Front. Med. 2022, 16(5): 714−722
https://doi.org/10.1007/s11684-021-0888-8

RESEARCH ARTICLE

New definition of metabolic dysfunction-associated fatty liver disease with elevated brachial-ankle pulse wave velocity and albuminuria: a prospective cohort study

Jialu Wang[1,2,*], Shanshan Liu[1,2,*], Qiuyu Cao[1,2], Shujing Wu[1,2], Jingya Niu[1,2], Ruizhi Zheng[1,2], Lizhan Bie[1,2], Zhuojun Xin[1,2], Yuanyue Zhu[1,2], Shuangyuan Wang[1,2], Hong Lin[1,2], Tiange Wang[1,2], Min Xu[1,2], Jieli Lu[1,2], Yuhong Chen[1,2], Yiping Xu[3], Weiqing Wang[1,2], Guang Ning[1,2], Yu Xu[1,2], Mian Li (✉)[1,2], Yufang Bi (✉)[1,2], Zhiyun Zhao (✉)[1,2]

[1]Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; [2]Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the PR China, Shanghai Key Laboratory for Endocrine Tumor, State Key Laboratory of Medical Genomics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; [3]Clinical Trials Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

Abstract **A new definition of metabolic dysfunction-associated fatty liver disease (MAFLD) has recently been proposed. We aim to examine the associations of MAFLD, particularly its discordance from non-alcoholic fatty liver disease (NAFLD), with the progression of elevated brachial-ankle pulse wave velocity (baPWV) and albuminuria in a community-based study sample in Shanghai, China. After 4.3 years of follow-up, 778 participants developed elevated baPWV and 499 developed albuminuria. In comparison with the non-MAFLD group, the multivariable adjusted odds ratio (OR) of MAFLD group for new-onset elevated baPWV was 1.25 (95% confidence interval (CI) 1.01–1.55) and 1.35 (95% CI 1.07–1.70) for albuminuria. Participants without NAFLD but diagnosed according to MAFLD definition were associated with higher risk of incident albuminuria (OR 1.77; 95% CI 1.07–2.94). Patients with MAFLD with high value of hepamet fibrosis score or poor-controlled diabetes had higher risk of elevated baPWV or albuminuria. In conclusion, MAFLD was associated with new-onset elevated baPWV and albuminuria independently of body mass index, waist circumference, and hip circumference. Individuals without NAFLD but diagnosed as MAFLD had high risk of albuminuria, supporting that MAFLD criteria would be practical for the evaluation of long-term risk of subclinical atherosclerosis among fatty liver patients.**

Keywords metabolic dysfunction-associated fatty liver disease; non-alcoholic fatty liver disease; fibrosis score; brachial-ankle pulse wave velocity; albuminuria

Introduction

Metabolic dysfunction-associated fatty liver (MAFLD), a novel concept proposed by an international consensus in early 2020 [1], is attracting the attention of many scholars and experts [2–6]. Unlike the former diagnostic criteria of non-alcoholic fatty liver disease (NAFLD), MAFLD does not need to exclude patients with alcohol intake or other chronic liver diseases [7], while emphasizing metabolic risk factors [8]. Cardiovascular disease (CVD) is the leading cause of mortality in patients with fatty liver [9,10], placing a huge burden on public health and highlighting the importance to investigate the effect of the new MAFLD definition on cardiovascular disease and related subclinical vascular abnormalities. Arterial stiffness according to an elevated brachial-ankle pulse wave velocity (baPWV) is a predictive marker of CVD [11], while albuminuria, as an indicator of microvascular

Received: April 22, 2021; accepted: July 31, 2021
Correspondence: Zhiyun Zhao, zzybrad@hotmail.com;
Yufang Bi, byf10784@rjh.com.cn;
Mian Li, limian39@aliyun.com

*The authors contributed equally to this work.

abnormality, is related to increased risk of CVD [12]. The associations of NAFLD with elevated baPWV and albuminuria have been illustrated in several previous studies [13–16]. However, the associations of the new definition of MAFLD and the discordant criteria from MAFLD and NAFLD definitions with the risk of new-onset elevated baPWV and albuminuria remain unknown. The effect of MAFLD according to the new definition with diverse fibrosis probability and glycemic status on the risk of new-onset elevated baPWV and albuminuria are also yet to be determined.

In this context, we aimed to examine the risk of MAFLD with different severities on incident elevated baPWV and albuminuria in middle-aged and elderly Chinese population. Furthermore, we focused on the discordant criteria from MAFLD and NAFLD definitions and detected its association with new-onset elevated baPWV and albuminuria.

Materials and methods

Subjects and study design

Participants in the current study were obtained from a prospective cohort study, which was conducted in a community-based population between March and August in 2010 in Jiading District, Shanghai, China. The details of baseline design, recruitment, and demographic characteristics have been published previously [17]. Between August 2014 and May 2015, all eligible participants were invited to complete a follow-up survey. For current analysis, we sequentially excluded subjects (1) without hepatic ultrasonic examination or laboratory tests at baseline (n = 246) and (2) without information on both baPWV and urinary albumin/creatinine ratio (ACR; n = 3735) at baseline and follow-up. A total of 6394 participants were included in the MAFLD analysis. Additionally, 382 participants with missing data on baPWV and 1505 participants with abnormal baPWV ($\geqslant$ 1773 cm/s) at baseline were further excluded, leaving 4507 participants for the analysis of baPWV, while 111 participants without data on ACR and 399 participants with ACR $\geqslant$ 30 mg/g at baseline were excluded to generate the study group of 5884 for the analysis of albuminuria (Fig. 1).

The study protocol was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and written informed consent was obtained from each participant.

Data collection

A standard questionnaire on demographic characteristics, education, history of chronic disease and medications, and lifestyle habits was administrated face-to-face by trained investigators. Body mass index (BMI) was calculated as the body weight divided by height squared (kg/m^2). Waist and hip circumferences were determined using a measuring tape positioned at the midway point between the lateral lower ribs and the iliac crests and at the widest point over the greater trochanters, respectively. Blood pressure was measured using an automated electronic device (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China), and the three readings of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were averaged for analysis. All participants underwent fasting for at least 10 h, followed by 75 g oral glucose tolerance test (OGTT). Biochemical parameters including fasting plasma glucose (FPG), OGTT 2-h plasma glucose (2h-PG), glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyl transferase (GGT), and serum insulin were measured using automated analyzers (Modular P800 and Modular E170; Roche, Basel, Switzerland). Peripheral hematological parameters were measured using an automated cell counter (Hematology analyzer 120; ABX, Montpellier, France). A first-voided, early-morning spot urine sample was obtained to measure urinary albumin (g/L) and creatinine (mmol/L) by using the immunoturbidimetric method (Beijing Atom High-Tech, Beijing, China) and Jaffe's kinetic method on an automatic analyzer (Hitachi 7600-020, Tokyo, Japan), respectively. For the homeostasis model assessment of insulin resistance, the following equation was used: fasting serum insulin (μIU/mL) × FPG (mmol/L) /22.5.

Definition of MAFLD, NAFLD, and severity categories

Hepatic ultrasonic examination was operated by two experienced specialists, who were blinded to the clinical characteristics, by using high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Italy) with a 3.5-MHz probe. An ultrasonographic diagnosis of fatty liver was defined by the presence of at least two of three abnormal findings as follows: (1) diffusely increased echogenicity of the liver relative to the kidney; (2) ultrasound beam attenuation; or (3) poor visualization of intrahepatic structures.

According to the new definition, MAFLD was diagnosed based on a hepatic ultrasonic diagnosed fatty liver and the presence of either overweight/obesity, evidence of metabolic dysregulation, or presence of diabetes [8]. Metabolic dysregulation was defined as the presence of two or more of the following conditions: (1) waist circumference $\geqslant$ 90 cm in men and 80 cm in women; (2) blood pressure $\geqslant$ 130/85 mmHg or specific medicine treatment; (3) triglycerides $\geqslant$ 1.70 mmol/L or specific

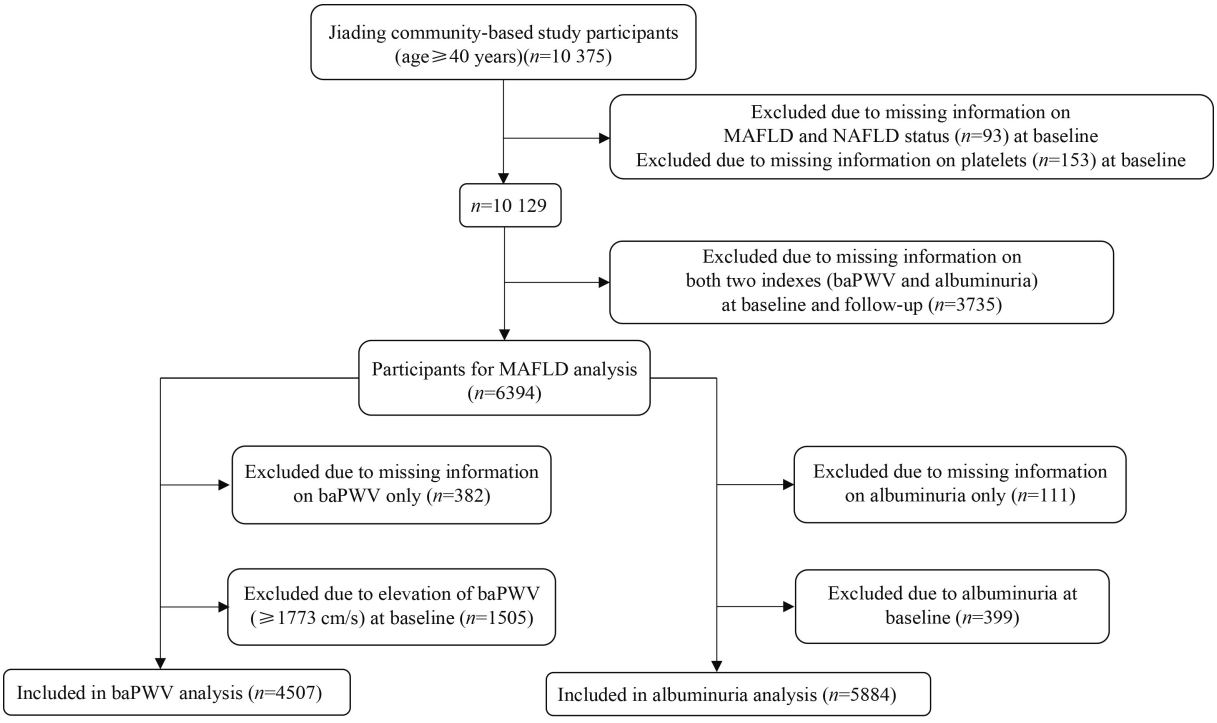

Fig. 1 Flow diagram of the study population.

medicine treatment; (4) HDL-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women or specific medicine treatment; (5) prediabetes (FPG 5.6 to 6.9 mmol/L, or 2h-PG 7.8 to 11.0 mmol or HbA1c 5.7% to 6.4%); and (6) homeostasis model assessment of insulin resistance score ⩾ 2.5.

In addition, NAFLD was diagnosed based on hepatic steatosis according to ultrasound examination after excluding alcohol abuse (alcohol consumption ⩾ 140 g/week for men or ⩾ 70 g/week for women) and other hepatic diseases, such as autoimmune hepatitis, viral hepatitis, and hepatic carcinoma [18].

According to the concordant or discordant from MAFLD and NAFLD definitions, we divided the included participants into four groups as follows: (1) NAFLD (−) and MAFLD (−) group: individuals without NAFLD or MAFLD; (2) NAFLD (−) and MAFLD (+) group: non-NAFLD individuals who were newly diagnosed according to MAFLD definition; (3) NAFLD (+) and MAFLD (−) group: NAFLD individuals who were reclassified into non-MAFLD group; and (4) NAFLD (+) and MAFLD (+) group: individuals met both MAFLD and NAFLD criteria.

In individuals with MAFLD, hepamet fibrosis score (HFS) was used to evaluate the probability of fibrosis. The score was calculated using the following formula: HFS [19]: $1/(1 + e^{y})$, where y = 5.390 – 0.986 × Age (45–64 years of age) – 1.719 × Age (⩾ 65 years of age) + 0.875 × Male sex – 0.896 × AST (35−69 IU/L) – 2.126 × AST (⩾ 70 IU/L) – 0.027 × Albumin (4–4.49 g/dL) – 0.897 ×Albumin (< 4g/dL) – 0.899 × Homeostatic model assessment (2–3.99 without diabetes) – 1.497 × Homeostatic model assessment (⩾ 4 without diabetes) – 2.184 × Diabetes – 0.882 × Platelets ((155–219) × 1000/μL) – 2.233 × Platelets (< 155 × 1000/μL). We considered a low probability of liver fibrosis as HFS < 0.12, a moderate probability as 0.12 ⩽ HFS ⩽ 0.47, and a high probability as HFS > 0.47 for statistical purposes.

According to the 2010 American Diabetes Association criteria, diabetes at baseline was diagnosed if at least one of the following criteria is met: (1) FPG level of 7 mmol/L or higher; (2) OGTT 2h-PG level of 11.1 mmol/L or higher; (3) HbA1c level of 6.5% or higher; or (4) self-reported diagnosis by professionals.

Measurements of baPWV and albuminuria

The same method and criteria were used to evaluate elevated baPWV and albuminuria at baseline and follow-up in the population.

baPWV, which indicates the brachial to ankle pulse wave velocity, was measured on a Colin VP-1000 (Model BP203RPE II, form PWV/ankle brachial index) after 10–15 min of rest. Pulse waves were obtained while placing suitable cuffs on the upper sides of both arms and ankles. The value of baPWV was calculated as the transit distance divided by the transit time. We adopted the greater value of bilateral baPWV for analysis at both baseline and follow-up. Individuals who did not have

these abnormalities at baseline but occurred during follow-up were defined as new-onset. New-onset elevated baPWV was defined as the upper quartile of baseline baPWV (⩾ 1773 cm/s).

Urinary ACR (mg/g) was calculated by dividing the urinary albumin concentration by the urinary creatinine concentration. New-onset albuminuria was defined as ACR ⩾ 30 mg/g.

Statistics analysis

Continuous variables were presented as mean ± standard deviation (SD) or as medians (interquartile ranges). Categorical variables were presented as numbers (percentages). Mean and percentages were compared using one-way ANOVA or χ^2 as appropriate. Considering that no interactions were found between sex and MAFLD for the risk of clinical outcomes (all P for interaction > 0.05), pooled analyses were presented. We conducted multivariable logistic regression analysis to explore the associations of MAFLD status with risk of incident elevated baPWV and albuminuria. Moreover, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for combined NAFLD and MAFLD status in relation to incident elevated baPWV and albuminuria were evaluated with multivariable logistic regression analyses. Notably, NAFLD (+) and MAFLD (−) group was not included in the analysis, because the total number of the group was exceedingly small (n= 4). Furthermore, we conducted stratified analyses according to the probability of fibrosis and glycemic status. Significance tests were two-tailed, and statistical significance was considered at $P < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute , Cary, North Carolina).

Results

Characteristics of study participants at baseline

NAFLD and MAFLD were observed in 26.8% and 30.6% of the total population (n = 6394), respectively. Participants with overlapping NAFLD and MAFLD accounted for 26.8% of the total population. Non-overlapping NAFLD and MAFLD accounted for 0.06% and 3.80% of the total population, respectively (Fig. S1). The baseline general and clinical characteristics of the participants according to MAFLD status are summarized in Table 1. Participants with MAFLD status are likely to have higher BMI, waist circumference, hip circumference, SBP, DBP, FPG, 2h-PG, HbA1c, triglycerides, total cholesterol, LDL-cholesterol, ALT, AST, GGT, proportions of diabetes, and antihypertensive medication and lower HDL-cholesterol than those without MAFLD (all $P < 0.0001$). Notably, participants with MAFLD status had a high level of baPWV and ACR (both $P < 0.0001$). No significant difference was observed between the two groups in terms of age, sex, education, smoking status, drinking status, insulin use and lipid-lowering medication.

Baseline MAFLD status in association with incident elevated baPWV and albuminuria

As shown in Table 2, MAFLD status at baseline was remarkably associated with new-onset elevated baPWV and albuminuria. The incidences of elevated baPWV and albuminuria in MAFLD participants were 20.3% and 11.1%, while those in the non-MAFLD group were 16.1% and 7.4%, respectively. Multivariable logistic regression analysis was applied to explore the associations of MAFLD status with the risk of new-onset abnormalities. After adjustments for age, sex, education, smoking status, drinking status, physical activity, BMI, waist circumference, hip circumference, and medication (insulin, antihypertensive medication, and lipid-lowering medication), OR (95% CI) of MAFLD group was 1.25 (95% CI 1.01–1.55) for incident elevated baPWV. Similarly, OR (95% CI) of MAFLD group for new-onset albuminuria was 1.35 (95% CI 1.07–1.70).

Association of concordant or discordant criteria from MAFLD and NAFLD definitions with incident elevated baPWV and albuminuria

Participants were divided into four groups according to the NAFLD and MAFLD status. Considering that the NAFLD (+) and MAFLD (−) group only had four participants, this group was not included in this analysis. Overall, participants in the NAFLD (+) and MAFLD (+) group were associated with higher risk of new-onset elevated baPWV and albuminuria (OR 1.27, 95% CI 1.01–1.58; OR 1.35, 95% CI 1.06–1.72; respectively). Notably, the NAFLD (−) and MAFLD (+) group comprised 3.9% of participants, which were associated with a 77% higher risk of incident albuminuria (OR 1.77, 95% CI 1.07–2.94) (Table 3). Furthermore, we investigated the characteristics according to the presence of NAFLD in MAFLD participants and explored the associations of diverse alcohol intake with new-onset albuminuria in MAFLD participants, and the results are shown in Tables S1 and S2.

Risks of incident elevated baPWV and albuminuria according to MAFLD with subtypes of fibrosis probability

We further investigated the associations of diverse probability of liver fibrosis with new-onset elevated baPWV and albuminuria (Fig. 2). After multivariable adjustment, we observed that higher HFS was associated with higher risk of incident elevated baPWV in MAFLD participants compared with non-MAFLD individuals (OR 2.41, 95% CI 1.15–5.08). However, this relationship was not observed between HFS and new-onset albuminuria. In

Table 1 General characteristics of the study population according to the presence of MAFLD at baseline

Characteristics	Overall (n = 6394)	Presence of MAFLD at baseline		
		No (n = 4439)	Yes (n = 1955)	P value
Age (year)	58.00 ± 8.72	58.00 ± 8.94	58.00 ± 8.19	0.99
Men, n (%)	2333 (36.5)	1609 (36.2)	724 (37.0)	0.55
⩾ 9 years of education, n (%)	4111 (64.6)	2841 (64.2)	1270 (65.4)	0.37
Current drinking, n (%)	622 (10.1)	427 (10.0)	195 (10.3)	0.70
Current smoking, n (%)	1240 (20.1)	856 (20.0)	384 (20.3)	0.80
Physical activity (MET-h/wk)	23.10 (4.95–93.1)	23.10 (4.95–102.20)	23.10 (3.30–74.20)	0.003
BMI (kg/m^2)	25.23 ± 3.26	24.20 ± 2.80	27.56 ± 3.00	<0.0001
Waist circumference (cm)	82.69 ± 8.86	79.87 ± 7.80	89.09 ± 7.74	<0.0001
Hip circumference (cm)	94.03 ± 5.78	92.58 ± 5.12	97.34 ± 5.82	<0.0001
SBP (mmHg)	141.43 ± 19.84	139.18 ± 19.75	146.53 ± 19.09	<0.0001
DBP (mmHg)	83.06 ± 10.31	81.81 ± 10.14	85.90 ± 10.12	<0.0001
Platelets (×1000/μL)	216.02 ± 63.21	212.83 ± 63.75	223.25 ± 61.37	<0.0001
FPG (mmol/L)	5.18 (4.79–5.75)	5.07 (4.72–5.53)	5.53 (5.01–6.43)	<0.0001
2h-PG (mmol/L)	6.97 (5.68–9.14)	6.54 (5.37–8.07)	8.57 (6.72–12.28)	<0.0001
HbA1c (%)	5.60 (5.40–6.00)	5.60 (5.40–5.80)	5.80 (5.50–6.30)	<0.0001
Triglycerides (mmol/L)	1.38 (0.99–1.95)	1.22 (0.90–1.68)	1.86 (1.36–2.59)	<0.0001
Total cholesterol (mmol/L)	5.36 ± 1.01	5.30 ± 0.96	5.51 ± 1.09	<0.0001
LDL-cholesterol (mmol/L)	3.21 ± 0.86	3.17 ± 0.84	3.31 ± 0.91	<0.0001
HDL-cholesterol (mmol/L)	1.32 ± 0.32	1.38 ± 0.32	1.21 ± 0.27	<0.0001
ALT (IU)	18.20 (14.00–25.50)	16.70 (13.00–22.10)	23.60 (17.50–34.50)	<0.0001
AST (IU)	21.60 (18.40–25.60)	21.10 (18.10–24.90)	22.40 (19.10–27.50)	<0.0001
GGT (IU)	21.00 (15.00–34.00)	19.00 (14.00–28.00)	30.00 (21.00–48.00)	<0.0001
ACR (mg/g)	4.88 (2.80–8.99)	4.55 (2.65–8.17)	5.83 (3.16–11.69)	<0.0001
baPWV (cm/s)	1603.62 ± 355.01	1573.85 ± 350.00	1671.27 ± 357.13	<0.0001
Diabetes, n (%)	1245 (19.5)	548 (12.4)	697 (35.7)	<0.0001
Insulin use, n (%)	44 (0.7)	33 (0.7)	13 (0.7)	0.88
Antihypertensive medication[a], n (%)	360 (5.6)	187 (4.2)	173 (8.9)	<0.0001
Lipid-lowering medication, n (%)	16 (0.3)	9 (0.2)	7 (0.4)	0.25

Data are expressed as mean ± SD, median (interquartile range), or as n (%) (there were missing values for some variables).
[a]Antihypertensive medication included the use of angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers.
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2h-PG, 2-h plasma glucose; HbA1c, glycated hemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, γ-glutamyl transferase; ACR, albumin/creatinine ratio; baPWV, brachial-ankle pulse wave velocity.

Table 2 Risk of incident elevated baPWV and albuminuria according to MAFLD status

	Cases/participants (%)	Model 1		Model 2		Model 3	
		Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Elevated baPWV							
No MAFLD	524/3257 (16.1%)	1.00 (ref.)	−	1.00 (ref.)	−	1.00 (ref.)	−
MAFLD	254/1250 (20.3%)	1.47 (1.23−1.75)	<0.0001	1.24 (1.01−1.54)	0.04	1.25 (1.01−1.55)	0.04
Albuminuria							
No MAFLD	304/4124 (7.4%)	1.00 (ref.)	−	1.00 (ref.)	−	1.00 (ref.)	−
MAFLD	195/1760 (11.1%)	1.60 (1.32−1.94)	<0.0001	1.35 (1.07−1.70)	0.01	1.35 (1.07−1.70)	0.01

Model 1: adjusted for sex and age at baseline.
Model 2: further adjusted for education, smoking status, drinking status, physical activity, BMI, waist circumference, hip circumference based on Model 1.
Model 3: further adjusted for medication (insulin, antihypertensive, and lipid-lowering medications) on Model 2.
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; ref., reference.

Table 3 Risk of incident elevated baPWV and albuminuria according to concordant or discordant criteria from MAFLD and NAFLD definitions

	Cases/participants (%)	Model 1		Model 2		Model 3	
		Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Elevated baPWV							
NAFLD (−) & MAFLD (−)	524/3253 (16.1%)	1.00 (ref.)	−	1.00 (ref.)	−	1.00 (ref.)	−
NAFLD (−) & MAFLD (+)	30/165 (18.2%)	1.47 (0.95−2.28)	0.08	1.21 (0.75−1.95)	0.44	1.20 (0.74−1.94)	0.46
NAFLD (+) & MAFLD (+)	224/1085 (20.7%)	1.47 (1.22−1.78)	<0.0001	1.25 (1.01−1.57)	0.05	1.27 (1.01−1.58)	0.04
Albuminuria							
NAFLD (−) &MAFLD (−)	304/4120 (7.4%)	1.00 (ref.)	−	1.00 (ref.)	−	1.00 (ref.)	−
NAFLD (−) &MAFLD (+)	25/229 (10.9%)	2.31 (1.46−3.64)	0.0003	1.81 (1.09−3.00)	0.02	1.77 (1.07−2.94)	0.03
NAFLD (+) &MAFLD (+)	170/1531 (11.1%)	1.53 (1.25−1.87)	<0.0001	1.35 (1.06−1.72)	0.02	1.35 (1.06−1.72)	0.02

Model 1: adjusted for sex and age at baseline.
Model 2: further adjusted for education, smoking status, drinking status, physical activity, BMI, waist circumference, hip circumference based on Model 1.
Model 3: further adjusted for medication (insulin, antihypertensive and lipid-lowering medications) on Model 2.
Abbreviations: NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; ref., reference.

comparison with non-MAFLD participants, with the increasement of HFS in MAFLD participants, the risk of new-onset albuminuria increased, but the change was not significant (OR 1.33, 95% CI 1.03–1.72 for MAFLD participants with HFS < 0.12; OR 1.48, 95% CI 1.02–2.14 for MAFLD participants with HFS of 0.12–0.47; OR 1.91, 95% CI 0.98–3.72 for MAFLD participants with HFS > 0.47, respectively).

Risks of incident elevated baPWV and albuminuria according to MAFLD with subtypes of glycemic status

As shown in Fig. 3, compared with the non-MAFLD participants, MAFLD participants with diabetes and HbA1c ⩾ 7.0% had a 192% higher risk of incident elevated baPWV (OR 2.92, 95% CI 1.94–4.40) and 166% higher risk of albuminuria (OR 2.66, 95% CI 1.78–3.99) after adjusting for age, sex, current smoking, current drinking, education, physical activity, BMI, waist circumference, hip circumference, and medications. Furthermore, MAFLD participants with diabetes and HbA1c < 7.0% were associated with higher risk of new-onset albuminuria (OR 1.61, 95% CI 1.12–2.33).

Discussion

Based on this prospective study, MAFLD was associated

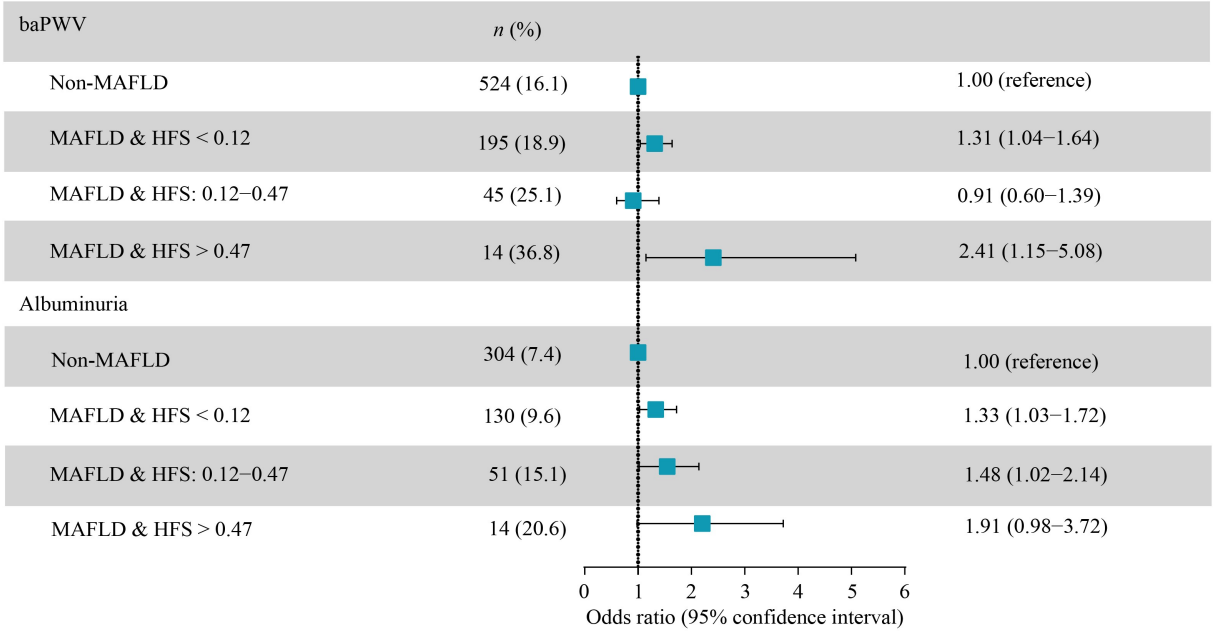

Fig. 2 Risks of incident elevated baPWV and albuminuria according to MAFLD status with different levels of HFS. ORs (95% CIs) were adjusted for age, sex, current smoking, current drinking, education, physical activity, BMI, waist circumference, hip circumference, and medications (insulin, antihypertensive, and lipid-lowering medications). baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; HFS, hepamet fibrosis score; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio.

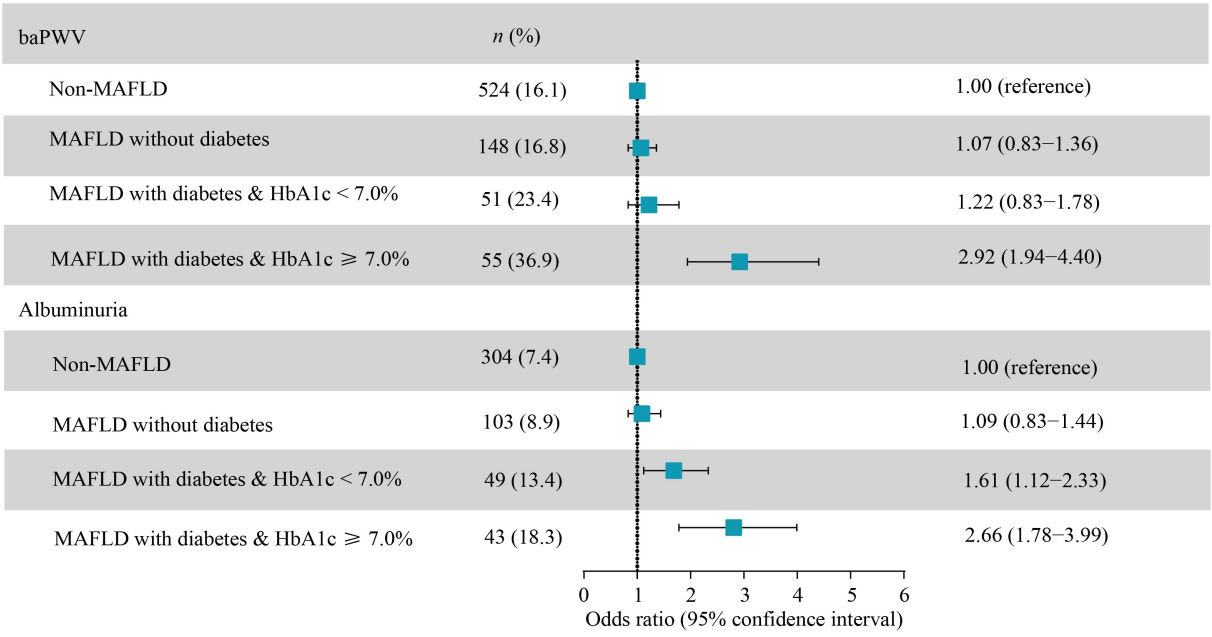

Fig. 3 Risks of incident elevated baPWV and albuminuria according to MAFLD with subtypes of glycemic status. ORs (95% CIs) were adjusted for age, sex, current smoking, current drinking, education, physical activity, BMI, waist circumference, hip circumference, and medications (antihypertensive and lipid-lowering medications). baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio.

with an increased risk of elevated baPWV and albuminuria independently of BMI, waist circumference, and hip circumference, which were very important and independent determinants of the cardiometabolic risk [20]. In addition, participants without NAFLD but diagnosed with MAFLD according to the new definition had a significantly higher risk of albuminuria, suggesting that the novel criteria of MAFLD was a more practical definition for detecting participants with fatty liver at high risk of microvascular abnormality. Moreover, stratified analyses of the data indicated that MAFLD participants with higher HFS or poor glycemic control are likely to develop elevated baPWV and albuminuria. To the best of our knowledge, this prospective study was the first to investigate the associations of MAFLD status and its discordance from NAFLD with long-term risk of subclinical atherosclerosis.

Several previous studies have widely illustrated the associations between former NAFLD definition and elevated baPWV and albuminuria [21–23]. However, limited studies have focused on the effect of MAFLD assessed by the new definition on the abnormal subclinical vascular markers. A prospective cohort study conducted by Liu *et al*. [24] demonstrated that participants with MAFLD were associated with an increased risk of CVD and renal diseases. Consistent with this previous study, we found that MAFLD was associated with higher risk of subclinical atherosclerosis indicated by elevated baPWV and albuminuria. Notably, this association was independent of BMI, waist circumference, and hip circumference. Although obesity and central obesity were important features and diagnostic criteria of the definition of MAFLD, the effect of liver fat deposition on subclinical atherosclerosis was independent of the obesity condition and fat distribution phenotypes. This result indicates the urgent need to identify participants with increased metabolic dysregulation in normal weight. Furthermore, the name changing from former NAFLD to the newly proposed MAFLD have stimulated a heated discussion. A cross-sectional study conducted by Lin *et al*. [25] in 13 083 subjects from the general population enrolled in the third National Health and Nutrition Examination Survey of the United States (NHANES III) compared the characteristics of participants with NAFLD versus MAFLD. Results show that the individuals with NAFLD but without MAFLD were younger, had less frequently metabolic abnormality, and non-invasively assessed liver fibrosis. More recently, Lee *et al*. [26] observed that NAFLD not meeting metabolic abnormality was associated with “healthier” characteristics and lower CVD risk compared with MAFLD based on a nationwide study of 9 million middle-aged Koreans. The results are possibly associated with the presence of metabolically healthy fatty liver, mostly related to risk alleles in PNPLA3 and TM6SF2, which are strongly associated with protective effect for CVD [27]. However, the effect of discordance between the two definitions of fatty liver on the risk of incident subclinical vascular abnormalities is unknown. Considering that the present study involved middle-aged and elderly population with high probability of metabolic dysregulation, few participants are involved in the NAFLD without metabolic abnormality group. Notably, participants who met the diagnostic criteria of

MAFLD but not NAFLD comprised 3.9% of the total population, showing a significantly higher risk of new-onset albuminuria. This finding consolidated the clinical applicability of the new MAFLD definition, indicating that the NAFLD-to-MAFLD change enhanced the ability to capture and identify individuals at risk for microvascular abnormality.

Advanced fibrosis, which is measured by non-invasive liver fibrosis score, is associated with subclinical atherosclerosis in patients with NAFLD [28]. By using the newly proposed criteria of MAFLD, Yamamura *et al*. [29] compared the diagnostic accuracy of MAFLD with NAFLD to identify the probability of liver fibrosis in Japanese participants, and the results showed that MAFLD performed better than NAFLD in identifying advanced fibrosis. In line with the previous cross-sectional findings, we also detected that MAFLD participants with high probability of fibrosis evaluated by HFS conferred higher risks of elevated baPWV. Our findings emphasized the need to detect and manage the cardiovascular-related risk at the early stage of MAFLD. Furthermore, the newly proposed criteria of MAFLD have emphasized diabetes as one of three important facets, indicating that MAFLD participants with diabetes should be paid more attention. In the present study, MAFLD patients with poorly controlled diabetes showed high risk of elevated baPWV and albuminuria, which were surrogate indicators for subclinical atherosclerosis. Our results highlighted the importance of stringent glycemic control specifically for MAFLD participants.

Several limitations need to be considered. First, the study was performed in a middle-aged and elderly Chinese population, which could not represent the general population. Second, hepatic ultrasound was used to diagnose liver steatosis, but not the liver biopsy. Finally, considering that high-sensitivity C-creative protein level is a metabolic risk abnormality, it was not measured in our study.

In conclusion, MAFLD was associated with an increased risk of elevated baPWV and albuminuria independently of BMI, waist circumference, and hip circumference. Our findings suggest that the diagnostic criteria of MAFLD was a more practical definition in identifying high risk of microvascular abnormality in participants with fatty liver than NAFLD. Further and more prospective studies with a wider age range are needed to further clarify the associations between MAFLD and subclinical atherosclerosis.

Acknowledgements

The investigators are grateful to all participants for their cooperation in the study. This work was supported by the grants from the National Key R&D Program of China (Nos. 2017YFC1310700, 2018YFC1311800, and 2018YFC1311705), the National Natural Science Foundation of China (Nos. 81870560, 82070880, 81941017, 81770842, 81970706, and 82022011), the National Science and Technology Major Project for "Significant New Drugs Development" (No. 2017ZX09304007), Shanghai Municipal Government (No. 18411951800), Shanghai Shenkang Hospital Development Center (Nos. SHDC12019101, SHDC2020CR1001A, and SHDC2020CR3069B), the Scientific and Technological Committee of Shanghai (No. 19411964200), Shanghai Jiao Tong University School of Medicine (No. DLY201801), Ruijin Hospital (No. 2018 CR002) and Shanghai Rising-Star Program (No. 21QA1408100).

Compliance with ethics guidelines

Jialu Wang, Shanshan Liu, Qiuyu Cao, Shujing Wu, Jingya Niu, Ruizhi Zheng, Lizhan Bie, Zhuojun Xin, Yuanyue Zhu, Shuangyuan Wang, Hong Lin, Tiange Wang, Min Xu, Jieli Lu, Yuhong Chen, Yiping Xu, Weiqing Wang, Guang Ning, Yu Xu, Mian Li, Yufang Bi, and Zhiyun Zhao have no conflict of interest to declare. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Electronic Supplementary Material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-021-0888-8 and is accessible for authorized users.

References

1. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020; 158(7): 1999–2014.e1
2. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, Zheng MH, Shiha G, Yilmaz Y, Gani R, Alam S, Dan YY, Kao JH, Hamid S, Cua IH, Chan WK, Payawal D, Tan SS, Tanwandee T, Adams LA, Kumar M, Omata M, George J. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020; 14(6): 889–919
3. Mendez-Sanchez N, Arrese M, Gadano A, Oliveira CP, Fassio E, Arab JP, Chávez-Tapia NC, Dirchwolf M, Torre A, Ridruejo E, Pinchemel-Cotrim H, Castellanos Fernández MI, Uribe M, Girala M, Diaz-Ferrer J, Restrepo JC, Padilla-Machaca M, Dagher L, Gatica M, Olaechea B, Pessôa MG, Silva M. The Latin American Association for the Study of the Liver (ALEH) position statement on the redefinition of fatty liver disease. Lancet Gastroenterol Hepatol 2021; 6(1): 65–72
4. Shiha G, Alswat K, Al Khatry M, Sharara AI, Örmeci N, Waked I, Benazzouz M, Al-Ali F, Hamed AE, Hamoudi W, Attia D, Derbala M, Sharaf-Eldin M, Al-Busafi SA, Zaky S, Bamakhrama K, Ibrahim N, Ajlouni Y, Sabbah M, Salama M, Anushiravani A, Afredj N, Barakat S, Hashim A, Fouad Y, Soliman R. Nomenclature and definition of metabolic-associated fatty liver disease: a consensus from the Middle East and north Africa. Lancet Gastroenterol Hepatol 2021; 6(1): 57–64

5. Spearman CW, Desalegn H, Ocama P, Awuku YA, Ojo O, Elsahhar M, Abdo AA, Ndububa DA, Fouad Y, Borodo MM, Ng' wanasayi M, Ally R, Elwakil R. The sub-Saharan Africa position statement on the redefinition of fatty liver disease: from NAFLD to MAFLD. J Hepatol 2021; 74(5): 1256–1258
6. Fouad Y, Elwakil R, Elsahhar M, Said E, Bazeed S, Ali Gomaa A, Hashim A, Kamal E, Mehrez M, Attia D. The NAFLD-MAFLD debate: eminence vs evidence. Liver Int 2021; 41(2): 255–260
7. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64(6): 1388–1402
8. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020; 73(1): 202–209
9. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015; 313(22): 2263–2273
10. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J Hepatol 2016; 65(3): 589–600
11. Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, Inoguchi T, Maeda Y, Kohara K, Tabara Y, Nakamura M, Ohkubo T, Watada H, Munakata M, Ohishi M, Ito N, Nakamura M, Shoji T, Vlachopoulos C, Yamashina A, Nagano M, Yukiyo O, Kabutoya T, Asayama K, Takashima N, Chowdhury TT, Mitsuki-Shinohara K, Yamashita T; Collaborative Group for J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies). Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. Hypertension 2017; 69(6): 1045–1052
12. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schöttker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Ärnlöv J; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol 2015; 3(7): 514–525
13. Zheng J, Zhou Y, Zhang K, Qi Y, An S, Wang S, Zhao X, Tang YD. Association between nonalcoholic fatty liver disease and subclinical atherosclerosis: a cross-sectional study on population over 40 years old. BMC Cardiovasc Disord 2018; 18(1): 147
14. Zhu WH, Fang LZ, Lu CR, Dai HL, Chen JH, Qiao QH, Chen LY. Correlation between non-alcoholic fatty liver with metabolic risk factors and brachial-ankle pulse wave velocity. World J Gastroenterol 2015; 21(35): 10192–10199
15. Li N, Zhang GW, Zhang JR, Jin D, Li Y, Liu T, Wang RT. Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. Nutr Metab Cardiovasc Dis 2015; 25(2): 218–223
16. Kang SH, Cho KH, Do JY. Non-alcoholic fatty liver disease is associated with low-grade albuminuria in men without diabetes mellitus. Int J Med Sci 2019; 16(2): 285–291
17. Li M, Xu Y, Xu M, Ma L, Wang T, Liu Y, Dai M, Chen Y, Lu J, Liu J, Bi Y, Ning G. Association between nonalcoholic fatty liver disease (NAFLD) and osteoporotic fracture in middle-aged and elderly Chinese. J Clin Endocrinol Metab 2012; 97(6): 2033–2038
18. Xin Z, Zhu Y, Wang S, Liu S, Xu M, Wang T, Lu J, Chen Y, Zhao Z, Wang W, Ning G, Bi Y, Xu Y, Li M. Associations of subclinical atherosclerosis with nonalcoholic fatty liver disease and fibrosis assessed by non-invasive score. Liver Int 2020; 40(4): 806–814
19. Ampuero J, Pais R, Aller R, Gallego-Durán R, Crespo J, García-Monzón C, Boursier J, Vilar E, Petta S, Zheng MH, Escudero D, Calleja JL, Aspichueta P, Diago M, Rosales JM, Caballería J, Gómez-Camarero J, Lo Iacono O, Benlloch S, Albillos A, Turnes J, Banales JM, Ratziu V, Romero-Gómez M; HEPAmet Registry. Development and validation of hepamet fibrosis scoring system—a simple, noninvasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. Clin Gastroenterol Hepatol 2020; 18(1): 216–225.e5
20. Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol 2020; 8(7): 616–627
21. Kim NH, Park J, Kim SH, Kim YH, Kim DH, Cho GY, Baik I, Lim HE, Kim EJ, Na JO, Lee JB, Lee SK, Shin C. Non-alcoholic fatty liver disease, metabolic syndrome and subclinical cardiovascular changes in the general population. Heart 2014; 100(12): 938–943
22. Hong HC, Hwang SY, Ryu JY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The synergistic impact of nonalcoholic fatty liver disease and metabolic syndrome on subclinical atherosclerosis. Clin Endocrinol (Oxf) 2016; 84(2): 203–209
23. Wijarnpreecha K, Thongprayoon C, Boonpheng B, Panjawatanan P, Sharma K, Ungprasert P, Pungpapong S, Cheungpasitporn W. Nonalcoholic fatty liver disease and albuminuria: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018; 30(9): 986–994
24. Liu Z, Suo C, Shi O, Lin C, Zhao R, Yuan H, Jin L, Zhang T, Chen X. The health impact of MAFLD, a novel disease cluster of NAFLD, is amplified by the integrated effect of fatty liver disease-related genetic variants. Clin Gastroenterol Hepatol 2020: S1542-3565(20)31729-8
25. Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, Wu Y, Wang X, Zhu Y. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int 2020; 40(9): 2082–2089
26. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol 2020; S1542-3565(20): 31717–1
27. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019; 7(4): 313–324
28. Chen Y, Xu M, Wang T, Sun J, Sun W, Xu B, Huang X, Xu Y, Lu J, Li X, Wang W, Bi Y, Ning G. Advanced fibrosis associates with atherosclerosis in subjects with nonalcoholic fatty liver disease. Atherosclerosis 2015; 241(1): 145–150
29. Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, Takahashi H, Anzai K, George J, Torimura T. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int 2020; 40(12): 3018–3030