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Original Article

# Comparing the Diagnostic Criteria of MAFLD and NAFLD in the Chinese Population: A Population-based Prospective Cohort Study

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## Abstract

***Background and Aims:*** Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new concept, proposed in 2020; however, its applicability in Asia populations has yet to be evaluated. Therefore, we aimed to compare the difference in epidemiological and clinical characteristics between MAFLD and non-alcoholic fatty liver disease (NAFLD) among Asian populations. ***Methods:*** Based on the Jinchang cohort, 30,633 participants were collected. The prevalence and incidence of MAFLD and NAFLD were used to analyze the epidemic characteristics and its overlapping effects. In addition, the corresponding clinical characteristics of the two diagnostic criteria populations were compared. ***Results:*** The prevalence rates of MAFLD and NAFLD were 21.03% and 18.83%, respectively. After an average 2.28-year follow-up, the incidence densities of MAFLD and NAFLD were 41.58 per 1,000 person-years and 37.69 per 1,000 person-years, respectively. With the increase of baseline age, body mass index (BMI), and waist circumference (WC) levels, the prevalence and incidence of MAFLD and NAFLD were on the rise (all $p_{trend}$<0.05). Among the total patients diagnosed at baseline or follow-up, most patients had both MAFLD and NAFLD, accounting for 78.84% and 82.88%, respectively. Compared with NAFLD, MAFLD patients had greater proportions of males and metabolic diseases (diabetes, dyslipidemia), and had higher BMI, WC, liver enzymes, blood glucose, and lipid levels in the baseline diagnosis patients ($p$<0.05). Additionally, lean MAFLD patients had higher metabolic disorders than lean NAFLD patients ($p$<0.05). ***Conclusions:*** Compared with NAFLD, the newly proposed definition of MAFLD is more practical and accurate, and it can help identify more fatty liver patients with high-risk diseases.

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## Introduction

Fatty liver disease (FLD) has become one of the major global public health problems in recent years.[1] FLD is currently divided into alcoholic fatty liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) based on the history of alcohol intake.[2] As NAFLD is a common cause of chronic liver disease, it has attracted more and more attention.[3] The global prevalence of NAFLD was 25.24%,[4] while it was 29.62% in Asia.[5] In China, the prevalence of NAFLD was 32.9% in 2018, which had increased by 9.1% compared to the beginning of the 20th century (23.8%).[6]

The diagnosis of NAFLD adopts exclusion criteria; that is, the secondary causes of liver fat accumulation need to be excluded on the basis of liver steatosis, such as excessive drinking, long-term use of steatogenic medication, chronic viral hepatitis, and so on.[7] With the deepening of people's understanding of the pathogenesis of NAFLD, the current criteria has been challenged. First, due to differences in the basic characteristics, living habits and genetic susceptibility of the population, the clinical manifestations, pathological characteristics and clinical outcomes of NAFLD are obviously heterogeneous.[8–11] Therefore, the original diagnostic criteria may affect the clinical prognosis of NAFLD. Second, at present, there is no uniform standard of calculating alcohol intake accurately. Due to information bias, it may not be possible to accurately estimate the

**Keywords:** MAFLD; NAFLD; Diagnostic criteria; Applicability; Prospective cohort study.

**Abbreviations:** ALB, albumin; ALD, alcoholic fatty liver disease; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBIL, direct bilirubin; FLD, fatty liver disease; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; GLO, globulin; IBIL, indirect bilirubin; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MN, those who meet both the definitions of MAFLD and NAFLD; NAFLD, non-alcoholic fatty liver disease; NMN, those who meet the definition of NAFLD but do not meet the definition of MAFLD; NNM, those who meet the definition of MAFLD but do not meet the definition of NAFLD; Scr, serum creatinine; T2DM, type 2 diabetes; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; WC, waist circumference.

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actual alcohol intake of the study subjects. Finally, some studies have shown NAFLD can coexist with chronic viral hepatitis, autoimmune liver disease, and ALD, which may contradict the original definition.[12,13] For the above reasons, an international expert panel composed of 30 experts from 22 countries proposed a new name for NAFLD, namely metabolic dysfunction-related fatty liver disease (MAFLD).[14,15]

The diagnosis of MAFLD is based on the evidence of hepatic steatosis and meeting one of the three conditions: overweight/obesity, type 2 diabetes (T2DM), and metabolic dysregulation.[15] The new diagnostic criteria are inclusive criteria, which mainly consider the role of metabolic dysfunction in the occurrence of fatty liver, and do not need to exclude excessive drinking and other related factors. Since the MAFLD consensus was proposed in early 2020, it has received a lot of support from experts, liver associations, nurses, and patient advocacy groups.[16–19] They all agreed to rename NAFLD to MAFLD. At present, the Association for the Study of the Liver in Latin America, Asia, Middle East, North Africa, and Sub-Saharan Africa have published clinical practice guidelines for MAFLD based on the characteristics of the local population.[20–23]

Although the MAFLD diagnostic criteria attracted much attention once they were proposed, there are relatively limited studies on the suitability of the criteria in different populations and the connection with NAFLD. Currently, there are only limited reports based on the American population,[24–27] but studies in Asian populations have not been reported similarly. Therefore, we aimed to compare the epidemiological and clinical characteristics of MAFLD and NAFLD, and reveal the overlapping effects of patients under the two diagnostic criteria based on a prospective cohort platform in Northwest China.

## Methods

### *Study population*

This study was based on the Jinchang cohort,[28] which was obtained from Jinchang City, Gansu Province, Northwest China. This represents an ongoing prospective population-based cohort study. The design and methods have been detailed elsewhere.[28] In brief, the baseline survey was conducted from June 2011 to December 2013 and the first follow-up was finished in December 2015. There are 33,355 participants who have finished both the baseline and first follow-up surveys. The average follow-up time was 2.28 years. Among these individuals, 2,722 participants were excluded because their B-ultrasound information at baseline and follow-up were missing. As such, 30,633 participants remained as subjects for the prevalence study. Among the 30,633 participants, people who already have fatty liver disease at the time of baseline survey were excluded ($n$=6,920). The remaining 23,713 participants were the subjects of the incidence study. The cumulative follow-up time was 52,693 person-years. Figure 1 shows the structure of the study participants. The study was approved by the Ethical Committees of School of Public Health, Lanzhou University (Ethical Approval Code: 2017-01), and all participants signed an informed consent form.

### *Data collection*

A standardized and structured questionnaire was used to conduct epidemiological investigation by trained investigators. The information included basic demographic characteristics (age, gender, education level, occupation, etc.), lifestyles (smoking, drinking, physical exercise, etc.), history of diseases, family history, and other health-related information.

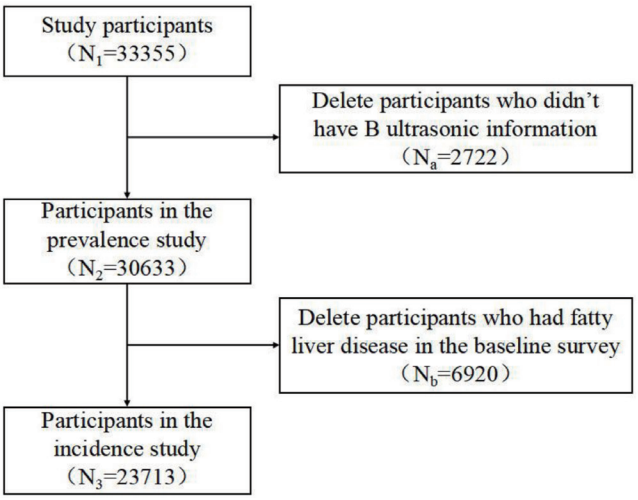


**Fig. 1. Flow charts for inclusion and exclusion of study participants.**

Physical examinations were performed by clinicians, which included measurements of weight, height, waist circumference (WC), abdominal ultrasound, and so on. Weight and height were measured by automatic recording instruments (SK-X80/TCS-160D-W/H; Sonka, China) in a standing position without shoes, and they were accurate to 0.1 kg with light clothing and 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. WC was measured with an inelastic tape at the middle of the subject's ribs and iliac crest, accurate to 0.1 cm. The subjects were put in a supine position and abdominal ultrasound was performed using ultrasound diagnostic apparatus (LOGIQ P5; GE Ultrasound, South Korea) by experienced radiologists who did not know the study aims.

Biochemical examinations were performed using a clinical chemistry automatic analyzer (7600-020; Hitachi, Japan) in the morning after overnight fasting (at least 8 to 10 hours without any food, except water). Indicators included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and so on.

### *Definition of variables*

According to the diagnostic criteria for obesity in the Asia-Pacific region recommended by the World Health Organization,[29] BMI was divided into normal weight (<23.0 kg/m$^2$), overweight (23.0 kg/m$^2$≤BMI<25.0 kg/m$^2$), and obesity (≥25.0 kg/m$^2$). WC was divided into normal (<90 cm (male)/<80 cm (female)) and central obesity (≥90 cm (male)/≥80 cm (female)).

### *Outcome ascertainment*

**MAFLD and nonNAFLD-MAFLD (NNM):** According to the latest consensus proposed by the international expert pan-

el and the diagnostic criteria recommended by the Asian Pacific Association for the Study of the Liver,[15,20] MAFLD was diagnosed based on B ultrasound-diagnosed hepatic steatosis, in addition to one of the following three criteria, namely overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation. The metabolic dysregulation was defined as the presence of at least two metabolic risk abnormalities: WC ≥90 cm for men and ≥80 cm for women; blood pressure ≥130/85 mmHg or specific drug treatment; plasma TG ≥1.70 mmol/L or specific drug treatment; plasma HDL-C <1.0 mmol/L for men and <1.3 mmol/L for women or specific drug treatment; prediabetes (FPG levels between 5.6 and 6.9 mmol/L, and self-report has not been clearly diagnosed as diabetes); and plasma high-sensitivity C-reactive protein level >2 mg/L.

The NNM individuals referred to those who meet the definition of MAFLD but did not meet the definition of NAFLD.

**NAFLD and nonMAFLD-NAFLD (NMN):** According to the diagnostic criteria recommended by the European Association for the Study of the Liver,[30] NAFLD was diagnosed according to the presence of all three conditions as follows, at the same time: B ultrasound showing excessive hepatic fat accumulation and the presence of steatosis in >5% of hepatocytes; no history of drinking or the amount of alcohol being <30 g/d for men and <20 g/d for women; and excluded secondary diseases that may cause liver steatoses, such as viral hepatitis (hepatitis B virus and hepatitis C virus), Wilson's disease, hemochromatosis, and autoimmune hepatitis.

The NMN were defined as those who meet the diagnostic criteria of NAFLD but did not meet the diagnostic criteria of MAFLD.

**MAFLD-NAFLD (MN):** This group included research subjects that met the diagnostic criteria of MAFLD and NAFLD at the same time. That is to say, they had liver steatosis, did not drink or drank less alcohol, and had any one of the following: overweight/obesity, T2DM, or metabolic dysregulation.

**Lean NAFLD and lean MAFLD:** Lean NAFLD was defined as lean individuals (BMI <23 kg/m$^2$) with the diagnosis of NAFLD. Lean MAFLD was defined as lean individuals (BMI <23 kg/m$^2$) with the diagnosis of MAFLD.

**Diabetes:** According to the diagnostic criteria recommended by the American Diabetes Association,[31] diabetes was defined as FPG ≥7.0 mmol/L or self-report clinical diagnosis of diabetes (subjects must provide the name of diagnosing hospital and time of diagnosis) or self-report used of anti-diabetes drugs.

**Dyslipidemia:** According to the guidelines for the prevention and treatment of dyslipidemia in Chinese adults (2016 Revised Edition),[32] plasma TC ≥6.2 mmol/L, TG ≥2.3 mmol/L, HDL-C <1.0mmol/L and LDL-C ≥4.1mmol/L were defined as TC, TG, HDL-C and LDL-C outside of normal range, respectively. Any of the above can be diagnosed as dyslipidemia.

### *Statistical analysis*

We used frequencies or percentages to describe categorical variables and means±standard deviations to describe continuous variables. Normally distributed variables used the two-sample independent *t*-test, non-normally distributed variables used the Mann-Whitney *U*-test, and categorical variables used the Chi-squared test (independent design and paired design) to compare the differences between the groups. The *p* values for all hypotheses tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 25.0 and R 3.5.1 statistical software.

## Results

### *General characteristics of the study participants*

Table 1 shows the general characteristics of study participants. There were 30,633 participants in the prevalence study, and 23,713 participants in the incidence study. Their average ages were 45.62±12.45 and 45.23±12.47 years-old, respectively. The average BMI and WC were 23.45±3.22 and 22.72±2.90 kg/m$^2$, and 84.07±8.94 and 82.42±8.39 cm, respectively. The proportion of males was 63.50% and 58.44%, respectively.

### *Prevalence and incidence of MAFLD and NAFLD*

The prevalence rates of MAFLD and NAFLD in the baseline population were 21.03% and 18.83%, respectively. After an average follow-up of 2.28 years, the incidence densities of MAFLD and NAFLD were 41.58 per 1,000 person-years and 37.69 per 1,000 person-years, respectively. As the population's age, BMI, and WC levels increase during the baseline survey, the prevalence and incidence of MAFLD and NAFLD were both on the rise ($p_{trend}<0.05$). Compared with females, non-diabetics, and non-dyslipidemia patients, the prevalence and incidence of MAFLD and NAFLD were higher than that among males, diabetics, and dyslipidemia patients ($p<0.05$) (Table 2).

### *Overlapping effects between the prevalence and incidence of MAFLD and NAFLD*

Figure 2 shows that a total of 6,828 people in the baseline population suffered from MAFLD and (or) NAFLD, of which 5,383 patients had both MAFLD and NAFLD, accounting for 78.84% (Fig. 2A). In addition, there were 1,893 patients that had both MAFLD and NAFLD among the 2,284 newly diagnosed patients, which accounted for 82.88% (Fig. 2B).

### *Comparison of MAFLD and NAFLD groups at related high-risk factors*

Compared with NAFLD, the MAFLD group had higher BMI and WC levels ($\chi^2$=108.160, $p<0.001$; $\chi^2$=27.864, $p<0.001$), were more likely to be male ($\chi^2$=16.348, $p<0.001$), and had higher prevalence of T2DM and dyslipidemia ($\chi^2$=12.968, $p<0.001$; $\chi^2$=7.330, $p<=.007$) at baseline (Fig. 3A).

For newly diagnosed MAFLD and NAFLD, patients with MAFLD had higher BMI level ($\chi^2$=6.142, $p$=0.046) and were more likely to be male ($\chi^2$=9.332, $p$=0.002) than the NAFLD patients. There were no statistical difference in the distribution of baseline age, WC, and dyslipidemia between the two groups ($p>0.05$) (Fig. 3B).

The comparison of high-risk factors among the three internal groups of patients is shown in Figure 3C–D. The NMN group had the least proportion of males, with normal BMI and WC, and the lowest proportion of T2DM and dyslipidemia in both the baseline patients and the follow-up new cases (all $p<0.05$). However, the levels of the above factors in the NNM group seemed to be the highest.

### *Clinical parameters in different groups of patients*

Table 3 shows the difference of clinical parameters between different groups of patients. The MAFLD group had higher

**Table 1. General characteristics of the study participants, *n* (%) / $\bar{x} \pm s$)**

| Variables | Prevalence study | Incidence study |
|---|---|---|
| Total, *n* | 30,633 (100) | 23,713 (100) |
| Age in years | 45.62±12.45 | 45.23±12.47 |
| <40 | 9,088 (29.67) | 7,338 (30.95) |
| 40–49 | 12,678 (41.38) | 9,924 (41.85) |
| 50–59 | 4,007 (13.08) | 2,831 (11.93) |
| ≥60 | 4,860 (15.87) | 3,620 (15.27) |
| Gender | | |
| Male | 19,451 (63.50) | 13,859 (58.44) |
| Female | 11,182 (36.50) | 9,854 (41.56) |
| BMI in kg/m$^2$ | 23.45±3.22 | 22.72±2.90 |
| <23.0 | 14,184 (46.30) | 13,175 (55.56) |
| 23.0–24.9 | 7,114 (23.23) | 5,508 (23.23) |
| ≥25.0 | 9,335 (30.47) | 5,030 (21.21) |
| WC in cm | 84.07±8.94 | 82.42±8.39 |
| Normal | 19,351 (63.17) | 16,799 (70.84) |
| Central obesity | 11,282 (36.83) | 6,914 (29.16) |
| T2DM | | |
| No | 28,529 (93.13) | 22,577 (95.21) |
| Yes | 2,104 (6.87) | 1,136 (4.79) |
| Dyslipidemia | | |
| No | 19,403 (63.34) | 16,647 (70.20) |
| Yes | 11,230 (36.66) | 7,066 (29.80) |
| ALT in U/L | 34.87±29.31 | 30.83±25.62 |
| AST in U/L | 34.53±19.50 | 32.80±17.49 |
| GGT in U/L | 37.20±47.29 | 30.25±40.27 |
| TBIL in μmol/L | 16.54±6.67 | 16.48±6.63 |
| DBIL in μmol/L | 4.28±2.63 | 4.24±2.67 |
| IBIL in μmol/L | 12.25±4.77 | 12.24±4.70 |
| TP in g/L | 76.18±4.46 | 75.98±4.45 |
| ALB in g/L | 48.13±2.80 | 47.99±2.80 |
| GLO in g/L | 28.12±3.78 | 28.07±3.77 |
| ALP in U/L | 67.96±20.65 | 66.73±20.76 |
| LDH in U/L | 190.46±36.64 | 189.03±36.16 |
| FPG in mmol/L | 5.32±1.38 | 5.18±1.15 |
| TC in mmol/L | 4.68±0.89 | 4.62±0.86 |
| TG in mmol/L | 1.96±1.56 | 1.74±1.33 |
| HDL-C in mmol/L | 1.36±0.35 | 1.41±0.35 |
| LDL-C in mmol/L | 3.05±0.74 | 3.03±0.71 |
| Scr in μmol/L | 70.24±15.13 | 69.44±15.52 |
| UA in μmol/L | 328.56±78.94 | 316.45±75.02 |
| BUN in mmol/L | 5.39±1.42 | 5.36±1.44 |

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBIL, direct bilirubin; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; GLO, globulin; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; T2DM, type 2 diabetes; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; WC, waist circumference.

**Table 2. Prevalence and incidence density of MAFLD and NAFLD at different levels of high-risk factors, %/per 1,000 person-years**

| Variables | Total | MAFLD | | NAFLD | | Person-years | MAFLD | | NAFLD | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | Pre, % | *n* | Pre, % | | Cases | ID | Cases | ID |
| Age in years | | | | | | | | | | |
| <40 | 9,088 | 1,557 | 17.13 | 1,487 | 16.36 | 15,054 | 505 | 33.55 | 468 | 31.09 |
| 40–49 | 12,678 | 2,556 | 20.16 | 2,299 | 18.13 | 21,342 | 878 | 41.14 | 814 | 38.14 |
| 50–59 | 4,007 | 1,119 | 27.93 | 982 | 24.51 | 6,655 | 376 | 56.50 | 333 | 50.04 |
| ≥60 | 4,860 | 1,210 | 24.90 | 1,001 | 20.60 | 9,642 | 432 | 44.80 | 371 | 38.48 |
| Total | 30,633 | 6,442 | 21.03* | 5,769 | 18.83 | 52,693 | 2,191 | 41.58# | 1,986 | 37.69 |
| $\chi^2$ | | 191.599 | | 79.853 | | | 114.071 | | 76.558 | |
| $p_{trend}$ | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |
| Gender | | | | | | | | | | |
| Male | 19,451 | 5,209 | 26.78 | 4,494 | 23.10 | 30,860 | 1,513 | 49.03 | 1,283 | 41.57 |
| Female | 11,182 | 1,233 | 11.03 | 1,275 | 11.40 | 21,833 | 678 | 31.05 | 703 | 32.20 |
| Total | 30,633 | 6,442 | 21.03 | 5,769 | 18.83 | 52,693 | 2,191 | 41.58 | 1,986 | 37.69 |
| $\chi^2$ | | 1,061.032 | | 636.058 | | | 111.094 | | 33.838 | |
| *p* | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |
| BMI in kg/m$^2$ | | | | | | | | | | |
| <23.0 | 14,184 | 531 | 3.74 | 816 | 5.75 | 29,202 | 522 | 17.88 | 539 | 18.46 |
| 23.0–24.9 | 7,114 | 1,606 | 22.58 | 1,362 | 19.15 | 12,271 | 662 | 53.95 | 582 | 47.43 |
| ≥25.0 | 9,335 | 4,305 | 46.12 | 3,591 | 38.47 | 11,220 | 1,007 | 89.75 | 865 | 77.09 |
| Total | 30,633 | 6,442 | 21.03 | 5,769 | 18.83 | 52,693 | 2,191 | 41.58 | 1,986 | 37.69 |
| $\chi^2$ | | 6,081.741 | | 3,911.219 | | | 1,185.337 | | 859.615 | |
| $p_{trend}$ | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |
| WC in cm | | | | | | | | | | |
| Normal | 19,351 | 2,106 | 10.88 | 2,149 | 11.11 | 37,376 | 1,019 | 27.26 | 977 | 26.14 |
| Central obesity | 11,282 | 4,336 | 38.43 | 3,620 | 32.09 | 15,317 | 1,172 | 76.52 | 1,009 | 65.87 |
| Total | 30,633 | 6,442 | 21.03 | 5,769 | 18.83 | 52,693 | 2,191 | 41.58 | 1,986 | 37.69 |
| $\chi^2$ | | 3,257.164 | | 2,052.417 | | | 692.075 | | 491.799 | |
| *p* | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |
| T2DM | | | | | | | | | | |
| No | 28,529 | 5,474 | 19.19 | 5,001 | 17.53 | 49,936 | 1,960 | 39.25 | 1,794 | 35.93 |
| Yes | 2,104 | 968 | 46.01 | 768 | 36.50 | 2,757 | 231 | 83.79 | 192 | 69.64 |
| Total | 30,633 | 6,442 | 21.03 | 5,769 | 18.83 | 52,693 | 2,191 | 41.58 | 1,986 | 37.69 |
| $\chi^2$ | | 848.728 | | 461.417 | | | 175.142 | | 113.034 | |
| *p* | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |
| Dyslipidemia | | | | | | | | | | |
| No | 19,403 | 2,375 | 12.24 | 2,310 | 11.91 | 36,838 | 1,068 | 28.99 | 988 | 26.82 |
| Yes | 11,230 | 4,067 | 36.22 | 3,459 | 30.80 | 15,855 | 1,123 | 70.83 | 998 | 62.95 |
| Total | 30,633 | 6,442 | 21.03 | 5,769 | 18.83 | 52,693 | 2,191 | 41.58 | 1,986 | 37.69 |
| $\chi^2$ | | 2,461.984 | | 1,661.532 | | | 531.316 | | 433.487 | |
| *p* | | <0.001 | | <0.001 | | | <0.001 | | <0.001 | |

* and # indicate that there was a difference in the prevalence and incidence of MAFLD and NAFLD ($p<0.05$). BMI, body mass index; ID, incidence density; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; Pre, prevalence; T2DM, type 2 diabetes; WC, waist circumference.

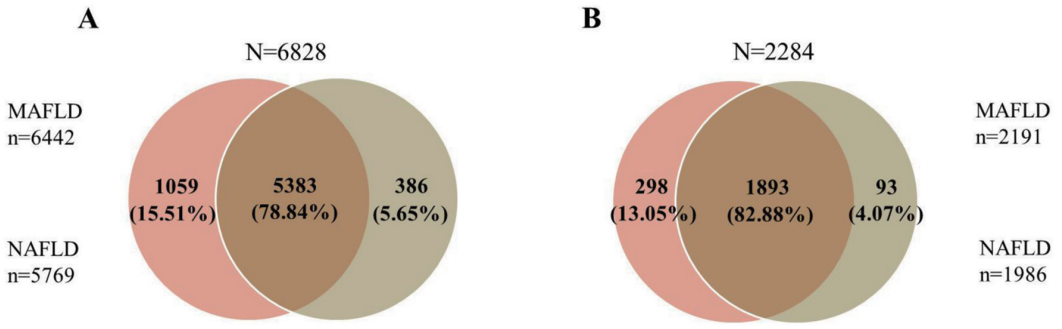


**Fig. 2. Schematic diagram of overlap effects between the prevalence and incidence of MAFLD and NAFLD.** (A) Overlapping effect of MAFLD and NAFLD patients in the baseline survey. (B) Overlapping effect of new cases of MAFLD and NAFLD in the follow-up population. Red represents the MAFLD patients, and grey-green represents the NAFLD patients. MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

ALT, AST, GGT, LDH, FPG, TG, serum creatinine (Scr) and uric acid (UA) levels than those in NAFLD group, but a lower level of HDL-C ($p$<0.05). Additionally, by comparing the MN and NMN and NNM groups, we found that NMN group had lower levels of liver enzymes, blood glucose, TC/TG/LDL-C, Scr/UA/blood urea nitrogen (BUN), and higher HDL-C levels than the other groups ($p$<0.05).

Table 4 shows a comparison of the differences in base-

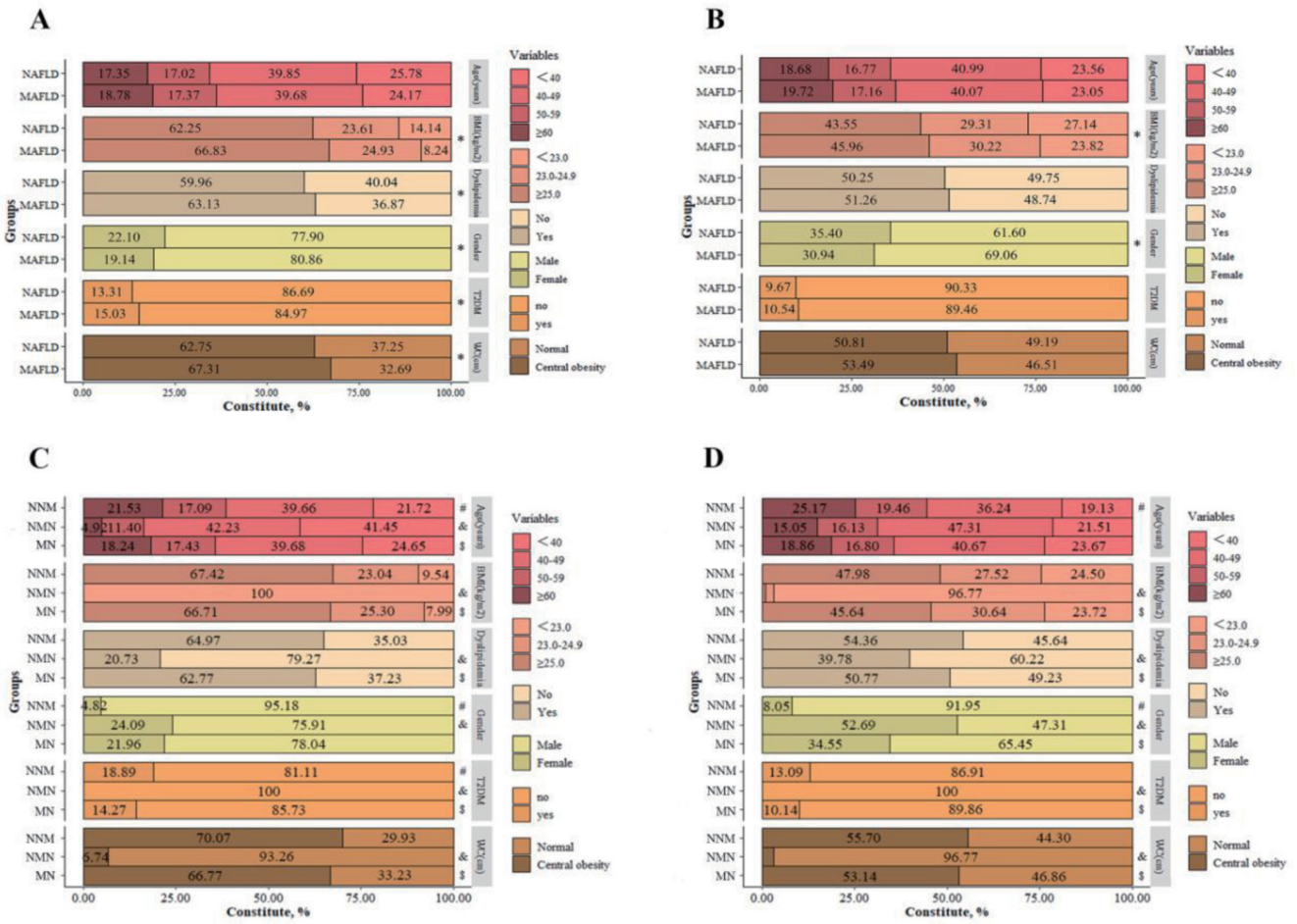


**Fig. 3. Comparison of related high-risk factors in different groups of patients.** (A) Comparison of MAFLD and NAFLD with different high-risk factors in the baseline diagnosed patients. (B) Comparison of MAFLD and NAFLD with different high-risk factors in the follow-up newly diagnosed cases. (C) Comparison of MN, NNM and NMN with different high-risk factors in the baseline diagnosed patients. (D) Comparison of MN, NNM and NMN with different high-risk factors in the follow-up newly diagnosed cases. $^{*}p$<0.05 for MAFLD vs. NAFLD; $^{\$}p$<0.05 for MN vs. NMN; $^{\#}p$<0.05 for MN vs. NNM; $^{\&}p$<0.05 for NMN vs. NNM. BMI, body mass index; MAFLD, metabolic dysfunction-associated fatty liver disease; MN, those who meet both the definitions of MAFLD and NAFLD; NAFLD, non-alcoholic fatty liver disease; NMN, those who meet the definition of NAFLD but do not meet the definition of MAFLD; NNM, those who meet the definition of MAFLD but do not meet the definition of NAFLD; T2DM, type 2 diabetes; WC, waist circumference.

**Table 3. Comparison of clinical parameters in different groups of patients, $\bar{x} \pm s$**

| Variables | MAFLD | NAFLD | $P_1$ | MN | NMN | NNM | $P_2$ | $P_3$ | $P_4$ |
|---|---|---|---|---|---|---|---|---|---|
| Total, *n* | 6,442 | 5,769 | – | 5,383 | 386 | 1,059 | – | – | – |
| Liver function metabolic | | | | | | | | | |
| ALT in U/L | 49.34±33.44 | 48.05±32.03 | 0.031 | 49.05±35.17 | 36.23±28.14 | 51.50±39.42 | <0.001 | 0.061 | <0.001 |
| AST in U/L | 40.64±23.90 | 39.54±22.10 | 0.008 | 39.80±21.88 | 35.67±24.71 | 44.82±31.96 | <0.001 | <0.001 | <0.001 |
| GGT in U/L | 55.28±63.80 | 50.00±48.59 | <0.001 | 51.00±48.70 | 36.14±44.92 | 77.05±110.225 | <0.001 | <0.001 | <0.001 |
| TBIL in μmol/L | 16.77±6.77 | 16.65±6.72 | 0.319 | 16.71±6.72 | 15.80±6.61 | 17.08±7.03 | 0.011 | 0.103 | 0.001 |
| DBIL in μmol/L | 4.41±2.48 | 4.37±2.47 | 0.382 | 4.36±2.47 | 4.47±2.47 | 4.65±2.56 | 0.403 | 0.001 | 0.250 |
| IBIL in μmol/L | 12.36±4.97 | 12.28±4.94 | 0.357 | 12.35±4.94 | 11.33±4.73 | 12.43±5.13 | <0.001 | 0.595 | <0.001 |
| TP in g/L | 76.91±4.45 | 76.87±4.44 | 0.598 | 76.91±4.44 | 75.85±4.37 | 76.73±4.47 | <0.001 | 0.223 | 0.001 |
| ALB in g/L | 48.63±2.74 | 48.64±2.74 | 0.801 | 48.64±2.74 | 48.61±2.69 | 48.55±2.75 | 0.838 | 0.341 | 0.720 |
| GLO in g/L | 28.34±3.79 | 28.29±3.75 | 0.470 | 28.35±3.76 | 27.29±3.48 | 28.21±3.91 | <0.001 | 0.263 | <0.001 |
| ALP in U/L | 72.19±19.64 | 71.88±19.41 | 0.382 | 71.88±19.38 | 69.42±20.01 | 72.70±21.04 | 0.016 | 0.217 | 0.008 |
| LDH in U/L | 196.43±37.95 | 194.99±38.02 | 0.036 | 195.97±38.08 | 178.50±33.24 | 197.28±37.40 | <0.001 | 0.305 | <0.001 |
| Glucose metabolism | | | | | | | | | |
| FPG in mmol/L | 5.88±1.93 | 5.78±1.84 | 0.002 | 5.84±1.89 | 4.85±0.44 | 6.07±2.15 | <0.001 | 0.001 | <0.001 |
| Lipid metabolism | | | | | | | | | |
| TC in mmol/L | 4.93±0.95 | 4.90±0.94 | 0.068 | 4.92±0.94 | 4.56±0.86 | 4.96±0.99 | <0.001 | 0.178 | <0.001 |
| TG in mmol/L | 2.81±2.01 | 2.69±1.91 | 0.001 | 2.77±1.94 | 1.51±0.92 | 3.00±2.35 | <0.001 | 0.003 | <0.001 |
| HDL-C in mmol/L | 1.20±0.29 | 1.21±0.29 | 0.041 | 1.19±0.28 | 1.43±0.34 | 1.22±0.32 | <0.001 | 0.002 | <0.001 |
| LDL-C in mmol/L | 3.18±0.80 | 3.15±0.80 | 0.110 | 3.18±0.79 | 2.76±0.80 | 3.15±0.82 | <0.001 | 0.270 | <0.001 |
| Renal function metabolic | | | | | | | | | |
| Scr in μmol/L | 73.18±13.52 | 72.65±13.47 | 0.029 | 72.85±13.60 | 69.70±11.03 | 74.81±13.01 | <0.001 | <0.001 | <0.001 |
| UA in μmol/L | 372.07±78.65 | 366.20±79.07 | <0.001 | 367.84±78.87 | 319.56±73.38 | 382.56±79.35 | <0.001 | <0.001 | <0.001 |
| BUN in mmol/L | 5.51±1.37 | 5.49±1.35 | 0.593 | 5.51±1.36 | 5.26±1.23 | 5.49±1.43 | <0.001 | 0.622 | 0.003 |

$P_1$: MAFLD vs. NAFLD; $P_2$: MN vs. NMN; $P_3$: MN vs. NNM; $P_4$: NMN vs. NNM. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DBIL, direct bilirubin; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; GLO, globulin; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MN, those who meet both the definitions of MAFLD and NAFLD; NAFLD, non-alcoholic fatty liver disease; NMN, those who meet the definition of NAFLD but do not meet the definition of MAFLD; NNM, those who meet the definition of MAFLD but do not meet the definition of NAFLD; Scr, serum creatinine; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid.

**Table 4. Comparison of baseline clinical parameters in different groups of new cases, $\bar{x} \pm s$**

| Variables | MAFLD | NAFLD | $P_1$ | MN | NMN | NNM | $P_2$ | $P_3$ | $P_4$ |
|---|---|---|---|---|---|---|---|---|---|
| Total, *n* | 2,191 | 1,986 | – | 1,893 | 93 | 298 | – | – | – |
| Liver function metabolic | | | | | | | | | |
| ALT in U/L | 36.73±23.33 | 35.73±22.15 | 0.153 | 36.31±23.94 | 27.79±16.07 | 41.55±32.27 | <0.001 | 0.008 | <0.001 |
| AST in U/L | 34.24±14.61 | 33.37±12.49 | 0.040 | 33.47±12.55 | 31.35±11.20 | 39.13±23.30 | 0.111 | <0.001 | <0.001 |
| GGT in U/L | 43.28±51.80 | 39.64±45.87 | 0.016 | 40.19±46.73 | 28.40±18.84 | 62.93±73.64 | <0.001 | <0.001 | <0.001 |
| TBIL in μmol/L | 16.38±6.52 | 16.13±6.35 | 0.210 | 16.17±6.42 | 15.32±4.67 | 17.71±7.01 | 0.095 | <0.001 | <0.001 |
| DBIL in μmol/L | 4.16±2.36 | 4.03±2.25 | 0.063 | 4.05±2.27 | 3.53±1.62 | 4.85±2.76 | 0.003 | <0.001 | <0.001 |
| IBIL in μmol/L | 12.22±4.76 | 12.10±4.69 | 0.425 | 12.12±4.73 | 11.79±3.65 | 12.87±4.90 | 0.514 | 0.012 | 0.024 |
| TP in g/L | 76.40±4.31 | 76.38±4.25 | 0.906 | 76.39±4.28 | 76.09±3.65 | 76.40±4.53 | 0.495 | 0.974 | 0.493 |
| ALB in g/L | 48.22±2.82 | 48.22±2.79 | 0.969 | 48.23±2.80 | 48.12±2.64 | 48.22±2.94 | 0.733 | 0.955 | 0.789 |
| GLO in g/L | 28.31±3.67 | 28.30±3.60 | 0.918 | 28.30±3.61 | 28.12±3.35 | 28.33±4.07 | 0.623 | 0.933 | 0.619 |
| ALP in U/L | 70.68±19.83 | 70.25±19.48 | 0.483 | 70.41±19.43 | 67.08±20.34 | 72.41±22.14 | 0.108 | 0.106 | 0.040 |
| LDH in U/L | 193.49±35.91 | 192.24±35.25 | 0.260 | 192.71±35.26 | 182.82±33.84 | 198.44±39.52 | 0.008 | 0.010 | 0.001 |
| Glucose metabolism | | | | | | | | | |
| FPG in mmol/L | 5.50±1.45 | 5.45±1.37 | 0.214 | 5.47±1.39 | 5.01±0.51 | 5.71±1.79 | <0.001 | 0.026 | <0.001 |
| Lipid metabolism | | | | | | | | | |
| TC in mmol/L | 4.83±0.91 | 4.83±0.91 | 0.996 | 4.83±0.91 | 4.88±0.83 | 4.84±0.90 | 0.611 | 0.779 | 0.753 |
| TG in mmol/L | 2.35±1.62 | 2.33±1.63 | 0.653 | 2.34±1.62 | 2.07±1.76 | 2.42±1.58 | 0.120 | 0.465 | 0.077 |
| HDL-C in mmol/L | 1.26±0.30 | 1.27±0.30 | 0.650 | 1.26±0.30 | 1.47±0.37 | 1.30±0.33 | <0.001 | 0.024 | <0.001 |
| LDL-C in mmol/L | 3.14±0.72 | 3.15±0.71 | 0.804 | 3.15±0.71 | 3.22±0.72 | 3.13±0.75 | 0.315 | 0.750 | 0.305 |
| Renal function metabolic | | | | | | | | | |
| Scr in μmol/L | 71.25±15.22 | 70.68±15.67 | 0.236 | 70.85±15.66 | 67.11±15.57 | 73.73±11.78 | 0.025 | <0.001 | <0.001 |
| UA in μmol/L | 346.18±78.40 | 342.58±78.50 | 0.139 | 343.98±78.41 | 314.25±75.26 | 360.17±76.97 | <0.001 | 0.001 | <0.001 |
| BUN in mmol/L | 5.52±1.44 | 5.53±1.46 | 0.947 | 5.54±1.46 | 5.34±1.40 | 5.45±1.35 | 0.205 | 0.320 | 0.513 |

$P_1$: MAFLD vs. NAFLD; $P_2$: MN vs. NMN; $P_3$: MN vs. NNM; $P_4$: NMN vs. NNM. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DBIL, direct bilirubin; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; GLO, globulin; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MN, those who meet both the definitions of MAFLD and NAFLD; NAFLD, non-alcoholic fatty liver disease; NMN, those who meet the definition of NAFLD but do not meet the definition of MAFLD; NNM, those who meet the definition of MAFLD but do not meet the definition of NAFLD; Scr, serum creatinine; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid.

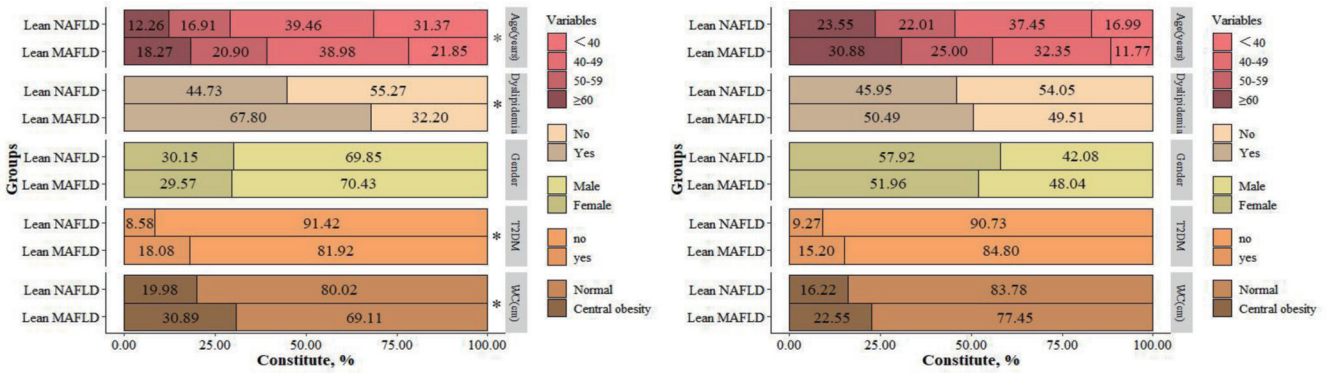


**Fig. 4. Comparison of lean MAFLD and lean NAFLD at different high-risk factors.** (A) Comparison of lean MAFLD and lean NAFLD with different high-risk factors in the baseline diagnosed patients. (B) Comparison of lean MAFLD and lean NAFLD with different high-risk factors in the follow-up newly diagnosed cases. *$p$<0.05 for lean MAFLD vs. lean NAFLD. T2DM, type 2 diabetes; WC, waist circumference.

line clinical parameters between different groups of new patients. Compared with the NAFLD group, the MAFLD group had higher AST and GGT levels ($p$<0.05), and there was no statistical difference in the distribution of other parameters ($p$>0.05). After comparing the three groups of MN and NMN and NNM, we found that NMN group had lower ALT, GGT, DBIL, LDH, FPG, Scr and UA levels, but a higher level of HDL-C than the other groups ($p$<0.05).

### *Comparison of lean MAFLD and lean NAFLD at baseline and follow-up*

There were 531 lean MAFLD patients and 816 lean NAFLD patients in the baseline population, and the prevalence rates were 1.73% and 2.66%, respectively. After an average follow-up of 2.28 years, the new cases of lean MAFLD and lean NAFLD were 204 and 259, and the incidence densities were 3.87 per 1,000 person-years and 4.92 per 1,000 person-years, respectively.

Among the patients diagnosed at baseline, compared with the lean NAFLD, the lean MAFLD group was significantly older ($\chi^2$=21.315, $p$<0001), had higher WC level ($\chi^2$=20.827, $p$<0001), and had higher prevalence of T2DM and dyslipidemia ($\chi^2$=26.872, $p$<0.001; $\chi^2$=68.862, $p$<0.001) (Fig. 4). Meanwhile, it also showed higher levels of liver enzymes, FPG, blood lipids, and UA than the lean group of NAFLD patients ($p$<0.05) (Table 5). Among newly diagnosed cases, the lean MAFLD patients had higher levels of AST (35.39±18.97 vs. 32.19±11.41, $p$=0.034) and FPG (5.84±1.77 vs. 5.50±1.48, $p$=0.030) than the lean NAFLD patients ($p$<0.05) (Table 5).

## Discussion

Based on the Jinchang cohort platform, this study explored the difference between the two diagnostic criteria of MAFLD and NAFLD. The prevalence and incidence density of MAFLD were 21.03% and 41.58/1,000 person-years, which were higher than that of NAFLD (18.83%, 37.69/1,000 person-years). Epidemiological studies based on MAFLD diagnostic criteria are relatively limited. A study from the US NHANES-III (1988–1994) database showed that the prevalence of MAFLD was lower than that of NAFLD (31.24% vs. 33.23%, $p$<0.05).[24] An analysis based on a random sample of 1,016 cases in Hong Kong showed that there were no significant differences in the prevalence of MAFLD and NAFLD (25.9% vs. 25.7%, $p$>0.05), and that the incidence of MAFLD was lower than that of NAFLD (2.8/100 person-years vs. 3.7/100 person-years, $p$<0.05).[26] In our cohort population, the prevalence of metabolic syndrome was highest,[33] which may cause the prevalence and incidence of MAFLD to be higher than those of NAFLD.

For existing and new cases, most patients met both diagnostic criteria, accounting for 78.84% and 82.88%, respectively. This phenomenon indicates that NAFLD is actually a metabolic disease.[34] In addition, the criteria of MAFLD could detect more fatty liver patients (13–15%) than the criteria of NAFLD and excluded some non-metabolic fatty liver patients. As an inclusive diagnostic criterion, MAFLD will more effectively contribute to managing this type of patient in terms of prevention, treatment, and disease prognosis.

The 2017 US Liver Disease Prevention and Control Guidelines suggested that obesity, T2DM, dyslipidemia, age, gender, and race were high-risk factors for fatty liver.[35] Based on this guideline, this study found that elderly, male, obese, and prevalence of T2DM and dyslipidemia were factors indicating a greater likelihood to develop MAFLD and NAFLD, which was consistent with the results conducted by Sulin *et al*.[24] In addition, the proportions of related indicators of abnormal metabolism (such as overweight/obesity, dyslipidemia, central obesity, etc.) in MAFLD patients were higher than those in the NAFLD group. This result indicated that the diagnostic criteria of MAFLD can fully reflect the current status of metabolic dysfunction.

Compared with NAFLD patients, MAFLD patients had higher levels of liver enzymes, blood lipids, and blood glucose. Sakura *et al*.[36] reported that MAFLD was more associated with patients with significant hepatic fibrosis than NAFLD. In addition, we also compared the relevant clinical indicators of each component of the two diagnostic criteria. The results showed that as long as the component contained MAFLD, the clinically relevant metabolic indicators were higher than those without the component. Therefore, this high-risk group should be given more attention.

Considering that obesity is one of the important factors leading to metabolic abnormalities, this study excluded the obese population and analyzed the applicability of the MAFLD diagnostic criteria in the normal-weight population. Lean MAFLD patients still showed higher levels of liver enzymes, FPG, and blood lipids than the lean NAFLD patients. Previous research studies have shown lean NAFLD and obese NAFLD had similar metabolic characteristics, such as insulin resistance and dyslipidemia.[37] It can be seen that the MAFLD diagnostic criteria proposed from the perspective of metabolic abnormalities had good applicability for the early detection of fatty liver.

Although this study found some significant results, there

**Table 5. Comparison of clinical parameters according to the presence of lean MAFLD and lean NAFLD**

| Variables | Baseline | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | Lean MAFLD | Lean NAFLD | $P_1$ | Lean MAFLD | Lean NAFLD | $P_2$ |
| Total, *n* | 531 | 816 | | 204 | 259 | |
| Liver function metabolic | | | | | | |
| ALT in U/L | 42.70±31.20 | 38.91±28.22 | 0.021 | 30.72±22.64 | 28.11±15.03 | 0.138 |
| AST in U/L | 41.60±35.20 | 37.27±25.79 | 0.015 | 35.39±18.97 | 32.19±11.41 | 0.034 |
| GGT in U/L | 66.94±137.62 | 44.78±69.37 | 0.001 | 42.27±83.25 | 33.29±68.56 | 0.204 |
| TBIL in μmol/L | 17.12±6.87 | 16.34±6.57 | 0.037 | 16.14±6.32 | 15.82±5.93 | 0.568 |
| DBIL in μmol/L | 4.25±2.61 | 4.26±2.47 | 0.938 | 3.88±2.31 | 3.61±2.02 | 0.184 |
| IBIL in μmol/L | 12.87±4.95 | 12.08±4.79 | 0.003 | 12.27±4.67 | 12.21±4.48 | 0.892 |
| TP in g/L | 77.53±4.48 | 76.83±4.51 | 0.005 | 76.82±4.10 | 76.48±3.91 | 0.363 |
| ALB in g/L | 48.88±2.72 | 48.81±2.69 | 0.617 | 47.92±2.53 | 48.04±2.58 | 0.606 |
| GLO in g/L | 28.74±3.67 | 28.11±3.58 | 0.002 | 28.94±3.72 | 28.52±3.44 | 0.208 |
| ALP in U/L | 74.24±22.46 | 71.50±21.03 | 0.023 | 69.41±20.29 | 68.30±20.22 | 0.557 |
| LDH in U/L | 191.47±39.20 | 185.06±36.91 | 0.002 | 189.28±31.58 | 187.58±32.55 | 0.573 |
| Glucose metabolism | | | | | | |
| FPG in mmol/L | 6.16±2.32 | 5.52±1.81 | <0.001 | 5.84±1.77 | 5.50±1.48 | 0.030 |
| Lipid metabolism | | | | | | |
| TC in mmol/L | 5.06±1.01 | 4.82±0.93 | <0.001 | 5.02±1.04 | 4.98±1.00 | 0.683 |
| TG in mmol/L | 2.86±1.76 | 2.20±1.51 | <0.001 | 2.26±1.37 | 2.20±1.53 | 0.635 |
| HDL-C in mmol/L | 1.27±0.38 | 1.34±0.36 | <0.001 | 1.37±0.33 | 1.40±0.35 | 0.464 |
| LDL-C in mmol/L | 3.21±0.83 | 3.00±0.82 | <0.001 | 3.28±0.71 | 3.27±0.72 | 0.920 |
| Renal function metabolic | | | | | | |
| Scr in μmol/L | 69.06±13.28 | 69.02±12.45 | 0.960 | 65.81±13.75 | 65.55±14.49 | 0.849 |
| UA in μmol/L | 352.96±84.39 | 334.02±78.98 | <0.001 | 316.66±76.60 | 309.81±75.07 | 0.334 |
| BUN in mmol/L | 5.28±1.35 | 5.30±1.27 | 0.868 | 5.21±1.41 | 5.27±1.44 | 0.671 |

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DBIL, direct bilirubin; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; GLO, globulin; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid.

are still some limitations. First, due to the lack of relevant data on fasting insulin and the diagnosis of diabetes being solely based on FPG or patient's self-report, the prevalence and incidence of MAFLD may be underestimated. Nevertheless, patients who self-reported diabetes were required to provide the name of the diagnosing hospital and the diagnosis time in order to ensure their accuracy. Second, hepatic steatosis was diagnosed by ultrasound in this study, which has limited sensitivity and does not reach 100% accuracy. When the subject's BMI was >40 kg/m$^2$, the detection result is not ideal. Although liver biopsy is the gold standard for diagnosing liver steatosis, it is not suitable for large-scale epidemiological investigations because of its invasive operation and safety issues.

In summary, the new definition of MAFLD is more suitable for describing liver diseases related to metabolic dysfunction, and compared to NAFLD, it can better identify fatty liver patients with high-risk diseases.

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## Conflict of interest

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

## Author contributions

Software, formal analysis, investigation, and writing of the original draft (CY), conceptualization, methodology, writing-

reviewing and editing, and study supervision (MW), conceptualization, methodology, investigation, and data curation (SZ), formal analysis and investigation (MX, HY), resources (DZ, CY, NC), and project administration and supervision (YB).

## Data sharing statement

The datasets used during the current study are available from the corresponding author on reasonable request.

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