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ORIGINAL ARTICLE

Impact of metabolic factors on risk of cardiovascular disease in nondiabetic metabolic dysfunction-associated fatty liver disease

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Abstract

Background and aim Changing terminology of non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD) is recently proposed by expert panels based on metabolic dysregulations. However, clinical evidences for the risk of cardiovascular disease (CVD) in MAFLD are limited. The aim of this study is evaluating the association of cardiovascular risk in these two terminology and subgroups of MAFLD.

Methods A total of 2133 individuals who underwent ultrasound and cardiac computed tomography contemporaneously were included at a single medical checkup center. Ultrasound was used to define fatty liver, and coronary artery calcification (CAC) defined a coronary artery calcium score above 0 was used to estimate the cardiovascular risk.

Results Overall, 911 participants were diagnosed with fatty liver. In the unadjusted analysis, NAFLD (OR = 1.4, 95% confidence interval [CI] = 1.05–1.85, $p = 0.019$) and MAFLD (OR = 1.55, 95% CI = 1.29–1.86, $p = 0.046$) were significantly associated with CAC. However, in sex and age-adjusted analyses, only MAFLD was associated with CAC (adjusted OR [aOR] = 1.38, 95% CI = 1.14–1.69, $p = 0.001$). Of the three subgroups of MAFLD (diabetic, nondiabetic overweight/obese, and nondiabetic normal weight/lean with at least two metabolic abnormalities), only diabetic MAFLD was associated with CAC (aOR = 2.65, 95% CI = 1.98–3.55, $p < 0.001$). When the minimal number of metabolic risk abnormalities increased to three, nondiabetic normal-weight/lean MAFLD was associated with CAC (aOR = 1.35, 95% CI = 1.02–1.77, $p = 0.034$).

Conclusion Diabetic MAFLD predicted high-risk CVD phenotypes the best. Metabolic risk abnormalities in nondiabetic MAFLD patients were independently associated with the risk of CVD. The proposed diagnostic criteria for nondiabetic MAFLD need further investigation in terms of CVD risk.

Keywords Metabolic abnormalities · Diabetes · Body mass index · Coronary artery calcification

Abbreviations

ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Serum aspartate aminotransferase
CAC	Coronary artery calcification
CVD	Cardiovascular disease
FIB-4	Fibrosis-4
FPG	Fasting plasma glucose
HDL-C	High-density lipoprotein cholesterol
hsCRP	High-sensitivity C reactive protein

Min Kyu Kang and Yu Rim Lee contributed equally to this study. Jung Gil Park and Soo Young Park are co-corresponding authors in this study.

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MAFLD	Metabolic dysfunction-associated fatty liver disease
NAFLD	Non-alcoholic fatty liver disease
NFS	NAFLD fibrosis score
T2DM	Type 2 diabetes mellitus
WC	Waist circumference

Introduction

Non-alcoholic fatty liver disease (NAFLD), characterized by ≥ 5% hepatic fat accumulation with no evidence of secondary causes of hepatic steatosis, manifests as simple steatosis, steatohepatitis, liver fibrosis, and cirrhosis [1]. Furthermore, it has been closely associated with metabolic dysfunction including type 2 diabetes mellitus (T2DM), dyslipidemia, and obesity, which can result in the development of liver fibrosis, cardiovascular disease (CVD), and increased liver-related and cardiovascular mortality [2–4].

In 2020, a panel of international experts proposed a new definition called metabolic dysfunction-associated fatty liver disease (MAFLD), which includes causes of chronic liver disease, such as viruses and excessive alcohol intake [5]. The definition of MAFLD is based on the presence of hepatic steatosis as a prerequisite and one of the following three features, including: (1) T2DM, (2) overweight or obesity, or (3) lean or normal weight with at least two metabolic risk abnormalities [5]. Based on the new nomenclature of MAFLD, comparative studies on clinical implication with NAFLD have been active recently [6]. In several studies, patients with MAFLD were more likely to have metabolic comorbidities, fibrosis progression, and incident cardiovascular disease risk analyzed using the traditional risk-scoring models [7–10].

Coronary artery calcium scoring with computed tomography (CT) is a noninvasive, reliable marker of coronary atherosclerotic burden [11]. The association between coronary artery calcification (CAC) and the risk of CVD has been well evaluated in the general population as well as in patients with NAFLD [12]. Additionally, the progression of coronary artery calcium scores was also associated with worsening coronary atherosclerosis, which predicts future CVD events, including myocardial infarction, ischemic stroke, and/or cardiovascular mortality, even in patients with NAFLD [13, 14]. However, little is known about the association between CAC and MAFLD.

This study aimed to investigate the association of the risk of CVD estimated by CAC with NAFLD and MAFLD. Furthermore, the association of CVD risk was investigated according to the three subgroups of MAFLD.

Patients and methods

Patients

This cross-sectional, retrospective study included individuals who underwent a medical checkup, including abdominal ultrasound and cardiac CT, from January 2017 to December 2021 at a health center in South Korea. The exclusion criterion was documented history of significant CVD, such as acute coronary syndrome, stable angina, history of angioplasty or stent placement, cerebrovascular disease, and peripheral vascular disease. However, no patient had significant CVD, because all relatively healthy individuals underwent medical checkups.

Data collection

We obtained medical records, including demographic variables, anthropometric measurements, laboratory findings, abdominal ultrasound, and coronary calcium scan at the time of the medical checkup. Variables, such as age, sex, comorbidities, history of alcohol, smoking, and medication use, were obtained based on self-reporting and direct interviews using standardized health questionnaires. Anthropometric assessments, including height, weight, waist circumference (WC), and blood pressure, were performed and recorded by trained nurses. Overweight and obesity were defined as a body mass index (BMI) ≥ 23 kg/m^2 and ≥ 25 kg/m^2 based on the Asia–Pacific region criteria, respectively [15]. Hypertension and T2DM were defined as current guideline [16, 17]. Metabolic syndrome was defined as the presence of three or more of the following factors by proposed criteria [18].

Blood biochemical tests and abdominal ultrasound were performed after overnight fasting. The patients' liver profiles, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and albumin levels; lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and TG levels; and platelet count, FPG, and HbA1c levels were measured.

The AST to platelet ratio index (APRI), fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and noninvasive fibrosis score were calculated according to previous publications, and low cut-off values of APRI ≥ 0.5, FIB-4 ≥ 1.3, and NFS ≥ -1.455 were used for dichotomous analysis[19, 20].

Diagnosis of NAFLD and MAFLD

The fatty liver was evaluated by experienced radiologists using abdominal ultrasonography based on the standard criteria [21]. A diagnosis of NAFLD was made by the clinical practice guidelines of European Association for the Study of Liver Diseases and American Association for the Study of Liver Diseases for the Management of NAFLD [22, 23]. A diagnosis of MAFLD was based on the criteria proposed by an international expert panel [5]. The criteria include evidence of fatty liver on ultrasonography in addition to one of the following three criteria: overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation. Metabolic dysregulation was defined as the presence of at least two metabolic risk abnormalities defined by an international expert panel (supplementary file 1) [5]. BMI and WC were determined using cut-off values for Asians, as all patients were Asian. Although the homeostasis model assessment of insulin resistance score ≥ 2.5 is one of the metabolic risk abnormalities, it was excluded in our study, because values of fasting insulin were unavailable.

Cardiac computed tomography for CAC

Non-contrast cardiac prospective electrocardiogram-triggered volumetric CT was performed using a 320-slice CT scanner (SOMATOM Force, Siemens Healthineers). At the end of inspiration, the patients held their breath as the scan ranged from the base of the heart to the carina; the field of view was 220 mm, whereas the scan collimation was 320×0.75 mm. As determined by the CARE Dose4D scanner software, a tube current ranging from 288 mA to 100–120 kVp was administered. The rotation time was 0.25 s. Using five filter revolutions, 3-mm-thick reconstruction slices were obtained. The Agatston scoring method, previously described by a fellowship-trained cardiac radiologist using independent post-processing software (*Syngo*.via, Siemens Healthineers), was used to quantify the coronary artery calcium scores. The presence of CAC was defined as a coronary artery calcium score > 0.

Statistical analysis

Data are presented as median with interquartile range (IQR) or number (%), as appropriate. No imputation was conducted for the missing data. Categorical variables were compared using the Chi-square test (or Fisher's exact test), whereas the Student's *t* test (or Mann–Whitney *U* test) after Shapiro–Wilk normality testing was used to compare continuous variables. Factors associated with CAC were identified using logistic regression analysis with stepwise backward elimination. Odds ratios (OR) and 95% confidence intervals (CI) were also calculated. A probability value of two-tailed $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the R software (version 3.0, http://cran.r-project.org/,install.packages("devtools')). Logistic regression model-based plotting for the probability of CAC presence was generated using ggplot2.

Results

Baseline characteristics

A total of 2133 individuals who underwent cardiac CT for coronary artery calcium and ultrasonography were included in this study. All cardiac CT and ultrasound examinations were performed on the same day. The median age and body mass index were 58 years and 22.0 kg/m^2, respectively. Overall, 911 (42.7%) individuals had fatty liver disease, and 794 (37.2%) had CAC with a median coronary artery calcium score of 46.4 [9.5–164.5]. The baseline characteristics of patients with and without fatty liver are shown in Table 1. Compared to individuals without fatty liver, those with fatty liver were predominantly male and more likely to have hypertension, T2DM, metabolic syndrome, and higher metabolic abnormality counts. Positivity of anti-HCV was not different with individuals with fatty liver and those without. The positivity of HBsAg is higher in individuals without fatty liver compared to those with it. However, ALT and FIB-4 is higher in those had HBsAg but not fatty liver compared to those had HBsAg and fatty liver (supplementary file 2).

Association of CAC with NAFLD and MAFLD

Prevalence of CAC in patients with NAFLD and MAFLD were 40.6% and 43.6%, respectively (Fig. 1a). The association between CAC and the type of fatty liver disease is shown in Table 2. In the unadjusted analysis, NAFLD (OR = 1.4, 95% CI = 1.05–1.85) and MAFLD (OR = 1.55, 95% CI = 1.29–1.86) were significantly associated with CAC. However, fatty liver without MAFLD was not associated with CAC. In sex- and age-adjusted analyses, only MAFLD was independently associated with CAC (adjusted OR [aOR] = 1.38, 95% CI = 1.14–1.69, $p = 0.001$).

Association of CAC with the metabolic subgroups of MAFLD

The baseline characteristics of MAFLD subgroups are shown in Table 3. Each subgroup had different clinical characteristics and values in the noninvasive fibrosis test. Of these, diabetic MAFLD had higher coronary artery calcium and noninvasive fibrosis test scores. Prevalence of CAC in patients with diabetic MAFLD was 57.0% (Fig. 1a). Though prevalence of CAC in patients with

Table 1 Baseline characteristics of entire study population

	Control ($N=1222$)	Fatty liver ($N=911$)	p Value
Male	698 (57.1%)	673 (73.9%)	< 0.001
Age, years	58.0 [51.0–63.0]	58.0 [51.0–64.0]	0.234
SBP, mmHg	123.0 [112.0–134.0]	129.0 [120.0–140.0]	< 0.001
DBP, mmHg	74.0 [67.0–82.0]	79.0 [72.0–86.0]	< 0.001
Coronary artery calcium score	0.0 [0.0–8.1]	0.0 [0.0–37.2]	< 0.001
Presence of CAC	407 (33.3%)	387 (42.5%)	< 0.001
BMI, kg/m^2	22.0 [21.0–22.0]	22.0 [22.0–22.0]	< 0.001
Use of hypertensive drug	82 (6.7%)	132 (14.5%)	< 0.001
T2DM	150 (12.3%)	221 (24.3%)	< 0.001
Smoking	255 (45.2%)	271 (58.9%)	< 0.001
Total cholesterol, mg/dL	187.0 [164.0–211.5]	196.0 [166.5–222.0]	< 0.001
HDL, mg/dL	58.0 [49.0–70.0]	51.0 [43.0–60.0]	< 0.001
LDL, mg/dL	126.0 [103.0–150.0]	134.0 [106.0–160.5]	< 0.001
Triglycerides, mg/dL	91.0 [63.0–125.5]	128.0 [92.0–186.0]	< 0.001
AST, U/L	24.0 [19.0–31.0]	26.0 [21.0–35.0]	< 0.001
ALT, U/L	20.0 [15.0–29.0]	28.0 [20.0–42.0]	< 0.001
Total bilirubin, mg/dL	0.7 [0.5–0.9]	0.7 [0.6–1.0]	0.008
Albumin, g/dL	4.8 [4.6–4.9]	4.8 [4.6–5.0]	< 0.001
Platelet $\times 10^9$/L	236.0 [203.0–275.5]	240.0 [205.0–281.0]	0.048
hsCRP, mg/dL	0.1 [0.0–0.1]	0.1 [0.0–0.1]	< 0.001
Fasting glucose, mg/dL	99.0 [91.0–107.5]	105.0 [95.0–120.0]	< 0.001
HbA1c, %	5.5 [5.3–5.8]	5.7 [5.4–6.1]	< 0.001
Positivity of HBsAg	59 (4.8%)	25 (2.7%)	0.020
Positivity of anti-HCV	11 (0.9%)	8 (0.9%)	1.000
Use of statin	85 (7.0%)	98 (10.8%)	0.003
Use of fibrate	0 (0.0%)	12 (1.3%)	< 0.001
Fatty liver without MAFLD		99 (10.9%)	
MAFLD Subtype			
T2DM		223 (27.5%)	
Overweight/obese		82 (10.1%)	
Normal weight/lean		507 (62.4%)	
NAFLD*	566 (100%)	335 (72.5%)	
Metabolic abnormality counts[§]	2 [1–3]	3 [2–4]	< 0.001
Metabolic syndrome	266 (21.8%)	488 (53.6%)	< 0.001

*1028 patients who could be assessed history of alcohol were evaluated

[§]Metabolic abnormalities include (1) WC ≥ 90/80 cm in male and female, (2) BP ≥ 130/85 mmHg or specific drug treatment, (3) plasma TG ≥ 150 mg/dL or specific drug treatment, (4) plasma HDL-cholesterol < 40 mg/dL for male and < 50 mg/dL for female or specific drug treatment, and (5) prediabetes (fasting glucose levels 100–125 mg/dL or 2-h post-load glucose levels 140–199 mg/dL or HbA1c 5.7–6.4%)

nondiabetic MAFLD was increasing up to three (Fig. 1b), mean coronary artery calcium score was constantly increasing according to number of metabolic risk abnormalities (Fig. 1c) in patients with nondiabetic MAFLD. In the unadjusted analysis, the subgroups of diabetic MAFLD and nondiabetic normal-weight/lean MAFLD with at least two and three metabolic risk abnormalities were significant factors associated with CAC, but nondiabetic overweight/obesity MAFLD was not (Table 2). In the sex- and age-adjusted analysis, the subgroup of diabetic MAFLD (aOR = 1.93, 95% CI = 1.42–2.64, $p < 0.001$) and nondiabetic normal-weight/lean MAFLD with at least three metabolic risk abnormalities were independently associated with CAC (aOR = 1.35, 95% CI = 1.02–1.77, $p = 0.034$), but those with at least two metabolic risk abnormalities were not (aOR = 1.18, 95% CI = 0.94–1.49, $p = 0.156$).

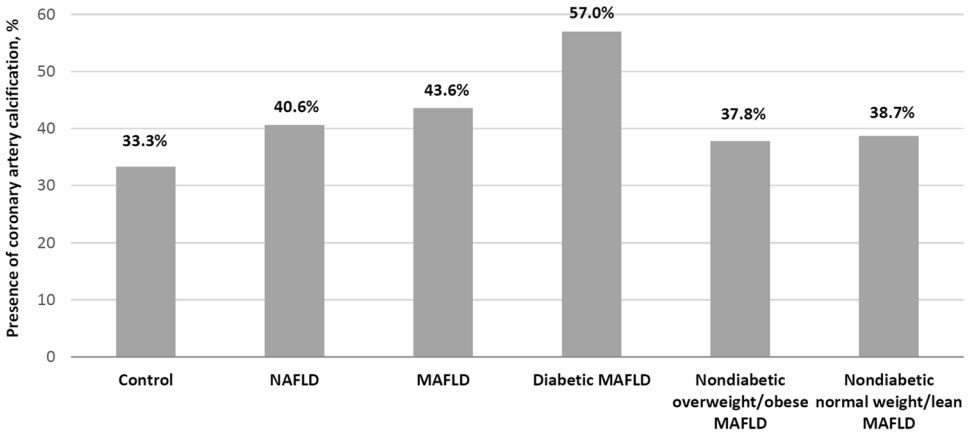

Fig. 1 Coronary artery calcification and coronary calcium score: **a** presence of coronary artery calcification according to presence of different fatty liver diseases, **b** presence of coronary artery calcification in patients with nondiabetic metabolic dysfunction-associated fatty liver disease, and **c** coronary artery calcium score in patients with nondiabetic metabolic dysfunction-associated fatty liver disease

Table 2 Association of presence of coronary artery calcification with NAFLD, MAFLD, and metabolic subtype of MAFLD

	Unadjusted analysis		Multivariable-adjusted analysis*	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
NAFLD	1.4 (1.05–1.85)	0.019	1.21 (0.88–1.65)	0.241
MAFLD	1.55 (1.29–1.86)	0.046	1.38 (1.14–1.69)	0.001
Fatty liver without MAFLD	1.00 (0.64–1.53)	0.996		
MAFLD, type 2 DM	2.65 (1.98–3.55)	< 0.001	1.93 (1.42–2.64)	< 0.001
[§]MAFLD, overweight/obesity	1.22 (0.76–1.92)	0.404		
[§]MAFLD, lean at least 2 metabolic risks	1.26 (1.26–3.29)	0.023	1.18 (0.94–1.49)	0.156
[§]MAFLD, lean at least 3 metabolic risks	1.48 (1.14–1.90)	0.003	1.35(1.02–1.77	0.034

*Adjusted by sex and age

[§]Nondiabetic

Association between CAC and number of metabolic risk abnormalities in individuals without T2DM

Sex- and age-adjusted analyses were performed to evaluate the association between CAC and the number of metabolic risk abnormalities among the control and nondiabetic MAFLD groups. In this analysis, the number of metabolic risk abnormalities was independently associated with CAC, irrespective of MAFLD (aOR = 1.23, 95% CI = 1.12–1.34, $p < 0.001$, Fig. 2).

Association between CAC and liver fibrosis in patients with MAFLD

To evaluate the association between CAC and liver fibrosis by FIB-4, multivariable-adjusted analysis, including values of the Framingham risk score, was performed in patients with MAFLD. In this analysis, liver fibrosis was independently associated with CAC (aOR = 2.08, 95% CI = 1.55–2.79, $p < 0.001$; Table 4). After further adjusted by positivity of HBsAg or anti-HCV, the association of CAC and liver fibrosis is not different (supplementary file 3).

Discussion

In this relatively healthy cohort, we demonstrated that MAFLD was independently associated with CAC using sex- and age-adjusted analyses. Among the three subgroups in the diagnostic criteria for MAFLD, only diabetic MAFLD was an independent predictor of CAC. However, when the minimal number of metabolic risk abnormalities increased to three, nondiabetic normal/lean MAFLD was associated with CAC, unlike the proposed diagnostic criteria of nondiabetic normal/lean MAFLD. Additionally, in nondiabetic MAFLD, the number of metabolic risk abnormalities was an independent predictor of CAC. In addition to these associations, liver fibrosis by FIB-4 was still an independent predictor of CAC using adjusted analysis of multiple cardiovascular risk factors.

These findings demonstrate that MAFLD is a better predictor of high-risk CVD phenotypes than NAFLD. However, most of these effects do not come from nondiabetic MAFLD but from diabetic MAFLD. We found that two metabolic risk abnormalities, which were defined as metabolic dysregulation in the proposed definition, were insufficient to

Table 3 Baseline characteristics of subgroups of MAFLD

MAFLD subgroup	T2DM ($N=223$)	Nondiabetic overweight/obese ($N=82$)	Nondiabetic normal weight/lean ($N=507$)	p Value
Male	167 (74.9%)	78 (95.1%)	349 (68.8%)	< 0.001
Age, year	60.6 ± 9.5	51.6 ± 10.8	57.2 ± 10.1	0.001
SBP	130.0 [122.0; 141.0]	128.0 [120.0; 137.0]	132.0 [121.0; 141.0]	0.201
Coronary artery calcium score	4.2 [0.0; 140.2]	0.0 [0.0; 25.1]	0.0 [0.0; 23.3]	< 0.001
Presence of CAC	127 (57.0%)	31 (37.8%)	196 (38.7%)	< 0.001
BMI, kg/m^2	22.0 [22.0; 22.0]	24.0 [23.6; 24.7]	22.0 [21.5; 22.0]	< 0.001
Use of hypertensive drug	51 (22.9%)	12 (14.6%)	67 (13.2%)	0.004
Smoking	73 (61.3%)	22 (66.7%)	142 (55.3%)	0.307
Total cholesterol, mg/dL	181.0 [147.5; 208.5]	191.0 [170.0; 219.0]	198.0 [171.0; 225.0]	< 0.001
HDL, mg/dL	50.0 [43.0; 59.0]	46.5 [40.0; 53.0]	51.0 [44.0; 60.5]	< 0.001
LDL, mg/dL	121.0 [91.5; 151.0]	132.0 [112.0; 164.0]	136.0 [110.0; 161.0]	< 0.001
Triglycerides, mg/dL	131.0 [94.5; 196.5]	154.0 [113.0; 213.0]	130.0 [90.0; 192.0]	0.059
AST, U/L	29.0 [23.0; 38.5]	25.0 [22.0; 32.0]	26.0 [21.0; 34.0]	0.002
ALT, U/L	31.0 [21.5; 47.0]	31.5 [22.0; 52.0]	27.0 [20.0; 39.5]	0.001
Total bilirubin, mg/dL	0.7 [0.5; 0.9]	0.8 [0.7; 1.1]	0.7 [0.6; 1.0]	< 0.001
Albumin, g/dL	4.9 [4.7; 5.1]	4.8 [4.7; 4.9]	4.8 [4.6; 5.0]	0.029
Platelet × 10^9/L	230.0 [193.0; 273.5]	238.5 [205.0, 270.0]	247.0 [215.0; 289.0]	0.001
hsCRP, mg/dL	0.1 [0.0; 0.1]	0.1 [0.1; 0.2]	0.1 [0.1; 0.1]	0.150
Fasting glucose, mg/dL	137.0 [127.0; 169.0]	103.0 [98.0; 113.0]	102.0 [93.5; 109.0]	< 0.001
HbA1c, %	6.8 [6.4; 7.6]	5.5 [5.3; 5.7]	5.6 [5.4; 5.8]	< 0.001
Positivity of HBsAg	8 (3.6%)	1 (1.2%)	13 (2.6%)	0.501
Positivity of anti-HCV	3 (1.3%)	1 (1.2%)	4 (0.8%)	0.762
Use of statin	39 (17.5%)	9 (11.0%)	50 (9.9%)	0.014
Use of fibrate	6 (2.7%)	0 (0.0%)	6 (1.2%)	0.200
Metabolic abnormality counts[§]	3.0 [2.0; 4.0]	3.0 [2.0; 4.0]	3.0 [2.0; 3.0]	0.021
MetS	153 (68.6%)	56 (68.3%)	279 (55.0%)	0.001
Noninvasive fibrosis test				
APRI	0.3 [0.2; 0.5]	0.3 [0.2; 0.4]	0.3 [0.2; 0.4]	< 0.001
APRI ≥ 0.5	45 (20.2%)	7 (8.5%)	58 (11.4%)	0.002
FIB-4	1.5 [1.0; 1.9]	1.0 [0.8; 1.3]	1.2 [0.9; 1.6]	< 0.001
FIB-4 ≥ 1.3	139 (62.3%)	22 (26.8%)	212 (41.8%)	< 0.001
NFS	− 3.5 [− 4.2; − 2.9]	− 4.5 [− 5.2; − 3.8]	− 4.3 [− 5.1; − 3.5]	< 0.001
NFS ≥ − 1.455	6 (2.7%)	0 (0.0%)	5 (1.0%)	0.141

[§]Metabolic abnormalities include (1) WC ≥ 90/80 cm in male and female, (2) BP ≥ 130/85 mmHg or specific drug treatment, (3) plasma TG ≥ 150 mg/dL or specific drug treatment, (4) plasma HDL-cholesterol < 40 mg/dL for male and < 50 mg/dL for female or specific drug treatment, and (5) prediabetes (fasting glucose levels 100–125 mg/dL or 2-h post-load glucose levels 140–199 mg/dL or HbA1c 5.7–6.4%)

determine the high-risk CVD phenotype in nondiabetic normal-weight/lean MAFLD, but instead three metabolic risk abnormalities were required. Thus, in terms of CVD risk, the number of metabolic risk abnormalities in normal-weight/lean nondiabetic MAFLD in the proposed diagnostic criteria may need to be further investigated. Furthermore, the addition of metabolic risk abnormalities in overweight/obese nondiabetic MAFLD may be considered. Consistent with a previous study on NAFLD, liver fibrosis remains an independent predictor of high-risk CVD phenotypes in MAFLD. As patients with diabetic MAFLD had higher scores on noninvasive fibrosis tests, liver fibrosis may independently increase the risk of CVD in diabetic MAFLD, which is consistent with a previous study on NAFLD.

Several studies have reported an association between NAFLD and CAC [14, 24, 25]. Although this association has been well evaluated in relatively large cohorts, it was not shown after adjusting for sex and age in the current study. A recent study reported that the association between NAFLD and CAC could be affected by sex and obesity [26]. This indicates that the impact of NAFLD on the risk of CAC could vary in cohorts with different BMIs. Unlike in other

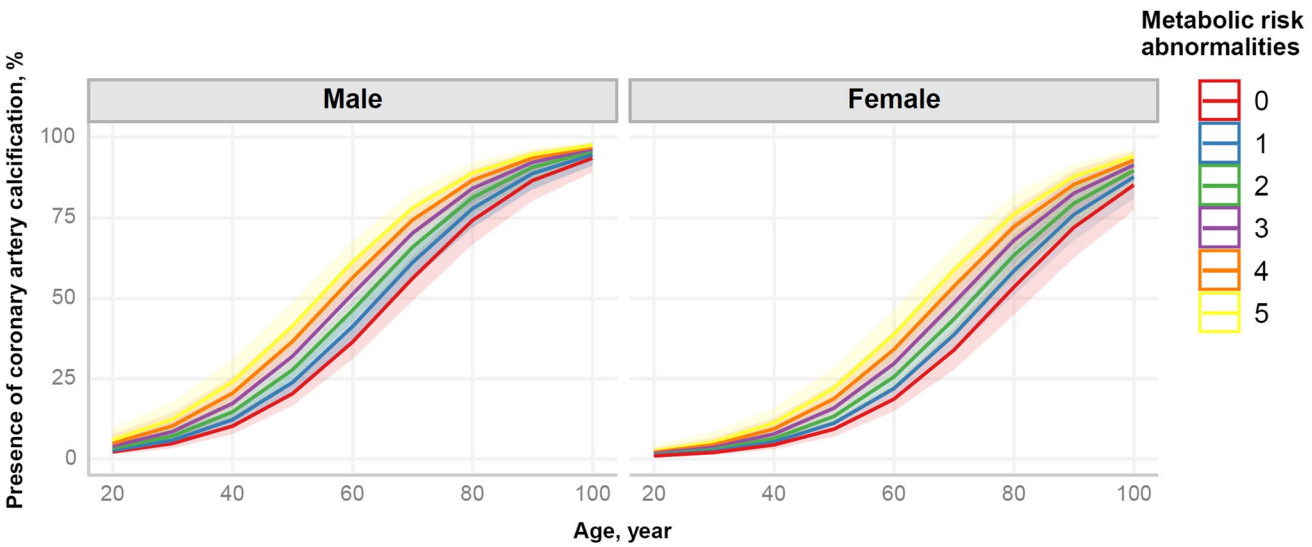

Fig. 2 Sex and age-adjusted predicted probability of the presence of coronary artery calcification (defined as coronary artery calcium score > 0) according to number of metabolic risk abnormalities in patient with metabolic dysfunction-associated fatty liver disease

Table 4 Association of presence of coronary artery calcification with liver fibrosis in patients with MAFLD*

	Unadjusted analysis		Multivariable-adjusted analysis§	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age	1.08 (1.06–1.10)	< 0.001		
Male	0.88 (0.64–1.20)	0.421		
Use of hypertensive drug	1.76 (1.21–2.58)	0.003	1.48 (1.00–2.19)	0.053
T2DM	2.17 (1.58–2.97)	< 0.001	1.82 (1.31–2.52)	< 0.001
Smoking	1.18 (0.79–1.76)	0.417		
Total cholesterol, mg/dL	1.00 (0.99–1.00)	0.034		
HDL, mg/dL	0.99 (0.98–1.00)	0.024	0.98 (0.97–1.00)	0.007
FIB-4 ≥ 1.3	2.23 (1.68–2.96)	< 0.001	2.08 (1.55–2.79)	< 0.001

*Number of patients reduced from 812 to 409 owing to lack of smoking data

§Age was excluded in multivariable-adjusted analysis, because the formula of FIB-4 included age, AST, ALT, and platelet count

cohorts (mean or median BMI of 23–26 kg/m^2), patients in our study cohort were relatively lean (median BMI was about 22 kg/m^2) [14, 24–26]. Especially, among patients with nondiabetic MAFLD, only 1.5% of patients were diagnosed with nondiabetic overweight/obese MAFLD. Thus, we believe that these differences may have been due to the relatively lean cohort in this study.

Some recent studies have reported that in terms of prediction of the risk of CVD, the definition of MAFLD is better than that of NAFLD [10, 27]. In these studies, patients with MAFLD were more likely to have higher CVD risk as assessed by the Korean 10-year atherosclerotic cardiovascular disease (ASCVD) risk score, Siuta score, or Framingham risk score (FRS). In addition, the incidence of CVD events, including myocardial infarction, ischemic stroke, heart failure, and CVD-related death assessed by reimbursement claim data, was higher in MAFLD than in NAFLD [10]. However, no study has evaluated the clinical characteristics of relevant subgroups. Thus, to overcome the heterogeneity of the disease, further studies are required to precisely define subgroups of MAFLD. A large-scale cohort study demonstrated that regardless of BMI, metabolically unhealthy individuals had higher CVD risk than did healthy individuals [28]. However, regardless of metabolic health, overweight/obese individuals had higher CVD risk than did lean individuals, and the hazard ratio of metabolic factors was much greater than that of related factor [28]. Furthermore, the association between metabolic dysregulation and severity of NAFLD has also been demonstrated in a biopsy-proven NAFLD cohort study [29]. In this previous study, the number of metabolic risk factors, including impaired fasting glucose or T2DM, hypertension (HTN), hypertriglyceridemia, and

low HDL-C, were also associated with the NAFLD activity score and fibrosis stage [29]. A recent large-scale retrospective cohort study demonstrated that at least two metabolic traits among obesity, dyslipidemia, HTN, and T2DM were associated with cirrhosis or HCC in patients with NAFLD [30]. However, the definition of metabolic health is heterogeneous and is not the same as factors in metabolic syndrome or traditional CVD risk assessments, such as FRS or ACC/AHA ASCVD risk estimator in various studies. In our study, patients with nondiabetic MAFLD had a relatively lower cardiovascular risk than those with diabetic MAFLD. According to a recently proposed definition of nondiabetic MAFLD, only normal-weight/lean MAFLD includes criteria for metabolic risk dysregulation, and overweight/obese MAFLD also have a relatively lower cardiovascular risk. Thus, we believe that additional metabolic criteria to define nondiabetic overweight/obese MAFLD are needed to determine the high-risk CVD phenotype.

The association between liver fibrosis and the risk of CVD in NAFLD has been reported in multiple studies [31–36]. The association between CAC and the risk of CVD has also been reported in many cohort studies; therefore, it can be an alternative option to assess the risk of CVD when traditional risk-scoring models, such as the FRS, are unclear [12, 37]. Additionally, because CAC is a highly specific feature of subclinical CVD, these associations are shown in early stage (stage ≥ 2) than in advanced fibrosis (stage ≥ 3) in patients with NAFLD regardless of their FRS [36]. In the current study, CAC was still an independent risk factor after adjusting for multiple risk factors, which were included in the FRS, and was consistent with the findings of a previous study. Recently, several studies have reported that changing NAFLD to MAFLD identifies more patients with significant liver fibrosis [7–9, 21]. In these previous studies, non-overlapping MAFLD had higher FIB-4 levels than non-overlapping NAFLD. Furthermore, one study reported higher CVD-related mortality in non-overlapping MAFLD than in non-overlapping NAFLD [8]. Thus, we think that liver fibrosis is an important risk factor for predicting CAC in MAFLD, as this study showed.

The strength of this study is that the risk of CVD and diagnosis of fatty liver were not assessed by a score-based test, such as the FRS and fatty liver index, but by imaging modalities, such as ultrasound and cardiac CT [10, 27]. Furthermore, although this was a single-center retrospective study, a well-organized cohort with no missing value was used to analyze the data. In this cohort, all values in the definition of MAFLD were included except fasting insulin levels and current medications, including antihypertensive, antidiabetic, and lipid-lowering agents. The present definition of nondiabetic lean/normal-weight MAFLD is relatively complicated and includes nonclinical friendly variables, such as fasting insulin and hsCRP; therefore, most previous studies did not include these metabolic risk abnormalities [10, 27].

This study has some limitations. First, almost all participants in this study were Korean. Thus, further studies are required to delineate our results in a multi-ethnic, multi-racial cohort. Second, the study population was relatively healthy and had normal weight or were lean, because this study was conducted using data from a health checkup center. Therefore, further studies are required in the general population.

In conclusion, changing from NAFLD to MAFLD could better predict the high-risk CVD phenotype. Of the three subgroups of MAFLD, diabetic MAFLD best predicted an increased risk of CVD. The number of metabolic risk abnormalities in patients with nondiabetic MAFLD was independently associated with the risk of CVD. The proposed diagnostic criteria for nondiabetic MAFLD may need to be further investigated in terms of CVD risk.

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Author contributions JGP and SYP is guarantor of integrity of the entire study. JGP designed the study and partially supervised by RL. All authors except RL collected data, which were reviewed by GJP, and analyzed by GJP based on the statistical analysis plan. GJP, MKG, and YLR drafted the manuscript, which was critically revised by SYP. All authors were responsible for collecting and interpretation of the data and approved the final version of manuscript.

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Data availability The data supporting findings of this study are available from the corresponding authors upon reasonable request.

Declarations

Conflict of interest RL serves as a consultant for Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharm, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer, and Sonic Incytes. He is also co-founder of Liponexus, Inc.

Ethical approval This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2013. The study protocol was approved by the institutional review board of the study center (IRB No. KNUH-2021-07-057-001). The requirement for informed consent from the study participants was waived by the ethics committee because of the retrospective nature of this study.

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