (0.5)	88 (0.3)	5 (0.2)	25 (0.4)	0.144
Fibrosis score						
NFS-defined advanced liver fibrosis	1,109 (2.6)	7 (0.2)	610 (2.0)	33 (1.3)	459 (6.6)	<0.001
FIB-4-defined advanced liver fibrosis	1,670 (3.9)	62 (2.0)	908 (3.0)	103 (3.9)	597 (8.6)	<0.001

Data are presented as mean±SD or number (%).

MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitive C-reactive protein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; FIB-4, fibrosis-4 index.

*Overweight or obese was defined as body mass index ≥23 kg/m^2; †Central obesity was defined as waist circumference ≥90 cm in males and ≥85 cm in females; ‡p<0.05 by *post hoc* analyses when compared to no MAFLD; §p<0.05 by *post hoc* analyses when compared to OW-MAFLD; ‖p<0.05 by *post hoc* analyses when compared to lean-MAFLD.

C-reactive protein, and HbA1c than patients with other MAFLD subtypes (all p<0.05).

The proportion of NFS-defined advanced liver fibrosis was the highest in the DM-MAFLD group (6.6%), followed by the OW-MAFLD (2.0%), lean-MAFLD (1.3%), and no MAFLD (0.2%) groups in descending order (Table 1, Fig. 2A). The proportion of FIB-4-defined advanced liver fibrosis was the highest in DM-MAFLD (8.6%), followed by the lean-MAFLD (3.9%), OW-MAFLD (3.0%), and no MAFLD (2.0%) subtypes in descending order (Table 1, Fig. 2B).

2. Comparison of participants with or without advanced liver fibrosis

A comparison of patients with and without NFS- or FIB-4-defined advanced liver fibrosis is presented in Table 2. Patients with NFS-defined advanced liver fibrosis were more likely to: be older; be female; have a higher BMI and waist circumference; be overweight or obese; have higher systolic blood pressure; have DM or hypertension; have central obesity; have a lower platelet count; have lower levels of ALT, albumin, total cholesterol, triglyceride, and low-density lipoprotein-cholesterol; and have higher levels of AST, fasting blood glucose, high-sensitivity C-reactive protein, and HbA1c (all p<0.05) than those without. The proportion of NFS-defined advanced liver fibrosis was the highest in OW-MAFLD patients (55.0%), followed by DM-MAFLD (41.4%), lean-MAFLD (2.9%), and no MAFLD patients (0.7%).

Trends in FIB-4-defined advanced liver fibrosis were similar to those of NFS-defined advanced liver fibrosis, except for a few variables. In patients with FIB-4-defined advanced liver fibrosis versus those without, BMI and the

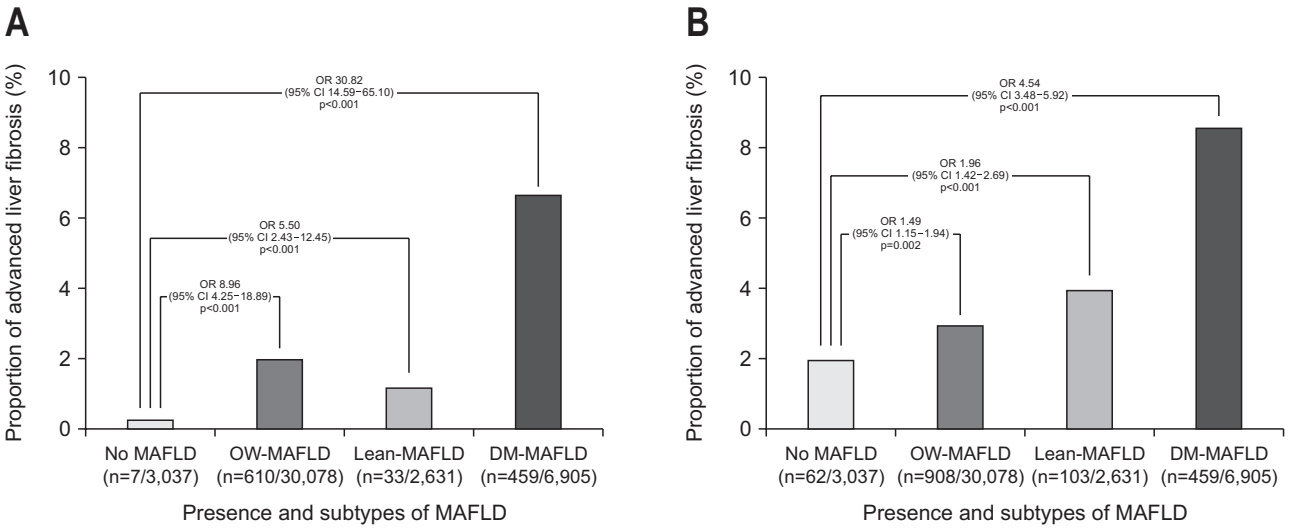

Fig. 2. Proportion of advanced liver fibrosis defined by NFS (A) and FIB-4 (B), according to the presence and subtypes of MAFLD.
OR, odds ratio; CI, confidence interval; NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; FIB-4, fibrosis-4 index; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; DM, diabetes mellitus.

frequency of being overweight or obese were not statistically different (all p>0.05). In addition, patients with FIB-4-defined advanced liver fibrosis had higher ALT and gamma-glutamyl transferase levels and higher frequencies of hepatitis B surface antigen positivity and hepatitis C virus antibody positivity than those without (all p<0.05). When defining advanced liver fibrosis by FIB-4, the proportion of each MAFLD subtype showed a similar trend as when defining by NFS. In patients with FIB-4-defined advanced liver fibrosis, the proportion of patients was highest in the order of OW-MAFLD (54.4%), DM-MAFLD (35.7%), lean-MAFLD (6.2%), and no MAFLD (3.7%).

3. Risk for advanced liver fibrosis according to the presence and subtypes of MAFLD

Unadjusted and adjusted odds ratios (ORs) for NFS- or FIB-4-defined advanced liver fibrosis, according to the presence and subtypes of MAFLD, are described in Table 3 and Fig. 2. In the unadjusted model (model 1), using "no MAFLD" was reference, OR (95% confidence interval [CI]) for NFS-defined advanced liver fibrosis was 8.96 (95% CI, 4.25 to 18.89) in OW-MAFLD, 5.50 (95% CI, 2.43 to 12.45) in lean-MAFLD, 30.82 (95% CI, 14.59 to 65.10) in DM-MAFLD, respectively. Unadjusted OR for FIB-4-defined advanced liver fibrosis were 1.49 (95% CI, 1.15 to 1.94) in OW-MAFLD, 1.96 (95% CI, 1.42 to 2.69) in lean-MAFLD, and 4.54 (95% CI, 3.48 to 5.92) in DM-MAFLD, respectively.

After adjustment for age (cutoff: 50 years old), sex, central obesity, viral hepatitis, and hypertension (model 4), the OR for NFS-defined advanced liver fibrosis were 4.46 (95% CI, 2.09 to 9.51) in OW-MAFLD, 2.81 (95% CI, 1.12 to 6.39) in lean-MAFLD, and 9.52 (95% CI, 4.46 to 20.36) in DM-MAFLD (Table 3). The adjusted OR for FIB-4-defined advanced liver fibrosis were 1.03 (95% CI, 0.78 to 1.36) in OW-MAFLD, 1.14 (95% CI, 0.82 to 1.57) in lean-MAFLD, and 1.97 (95% CI, 1.48 to 2.62) in DM-MAFLD (Table 3). The risk factors for NFS- and FIB-4-defined liver fibrosis are presented in Supplementary Table 3.

4. Sensitivity analyses

First, using a single cutoff value regardless of age, similar results were maintained as follows: the adjusted ORs (95% CI) for NFS-defined advanced liver fibrosis were 2.74 (1.11 to 6.75), 2.17 (0.80 to 5.86), and 6.12 (2.47 to 15.14) in OW-MAFLD, lean-MAFLD, and DM-MAFLD, respectively; and the adjusted ORs for FIB-4-defined advanced liver fibrosis were 1.10 (0.81 to 1.49), 1.26 (0.89 to 1.79), and 2.02 (1.48 to 2.76) in OW-MAFLD, lean-MAFLD, and DM-MAFLD, respectively (Supplementary Table 4, Supplementary Fig. 1). Second, non-obese patients from those with DM-MAFLD were analyzed again to determine whether DM-MAFLD had a high risk of advanced liver fibrosis due to DM. Finally, non-obese DM-MAFLD group had the highest risk subtype for advanced liver fibrosis as follows: the adjusted ORs (95% CI) for NFS-defined advanced liver fibrosis were 4.92 (2.29 to 10.54), 2.85 (1.25 to 6.48), and 5.58 (2.42 to 12.90) in OW-MAFLD, lean-MAFLD, and non-obese DM-MAFLD, respectively; and the adjusted ORs (95% CI) for FIB-4-defined advanced liver fibrosis were 1.05 (0.79 to 1.40), 1.11 (0.80 to 1.54), and 1.97 (1.39 to 2.80) in OW-MAFLD, lean-MAFLD, and non-obese DM-MAFLD, respectively (Supplementary Table 5, Supplementary Fig. 2). Third, advanced liver fibrosis defined by FAST score showed a similar trend to NFS-

Table 2. Comparison between Patients with and without NFS- or FIB-4-Defined Advanced Liver Fibrosis

Variable	Without NFS-defined advanced liver fibrosis (n=41,542)	With NFS-defined advanced liver fibrosis (n=1,109)	p-value	Without FIB-4-defined advanced liver fibrosis (n=40,981)	With FIB-4-defined advanced liver fibrosis (n=1,670)	p-value
Demographic variable						
Age, yr	49.6±10.2	69.3±7.8	<0.001	49.4±10.1	67.5±8.8	<0.001
Male sex	30,899 (74.4)	694 (62.6)	<0.001	10,496 (74.4)	1,097 (65.7)	<0.001
Body mass index, kg/m^2	25.9±3.1	27.3±3.7	<0.001	26.0±3.2	25.9±3.1	0.206
Overweight or obese*	35,033 (84.3)	1,041 (93.9)	<0.001	34,647 (84.5)	1,427 (85.4)	0.315
Waist circumference, cm	88.9±9.0	92.9±9.9	<0.001	89.0±9.1	89.6±9.0	0.003
Systolic blood pressure, mm Hg	124.1±13.7	130.5±15.0	<0.001	124.0±13.7	129.0±15.2	<0.001
Diastolic blood pressure, mm Hg	80.4±10.8	78.9±10.3	<0.001	80.4±10.7	79.1±10.7	<0.001
DM	6,446 (15.5)	459 (41.4)	<0.001	6,308 (15.4)	597 (35.7)	<0.001
Hypertension	15,544 (37.4)	695 (62.7)	<0.001	15,263 (37.2)	976 (58.4)	<0.001
Dyslipidemia	22,149 (53.3)	559 (50.4)	0.055	21,852 (53.3)	856 (51.3)	0.097
Central obesity†	22,829 (55.0)	840 (75.7)	<0.001	22,625 (55.2)	1,044 (62.5)	<0.001
Laboratory variable						
Platelet, 10^9/L	248.0±54.1	177.7±40.6	<0.001	248.8±53.7	181.7±42.8	<0.001
Aspartate aminotransferase, IU/L	30.6±16.5	36.4±29.2	<0.001	29.9±13.6	51.9±48.5	<0.001
Alanine aminotransferase, IU/L	36.8±26.5	28.7±19.5	<0.001	36.3±25.3	43.3±43.6	<0.001
Albumin, g/dL	4.6±0.3	4.4±0.3	<0.001	4.6±0.3	4.4±0.3	<0.001
Gamma-glutamyl transferase, mg/dL	44.3±49.5	45.5±86.8	0.646	43.5±45.3	65.3±118.4	<0.001
Total cholesterol, mg/dL	202.3±49.0	175.5±37.4	<0.001	202.5±38.4	179.8±38.8	<0.001
Triglyceride, mg/dL	156.5±100.2	132.0±73.0	<0.001	156.7±100.0	136.4±88.9	<0.001
HDL-cholesterol, mg/dL	49.9±11.3	49.3±11.6	0.088	49.9±11.2	50.3±13.0	0.283
LDL-cholesterol, mg/dL	125.7±34.5	102.4±32.9	<0.001	125.9±34.5	105.8±33.8	<0.001
Fasting blood glucose, mg/dL	104.7±22.5	116.0±27.0	<0.001	104.6±22.4	113.3±28.3	<0.001
hs-CRP, mg/L	1.5±3.9	1.7±3.3	0.230	1.5±3.8	1.6±4.5	0.606
Hemoglobin A1c, %	5.7±0.8	6.2±0.9	<0.001	5.7±0.8	6.1±1.0	<0.001
HBsAg positivity	1,060 (2.6)	28 (2.5)	0.955	1,030 (2.5)	58 (3.5)	0.015
HCV antibody positivity	126 (0.3)	7 (0.6)	0.053	115 (0.3)	18 (1.1)	<0.001
MAFLD subtype			<0.001			<0.001
No MAFLD	3,030 (7.3)	8 (0.7)		2,975 (7.3)	62 (3.7)	
OW-MAFLD	29,468 (70.9)	610 (55.0)		29,170 (71.2)	908 (54.4)	
Lean-MAFLD	2,598 (6.3)	32 (2.9)		2,528 (6.2)	103 (6.2)	
DM-MAFLD	6,446 (15.5)	459 (41.4)		6,308 (15.4)	597 (35.7)	

Data are presented as mean±SD or number (%).

NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; FIB-4, fibrosis-4 index; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitive C-reactive protein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.

*Overweight or obese was defined as body mass index ≥23 kg/m^2; †Central obesity was defined as waist circumference ≥90 cm in males and ≥85 cm in females.

defined advanced liver fibrosis as follows: the adjusted ORs (95% CI) for NFS-defined advanced liver fibrosis were 0.96 (0.45 to 2.04), 1.18 (0.44 to 3.12), and 2.46 (1.14 to 5.31) (Supplementary Tables 2 and 6, Supplementary Fig. 3).

DISCUSSION

In this large cross-sectional multicenter study (n=42,651), we investigated whether fibrotic burden in liver differs across the subtypes of MAFLD, based on cohorts of subjects who underwent a comprehensive medical health checkup. Finally, we found that fibrotic burden in liver differed significantly across MAFLD subtypes. The proportion and risk of NFS-4-defined advanced liver fibrosis were the highest in DM-MAFLD, and this risk decreased in the order of OW-MAFLD, lean-MAFLD, and no MAFLD. The proportion and risk of FIB-4-defined advanced liver fibrosis were the highest in DM-MAFLD, and this risk decreased in the order of lean-MAFLD, OW-MAFLD, and no MAFLD.

Our study has several clinical implications. First, a re-

Table 3. Unadjusted and Adjusted Odds Ratios for NFS- or FIB-4-Defined Advanced Liver Fibrosis According to the Presence and Subtypes of MAFLD

Multivariate analysis	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
NFS-defined advanced liver fibrosis								
No MAFLD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
OW-MAFLD	8.96 (4.25–18.89)	<0.001	8.67 (4.10–18.32)	<0.001	5.07 (2.38–10.79)	<0.001	4.46 (2.09–9.51)	<0.001
Lean-MAFLD	5.50 (2.43–12.45)	<0.001	3.66 (1.61–8.30)	0.002	3.17 (1.40–7.20)	0.006	2.81 (1.12–6.39)	0.014
DM-MAFLD	30.82 (14.59–65.10)	<0.001	19.36 (9.15–40.98)	<0.001	11.54 (5.41–24.60)	<0.001	9.52 (4.46–20.36)	<0.001
FIB-4-defined advanced liver fibrosis								
No MAFLD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
OW-MAFLD	1.49 (1.15–1.94)	0.002	1.38 (1.06–1.79)	0.018	1.17 (0.89–1.53)	0.277	1.03 (0.78–1.36)	0.815
Lean-MAFLD	1.96 (1.42–2.69)	<0.001	1.32 (0.96–1.83)	0.092	1.28 (0.93–1.77)	0.137	1.14 (0.82–1.57)	0.448
DM-MAFLD	4.54 (3.48–5.92)	<0.001	2.76 (2.11–3.62)	<0.001	2.36 (1.78–3.12)	<0.001	1.97 (1.48–2.62)	<0.001

Model 1: unadjusted; Model 2: adjusted by age (cutoff: 50 years of age) and sex; Model 3: adjusted by age (cutoff: 50 years of age), sex, central obesity, and viral hepatitis; Model 4: adjusted by age (cutoff: 50 years of age), sex, central obesity, viral hepatitis, and hypertension.
NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; FIB-4, fibrosis-4 index; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval; OW, overweight/obese; DM, diabetes mellitus.

cent prospective population-based cohort study suggested that patients with high fibrotic burden can be better detected by MAFLD, assessed by transient elastography.[11] In spite of being not confirmative due to the small number of patients with the NAFLD-only group (n=57), no significant fibrosis was observed in patients with NAFLD-only.[11] Similarly, our "no MAFLD" group had the lowest risk for both NFS- and FIB-4-defined advanced liver fibrosis. High fibrotic burden in patients with FLD is a major risk factor for developing HCC and liver-related mortality,[27,28] and other studies have shown that a high fibrotic burden in liver is independently associated with an increased CVD risk in patients with FLD.[16,17,19] Based on these findings, it might be suggested that no MAFLD group with the lowest fibrotic burden in our study might have the lowest risk of HCC, liver-related mortality, and CVD, although additional longitudinal or mechanistic analyses were not performed.

Second, in our study, DM-MAFLD had the highest risk of advanced liver fibrosis. DM is a major risk factor for liver fibrosis in patients with NAFLD.[29] In patients with DM with FLD, excess free fatty acid induced by insulin resistance in adipocytes is associated with inflammation, mitochondrial dysfunction, and increased oxidative stress, which consequently promotes a fibrotic response in hepatic stellate cells.[30] DM is one of the major risk factors for HCC,[31] and is known to increase the risk of liver-related mortality[32] and CVD risk in patients with FLD.[10] A recent study supports our findings, which revealed that DM-MAFLD is also the highest risk subtype for significant liver fibrosis assessed by magnetic resonance elastography.[33] Our study confirmed that fibrotic burden defined by NFS and FIB-4 is significantly higher in DM-MAFLD than in other subtypes, and it suggests that more attention in surveillance and evaluation of liver fibrosis might be required in patients with DM-MAFLD subtype. Our study included overweight or obese patients with DM-MAFLD with reference to other studies on previous MAFLD subtypes.[33,34] Further analysis showed that DM-MAFLD was also the highest risk subtype, except in obese patients.

Third, we compared the differences in fibrotic burden between OW-MAFLD and lean-MAFLD. The risk and proportion of NFS-defined advanced liver fibrosis were higher in OW-MAFLD than in lean-MAFLD, whereas the risk and proportion of FIB-4-defined advanced liver fibrosis were higher in lean-MAFLD than in OW-MAFLD. However, there was no statistical difference in the OR for advanced liver fibrosis defined as both NFS and FIB-4 between these two subtypes. Studies evaluating the characteristics and outcomes of lean and obese NAFLD presented disputable conclusion. In two meta-analyses, non-obese patients with NAFLD showed a more favorable histological profile regarding steatohepatitis and fibrosis stage than did obese patients with NAFLD.[35,36] Other studies showed that lean NAFLD is associated with high CVD risk and CVD-related mortality.[37,38] Another study reported similar event-free survival between non-obese and obese patients with NAFLD.[39] The similar fibrotic burden between OW-MAFLD and lean-MAFLD in our study may be because lean-MAFLD included only "metabolically unhealthy" patients, such as those with central obesity, hypertension, and dyslipidemia. On the other hand, lean patients with NAFLD in the former meta-analyses also included "metabolically healthy" patients, classified as "no MAFLD" in our study, which may be the reason for the favorable histological results in lean compared to obese NAFLD patients.[35,36] A recent study on biopsy-confirmed NAFLD reported that there was no difference in liver-related events and survival between obese and lean NAFLD, despite the

less severe histology in lean patients than obese patients.[40] Another study showed that both lean- and DM-MAFLD have a similar, higher risk for all-cause mortality than OW-MAFLD does.[34] Therefore, combining our study and previous studies, FLD in lean patients is clearly not a benign condition. The presence of metabolic abnormalities in lean subjects with FLD may be a key factor in determining histological characteristics and prognosis.

Fourth, we used well-known scoring tests to define advanced liver fibrosis. Although noninvasive imaging surrogates (such as transient elastography or magnetic resonance elastography) have greater diagnostic accuracy,[41,42] NFS and FIB-4 are simple-to-calculate tools to evaluate advanced liver fibrosis and are readily applied in primary clinics. Accordingly, most guidelines recommend NFS and FIB-4 as one of the first tests to evaluate advanced liver fibrosis in patients with FLD.[43-45] NFS and FIB-4 can also determine whether referral to specialists in primary clinics is needed.[44] A recent study showed that the specificity of FIB-4 or NFS for significant liver fibrosis is unacceptably low in patients aged ≥65 years. In addition, the study also presented new cutoffs (NFS: >0.676 in patients <65 years of age and >0.12 in patients ≥65 years of age, FIB-4: >2.67 in patients <65 years of age and >2.0 in patients ≥65 years of age) which improved specificity without adversely affecting sensitivity in these populations.[21] A review article also supported these new cutoffs according to age.[46] Based on these results, we assessed liver fibrosis using FIB-4 or NFS with two different cutoff values. In our study, the proportion of NFS-defined advanced liver fibrosis was higher in OW-MAFLD than in lean-MAFLD and vice versa for that of FIB-4-defined advanced liver fibrosis. Similar results were shown in sensitivity analyses using a single cutoff value. Although the reason for this discrepancy is unclear, the difference in constituent variables of NFS and FIB-4, such as BMI, might be partly attributable. In addition, as subgroup analysis, FAST-defined advanced liver fibrosis was evaluated in subjects who underwent transient elastography. The FAST score is calculated by combining liver stiffness measurement and controlled attenuation parameter measured by transient elastography and AST levels. In a recent study, the FAST score showed satisfactory performance in identifying advanced liver fibrosis (area under the receiver operating curve, 0.80).[27] In our study, FAST-defined advanced liver fibrosis showed a similar trend to NFS-defined advanced liver fibrosis.

Although the findings of our study might provide the necessity in establishing different surveillance or interventional strategy according to MAFLD subtypes, our study also has several limitations. First, we did not include liver biopsy data. Various noninvasive tests to assess liver fibrosis have been developed, but liver biopsy is still the "gold standard" method.[47] Second, although we included consecutive patients with FLD who received comprehensive medical health checkup, there may be selection bias: only subjects who could afford to pay for health checkups might have been included in our study. Third, we did not evaluate alcohol consumption owing to data insufficiency. Although MAFLD can be diagnosed as "positive criteria" related to metabolic dysfunction without alcohol history, alcohol might have affected fibrotic burden in our study, which might be further assessed in following future studies. Lastly, owing to the absence of data on insulin levels, metabolic abnormalities were defined with the remaining factors.

In conclusion, fibrotic burden in liver differs across MAFLD subtypes. Optimized surveillance strategies and therapeutic options might be needed for different MAFLD subtypes.

CONFLICTS OF INTEREST

S.U.K. has served as an advisory committee member Gilead Sciences, GSK, Bayer, and Eisai. He is a speaker for Gilead Sciences, GSK, Bayer, Eisai, Abbvie, Echosens, MSD, and Bristol-Myers Squibb. He has also received a research grant from Abbvie, Bristol-Myers Squibb. The other authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

Study conception and design: S.U.K., J.Y.C. Data acquisition: H.S.C., S.S.K., J.K.K., M.L., H.J.C., S.U.K., J.Y.C. Data analysis and interpretation: T.S.L., H.S.C., S.S.K., J.K.K., M.L., H.J.C., S.U.K., J.Y.C. Drafting the manuscript: T.S.L., H.S.C. Critical revision of the manuscript for important intellectual content: T.S.L, H.S.C., S.U.K., J.Y.C. Statistical analysis: T.S.L., H.S.C. Obtained funding: J.Y.C. Administrative, technical, or material support; study supervision: S.U.K., J.Y.C. Approval of final manuscript: all authors. S.U.K., J.Y.C. are the guarantors, and as such, had full ac-

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SUPPLEMENTARY MATERIALS

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