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Original Article

Comparison of Clinical Characteristics and Outcomes of MAFLD and NAFLD in Chinese Health Examination Populations

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Abstract

Background and Aims: The recently proposed concept of metabolic dysfunction-associated fatty liver disease (MAFLD) has remained controversial. We aimed to describe the features and associated outcomes to examine the diagnostic ability of MAFLD for identifying high-risk individuals. ***Methods:*** In this retrospective cohort study, we enrolled 72,392 Chinese participants between 2014 and 2015. Participants were classified as MAFLD, nonalcoholic fatty liver disease (NAFLD), non-MAFLD-NAFLD, and a normal control group. The primary outcomes were liver-related and cardiovascular disease (CVD) events. Person-years of follow-up were calculated from enrolment to the diagnosis of the event, or the last date of data (June, 2020). ***Results:*** Of the 72,392 participants, 31.54% (22,835) and 28.33% (20,507) qualified the criteria for NAFLD or MAFLD, respectively. Compared with NAFLD, MAFLD patients were more likely to be male, overweight, and have higher biochemical indices including liver enzyme levels. Lean MAFLD diagnosed with ≥2 or ≥3 metabolic abnormalities presented similar clinical manifestations. During the median follow-up of 5.22 years, 919 incident cases of severe liver disease and 2,073 CVD cases were recorded. Compared with the normal control group, the NAFLD and MAFLD groups had a higher cumulative risk of liver failure and cardiac-cerebral vascular diseases. There were no significant differences in risk between the non-MAFLD-NAFLD and normal group. Diabetes-MAFLD group had the highest incidence of liver-related and cardiac-cerebral vascular diseases, lean MAFLD came second, and obese-MAFLD had the lowest incidence. ***Conclusions:*** This real-world study provided evidence for rationally assessing the benefit and practicability of the change in terminology from NAFLD to MAFLD. MAFLD may be better than NAFLD in identifying fatty liver with worse clinical features and risk profile.

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Introduction

Over the past decades, nonalcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in the world, affecting nearly 1 billion people globally.[1–3] NAFLD is a multisystem disorder and the clinical burden of the disease is not limited to liver-related complications, but also involves extrahepatic diseases.[4,5] In 2020, an international expert consensus panel proposed a novel concept of Metabolic dysfunction-associated fatty liver disease (MAFLD) to describe liver disease associated with known metabolic dysfunction.[6] The new concept is defined by a set of positive diagnostic criteria for fatty liver disease (FLD) associated with metabolic dysfunction, rather than by exclusion criteria. The increasing prevalence of MAFLD coexists with other chronic liver diseases, and has the critical importance of proposing a diagnosis based on inclusion criteria. Younossi *et al*.[7,8] reckoned that the term is ambiguous, as it is never accurate to assign a single name to a disease as heterogeneous as NAFLD. Hence, there is no clear consensus on the change in definition from NAFLD to MAFLD.

Keywords: Metabolic-associated fatty liver disease; Non-alcoholic fatty liver disease; Liver-related disease; Cardiac vascular disease; Cerebral vascular disease.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; FLD, fatty liver disease; GGT, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICD-10, International Classification of Diseases-Tenth Revision; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride.

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While cross-sectional studies point to the difference in the features of MAFLD and NAFLD,[9,10] it is not clear whether the MAFLD definition is more practical for identifying patients with worse clinical features. Inconsistencies in cross-sectional studies may have many reasons, including limitation of study design, small sample size, and reverse causation. A cohort study, which is prospectively designed from cause to outcome, can examine the causal association between FLD groups and the long-term outcome. Therefore, risk assessment of long-term outcomes based on cohort study data may provide real-world evidence to provide the reasoning for the change in definition. To fill this gap in the literature, we conducted a large retrospective cohort study of 72,392 Chinese adults to evaluate the rationality of the MAFLD definitions by assessing the risk of liver-related and cardiac-cerebral vascular diseases. The median follow-up in our cohort was 5.22 years.

Methods

Study participants

This was a single-center, retrospective cohort study conducted in China. We enrolled 121,020 health check examinees who visited the Health Promotion Center of the First Affiliated Hospital of Nanjing Medical University in Jiangsu between January 2014 and December 2015. All patients underwent abdominal ultrasonography as part of their routine health examination. Of those, 31,886 were excluded because of duplicate records, lack of data for the diagnosis of MAFLD (n=11,893), lack of data for alcohol consumption (n=3,310), having a history of hepatocellular carcinoma (HCC), cirrhosis, liver failure, cardiovascular or cerebrovascular disease (n=1,539). The study cohort thus comprised 72,392 participants (Supplementary Fig. 1). The First Affiliated Hospital with Nanjing Medical University Ethics Review Board approved the study protocol and informed consent was obtained from all subjects.

Group definitions

According to the guidelines for the prevention and treatment for NAFLD (2018 update), abdominal ultrasonography was performed for hepatic steatosis.[11] The severity of hepatic steatosis (negative, mild, moderate, and severe) was assessed based on the imaging findings retrieved from medical records. The MAFLD group included participants with fatty liver with the following three conditions: overweight or obese, a body mass index (BMI) ≥23 kg/m^2 in Asians, type 2 diabetes mellitus (T2DM), or two or more of the following metabolic conditions:[6] (1) waist circumference ≥90 cm in men and ≥80 cm in women (central obesity); (2) blood pressure ≥130/85 mmHg or receiving antihypertension medication; (3) plasma triglycerides ≥1.7 mmol/L or receiving lipid-lowering drugs; (4) plasma high-density lipoprotein-cholesterol (HDL-C) < 1.0 mmol/L in men and <1.3 mmol/L in women, or receiving specific drug treatment; (5) prediabetes, a fasting plasma glucose (FPG) of 5.6–6.9 mmol/L or a hemoglobin A1c (HbA1c) of 5.7–6.4%; (6) a homeostasis model assessment of insulin resistance (HOMA-IR) score ≥2.5; and (7) plasma high-sensitivity C-reactive protein level >2 mg/L. Participants with a BMI <23.0 kg/m^2 who had ≥2 or ≥3 metabolic abnormalities were recorded as thinner with ≥2 metabolic abnormalities (1,242 participants) or thinner with ≥3 metabolic abnormalities (457 participants).

The definition of NAFLD was based on ultrasound evidence of fatty liver and the exclusion of both secondary causes such as viral hepatitis or drug-induced hepatitis, and excessive alcohol consumption (≥30 g/d for men and ≥20 g/d for women) based on the detailed medical history including medications, alcohol consumption, and laboratory data. The non-MAFLD-NAFLD group included those who satisfied the diagnostic criteria for NAFLD but not the definition of MAFLD. The group was characterized by fatty liver without competing causes of steatosis (e.g., alcohol, viral hepatitis, or other causes), obesity, metabolic dysfunction, and diabetes. Similarly, the non-NAFLD-MAFLD group included those who met the diagnostic criteria for MAFLD but not those of NAFLD. The non-NAFLD-MAFLD group included fatty liver patients with obesity, metabolic dysfunction, or diabetes regardless of having other competing causes of steatosis. The MAFLD with NAFLD group included those who met the diagnostic criteria for both MAFLD and NAFLD, and the non-NAFLD with non-MAFLD group included those not satisfying the diagnostic criteria of either MAFLD or NAFLD.

Demographic and clinical characteristics

Demographic and clinical variables were obtained from the health examination database, including age, sex, alcohol consumption, weight, height, waist circumference, severity of hepatic steatosis estimated by ultrasound (mild, moderate, or severe hepatic steatosis), history of diabetes and hypertension, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, laboratory indices (related metabolic indices, liver biochemistry, and tumor markers), and BMI (kg/m^2). Venous blood samples for laboratory testing were collected after overnight fasting of at least 8 h. The metabolic indices included blood urea nitrogen (BUN), creatinine, albumin, HbA1c, FPG, total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and HDL-C. Liver biochemistry included total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), and lactic dehydrogenase (LDH). Tumor markers included alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA). Two noninvasive liver fibrosis scores with published formulae and cutoffs were calculated to evaluate liver fibrosis, AST-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4). The APRI index was calculated as (AST level/upper limit of normal) / platelet count (10^9/L) × 100. The higher cutoff value (1.50) was identified as the criteria for significant fibrosis.[12] The FIB-4 index was derived by age (years), serum levels of AST (U/L), ALT (U/L), and platelet count (10^9/L) as previously described.[13] The low cut-off value (1.30) was found to have good diagnostic accuracy for discriminating advanced fibrosis.

Outcomes

For each participant, hospitalization information was obtained by telephone interviews conducted yearly. We collected the diagnoses and International Classification of Diseases–Tenth Revision (ICD-10) codes from electronic medical records (EMR). The primary outcomes were liver-related and cardiac-cerebral vascular event, including cirrhosis (ICD-10 K70.2-K70.3, K74.1-K74.6), HCC; ICD-10 C22.1, C24.0, and C24.8-C24.9), liver failure (hepatic failure; ICD-10 K72.0, K72.1, and K72.9), coronary heart disease (ICD-10 I24.0-I24.1, I25.0-I25.1), stroke (ICD-10 I63, I69.3-I69.4, and G46.3-G46.4), heart failure (ICD-10 I11.0, I11.9, I13.0, I13.2, and I50), and cardiomyopathy (ICD-10 I40-I43). Person-years of follow-up were calculated as the time from enrolment to the diagnosis of the event, or the date at death, or the last date of data collection (June, 2020), whichever came first. Median follow-up was calculated using the more robust reverse Kaplan–Meier method.

Statistical analysis

Continuous variables were reported as means ± standard deviation (SD) and between-group differences were assessed using the Student's *t*-test, Welch's *t*-test, or the Wilcoxon rank-sum (Mann-Whitney U) test. Multigroup comparisons were performed using one-way analysis of variance or the linear mixed-effects model depending on whether the assumption of variance equality for analysis of variance was confirmed, followed by post-hoc Bonferroni's correction. Multiple comparisons and the unequal sample size between groups increase the probability of type I error. Categorical variables were reported as frequency and percentage, and between-group differences were assessed using chi-squared or Fisher's exact tests. Comparisons of categorical variables between multiple groups were followed by Bonferroni's correction. Survival analysis was performed using Cox proportional hazards models or the accelerated failure time (AFT) model. Multivariable analysis was used to estimate the association between the FLD groups and outcomes, adjusting for age at baseline (continuous) and sex (female or male). As previously described, the multivariable model was adjusted by sociodemographic indices including age, sex, race, income, and marital status.[14,15] However, owing to the lack of availability of data for other sociodemographic features, only age and sex were adjusted for in the model.

We performed stratified analysis by sex and HBV infection status. The statistical analysis was performed with Stata version 15.0 (Stata Corp, TX, United States) and R version 4.0.3. Two-sided *p*-values <0.05 were considered statistically significant. For comparisons among four groups in Table 1 and among five groups in Supplementary Table 1, all *p*-values shown are the Bonferroni-corrected with six and ten multiple tests in consideration of convenience. Statistical tests were performed for six or ten comparisons, with a type I error threshold of $p'<0.0083$ and 0.005 ($\alpha=0.05$ with Bonferroni's correction for multiple comparisons).

Results

Baseline characteristics

Of the 72,392 eligible participants, 22,835 (31.54%) satisfied the NAFLD criteria. The prevalence of FLD was lower when defined by MAFLD (28.33%, Table 1), and 2,574 participants previously classified as NAFLD did not meet the MAFLD criteria (non-MAFLD-NAFLD), 246 (0.34%) classified as MAFLD did not satisfy the NAFLD criteria (non-NAFLD-MAFLD), and 20,261 (27.99%) who met the criteria for both NAFLD and MAFLD (Supplementary Table 1). Compared with the NAFLD group, the MAFLD group was more likely to be male, overweight, and have severe hepatic steatosis and higher biochemical indices, including serum levels of ALT, GGT, FGP, TG, and HDL-C (Table 1). Besides. Only 84 patients in the MAFLD group had alcohol-associated liver disease. Although not satisfying the conditions for NAFLD, the non-NAFLD-MAFLD group were also predominantly male, overweight, had worse hepatic steatosis, and higher non-invasive liver fibrosis scores, and had significantly worse biochemical indices, including serum levels of liver enzymes and related metabolic and liver biochemical indices compared with the non-FLD (normal) group and the non-MAFLD-NAFLD group (Supplementary Table 1). Of note, after excluding patients with concurrent diagnosis of NAFLD and MAFLD, differences of the biochemical indices between the non-MAFLD-NAFLD and the non-NAFLD-MAFLD group were greater than those between the NAFLD and MAFLD group (Table 1 and Supplementary Table 1). The non-MAFLD-NAFLD group versus non-NAFLD-MAFLD group: mean ALT, 26.59 vs. 43.65, mean GGT, 33.69 vs. 54.85, and mean TG, 1.56 vs. 2.04; NAFLD versus MAFLD group: mean ALT, 33.47 vs. 34.45, mean GGT, 43.15 vs. 44.52, and mean TG, 2.13 vs. 2.19. Comparatively, the non-MAFLD-NAFLD group had a more modest clinical features than the NAFLD and MAFLD groups. The results of the comparison indicated the capacity of packing more severe cases of the new FLD definition.

The clinical indices of different MAFLD subtypes were compared (Supplementary Table 2). Among the 20,507 MAFLD patients, 19,053 with BMIs ≥23.0 kg/m^2 were assigned to the BMI-related MAFLD group (obese-MAFLD), and 2,763 with diabetes assigned to the diabetes-related MAFLD group (diabetes-MAFLD). We found that the two groups had similar clinical manifestations, except for metabolic abnormalities. The thinner with ≥2 metabolic abnormalities group was characterized by generally worse clinical features compared with the participants without fatty livers, including serum levels of liver enzymes, HbA1c, FPG, serum lipids, and indicators of hepatic fibrosis.

Risk of liver-related and cardiac-cerebrovascular disease

In the 72,392 participants, 1,274 stroke, 952 coronary heart disease, 793 liver failure, 522 heart failure, 123 cirrhosis, 40 cardiomyopathy, and 39 hepatocellular carcinoma (HCC) events occurred during the median follow-up of 5.22 (interquartile range: 5.21–5.22) years. The incidence rates of the events were 357.49/100,000, 280.07/100,000, 229.34/100,000, 147.60/100,000, 31.22/100,000, 12.05/100,000, and 10.47/100,000 participant years, respectively (Supplementary Fig. 2).

Supplementary Figure 3 shows the incident rates of liver-related and cardiac-cerebral vascular diseases in the FLD groups. The association of different FLD groups with the risk of liver-related and cardiac-cerebral vascular diseases was examined by the Kaplan-Meier method (Fig. 1). The MAFLD and NAFLD groups had a higher cumulative risk of stroke, CHD, liver failure, and heart failure than the normal group. Multivariable Cox regression analysis showed that MAFLD and NAFLD were significantly associated with increased risk of the diseases. The adjusted hazard ratios (HRs) for stroke were 1.27 and 1.23 (95% CI, 1.13–1.42 and 1.10–1.38, respectively; both $p<0.001$). The adjusted HRs for stroke were 1.27 and 1.23 (95% CI, 1.13–1.42 and 1.10–1.38, respectively; both $p<0.001$). The adjusted HRs for CHD were 1.68 (95% CI, 1.48–1.92; $p<0.001$) and 1.63 (95% CI, 1.43–1.85; $p<0.001$). The adjusted HRs for liver failure were 1.61 (95% CI, 1.39–1.86; $p<0.001$) and 1.61 (95% CI, 1.40–1.85; $p<0.001$). The adjusted HRs for heart failure were 1.34 (95% CI, 1.13–1.60; $p=0.001$) and 1.30 (95% CI, 1.00–1.55; $p=0.003$) (Fig. 2). Similar results were seen after adjusting for age and sex ($p<0.05$, Supplementary Table 3). We did not observe significant differences in the risk of HCC or cirrhosis, mostly because of insufficient outcomes. We did not detect significant differences in the risk of liver-related or cardiac-cerebral vascular disease in the non-MAFLD-NAFLD and normal groups.

The MAFLD participants were assigned to three subtypes, obese-MAFLD, diabetes-MAFLD, and lean-MAFLD (participants with BMIs <23.0 kg/m^2 and with ≥2 metabolic abnormalities) (Table 2). Diabetes-MAFLD had the highest incidence of liver-related and cardiac-cerebral vascular disease, lean MAFLD had the second-highest incidence, and obese-MAFLD had the lowest incidence. Unadjusted logistic regression results showed that the three subtypes were significantly associated with increased risk of liver failure, coronary

Table 1. Comparison of clinical parameters according to presence of MAFLD, NAFLD, and non-MAFLD-NAFLD

Variables	Normal (n=48 790)	NAFLD (n=22 835)	MAFLD (n=20 507)	non-MAFLD-NAFLD (n=2 574)	*P*[a] for MAFLD vs. NAFLD	*P*[a] for MAFLD vs. non-MAFLD-NAFLD	*P*[a] for non-MAFLD-NAFLD vs. normal
Age, years	43.04±15.54	48.60±14.42	48.83±14.39	46.70±14.31	0.520	<0.001***	<0.001***
Male, %	25 389 (52.04)	15 975 (69.96)	14 801 (72.18)	1 383 (53.73)	<0.001***	<0.001***	0.563
Severity of fatty liver							
Mild, %	0 (0)	13 316 (58.31)	11 506 (56.11)	1 959 (76.11)			
Moderate, %	0 (0)	9 293 (40.70)	8 790 (42.86)	599 (23.27)			
Severe, %	0 (0)	226 (0.99)	211 (1.03)	16 (0.62)			
BMI, Kg/m^2	22.49±10.73	26.03±2.96	26.38±2.79	21.75±1.13	<0.001***	<0.001***	<0.001***
Excess Alcohol Use, %	110 (0.23)	0 (0)	84 (0.41)	0 (0)	<0.001***	<0.001***	0.042*
Diabetes, %	1 953 (4.17)	2 726 (12.12)	2 763 (13.67)	0 (0)	<0.001***	<0.001***	<0.001***
Hypertension, %	10 139 (20.78)	10 171 (44.54)	9 941 (48.48)	350 (13.60)	<0.001***	<0.001***	<0.001***
Platelets, 10^9/L	222.39±54.91	226.39±56.24	225.53±56.57	231.52±53.54	0.692	<0.001***	<0.001***
BUN, mmoL	4.87±1.79	5.09±1.23	5.11±1.24	4.90±1.17	0.292	<0.001***	1.000
Creatinine, μmolL	69.24±19.78	72.73±16.76	73.29±16.88	68.36±14.65	0.003*	<0.001***	0.025*
TBIL, μmolL	13.30±5.47	13.07±5.21	13.10±5.19	12.93±5.48	1.000	1.000	0.030*
ALT, U/L	20.62±19.30	33.47±24.68	34.45±25.27	26.59±19.63	<0.001***	<0.001***	<0.001***
AST, U/L	22.15±11.43	26.27±15.82	26.60±16.13	24.05±12.97	0.230	<0.001***	<0.001***
GGT, U/L	26.44±34.74	43.15±39.53	44.52±40.30	33.69±33.28	0.008**	<0.001***	<0.001***
ALP, U/L	74.58±22.36	81.55±22.07	81.86±22.06	78.56±21.80	1.000	<0.001***	<0.001***
LDH, U/L	181.79±34.03	190.83±36.43	191.42±36.73	185.86±32.88	0.894	<0.001***	<0.001***
Albumin, g/L	45.51±2.85	45.69±2.75	45.72±2.75	45.50±2.79	1.000	0.011*	1.000
HbA1c, %	5.53±0.62	5.83±0.87	5.87±0.89	5.47±0.36	0.554	<0.001***	0.031*
FPG, mmol/L	5.18±0.90	5.66±1.37	5.72±1.43	5.16±0.50	<0.001***	<0.001***	0.254
TC, mmol/L	5.00±0.95	5.34±1.02	5.35±1.02	5.29±1.00	1.000	0.026*	<0.001***
TG, mmol/L	1.23±0.84	2.13±1.70	2.19±1.74	1.56±1.18	<0.001***	<0.001***	<0.001***
LDL-C, mmol/L	3.15±0.75	3.48±0.77	3.49±0.77	3.42±0.78	1.000	<0.001***	<0.001***
HDL-C, mmol/L	1.41±0.32	1.22±0.26	1.20±0.26	1.34±0.29	<0.001***	<0.001***	<0.001***
APRI score, mean ± SD	0.27±0.23	0.31±0.23	0.32±0.24	0.28±0.18	0.137	<0.001***	0.395
APRI score >1.5, n (%)	81 (0.20)	58 (0.29)	56 (0.31)	4 (0.17)	1.000	1.000	1.000
FIB-4 score, mean ± SD	1.13±1.09	1.15±0.68	1.16±0.68	1.11±0.70	1.000	0.030*	1.000
FIB-4 score >1.3, n (%)	11 531 (28.05)	6 335 (31.16)	5 777 (31.67)	643 (27.75)	1.000	<0.001***	1.000
AFP	3.10±6.19	3.13±2.22	3.13±2.26	3.12±1.82	1.000	1.000	1.000
CEA	2.05±5.51	2.21±3.33	2.23±2.94	2.05±5.43	1.000	0.611	1.000

[a]*p* value was the Bonferroni-corrected with six multiple comparisons. *p<0.05, **p<0.01 and ***p<0.001. AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, alanine aminotransferase -to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; FIB-4, Fibrosis-4 index; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDH, lactic dehydrogenase; LDL-C, low-density lipoprotein-cholesterol; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride.

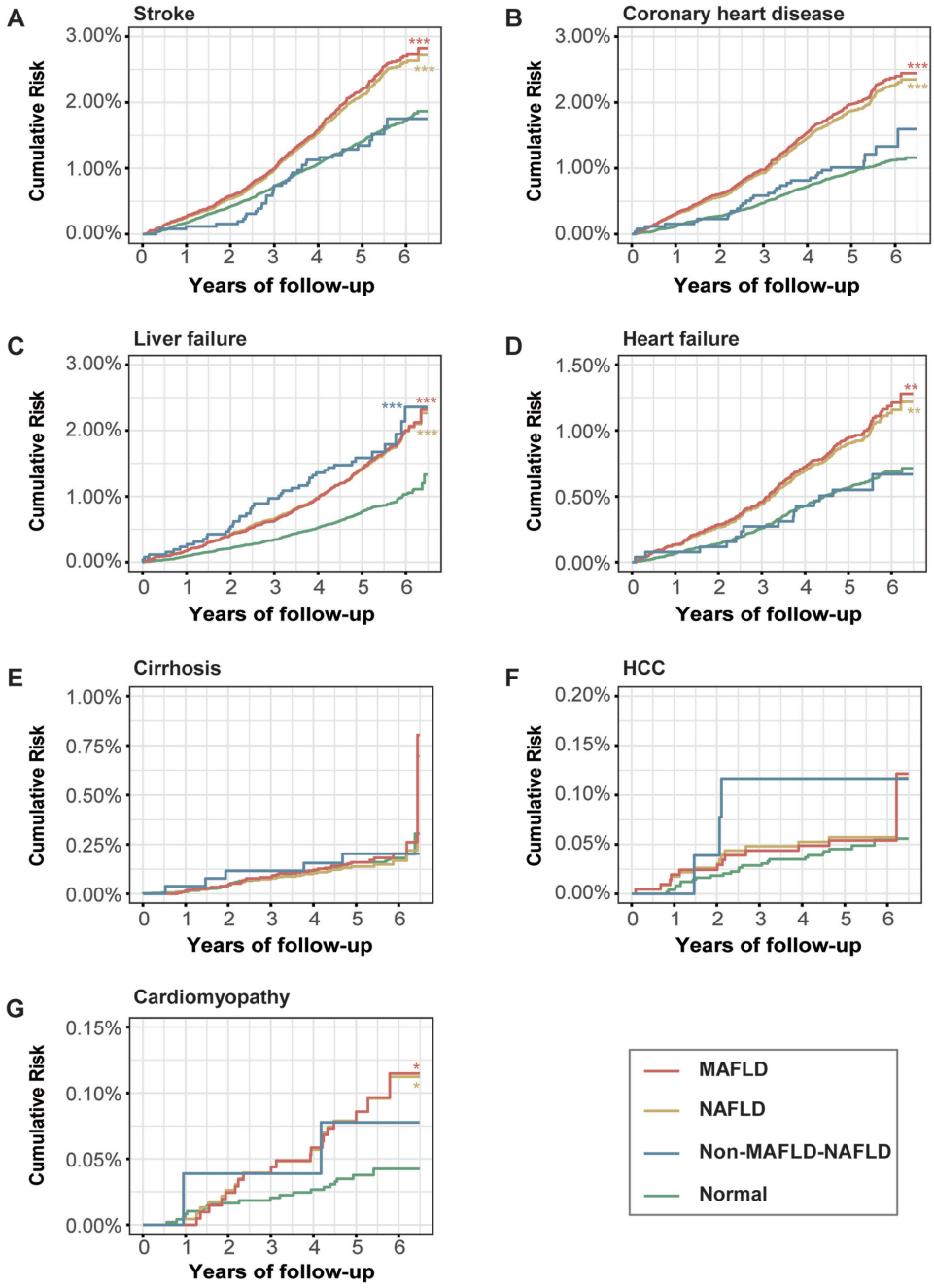

Fig. 1. Cumulative risk of developing incident (A) Stroke, (B) Coronary heart disease, (C) Liver failure, (D) Heart failure, (E) Cirrhosis, (F) Hepatocellular carcinoma, (G) Cardiomyopathy in four different classifications of fatty liver. The normal group was the reference. Survival models were adjusted for age and sex. $^{*}p<0.05$, $^{**}p<0.01$. $^{***}p<0.001$.

heart disease, and stroke. In addition, diabetes-MAFLD and lean MAFLD were associated with significantly higher risk.

Association of steatosis severity with liver-related and cardiac-cerebral vascular outcomes is shown in Supplementary Table 4. The moderate and severe FLD group had higher cumulative risks of stroke, CHD, liver failure, heart failure, and cirrhosis than the non-FLD group (Fig. 3). Multivariable Cox regression analysis found that moderate and severe FLD patients had a significant association with increased risk of the diseases [adjusted HR for stroke: 1.24 (95% CI, 1.07–1.44) and 1.35 (95% CI, 0.50–3.60), p=0.005 and 0.552, respectively; adjusted HR for CHD: 1.54 (95% CI, 1.30–1.83) and 2.42 (95% CI, 1.00–5.84), p<0.001 and p<0.049, respectively]. The adjusted HRs for liver failure were 1.99 (95% CI, 1.67–2.38; p<0.001) and 2.68 (95% CI, 1.11–6.47; p<0.029). The adjusted HRs for heart failure were 1.34 (95% CI, 1.06–1.68; p=0.014) and 0.78 (95% CI, 0.11–5.54; p=0.802) (Supplementary Table 4). We conducted sensitivity analyses stratified by sex (Supplementary Table 5) and HBV infection (Supplementary Table 6). The associations of

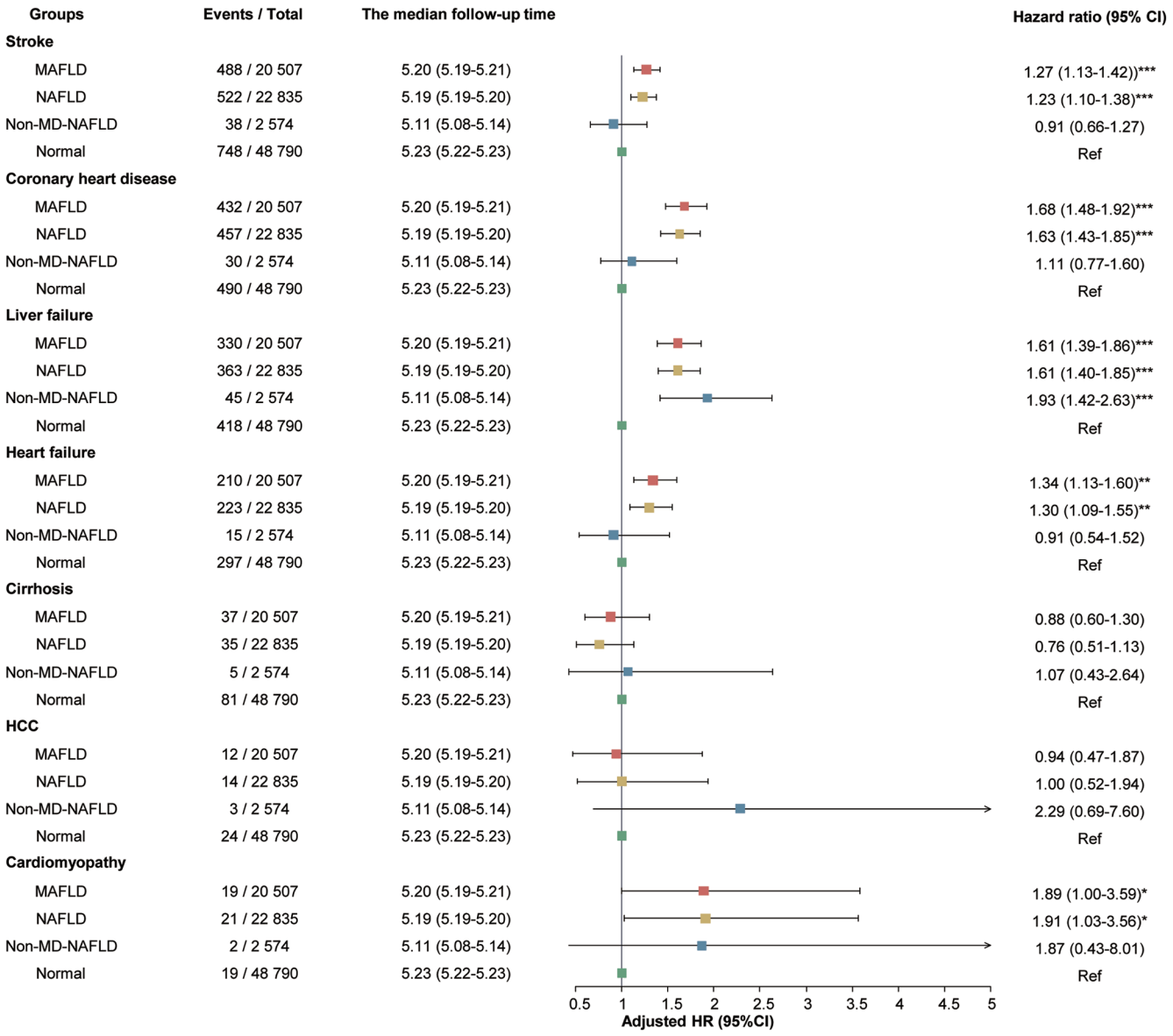

Fig. 2. Impact of four different classifications of fatty liver on liver-related and cardiovascular disease outcomes. Hazard ratios were obtained from adjusted survival models with the normal group as reference.

MAFLD and NAFLD with liver failure and individual cardiac-cerebral vascular diseases were statistically significant in all subgroups. We did not observe significant differences in risk in the non-MAFLD-NAFLD and normal group in any subgroup.

Discussion

The principal finding of this study was that MAFLD definition had better ability to identify patients with clinical characteristics significantly worse than the NAFLD definition. Although a significant proportion of patients qualified the diagnostic criteria for both NAFLD and MAFLD, non-NAFLD-MAFLD group showed significantly worse clinical manifestations. In addition, thin patients diagnosed with ≥2 or ≥3 metabolic abnormalities presented a similar clinical manifestation. We saw that FLD was associated with a higher risk of cardiac-cerebral vascular events, despite whether defined as MAFLD or NAFLD. Participants with NAFLD but not MAFLD had a similar risk with those without fatty liver, but were at risk lower than those with MAFLD.

Ever since the introduction of MAFLD to replace NAFLD by a panel of international experts, the novel terminology of MAFLD has sparked widespread discussion and concern, but has gained increasing acceptance and endorsement.[6,16–19] Real-world studies on MAFLD must provide strong evidence for rationally assessing the benefit and practicability of the change in terminology. Our study confirmed the rationality of the term change from three parts: 1) MAFLD was found more sensitive than NAFLD in discriminating patients with poorer clinical features and fibrosis at risk. Our results followed an earlier cross-sectional study based on the third National Health and Nutrition Examination Surveys of the United States (NHANES III).[9] The study found that compared with NAFLD, MAFLD patients were significantly older, had higher

Table 2. Adjusted hazard ratios of incident severe liver disease and cardio-cerebrovascular disease in MAFLD defined by different criteria

Outcomes	No. of total	The median follow-up time [Years (95%CI)]	PYs	No. of events	Incidence rate per 100 000 PYs	HR (95% CI)	*P*	aHR[a] (95% CI)	*P*	*P*[b]
Cirrhosis [c]										0.606
Normal	48 790	5.23 (5.22 - 5.23)	261,514.7	81	30.97	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.20 (5.20 - 5.21)	101,733.5	35	34.40	1.12 (0.75–1.66)	0.579	0.91 (0.61–1.36)	0.645	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.32)	14,829.4	10	67.43	2.20 (1.14–4.25)	0.018*	1.13 (0.58–2.20)	0.715	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,559.5	2	30.49	1.00 (0.25–4.09)	0.994	0.62 (0.15–2.52)	0.501	
HCC[c]										0.833
Normal	48 790	5.23 (5.22 - 5.23)	261,644.7	24	9.17	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.20 (5.20 - 5.21)	101,772.1	11	10.81	1.18 (0.58–2.41)	0.652	0.93 (0.46–1.91)	0.847	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.32)	14,839.9	3	20.22	2.20 (0.66–7.31)	0.198	0.98 (0.29–3.27)	0.975	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,560.4	1	15.24	1.67 (0.23–12.32)	0.617	1.08 (0.15–8.02)	0.940	
Liver failure[d]										0.004**
Normal	48 790	5.23 (5.22 - 5.23)	260,823.5	418	160.26	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.20 (5.20 - 5.22)	101,168.1	302	298.51	1.87 (1.60–2.18)	<0.001***	1.62 (1.39–1.89)	<0.001***	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.31)	14,668.9	69	470.38	2.94 (2.25–3.83)	<0.001***	1.87 (1.44–2.44)	<0.001***	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,529.5	25	382.88	2.40 (1.60–3.61)	<0.001***	1.66 (1.10–2.49)	0.015*	
Coronary heart disease[c]										0.215
Normal	48 790	5.23 (5.22 - 5.23)	260,513.7	490	188.09	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.21 (5.20 - 5.21)	100,852.4	389	385.71	2.05 (1.79–2.34)	<0.001***	1.69 (1.48–1.93)	<0.001***	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.32)	14,487.7	144	993.95	5.29 (4.39–6.37)	<0.001***	2.32 (1.93–2.80)	<0.001***	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,502.0	30	461.40	2.45 (1.70–3.54)	<0.001***	1.38 (0.96–2.00)	0.086	
Stroke[c]										0.579
Normal	48 790	5.23 (5.22 - 5.23)	259,944.7	748	287.75	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.21 (5.20 - 5.21)	100,816.0	439	435.45	1.52 (1.35–1.70)	<0.001***	1.28 (1.14–1.44)	<0.001***	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.33)	14,439.3	172	1,191.20	4.15 (3.52–4.90)	<0.001***	1.77 (1.50–2.09)	<0.001***	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,485.6	38	585.91	2.04 (1.47–2.83)	<0.001***	1.07 (0.77–1.49)	0.670	
Heart failure[c]										0.309
Normal	48 790	5.23 (5.22 - 5.23)	261,016.5	297	113.79	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.20 (5.19 - 5.21)	101,347.8	192	189.45	1.66 (1.39–2.00)	<0.001***	1.38 (1.15–1.65)	0.001**	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.32)	14,658.9	70	477.53	4.19 (3.23–5.44)	<0.001***	1.87 (1.44–2.43)	<0.001***	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,538.5	12	183.53	1.61 (0.90–2.87)	0.105	0.89 (0.50–1.59)	0.699	
Cardiomyopathy[c]										0.527
Normal	48 790	5.23 (5.22 - 5.23)	261,659.8	19	7.26	Ref	Ref	Ref	Ref	
Obese-MAFLD	19 053	5.20 (5.20 - 5.21)	101,768.6	18	17.69	2.44 (1.28–4.64)	0.007**	1.94 (1.02–3.71)	0.044*	
Diabetes-MAFLD	2 763	5.27 (5.25 – 5.32)	14,840.1	4	26.95	3.71 (1.26–10.91)	0.017*	1.81 (0.61–5.35)	0.287	
Lean MAFLD	1 242	5.11 (5.06 - 5.18)	6,562.3	1	15.24	2.10 (0.28–15.67)	0.470	1.31 (0.17–9.83)	0.794	

[a]Models were adjusted for age at baseline (continuous) and sex (female or male). [b]Tests of proportional hazards assumption for adjusted models. [c]Survival analysis was started by Cox proportional hazards models. [d]Survival analysis was started by AFT model. *p<0.05, **p<0.01 and ***p<0.001. aHR, adjusted hazard ratio; HCC, hepatocellular carcinoma; HR, hazard ratio; MAFLD, metabolic associated fatty liver disease; PYs, person-years.

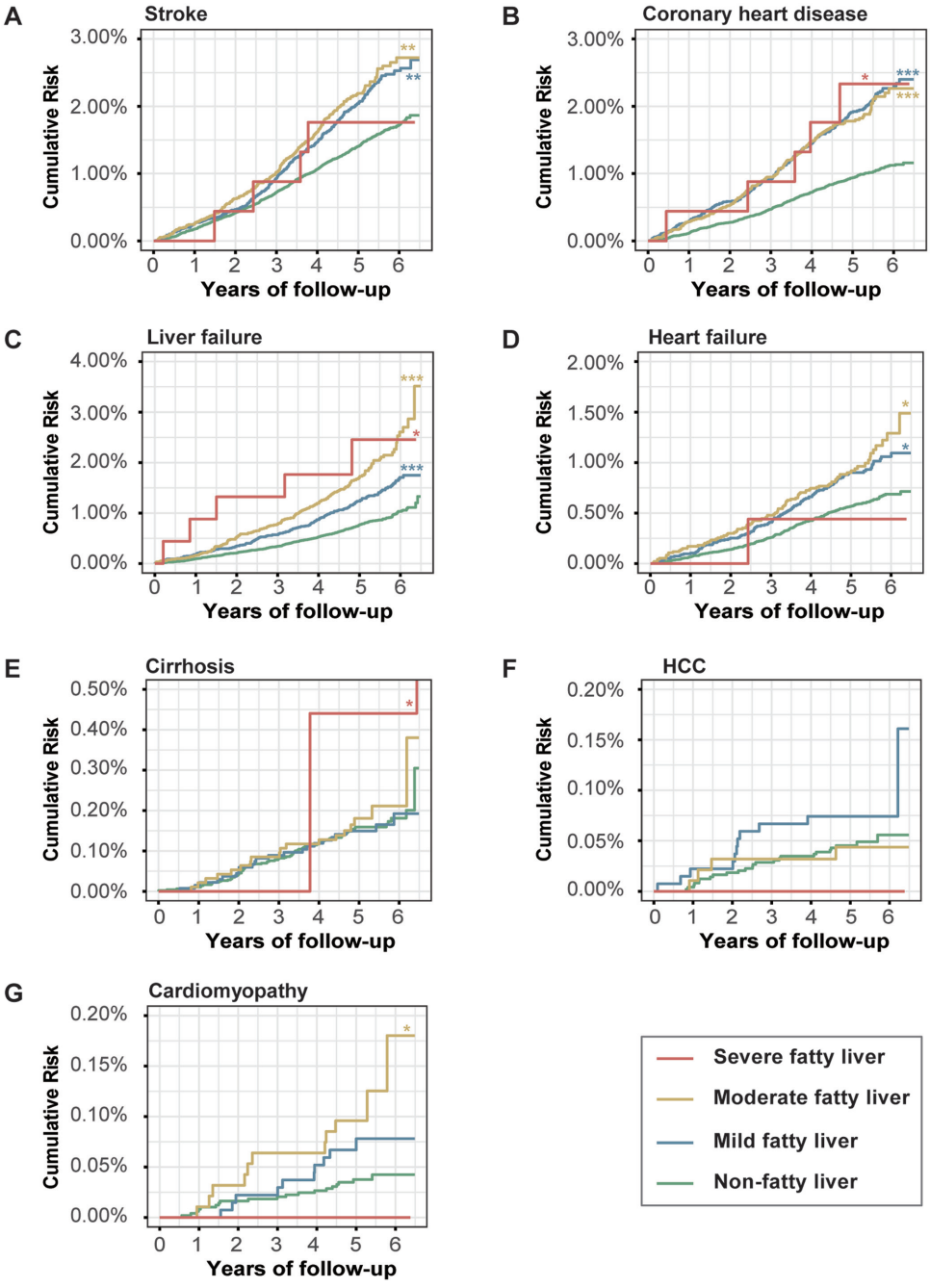

Fig. 3. Cumulative risk of developing incident (A) Stroke, (B) Coronary heart disease, (C) Liver failure, (D) Heart failure, (E) Cirrhosis, (F) Hepatocellular carcinoma, (G) Cardiomyopathy in four groups by steatosis severity. Non-fatty liver was the reference. Survival models were adjusted for age and sex. $^{*}p<0.05$, $^{**}p<0.01$. $^{***}p<0.001$.

BMI level, higher proportions of metabolic comorbidities, and were at a higher risk of disease progression. Another study of 765 Japanese patients also showed that the MAFLD definition better identified patients with significant fibrosis evaluated by non-invasive tests, which follows our results.[20] 2) Patients diagnosed with NAFLD but without MAFLD had a similar risk of liver-related and cardio-cerebral vascular diseases as in those without fatty liver. Similarly, in recent studies, the NAFLD-only group was associated with lower CVD risk and CVD-related mortality and all-cause mortality.[14,21] the NAFLD-only patients had a generally "healthier" characteristics when compared with MAFLD patients. 3) Another concern is the cut-off threshold for the number of metabolic abnormalities. To date, this is among the few studies reporting that lean-MAFLD with ≥2 metabolic abnormalities has similar clinical features as those with ≥ 3 metabolic abnormalities. On the whole, the new definition of MAFLD can identify patients with metabolically complicated fatty liver, and leaves out a small fraction of individuals with metabolically uncomplicated fatty liver, which confers a lower risk of

disease progression.

NAFLD is strongly associated with metabolic conditions such as overweight/obesity and T2DM.[22] However, NAFLD can be diagnosed in so-called lean (non-obese) individuals with BMI < 23 kg/m^2, the prevalence of which ranges between 3.7% and 7.0% in the general population.[23] A meta-analysis suggested that the non-obese or lean NAFLD population was more likely to die from causes related to cardiovascular disease than the obese NAFLD population [cardiovascular-related mortality (per 1,000 PY), 4.0 (0.1–14.9) vs 2.4 (0.0–13.3)], indicating that individuals with BMI < 23 kg/m^2 cannot be overlooked.[23] In our analysis, the cardiac-cerebral vascular disease incidence rate was higher in the lean MAFLD group than in the obese MAFLD group, which follows the previous findings. Of note, the diabetes-MAFLD group had the highest risk of cardiac-cerebral vascular disease, which should be further elucidated.

Another recently published research based on NHANES III (1988–1994) data and the NHANES survey cycle (2017–2018) showed different findings from our study.[24] This discrepancy may be attributable to the vast differences in the study population, classification details and the study outcomes. The participants in our study were Chinese (predominantly Han ethnicity) and had a greater proportion of males (57.89%) and lesser proportion of alcohol-drinkers (0.26%). In contrast, the study population in the previous study comprised of 76.0% non-Hispanic White, 49.5% males, and 15.0% excessive drinkers. The proportion of excessive drinkers in our study was similar to that in a cohort study exploring the epidemiological impact of MAFLD which randomly sampled from the census database of the Hong Kong Government, in which the proportion was only 0.9%.[10] Beyond that, in our study, only 34.15% patients in non-NAFLD-MAFLD group were noted to have alcoholic fatty liver (ALD), but in the research, 99% patients in non-NAFLD-MAFLD group had ALD and the identification ability of MAFLD for high-risk FLD patients was attributed to the impact of ALD on poor outcomes. On the other hand, when diagnosing FLD, our study included all patients with hepatic steatosis, which follows previous studies,[9,14,20] despite the severity (mild, moderate, or severe), but the research only focused on individuals with moderate or severe hepatic steatosis. In addition, the grouping approach based on NAFLD, MAFLD, and non-MAFLD-NAFLD in our study is similar to that in earlier studies but different from the research.[9] Considering the overlapping patients in the NAFLD and MAFLD groups, we also compared the non-MAFLD-NAFLD group and the non-NAFLD-MAFLD group, and the significant differences of biochemical indices were still seen. Moreover, our study focused on the incidence risk of liver-related and cardio-cerebral vascular disease while the outcomes of the research were mortality from any cause and specific causes.

To the best of our knowledge, this is the first large-size Chinese population study to describe the distinctions in clinical features and disease progression between MAFLD and NAFLD. This study confirms the diagnostic ability and the efficacy of the new diagnostic criteria in identifying high-risk individuals and supports the redefinition of the nomenclature considering the inclusive and clinically practical value of MAFLD. However, some limitations of our study should be considered while interpreting the results. First, the study population was derived from physical examinees at a single hospital. This may have limited the representativeness of our findings and our results may have been affected by referral bias. However, the relatively long enrolment period and follow-up time and the large-size of the cohort add to the robustness of the correlation results. Second, all hepatic steatosis patients were diagnosed by ultrasonography examination instead of liver biopsy, the gold-standard. Liver biopsy is not recommended and practiced for the diagnosis of hepatic steatosis because of its invasiveness, high costs, sampling variability, and poor acceptability.[25] Ultrasonography examination is the most commonly used imaging method because of its wider availability, low-cost, convenience, and acceptability.[25] Besides, ultrasonography has an acceptable diagnostic accuracy for hepatic steatosis, with sensitivity and specificity of 84.8% and 93.6% for moderate to severe steatosis and 82% and 80% for ≥5% histologically defined steatosis.[26,27]

Conclusions

In a large-sized longitudinal Chinese cohort, MAFLD definition showed a distinct advantage over NAFLD in identifying a significant subset of patients with worrying clinical manifestations and worse prognosis. Participants with NAFLD but without MAFLD did not show a significantly higher risk of poor prognosis than those without fatty liver. The proposed concept of MAFLD can promote early identification and interventions for hepatic steatosis patients at a higher risk of intrahepatic and extrahepatic complications. The redefinition can help reduce the long-term risks of cardiovascular and cerebrovascular diseases.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Data curation, formal analysis, methodology, roles/writing original draft, formal analysis, methodology (XX), data curation, investigation (XZ), formal analysis (YD), methodology (CY), data curation (LJ, WZ), investigation (XW, JL, WG, QW), data curation, conceptualization, project administration, supervision (QZ), funding acquisition, conceptualization, project administration, methodology, writing, review, and editing (CS).

Ethical statement

The First Affiliated Hospital with Nanjing Medical University Ethics Review Board approved the study protocol and informed consent was obtained from all subjects.

Data sharing statement

Individual participant data will not be shared on public, but be available from the correspondence authors on request through E-mail.

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