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Metabolic dysfunction–associated fatty liver disease indicates more hepatic fibrosis than nonalcoholic fatty liver disease

Shan Hong, MD[a], Zifan Hong, BSc[b], Yiwei Hao, DEco[c], Lei Sun, PhD[d], Hongshan Wei, PhD[a,*]

Abstract

The term metabolic dysfunction–associated fatty liver disease (MAFLD) has been proposed based on a redefinition of the nonalcoholic fatty liver disease (NAFLD) criteria. Our study aimed to address the knowledge gap by comparing the diagnostic accuracy of MAFLD and NAFLD criteria in identifying significant fibrosis among patients with hepatic steatosis. A cross-sectional study was conducted on 2626 patients with hepatic steatosis treated at Beijing Ditan Hospital between January 2009 and December 2022. Patients with viral hepatitis were excluded. Significant fibrosis was defined as a Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) score $F \geq 2$. MAFLD and NAFLD were diagnosed in 478 and 428 patients, respectively. Clinicopathological characteristics were compared between the MAFLD+ NAFLD– group (patients who met the criteria for MAFLD but not NAFLD) and MAFLD– NAFLD+ group (patients who met the criteria for NAFLD but not MAFLD). A total of 743 patients with histologically verified hepatic steatosis were analyzed. The MAFLD+ NAFLD– group comprised 163 (21.9%) and the MAFLD– NAFLD+ group comprised 113 (15.2%) patients. Patients in the MAFLD+ NAFLD– group were older and more likely to be male and had higher body mass index and liver stiffness levels than those in the MAFLD– NAFLD+ group. The prevalence of significant fibrosis was higher in the MAFLD+ NAFLD– group than in the MAFLD– NAFLD+ group (43.6% vs 15.9%, $P < .001$). The MAFLD criteria may be a better indicator of fibrosis than the NAFLD criteria. Fibrosis in patients with MAFLD can be determined by metabolic disorders, not excessive alcohol consumption.

Abbreviations: Alc– = excessive alcohol consumption negative, Alc+ = excessive alcohol consumption positive, BMI = body mass index, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, LSM = liver stiffness measurement, MAFLD = metabolic dysfunction–associated fatty liver disease, NAFLD = nonalcoholic fatty liver disease, NAS = NAFLD activity score, PLT = platelet count, T2DM = type 2 diabetes mellitus, TCHO = total cholesterol, TG = total triglyceride.

Keywords: diagnosis, metabolic syndrome, nonalcoholic fatty liver disease, significant hepatic fibrosis

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) affects 25% to 33% of the global population, making it the most common chronic liver disease.[1-3] In 2021, the incidence of NAFLD in the world population was 3.7 per 100 person-years[4] and is projected to reach ≈314 million cases by 2030.[5-7] Owing to its high prevalence, NAFLD is one of the leading causes of cirrhosis, hepatocellular carcinoma, and liver transplantation worldwide.[8,9] Consequently, it is anticipated to become the most rapidly growing contributor to liver-related mortality and morbidity in the coming decades.[7,10-12]

Metabolic dysfunction–associated fatty liver disease (MAFLD) has been proposed as a new definition for NAFLD because the former focuses on metabolic risk profiles without excluding other etiologies.[13] Recently, a new nomenclature for NAFLD was developed and finalized by the American Association for Study of Liver Disease and the European Association for the Study of the Liver.[14] However, in the Asia-Pacific region, MAFLD has already been recognized, as indicated by an increased awareness of fatty liver diseases,[2,15] where the actual nomenclature is less important than the underlying pathophysiological mechanism behind the disease. In this manuscript, we therefore continue to use the nomenclature "MAFLD," as it is commonly used in China. The prevalence of MAFLD has been found to range from 21.0% to 46.7% in China, which is notably higher than the prevalence of NAFLD, ranging from 29.3% to 32.9%.[15]

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[a] Department of Gastroenterology, Beijing Ditan Hospital, Capital Medical University, Beijing, China, [b] Department of Applied Information, Tomsk State University, Tomsk, Russia, [c] Department of Medical Records and Statistics, Beijing Ditan Hospital, Capital Medical University, Beijing, China, [d] Department of Pathology, Beijing Ditan Hospital, Capital Medical University, Beijing, China.

** Correspondence: Hongshan Wei, Department of Gastroenterology, Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China (e-mail: drwei@ccmu.edu.cn).*

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Fibrosis progression in the liver, particularly significant fibrosis, is the strongest histological predictor of morbidity and mortality[16-25] and is a major target of pharmacological interventions.[26] However, most prior studies have evaluated the fibrosis burden of MAFLD using the Fibrosis-4 index,[27,28] NAFLD fibrosis score,[29,30] or transient elastography,[31,32] with few studies using pathological data. Currently, there is still debate over the similarities and differences among the clinicopathological features of MAFLD and NAFLD.[6,33-35] In these studies, the MAFLD population had a high proportion of concomitant viral hepatitis B or C infections, which are established causes of advanced liver disease.[36,37] Consequently, confounding factors should be considered when evaluating hepatic fibrosis in patients with fatty liver disease, particularly viral hepatitis.

In the present study, we highlight the association between MAFLD and the increased prevalence of histologically significant fibrosis (stages F2–F4) when compared with that of conventional NAFLD. When adopting a decision-tree algorithm, we found that the risk factors for significant fibrosis in MAFLD vary from those in NAFLD. MAFLD may be beneficial for the risk stratification of patients with progressive fibrosis.

2. Methods

2.1. Study population

This cross-sectional, retrospective study included patients who underwent liver biopsy between January 2009 and December 2022 at Beijing Ditan Hospital, Capital Medical University, Beijing, China. The study protocol was approved by the Ethics Committee of Beijing Ditan Hospital (DTEC-KT2023-006-01) and conformed to the guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Informed consent for liver biopsy was obtained from all participants before the procedure, and anonymous clinical data were used for analysis.

All patients who underwent liver biopsy with histologically confirmed hepatic steatosis were included. The exclusion criteria were as follows: viral hepatitis, malignancy, incomplete data of relevant parameters, and <15 mm of biopsy tissue or biopsy containing fewer than 6 portal areas.

2.2. Diagnostic criteria for MAFLD

MAFLD was diagnosed if at least 1 of the following 3 criteria reported by Eslam et al.[38] were met, in addition to having an intrahepatic triglyceride concentration of >5%: type 2 diabetes mellitus (T2DM), overweight/obesity (i.e., body mass index [BMI]: ≥23 kg/m^2 in Asians), or 2 or more of the following metabolic risk factors: waist circumference ≥90/80 cm in Asian men/women, blood pressure ≥130/85 mm Hg or specific drug treatment, plasma triglycerides ≥1.70 mmol/L or specific drug treatment, plasma high-density lipoprotein cholesterol <1.0 mmol/L for men or <1.30 mmol/L for women or specific drug treatment, prediabetes (fasting plasma glucose: 5.6–6.9 mmol/L, 2-hour glucose: 7.8–11.0 mmol/L, glycosylated hemoglobin: 5.7%–6.4%), homeostasis model assessment of insulin resistance score ≥2.5, and plasma high-sensitivity C-reactive protein level >2 mg/L.

2.3. Diagnostic criteria for NAFLD

NAFLD was diagnosed based on the identification of hepatic steatosis (>5%) on liver biopsy in the absence of excessive alcohol consumption (defined as alcohol consumption of >20 g/d for men or >10 g/d for women)[39] and other chronic liver diseases such as viral hepatitis, autoimmune hepatitis, or steatogenic drug use (i.e., corticosteroids).

2.4. Study groups

Patients were classified as meeting the definitions of MAFLD (MAFLD+) or NAFLD (NAFLD+).

We further allocated all patients into 4 mutually exclusive subgroups by combining the 2 definitions: MAFLD+ NAFLD–: patients with MAFLD but no NAFLD, MAFLD– NAFLD+: patients with NAFLD but no MAFLD, MAFLD+ NAFLD+: simultaneous adherence to the MAFLD and NAFLD criteria, and MAFLD– NAFLD–: patients excluded by both definitions.

2.5. Histologic evaluation

All patients enrolled in the current study underwent percutaneous liver biopsy using a 16-gauge needle. Only biopsy tissues with at least 6 portal areas and a minimum length of 15 mm were considered sufficient. All specimens were independently reviewed by 2 experienced pathologists who were blinded to the clinical details. The degree of liver fibrosis was graded on a scale of 0 to 4.[40] Hepatic fibrosis at stages 2 to 4 was defined as significant fibrosis, while that at stages 3 to 4 was defined as advanced fibrosis. Histological scoring of NAFLD was performed using the NAFLD activity score (NAS), as proposed by the NASH Clinical Research Network.[41-43]

2.6. Demographic variables and laboratory parameters

Data regarding the history of hypertension, T2DM, dyslipidemia, medications, and alcohol intake were obtained from medical records, including the liver biopsy. Anthropometric measurements included waist circumference, blood pressure, height, and weight. Blood samples were collected and abdominal ultrasonography was performed, with the inclusion of the liver biopsy. Liver stiffness measurements (LSMs) were obtained for some patients. LSM values were recorded at the time of liver biopsy using vibration-controlled transient elastography (FibroScan; Echosens, Paris, France). These measurements were documented in the medical records and retrospectively included in the study analysis. At least 10 measurements were obtained at the time of liver biopsy using the M or XL probe. Measurements were discarded according to the Boursier criteria.[44] LSM ≥8 kPa indicated hepatic fibrosis. Fasting serum glucose, blood lipids, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, total cholesterol (TCHO), total triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and platelet count (PLT) were assessed, and the homeostasis model assessment of insulin resistance score was calculated as the glucose concentration (mmol/L) multiplied by the insulin concentration (mmol/L) divided by 22.5.[45] Patients without key diagnostic parameters such as BMI values were removed from the final analysis cohort. This exclusion process was crucial for minimizing bias and enhancing the validity of our findings.

2.7. Statistical analysis

Statistical analyses were performed using SPSS25.0 (IBM Corp., Armonk) and R (4.1.2, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as medians with interquartile ranges (IQRs). In this study, we conducted normality testing to assess the distribution of our data using the Shapiro–Wilk test, a widely recognized method for evaluating the normality of datasets. For data that conformed to a normal distribution, we employed parametric tests such as the Student *t* test and analysis of variance. Conversely, for data that exhibited nonnormal distributions, we utilized nonparametric tests, including the Mann–Whitney *U* test for 2-group comparisons and the Kruskal–Wallis test for comparisons among more than 2 groups. Categorical variables are described as frequencies with percentages and analyzed using the χ^2 test. We assessed the prevalence of significant fibrosis in all patients with hepatic steatosis, stratified

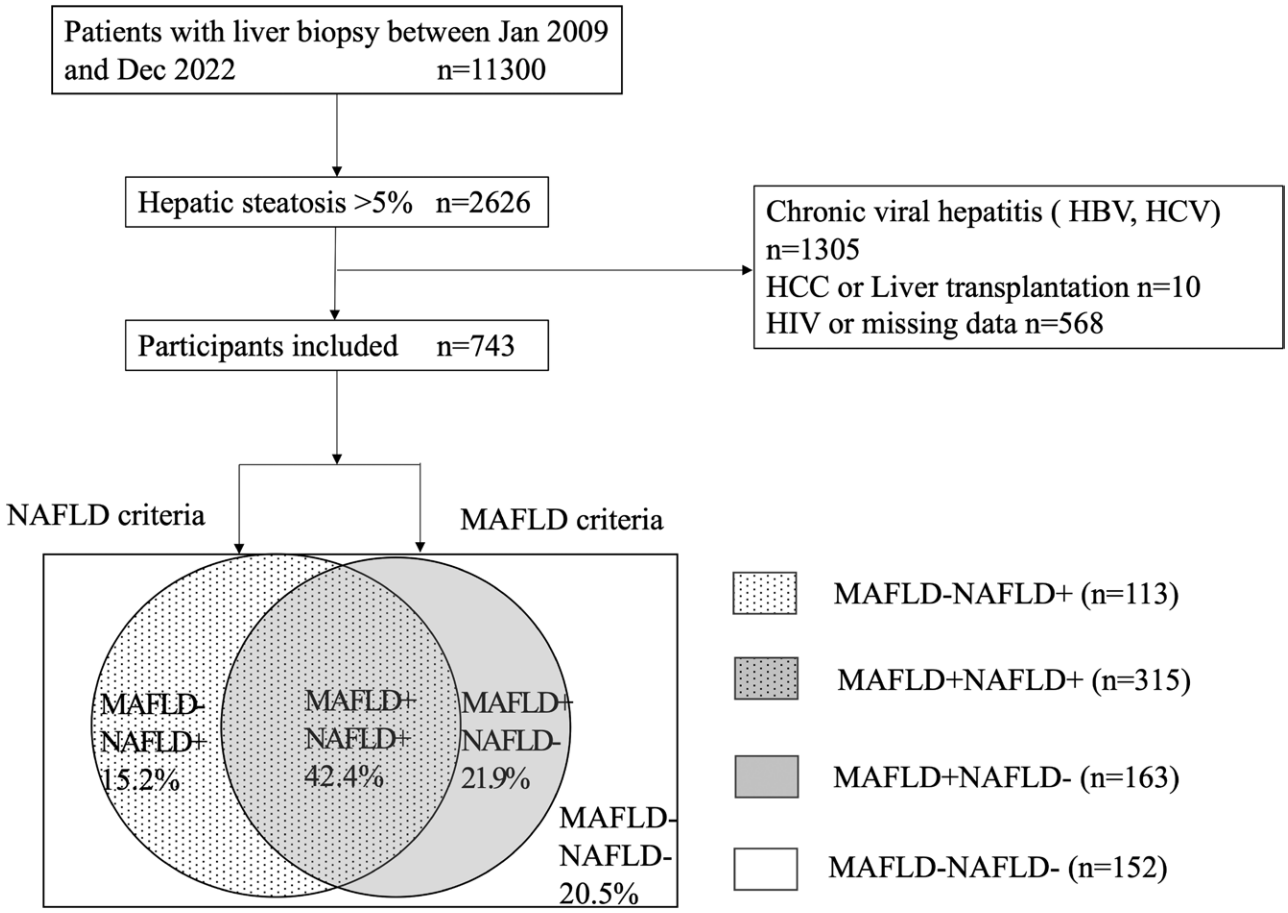

Figure 1. Overview of the study design. HBV = hepatitis B virus, HCV = hepatitis C virus, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, MAFLD = metabolic dysfunction–associated fatty liver disease, NAFLD = nonalcoholic fatty liver disease.

by the presence of MAFLD or NAFLD. As excessive alcoholic consumption limits of ≥20 g/d for women and 40 g/d for men were set in China as the current threshold of alcohol consumption for the criteria of alcoholic liver disease, we used a more stringent threshold for excessive alcohol consumption to diagnose alcoholic+ (Alc+).[46] The prevalence of significant fibrosis was quantified for the 4 mutually exclusive groups based on MAFLD and the diagnosis of alcoholic liver disease: MAFLD+ Alc+, MAFLD+ excessive alcohol consumption negative (Alc–), and MAFLD– Alc–. Analysis of variance was used to compare multiple groups. All tests were 2-tailed, and statistical significance was set at $P < .05$. The P values for multiple comparisons were adjusted using Bonferroni correction, according to the number of comparisons.

Histologic findings were quantified for the 4 mutually exclusive groups based on MAFLD and NAFLD definitions. Diagnostic accuracy was compared using the area under the receiver operating curve. To identify factors associated with significant fibrosis, factors with $P < .1$ in the univariate analysis were subjected to multivariable binary logistic regression. Decision-tree algorithms were constructed using the "rpart" package in R (4.1.2), with a complexity parameter of 0.02 for both MAFLD and NAFLD, to reveal profiles associated with significant hepatic fibrosis previously selected by logistic regression.

3. Results

3.1. Study design

From January 2009 to December 2022, 11,300 patients underwent liver biopsy at Beijing Ditan Hospital, Capital Medical University. Among these patients, 2626 were diagnosed with hepatic steatosis (>5%). A total of 1883 patients were excluded based on specific criteria (e.g., viral hepatitis, hepatocellular carcinoma, history of liver transplantation, human immunodeficiency virus infection, or significant missing data). Ultimately, 743 patients met the eligibility criteria (Fig. 1) and were categorized into 4 mutually exclusive groups: MAFLD+ NAFLD+ (n = 315), MAFLD+ NAFLD– (n = 163), MAFLD– NAFLD+ (n = 113), and MAFLD– NAFLD– (n = 152). In total, 478 patients were diagnosed with MAFLD+, and 428 patients were diagnosed with NAFLD+.

The baseline characteristics are listed in Table 1. There were 446 (60%) men, with a mean age of 42.3 ± 13.5 years and a mean BMI of 26.9 ± 4.2 kg/m^2. Among them, 29.5% (n = 219) had significant fibrosis and 11.7% (n = 87) had advanced fibrosis, as confirmed by liver biopsy. MAFLD was diagnosed in 478 (64.3%) participants, while NAFLD was diagnosed in 428 (57.6%) among the overall population. Reliable LSM was available for 52.8% (392/743) of all participants, 34% (109/321) of those with MAFLD, and 24.3% (73/301) of those with NAFLD, with fibrosis defined by LSM. Excessive alcohol consumption (Alc+) was present in 10.7% of the patients with MAFLD, resulting in the following distribution of mutually exclusive groups: MAFLD+ Alc+ (51/478) and MAFLD+ Alc– (427/478).

3.2. Differences in characteristics between MAFLD and NAFLD

The MAFLD criteria captured an additional 163 individuals (MAFLD+ NAFLD– group, 21.9%) with metabolic abnormality and alcohol use or other concomitant liver diseases, while excluding 113 individuals (15.2%).

Table 1

Comparison of participants' characteristics stratified by NAFLD and MAFLD status.

	MAFLD+ NAFLD– n = 163	MAFLD+ NAFLD+ n = 315	MAFLD– NAFLD+ n = 113	P*
Age (yr)	44 (35–53)	43 (31–53)	36 (26–50)	.002
Male, n (%)	118 (72.4)	188 (59.7)	66 (58.4)	.015
BMI (kg/m^2)	28.2 ± 3.8	28.0 ± 3.9	22.0 ± 1.5	<.001
Hypertension, n (%)	61 (37.4)	103 (32.7)	35 (31)	.269
T2DM, n (%)	41 (25.2)	80 (25.4)	0 (0)	<.001
Prediabetes	49 (30.1)	86 (27.3)	15 (13.3)	.005
AST (U/L)†	40.6 (32.9–51.0)	36.6 (25.9–62.8)	46.8 (29.8–80.4)	.078
ALT (U/L)‡	75.0 (62.9–89.8)	64.4 (33.7–121.8)	80.4 (35.1–165.3)	.375
ALB (g/L)§	46.3 (42.9–48.3)	45.6 (42.3–48.7)	47.0 (43.5–48.9)	.257
GGT (U/L)	51.1 (25.4–99.6)	60.0 (31.5–117.0)	54.0 (30.8–95.8)	.444
TCHO (mmol/L)‖	4.5 (3.8–5.3)	4.7 (4.1–5.3)	4.4 (1.4–5.1)	.040
TG (mmol/L)	1.4 (1.0–2.1)	1.8 (1.2–2.6)	1.3 (1.0–2.1)	.172
HDL-C (mmol/L)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.1 (1.1–1.3)	.645
LDL-C (mmol/L)¶	2.9 ± 0.9	2.9 ± 0.8	2.4 ± 1.1	<.001
PLT (10^9/L)	189.4 ± 64.2	222.3 ± 70.9	221.7 ± 73.3	.021
LSM (kPa)#	7.5 (5.5–11.4)	6.7 (5.1–9.0)	5.4 (5.0–6.1)	<.001

Age, BMI, AST, ALT, ALB, GGT, TCHO, TG, and LSM are presented with median and interquartile ranges, as these are not normally distributed according to the Shapiro–Wilk test. LDL-C and PLT are presented with mean and standard deviation, as these are normally distributed according to the Shapiro–Wilk test. Categorical variables like male, hypertension, prediabetes, and T2DM are presented as counts and percentages. None of the patients included in the study had undergone bariatric surgery.

Subjects were classified as meeting the definitions of MAFLD or NAFLD: MO: patients who meet only MAFLD criteria but not NAFLD, MAFLD– NAFLD+: patients who meet only NAFLD but not MAFLD, MAFLD+ NAFLD+: patients who meet simultaneous MAFLD and NAFLD criteria.

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = gamma-glutamyl transpeptidase, HDL-C = high-density lipoprotein cholesterol, kPa = kilopascals, LDL-C = low-density lipoprotein cholesterol, LSM = liver stiffness measurement, MAFLD = metabolic dysfunction-associated fatty liver disease, NAFLD = nonalcoholic fatty liver disease, PLT = platelet, T2DM = type 2 diabetes mellitus, TCHO = total cholesterol, TG triglyceride.

**P* value was used to compare between the groups MAFLD+ NAFLD– versus MAFLD– NAFLD+.

†AST value were invalid in 13 cases in MAFLD+ NAFLD– group, 23 cases in MAFLD– NAFLD+ group.

‡ALT value were invalid in 13 cases in MAFLD+ NAFLD– group, 23 cases in MAFLD– NAFLD+ group.

§ALB value were invalid in 13 cases in MAFLD+ NAFLD– group.

‖TCHO value were invalid in 3 cases in MAFLD+ NAFLD– group.

¶LDL-C value were invalid in 13 cases in MAFLD+ NAFLD– group.

#LSM value were invalid in 72 cases in MAFLD+ NAFLD– group, 85 cases in MAFLD+ NAFLD+ group, 42 cases in MAFLD– NAFLD+ group.

Good concordance (n = 315, 42.4%) was observed between the NAFLD and MAFLD groups. Patients with MAFLD but no NAFLD (MAFLD+ NAFLD– group) were older and more likely to be male and had higher BMI, TCHO, low-density lipoprotein cholesterol, and LSM values than those with NAFLD but no MAFLD (MAFLD– NAFLD+ group). The demographic and clinical characteristics of the participants in the MAFLD– NAFLD+, MAFLD+ NAFLD+, and MAFLD+ NAFLD– groups are summarized in Table 1.

3.3. Differences in histologic features between MAFLD and NAFLD

The prevalence of significant hepatic fibrosis in the MAFLD+ and NAFLD+ groups were 38.1% (182/478) and 30.1% (129/428), respectively. Excessive alcohol consumption was observed in 51 (10.7%) patients with MAFLD. The difference in the prevalence of significant fibrosis between the MAFLD+ Alc+ and MAFLD+ Alc–groups (43.1% vs 37.5%, respectively) was not statistically significant ($P = .448$).

To examine the differences in histological features between MAFLD and NAFLD, nonoverlapping groups were investigated (Fig. 2 and Supplementary Table S1, Supplemental Digital Content, http://links.lww.com/MD/O354). The NAS was significantly higher in the MAFLD+ NAFLD– group than in the MAFLD– NAFLD+ group (4.05% vs 3.21%, $P < .001$). The MAFLD+ NAFLD– group had the highest stage of fibrosis, followed by the MAFLD+ NAFLD+ group, while the MAFLD– NAFLD+ group had the lowest rate of significant fibrosis ($P < .001$). The prevalence of significant fibrosis in the MAFLD– NAFLD+ group was similar to that in the MAFLD– NAFLD– group (15.9% vs 12.5%, $P = .426$). The NAS was positively correlated with the fibrosis stage in all patients (Spearman $\rho = 0.279$, $P < .001$).

Furthermore, after adjusting for age, the MAFLD+ NAFLD– group had a higher prevalence of significant fibrosis (adjusted odds ratio: 5.911, 95% confidence interval [CI]: 3.306–10.570, $P < .001$) than the MAFLD– NAFLD+ group (adjusted odds ratio: 1.612, 95% CI: 0.794–3.273, $P < .001$) (Table 2).

To compare the different risks for significant fibrosis according to MAFLD+ and NAFLD+ definitions, receiver operating characteristic curves for the diagnosis of significant fibrosis stratified by MAFLD and NAFLD criteria, and a subsequent analysis of multivariable binary logistic regression were performed. Overall, the MAFLD criteria showed a better area under the receiver operating curve (0.62, 95% CI: 0.59–0.65) than the NAFLD criteria (0.51, 95% CI: 0.47–0.55, $P < .001$) at identifying significant fibrosis.

3.4. Alcohol consumption and MAFLD

Among patients with MAFLD having drinking habits (all in the MAFLD+ NAFLD– group), 60 (36.8%) had excessive alcohol consumption, with a median intake of 80 g/d (IQR: 40–100 g/d) for women and 80 g/d (IQR: 50–200 g/d) for men. Subsequently, we used a more stringent threshold for excessive alcohol consumption (≥40 g/d in men and ≥20 g/d in women) to diagnose Alc+. Among the 60 patients deemed to have excessive alcohol consumption, 51 (85%) were diagnosed with Alc+ using the more stringent criterion, with a median intake of 80 g/d (IQR: 65–300 g/d) for women and 100 g/d (IQR: 71–200 g/d) for men. To further investigate the impact of alcohol consumption and metabolic disorders in MAFLD on significant fibrosis, we compared the distribution of significant fibrosis among 4 mutually exclusive groups: MAFLD+

Alc+, 43.1%; MAFLD+ Alc–, 37.5%; MAFLD– Alc+, 14.2%; and MAFLD– Alc–, 13.9% ($P = .013$). Subsequently, in an age- and sex-adjusted model, we demonstrated that the prevalence of fibrosis was significantly higher in the MAFLD+ Alc+ group than in the MAFLD+ Alc– and MAFLD– Alc+ groups ($P < .001$; Table 3).

3.5. Profiles associated with significant hepatic fibrosis using NAFLD and MAFLD definitions

To identify independent predictors of significant fibrosis in the MAFLD and NAFLD groups, we performed a decision tree based on the results of multivariable logistic regression. PLT and age were identified as initial classifiers of significant fibrosis in both groups. This was followed by TCHO in patients with MAFLD (Fig. 3A). TCHO was not a predictor of decision-tree pruning in patients with NAFLD (Fig. 3B).

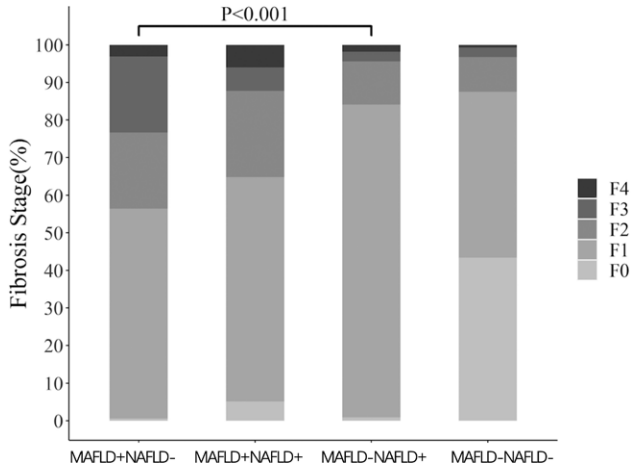

Figure 2. Distribution of fibrosis categories by NAFLD and MAFLD criteria. The degree of liver fibrosis was graded from 0 to 4 according to METAVIR. Hepatic fibrosis in stages 2 to 4 was defined as significant. The percentages of significant fibrosis were as follows: MAFLD+ NAFLD–, 43.6%; MAFLD+ NAFLD+, 35.2%; MAFLD– NAFLD+, 15.9%; and MAFLD– NAFLD–, 12.5%. Statistical analysis was performed using a χ^2 test to assess the significance of differences in fibrosis distribution among the groups. The distribution of fibrosis was significantly different between the MAFLD+ NAFLD– and MAFLD– NAFLD+ groups ($P < .001$). BMI = body mass index, MAFLD = metabolic dysfunction-associated fatty liver disease, METAVIR = Meta-analysis of Histological Data in Viral Hepatitis, NAFLD = nonalcoholic fatty liver disease, MAFLD+ NAFLD– = patients meeting the diagnostic criteria for MAFLD but not NAFLD, MAFLD– NAFLD = patients meeting the diagnostic criteria for NAFLD but not MAFLD, MAFLD+ NAFLD+ = patients meeting the diagnostic criteria for MAFLD and NAFLD, MAFLD– NAFLD– = patients meeting the criteria for neither MAFLD nor NAFLD, PLT = platelet, TCHO = total cholesterol.

4. Discussion

In this study, we assessed the clinical and pathological characteristics of MAFLD and NAFLD in a large biopsy-verified cohort. Patients excluded by the NAFLD definition but included by the MAFLD definition had higher odds of significant fibrosis than those excluded by the MAFLD definition but included by the NAFLD definition.

A major strength of this study is the use of a systematic approach for comparing the clinicopathological characteristics of MAFLD and NAFLD. This is, to the best of our knowledge, the largest cohort to compare various risk variables for significant fibrosis between the 2 nomenclatures. MAFLD consistently outperformed NAFLD in identifying higher stages of fibrosis across multiple analyses. Early identification of patients at a risk of fibrosis is crucial for referring them to specialists for monitoring and potential future treatments.[18] Notably, more liver-related deaths have been reported in MAFLD.[34,47] Several studies have shown that patients with MAFLD but not NAFLD have a higher risk of cirrhosis and mortality.[31,36,48-51] In contrast, patients with NAFLD but not MAFLD have a lower risk of developing advanced liver disease at baseline and long-term adverse outcomes.[47] A recent study[52] indicated that in patients with NAFLD and T2DM, who can be diagnosed as having MAFLD, LSM was higher than that in patients with NAFLD but not T2DM, mirroring our findings.

Interestingly, the prevalence of significant fibrosis was similar between the MAFLD– NAFLD+ and MAFLD– NAFLD– groups, indicating that the MAFLD criteria effectively identified patients with a higher likelihood of fibrosis. This suggests that the MAFLD criteria encompass patients with a higher prevalence of significant fibrosis.

Another hallmark of our study is the exclusion of patients with viral hepatitis but not those with excessive alcohol consumption, allowing us to differentiate the roles of metabolic dysfunction and alcohol consumption. Although the MAFLD criteria do not require the exclusion of concomitant liver disease, we excluded patients with chronic hepatitis B (CHB), which is relatively common in Asia,[53] to provide more decisive evidence of potential associations. In another study involving 974 patients with MAFLD and CHB, 35.5% of them had significant hepatic fibrosis.[54] As CHB is a major risk factor of liver fibrosis and cirrhosis, excluding patients with concomitant viral hepatitis allowed us to focus on metabolic factors. The prevalence of fibrosis was not significantly different between the MAFLD+ Alc+ and MAFLD+ Alc– groups, which is also consistent with a previous report.[55] However, several studies have reported conflicting results, in which the prognosis of patients with MAFLD and excessive alcohol consumption is not determined by metabolic disorders, but by harmful alcohol intake.[56] In the present study, MAFLD and excessive alcohol consumption were independent and simultaneous predictors of significant fibrosis. This suggests that even in individuals who consume alcohol, metabolic dysregulation is a key driver. Nevertheless, further well-designed studies are required to investigate whether the risk of hepatic fibrosis or all-cause mortality is increased by

Table 2

Significant fibrosis risk according to the presence of MAFLD or NAFLD.

	B	SE	Wald	*df*	Sig	aOR	95% CI
MAFLD+ NAFLD–-	1.777	0.297	35.908	1	<0.001	5.911	3.306–10.570
MAFLD+ NAFLD+	1.465	0.277	27.922	1	<0.001	4.434	2.512–7.440
MAFLD– NAFLD+	0.477	0.362	1.743	1	<0.001	1.612	0.794–3.273
MAFLD– NAFLD–	Reference						

Results were obtained by forward stepwise Logistic regression with Wald method. Results were adjusted for age. Hepatic fibrosis with stage 2 to 4 was defined as significant fibrosis.

aOR = adjusted odds ratio, CI = confidence interval, MAFLD = metabolic dysfunction–associated fatty liver disease, MAFLD+ NAFLD– = subjects meet the diagnostic criteria for MAFLD only but not NAFLD, MAFLD+ NAFLD+ = subjects with simultaneous MAFLD and NAFLD, MAFLD– NAFLD+ = subjects meet the diagnostic criteria for NAFLD only but not MAFLD, NAFLD = nonalcoholic fatty liver disease, SE = standard error.

the simultaneous presence of metabolic disorders and alcohol consumption.

Consistent with previous studies, our results showed that PLT is a significant predictor of fibrosis in both the MAFLD and NAFLD groups. Liu et al[57] observed a significant decrease in PLT after 5 years of follow-up for NAFLD, likely owing to oxidative stress affecting thrombopoietin production and mitochondrial function.[58] Moreover, platelets play a role in metabolic syndromes and in bridging innate and adaptive immune cells in nonalcoholic steatohepatitis.[59] During these processes, the peripheral PLT may decrease.

However, the present study had some limitations. First, it was conducted at a single center in China, and validation studies are therefore required. Furthermore, the patients in the MAFLD– NAFLD+ group were young (mean age, 42.3 years) and were 7 years younger on average than those who met the criteria for MAFLD. It is plausible that metabolic disorders, such as insulin resistance, are not obvious at a young age and take time to become apparent. While the MAFLD– NAFLD+ group had a low cross-sectional association with advanced fibrosis, the long-term risk might be higher. Properly designed future studies are needed to determine whether the MAFLD– NAFLD+ group has a lower prevalence of advanced liver disease or all-cause mortality than the MAFLD+ NAFLD– group.

Second, only patients who underwent liver biopsy were included in our study, introducing selection bias as liver biopsies are typically performed when significant liver injury is suspected. Despite being the gold standard for diagnosing steatosis and fibrosis, liver biopsy is prone to sampling errors.[60]

Third, the small number of patients in the MAFLD+ NAFLD– group limited our ability to analyze subgroups such as MAFLD+ T2DM in detail. Our understanding of disease progression in different subgroups of MAFLD remains unclear. The answers to these questions will form the basis for mapping new, effective preventive treatments and more comprehensive approaches for patients with MAFLD and metabolic disorders.

Fourth, due to the retrospective nature of this study, over 500 patients were excluded for lacking MAFLD essential diagnostic criteria, potentially introducing bias into our findings. Future prospective studies are needed to validate our findings and minimize potential biases associated with data incompleteness. The absence of LSM data for some patients prevented its inclusion in multivariable models and decision trees. However, LSM, for which access is limited across Asia, is not widely covered by public healthcare insurance. Otherwise, interpretation of the decision analysis must be considered in the context of the model used. LSM and its related scores, such as AGILE 3+, have lower accuracy for the diagnosis of advanced fibrosis in patients who are obese and those with elevated alanine aminotransferase levels.[51] The optimal

Table 3

Prevalence of significant fibrosis for the 4 mutually exclusive groups based on MAFLD and the stringent definition of excessive alcohol consumption.

	aOR	95% CI	*P*
MAFLD– Alc–	Reference		
MAFLD– Alc+	1.028	0.218–4.847	.972
MAFLD+ Alc–	3.806	2.516–5.756	<.001
MAFLD+ Alc+	5.050	3.806–2.516	<.001

Stringent definition of excessive alcohol consumption was defined as ≥20 and 40 g/d in females and males. Results were adjusted for age and sex.

Alc+ = excessive alcohol consumption positive, Alc–, excessive alcohol consumption negative, aOR = adjusted odds ratio, CI = confidence interval, MAFLD = metabolic dysfunction–associated fatty liver disease.

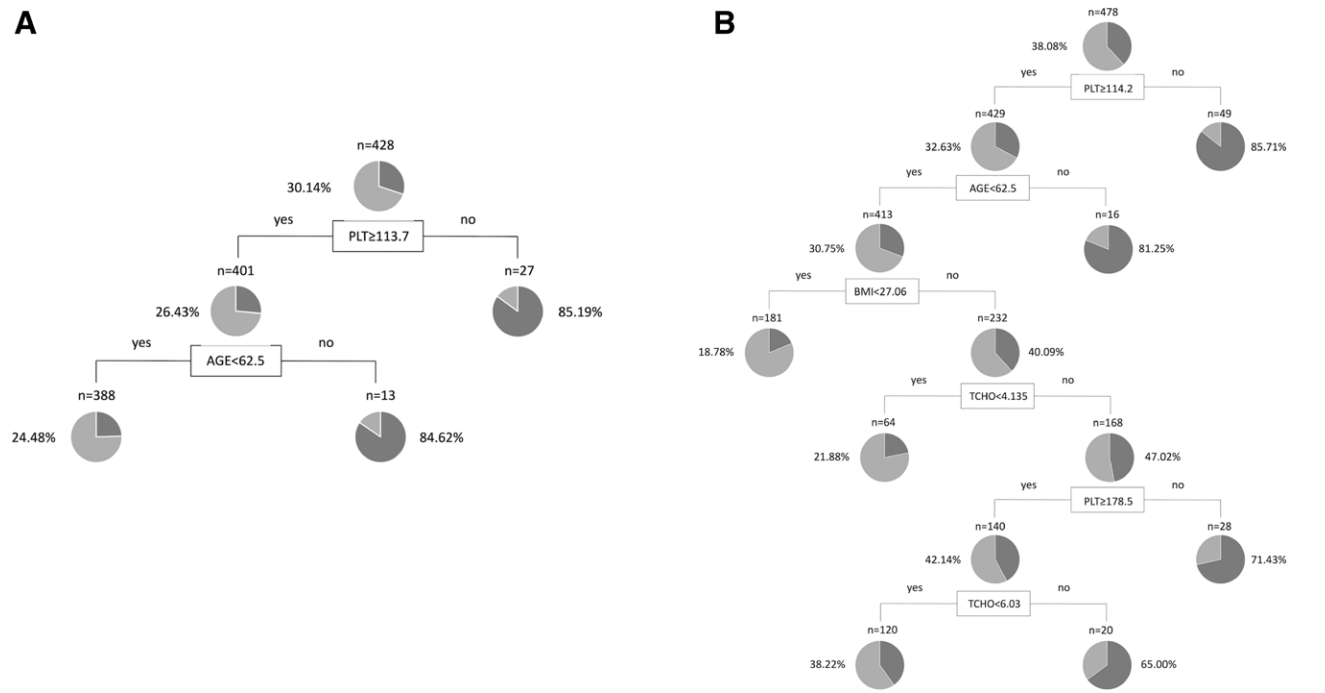

Figure 3. Profiles of significant fibrosis analyzed by decision-tree analysis stratified by patients meeting the (A) NAFLD and (B) MAFLD criteria. The pie graphs indicate the proportion of patients with significant hepatic fibrosis (dark). The decision tree was constructed using the "rpart" package in R (version 4.1.2) to identify profiles associated with significant hepatic fibrosis. The complexity parameter was set at 0.02 for both MAFLD and NAFLD. The tree was generated based on the results of multivariable binary logistic regression, which identified factors significantly associated with significant fibrosis ($P < .1$ in univariate analysis). Each node in the tree represents a decision point based on a specific variable, and the branches illustrate the outcomes of these decisions. The final leaves of the tree indicate the predicted presence or absence of significant fibrosis, providing a visual representation of the complex relationships between the identified factors and the outcome of interest. HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HIV = human immunodeficiency virus, MAFLD = metabolic dysfunction-associated fatty liver disease, NAFLD = nonalcoholic fatty liver disease.

strategy regarding the inclusion of LSM for risk stratification using the MAFLD criteria should be further investigated and validated in a large sample.

5. Conclusions

MAFLD serves as a superior clinical marker for identifying significant fibrosis. Our results showed that MAFLD contributes to hepatic fibrosis independently of viral hepatitis or excessive alcohol consumption. The adoption of MAFLD has profound implications for clinical practice, particularly in avoiding overdiagnosis or misclassification of patients with low metabolic risk. However, further longitudinal studies are essential to elucidate the temporal progression of MAFLD subtypes and their responses to various lifestyle and pharmacological interventions. Future studies and practical applications will shed light on the applicability and consequences of these changing classifications for the treatment of this major global health issue.

Author contributions

Data curation: Shan Hong, Lei Sun.
Formal analysis: Shan Hong, Yiwei Hao.
Investigation: Shan Hong.
Writing – original draft: Shan Hong.
Methodology: Zifan Hong, Yiwei Hao.
Resources: Lei Sun.
Writing – review & editing: Lei Sun, Hongshan Wei.
Conceptualization: Hongshan Wei.

References

[1] Muthiah MD, Han N C, Sanyal AJ. A clinical overview of non-alcoholic fatty liver disease: a guide to diagnosis, the clinical features, and complications—what the non-specialist needs to know. Diabetes Obes Metab. 2022;24:3–14.
[2] Eslam M, Sarin SK, Wong VW, et al. 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;14:889–919.
[3] Yuan Q, Wang H, Gao P, et al. Prevalence and risk factors of metabolic-associated fatty liver disease among 73,566 individuals in Beijing, China. Int J Environ Res Public Health. 2022;19:2096.
[4] Wong VW, Wong GL, Woo J, et al. Impact of the new definition of metabolic associated fatty liver disease on the epidemiology of the disease. Clin Gastroenterol Hepatol. 2021;19:2161–71.e5.
[5] Kaya E, Yılmaz Y. Non-alcoholic fatty liver disease: a growing public health problem in Turkey. Turk J Gastroenterol. 2019;30:865–71.
[6] Alharthi J, Gastaldelli A, Cua IH, Ghazinian H, Eslam M. Metabolic dysfunction-associated fatty liver disease: a year in review. Curr Opin Gastroenterol. 2022;38:251–60.
[7] Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology. 2020;72:1605–16.
[8] Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10:330–44.
[9] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57.
[10] Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors, and prevention. Nat Rev Gastroenterol Hepatol. 2018;15:11–20.
[11] Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. Gastroenterology. 2019;157:590–3.
[12] Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2020;5:167–228.
[13] Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology. 2020;158:1999–2014.e1.
[14] Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79:1542–56.
[15] Huang X, Yu R, Tan X, et al. Comparison of NAFLD, MAFLD, and MASLD prevalence and clinical characteristics in Asia adults. J Clin Exp Hepatol. 2025;15:102420.
[16] Younossi ZM, Noureddin M, Bernstein D, et al. Role of noninvasive tests in clinical gastroenterology practices to identify patients with nonalcoholic steatohepatitis at high risk of adverse outcomes: expert panel recommendations. Am J Gastroenterol. 2021;116:254–62.
[17] Kwok R, Tse YK, Wong GL, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease—the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther. 2014;39:254–69.
[18] Ekstedt M, Hagström H, Nasr P, et al. The fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61:1547–54.
[19] Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology. 2020;158:1611–25.e12.
[20] Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol. 2017;67:1265–73.
[21] Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149:389–97.e10.
[22] Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. Cells. 2020;9:875.
[23] Piscaglia F, Svegliati-Baroni G, Barchetti A, et al; HCC-NAFLD Italian Study Group. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology. 2016;63:827–38.
[24] Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. Clin Gastroenterol Hepatol. 2015;13:594–601.e1.
[25] Vilar-Gomez E, Calzadilla-Bertot L, Wong VW-S, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018;155:443–57.e17.
[26] Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53:362–76.
[27] Yamamura S, Eslam M, Kawaguchi T, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int. 2020;40:3018–30.
[28] Nguyen VH, Le MH, Cheung RC, Nguyen MH. Differential clinical characteristics and mortality outcomes in persons with NAFLD and/or MAFLD. Clin Gastroenterol Hepatol. 2021;19:2172–81.e6.
[29] Park H, Yoon EL, Kim M, et al. Comparison of diagnostic performance between FIB-4 and NFS in metabolic-associated fatty liver disease era. Hepatol Res. 2022;52:247–54.
[30] Liu Q, Zhao G, Li Q, Wu W, Zhang Y, Bian H. A comparison of NAFLD and MAFLD diagnostic criteria in contemporary urban healthy adults in China: a cross-sectional study. BMC Gastroenterol. 2022;22:471.
[31] Kim M, Yoon EL, Cho S, et al. Prevalence of advanced hepatic fibrosis and comorbidity in metabolic dysfunction-associated fatty liver disease in Korea. Liver Int. 2022;42:1536–44.
[32] Mantovani A. MAFLD vs NAFLD: where are we? Dig Liver Dis. 2021;53:1368–72.
[33] Younossi ZM, Paik JM, Shabeeb RA, et al. Are there outcome differences between NAFLD and metabolic-associated fatty liver disease? Hepatology. 2022;76:1423–37.
[34] Attia D, Aty NA, Shawket A, Said E, Fouad Y. MAFLD not NAFLD is associated with impairment of health-related quality of life. J Clin Transl Hepatol. 2022;10:4–5.
[35] Ayada I, van Kleef LA, Alferink LJM, Li P, de Knegt RJ, Pan Q. Systematically comparing epidemiological and clinical features of MAFLD and NAFLD by meta-analysis: focusing on the non-overlap groups. Liver Int. 2022;42:277–87.
[36] Wang X, Wu S, Yuan X, et al. Metabolic dysfunction-associated fatty liver disease and mortality among Chinese adults: a prospective cohort study. J Clin Endocrinol Metab. 2022;107:e745–55.
[37] Huang J, Xue W, Wang M, et al. MAFLD criteria may overlook a subtype of patient with steatohepatitis and significant fibrosis. Diabetes Metab Syndr Obes. 2021;14:3417–25.

[38] Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73:202–9.
[39] 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;64:1388–402.
[40] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24:289–93.
[41] Rinella ME, Tacke F, Sanyal AJ, Anstee QM; Participants of the AASLD/EASL Workshop. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. J Hepatol. 2019;71:823–33.
[42] Kleiner DE, Brunt EM, Van Natta M, et al; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41:1313–21.
[43] Bedossa P, Patel K. Biopsy and noninvasive methods to assess progression of nonalcoholic fatty liver disease. Gastroenterology. 2016;150:1811–22.e4.
[44] Boursier J, Zarski JP, de Ledinghen V, et al; Multicentric Group from ANRS/HC/EP23 FIBROSTAR Studies. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology. 2013;57:1182–91.
[45] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
[46] Fan JG, Jia JD, Li YM, et al; Chinese Association for the Study of Liver Disease. Guidelines for the diagnosis and management of non-alcoholic fatty liver disease: update 2010 guidelines for the diagnosis and management of alcoholic liver disease: update 2010: (published in Chinese on Chinese Journal of Hepatology 2010; 18: 163–166). J Dig Dis. 2011;12:38–44.
[47] Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol. 2021;75:1284–91.
[48] Niriella MA, Ediriweera DS, Kasturiratne A, et al. Outcomes of NAFLD and MAFLD: results from a community-based, prospective cohort study. PLoS One. 2021;16:e0245762.
[49] van Kleef LA, Ayada I, Alferink LJM, Pan Q, de Knegt RJ. Metabolic dysfunction-associated fatty liver disease improves detection of high liver stiffness: the Rotterdam Study. Hepatology. 2022;75:419–29.
[50] van Kleef LA, de Knegt RJ. The transition from NAFLD to MAFLD: one size still does not fit all—time for a tailored approach? Hepatology. 2022;76:1243–5.
[51] Huang Q, Zou X, Wen X, Zhou X, Ji L. NAFLD or MAFLD: which has closer association with all-cause and cause-specific mortality?—results from NHANES III. Front Med (Lausanne). 2021;8:693507.
[52] Pennisi G, Enea M, Falco V, et al. Noninvasive assessment of liver disease severity in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes [published online ahead of print, 2023 Mar 17]. Hepatology. 2023;78:195–211.
[53] Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
[54] Hong S, Hao Y, Sun L, et al. Prevalence and risk factors of significant fibrosis in chronic hepatitis B patients with concurrent metabolic dysfunction-associated steatotic liver disease. Ann Hepatol. 2024;30:101589.
[55] van Kleef LA, de Knegt RJ, Brouwer WP. Metabolic dysfunction-associated fatty liver disease and excessive alcohol consumption are both independent risk factors for mortality. Hepatology. 2023;77:942–8.
[56] De A, Ahmad N, Mehta M, Singh P, Duseja A. NAFLD vs. MAFLD—it is not the name but the disease that decides the outcome in fatty liver. J Hepatol. 2022;76:475–7.
[57] Liu F, Zhou H, Cao L, et al. Risk of reduced platelet counts in patients with nonalcoholic fatty liver disease (NAFLD): a prospective cohort study. Lipids Health Dis. 2018;17:221.
[58] Kawasaki T, Takeshita A, Souda K, et al. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. Am J Gastroenterol. 1999;94:1918–22.
[59] Peiseler M, Schwabe R, Hampe J, Kubes P, Heikenwälder M, Tacke F. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease—novel insights into cellular communication circuits. J Hepatol. 2022;77:1136–60.
[60] Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156:1264–81.e4.