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Original Article

# Clinical characteristics of lean metabolic-associated fatty liver disease and the impact of concurrent diabetes mellitus

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## Abstract

**Objectives:** Metabolic-associated fatty liver disease (MAFLD) was proposed in 2020 to replace the original term nonalcoholic fatty liver disease (NAFLD) with new diagnostic criteria. The disease risks of lean and overweight/obese MAFLD patients remain controversial. **Materials and Methods:** The participants from the Taiwan biobank cohort were included. Advanced liver fibrosis is defined as NAFLD fibrosis score (NFS) >0.675. We use carotid plaques of duplex ultrasounds to diagnose atherosclerosis. **Results:** A total of 20,058 participants (age 55.67 ± 10.32; males 37.6%) were included in the final analysis. Seven thousand eight hundred and forty-three (39.1%) participants were diagnosed with MAFLD. Of them, 965 (12.3%) were lean MAFLD patients. Among lean MAFLD patients, 25.6% were comorbid with diabetes mellitus (DM). Lean MAFLD patients were older and had higher percentages of females and DM than overweight/obese MAFLD patients. After propensity score matching for age and sex, they had lower levels of NFS but a higher percentage of carotid plaques. Among four subtypes of MAFLD including "lean with DM," "lean without DM," "overweight/obese with DM," and "overweight/obese without DM," logistic regression showed that "lean with DM" subjects had the highest risk of atherosclerosis and "overweight/obese with DM" subjects had the highest risk of advanced liver fibrosis in MAFLD patients. **Conclusion:** The population-based study revealed that lean MAFLD patients make up 12.3% of all MAFLD patients, and they have a higher proportion of coexisting diabetes. Among lean MAFLD patients concurrent with diabetes, they have the highest risk of atherosclerosis and should receive special attention clinically.

**Keywords:** *Carotid artery plaque, Liver fibrosis, Metabolic-associated fatty liver disease, Nonalcoholic fatty liver disease, Nonalcoholic fatty liver disease fibrosis score*

## Introduction

Metabolic (dysfunction)-associated fatty liver disease (MAFLD) was proposed to replace the original term of nonalcoholic fatty liver disease (NAFLD) by international consensus in 2020 [1,2]. NAFLD is an exclusive diagnosis without underlying causes in diagnostic criteria, which can increase heterogeneity in the included patients [3]. The updated disease name is an "inclusive" diagnosis and metabolic dysfunction is included in the diagnostic criteria, in addition to the previous criteria of hepatic steatosis. Metabolic dysfunction includes three criteria: overweight/obesity, type 2 diabetes mellitus (DM), or lean subjects with more than two metabolic abnormalities. Furthermore, the patients with viral, alcoholic, or other known chronic liver diseases were not excluded. Hence, MAFLD not only is an updated disease name but also includes new diagnostic criteria. Although the new disease name and diagnostic criteria can accurately reflect the underlying pathogenesis of the fatty liver disease, it was not very well justified by all societies over the world. The Asian-Pacific Association for the Study of the Liver first published the clinical practice guideline for the diagnosis and management of MAFLD [4]. Furthermore, the representatives of multiple stakeholders including hepatologists, cardiologists, nutritionists, nurses, and patient advocates from over 134 countries endorsed the name and its definition [5]. In addition, increasing evidence showed the superiority of

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the MAFLD definition in identifying patients with significant hepatic fibrosis and better predicting the progression of atherosclerotic cardiovascular risk compared to the previous NAFLD definition [6-9].

There is a significant correlation between NAFLD and obesity [10]. However, a small subset of patients with NAFLD does not exhibit overweight symptoms, and this subgroup is termed as lean NAFLD [11]. The definition of lean NAFLD is primarily based on body mass index (BMI), with a threshold of <23 kg/m$^2$ in Asian populations and <25 kg/m$^2$ in non-Asian populations. Therefore, individuals meeting the diagnostic criteria for NAFLD and having a BMI within the defined lean range for their respective regions were previously referred to as lean NAFLD in prior research [11]. However, due to changes in diagnostic terminology, they are now referred to as lean MAFLD. The pathophysiology of this specific subtype is not yet fully understood, and its clinical outcomes, management, and prognosis remain uncertain and require further investigation. In addition, no studies have reported on the clinical characteristics and outcomes of lean MAFLD patients since the update of the disease name and diagnostic criteria. This subgroup of lean MAFLD patients includes two subcategories: those without DM but having more than two metabolic abnormalities and those with concurrent DM. Using data from a Taiwan biobank cohort, a large, population-based study was conducted to examine the clinical outcomes including advanced liver fibrosis and atherosclerosis of lean MAFLD patients, compared with overweight/obese MAFLD patients, after stratification by the status of DM.



## Materials and methods

### Taiwan biobank cohort

Taiwan biobank, a general population-based research database in Taiwan, was conducted ever since 2008. The participants were enrolled through 43 recruitment stations. Till October 31, 2022, the participants increased to approximately 181,635. The methodologies of data collection from all participants were in standardized procedure and were described in previous studies [12,13]. Briefly, after obtaining informed consent, a formal questionnaire was performed by an experienced nurse. The questionnaire includes individuals who have been diagnosed with hypertension or are using drug treatment for hypertension, categorizing them as having a hypertension history. Similarly, a similar criterion is applied to a hyperlipidemia history. It also categorizes individuals based on their alcohol consumption history into three major groups: the first group consisted of non/social drinkers, the second group included individuals who had quit drinking, and the third group comprised those who continued to drink for at least 3 months or more. Demographic, clinical, and laboratory data were collected. The samples of DNA, blood, and urine were optionally obtained. All participants were invited to receive a follow-up at the intervals of 2–4 years. At the first follow-up, additional examinations including abdominal ultrasound, bone density measurement, and carotid duplex ultrasound were performed.

### Patients and study design

In the present study, the participants with the data of liver ultrasound were recruited. The diagnosis of MAFLD was based on the evidence of hepatic steatosis on liver ultrasound plus metabolic dysfunction including any of the following three criteria: overweight/obesity (BMI ≥23 kg/m$^2$), type 2 DM, and at least 2 metabolic risk abnormalities in lean/normal weight subjects. The name and diagnostic criteria of MAFLD were proposed in 2020 and approved by the Asia-Pacific Association for the Study of Liver (APASL), which subsequently established clinical guidelines [4]. Over the past 3 years, numerous published papers globally have affirmed its clinical feasibility. As for the diagnostic name and criteria of metabolic-associated steatotic liver disease proposed in 2023 by the American Association for the Study of Liver Diseases, there is currently limited clinical evidence, and the name has not been accepted by the APASL. Achieving unified disease names and diagnostic criteria in the future will require further research confirmation and communication and discussion among the three international liver associations including the European Association for the Study of the Liver. It is believed that there will be a consensus on disease names and diagnostic criteria in the future.

"Lean" MAFLD is defined as MAFLD with BMI <23 kg/m$^2$. DM is defined as having a history of DM or serum glycated hemoglobin (HbA1c) >6.5%. The fatty liver index (FLI) was utilized to predict the grade of hepatic steatosis [14]. NAFLD fibrosis score (NFS) >0.675 was defined as advanced liver fibrosis [15,16]. We use carotid plaques of duplex ultrasound to diagnose atherosclerosis [17]. According to the diagnostic criteria for MAFLD, this study did not exclude patients with chronic hepatitis B, chronic hepatitis C infection, and alcoholic liver disease. Therefore, the patients who have persistent drinking were not excluded. The clinical characteristics and adverse outcomes were compared between lean MAFLD patients and lean healthy controls, between lean MAFLD and overweight/obese MAFLD patients, and between lean MAFLD patients with DM and those without.

### Ethical considerations

This study was performed in accordance with the principles of the 1975 Declaration of Helsinki and was approved with waived informed consent by the Research Ethics Committee of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approval numbers: 10-XD-055 and 11-X-074), and the Ethics and Governance Council of the TWB (approval numbers: TWBR11102-03).

### Statistical analyses

The data were expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The clinical characteristics and outcomes were compared between lean MAFLD patients and lean healthy controls, between lean and overweight/obese MAFLD patients, and between lean MAFLD patients with DM and those without.

These data were analyzed by Chi-squared test and Student's *t*-test. $P < 0.05$ was considered statistically significant. The MAFLD patients were divided into four subtypes according to the status of DM and lean including "overweight/obese with DM," "overweight/obese without DM," "lean with DM," and "lean without DM" groups. The risk of advanced liver fibrosis and atherosclerosis for four subtypes was calculated by logistic regression.

## Results

A total of 22,909 participants with liver ultrasonography were enrolled from the Taiwan biobank database. After excluding participants with missing data, 20,058 participants (age: 55.67 ± 10.32; males: 37.6%) were included in the final analysis. Seven thousand eight hundred and forty-three (39.1%) participants were diagnosed as MAFLD. Of them, there were 965 (12.3%) lean MAFLD patients. Among lean MAFLD patients, 247 (25.6%) lean MAFLD patients were concurrent with DM [Figures 1 and 2].

### Comparison of clinical characteristics and outcomes between lean metabolic-associated fatty liver disease patients and lean healthy controls

Compared with lean healthy controls, lean MAFLD patients were older and had greater percentages of DM and carotid plaques but lower percentages of coexisting chronic hepatitis B virus (HBV) infection. Moreover, they had higher levels of BMI, glucose, HbA1c, triglyceride (TG), total cholesterol (CHO), low-density lipoprotein (LDL), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), uric acid, and NFS but lower levels of high-density lipoprotein (HDL). There is no significant difference in the levels of aspartate aminotransferase (AST) between the two groups. In addition, the percentage of male gender, chronic hepatitis C virus (HCV) infection, and persistent drinking was comparable between the two groups [Table 1].

### Comparison of clinical characteristics and outcomes between lean and overweight/obese metabolic-associated fatty liver disease patients

Compared with overweight/obese MAFLD patients, lean MAFLD patients had an older age and higher percentages of females. Moreover, they had lower levels of BMI, TG,

**Table 1: Clinical characteristics and outcomes between lean metabolic-associated fatty liver disease patients and lean healthy controls**

| | Lean controls (*n*=6813) | Lean MAFLD (*n*=965) | *P* |
|---|---|---|---|
| Male, *n* (%) | 1570 (23.0) | 225 (23.3) | 0.851 |
| Age (year) | 54.64±10.48 | 58.83±8.82 | <0.001 |
| DM, *n* (%) | 337 (4.9) | 247 (25.6) | <0.001 |
| HBV, *n* (%) | 747 (11.0) | 76 (7.9) | 0.004 |
| HCV, *n* (%) | 195 (2.9) | 20 (2.1) | 0.161 |
| Persistent drinking, *n* (%) | 307 (4.5) | 49 (5.1) | 0.426 |
| BMI (kg/m$^2$) | 20.81±1.53 | 21.65±1.08 | <0.001 |
| Glucose (mg/dL) | 92.41±13.51 | 104.56±28.60 | <0.001 |
| HbA1c (%) | 5.66±0.55 | 6.22±1.08 | <0.001 |
| TG (mg/dL) | 85.33±47.01 | 152.15±103.15 | <0.001 |
| Cholesterol (mg/dL) | 197.66±36.06 | 202.11±39.96 | 0.001 |
| HDL (mg/dL) | 62.34±13.87 | 51.76±12.65 | <0.001 |
| LDL (mg/dL) | 117.37±31.08 | 123.30±34.12 | <0.001 |
| Uric acid (mg/dL) | 4.76±1.15 | 5.29±1.26 | <0.001 |
| AST (U/L) | 24.37±11.64 | 25.74±22.35 | 0.062 |
| ALT (U/L) | 18.81±15.63 | 25.58±40.30 | <0.001 |
| GGT (U/L) | 18.32±29.15 | 26.99±55.11 | <0.001 |
| FLI | 11.30±9.62 | 21.79±15.27 | <0.001 |
| NFS | −2.17±1.06 | −2.02±1.11 | <0.001 |
| Carotid plaque, *n* (%) | 1769 (26.0) | 382 (39.6) | <0.001 |

MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BMI: Body mass index, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, FLI: Fatty liver index, TG: Triglyceride, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, NFS: Nonalcoholic fatty liver disease fibrosis score

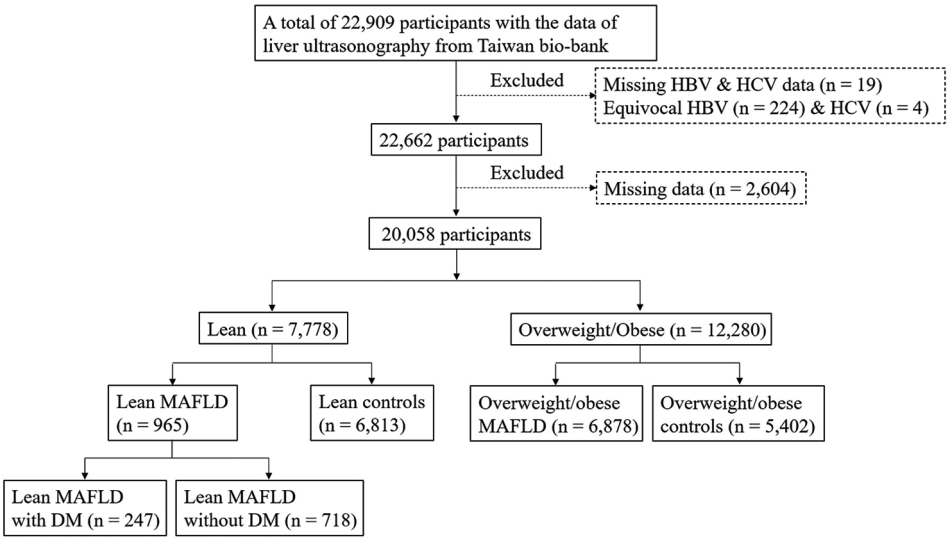


**Figure 1:** Study flowchart. HBV: Hepatitis B virus, HCV: Hepatitis C virus, MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus

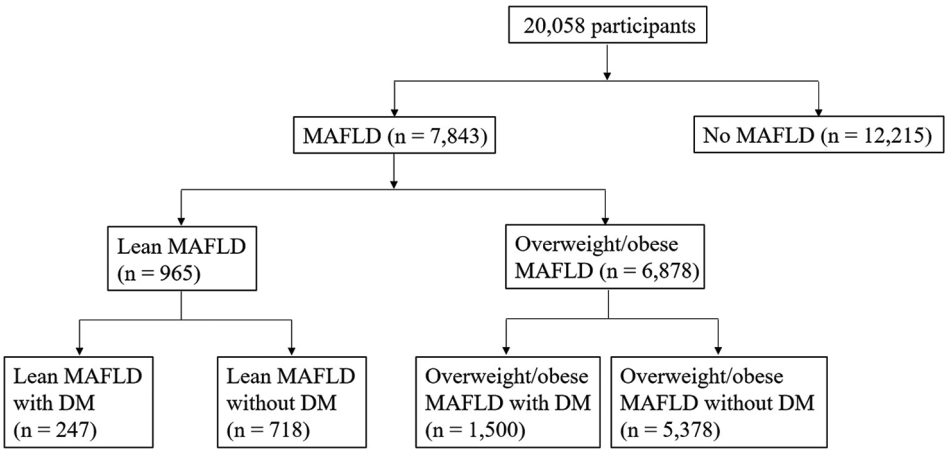


**Figure 2:** Metabolic-associated fatty liver disease patients were distributed to four groups according to the status of diabetes mellitus and the cutoff value of 23 in kg/m$^2$ in body mass index. MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus

LDL, uric acid (UA), AST, ALT, GGT, FLI, NFS, and lower percentage of persistent drinking but higher levels of CHO, HDL and higher percentage of carotid plaques and DM. The percentage of chronic HBV infection and chronic HCV infection was comparable between the two groups. The levels of glucose, HbA1c, and LDL were comparable between the two groups [Table 2].

### Comparison of clinical outcomes between lean and overweight/obese metabolic-associated fatty liver disease patients using propensity score matching for age and sex

Compared with overweight/obese MAFLD patients, lean MAFLD patients had higher percentages of DM, persistent drinking, and carotid plaques. Moreover, they had lower levels of BMI, HDL, and NFS but higher levels of glucose, HbA1c, TG, CHO, GGT, and FLI. The percentage of chronic HBV infection and chronic HCV infection was comparable between the two groups. The levels of LDL, uric acid, AST, and ALT were comparable between the two groups [Table 3].

### Comparison of clinical characteristics and outcomes between lean metabolic-associated fatty liver disease patients with diabetes mellitus and those without

Compared with nondiabetic lean MAFLD patients, lean MAFLD patients with DM had an older age and higher percentages of males. Moreover, they had higher levels of glucose, HbA1c, and NFS and a higher percentage of carotid plaques but lower levels of CHO, HDL, and LDL. There is no significant difference in the levels of BMI, TG, uric acid, and liver inflammatory markers between the two groups. The percentage of chronic HBV infection, chronic HCV infection, and persistent drinking was comparable between the two groups [Table 4].

### The risk of advanced liver fibrosis and atherosclerosis stratified by the status of lean and diabetes mellitus in metabolic-associated fatty liver disease patients

According to the status of lean and DM, MAFLD patients were distributed into four groups: "overweight/obese with DM," "overweight/obese without DM," "lean with DM," and "lean without DM" groups [Figure 2]. Advanced liver fibrosis is defined as NFS >0.675. Utilizing the "lean without DM" group as a reference, the adjusted odds ratios (AORs) of advanced liver fibrosis are 19.27 and 10.17 in the "overweight/obese with DM" and "lean with DM" groups, respectively [Table 4]. The risk of atherosclerosis is defined as the presence of carotid plaques. Utilizing the "lean without DM" group as a reference for comparison, the AORs of atherosclerosis are 1.31, 3.0, and 3.72 in the "overweight/

**Table 2: Comparison between lean metabolic-associated fatty liver disease and overweight/obese metabolic-associated fatty liver disease patients**

| | Lean MAFLD (*n*=965) | Overweight/obese MAFLD (*n*=6878) | *P* |
|---|---|---|---|
| Male, *n* (%) | 225 (23.3) | 3397 (49.4) | <0.001 |
| Age (year) | 58.83±8.82 | 55.78±10.13 | <0.001 |
| DM, *n* (%) | 247 (25.6) | 1500 (21.8) | 0.008 |
| HBV, *n* (%) | 76 (7.9) | 616 (9.0) | 0.268 |
| HCV, *n* (%) | 20 (2.1) | 151 (2.2) | 0.807 |
| Persistent drinking, *n* (%) | 49 (5.1) | 624 (9.1) | <0.001 |
| BMI (kg/m$^2$) | 21.65±1.08 | 27.23±3.24 | <0.001 |
| Glucose (mg/dL) | 104.56±28.60 | 103.63±26.44 | 0.339 |
| HbA1c (%) | 6.22±1.08 | 6.15±1.01 | 0.061 |
| TG (mg/dL) | 152.15±103.15 | 163.69±140.52 | 0.014 |
| Cholesterol (mg/dL) | 202.11±39.96 | 198.36±37.28 | 0.006 |
| HDL (mg/dL) | 51.76±12.65 | 48.36±10.89 | <0.001 |
| LDL (mg/dL) | 123.30±34.12 | 124.11±33.33 | 0.480 |
| Uric acid (mg/dL) | 5.29±1.26 | 6.04±1.42 | <0.001 |
| AST (U/L) | 25.74±22.35 | 27.55±13.77 | 0.015 |
| ALT (U/L) | 25.58±40.30 | 31.59±24.25 | <0.001 |
| GGT (U/L) | 26.99±55.11 | 30.91±29.43 | 0.001 |
| FLI | 21.79±15.27 | 39.16±21.72 | <0.001 |
| NFS | −2.02±1.11 | −1.84±1.15 | <0.001 |
| Carotid plaque, *n* (%) | 382 (39.6) | 2390 (34.7) | 0.003 |

MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BMI: Body mass index, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, FLI: Fatty liver index, TG: Triglyceride, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, NFS: Nonalcoholic fatty liver disease fibrosis score

**Table 3: Comparison between lean metabolic-associated fatty liver disease and overweight/obese metabolic-associated fatty liver disease patients after propensity score matching for age and sex**

| | Lean MAFLD (*n*=965) | Overweight/obese MAFLD (*n*=965) | *P* |
|---|---|---|---|
| Male, *n* (%) | 225 (22.3) | 225 (22.3) | 1.000 |
| Age (year) | 58.83±8.82 | 58.83±8.82 | 1.000 |
| DM, *n* (%) | 247 (25.6) | 137 (14.2) | <0.001 |
| HBV, *n* (%) | 76 (7.9) | 96 (9.9) | 0.110 |
| HCV, *n* (%) | 20 (2.1) | 34 (3.5) | 0.053 |
| Persistent drinking, *n* (%) | 49 (5.1) | 0 | <0.001 |
| BMI (kg/m$^2$) | 21.65±1.08 | 25.16±1.69 | <0.001 |
| Glucose (mg/dL) | 104.56±28.60 | 98.66±19.68 | <0.001 |
| HbA1c (%) | 6.22±1.08 | 5.95±0.77 | <0.001 |
| TG (mg/dL) | 152.15±103.15 | 92.33±35.26 | <0.001 |
| Cholesterol (mg/dL) | 202.11±39.96 | 196.56±37.42 | 0.002 |
| HDL (mg/dL) | 51.76±12.65 | 55.76±11.44 | <0.001 |
| LDL (mg/dL) | 123.30±34.12 | 123.98±33.30 | 0.658 |
| Uric acid (mg/dL) | 5.29±1.26 | 5.33±1.16 | 0.482 |
| AST (U/L) | 25.74±22.35 | 24.24±11.83 | 0.066 |
| ALT (U/L) | 25.58±40.30 | 22.68±26.59 | 0.063 |
| GGT (U/L) | 26.99±55.11 | 16.11±6.20 | <0.001 |
| FLI | 21.79±15.27 | 12.68±4.69 | <0.001 |
| NFS | −2.02±1.11 | −1.75±1.05 | <0.001 |
| Carotid plaque, *n* (%) | 382 (39.6) | 329 (34.1) | 0.012 |

MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BMI: Body mass index, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, FLI: Fatty liver index, TG: Triglyceride, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, NFS: Nonalcoholic fatty liver disease fibrosis score

obese without DM," "overweight/obese with DM," and "lean with DM" groups, respectively [Table 5]. Through logistic regression analysis, the AORs of atherosclerosis indeed showed the highest value in the "lean with DM" group, surpassing the "overweight/obese and DM" group.

### Factors associated with carotid plaque in metabolic-associated fatty liver disease patients using binary logistic regression

The factors associated with carotid plaque were evaluated using binary logistic regression. Univariate analysis found that male gender, age, DM, HBV, persistent drinking, BMI, glucose, HbA1c, HDL, LDL, UA, AST, and NFS were factors associated with carotid plaque. In multivariate analysis, 8 independent risk factors were identified for the carotid plaque: male (AOR = 1.62 [1.44–1.82]; $P < 0.001$), age (AOR = 1.11 [1.099–1.12]; $P < 0.001$), DM (AOR = 1.48 [1.24–1.77]; $P < 0.001$), HBV (AOR = 0.79 [0.65–0.95]; $P = 0.015$), persistent drinking (AOR = 1.34 [1.11–1.61]; $P = 0.003$), HDL (AOR = 0.993 [0.988–0.999]; $P = 0.012$), LDL (AOR = 1.004 [1.002–1.005]; $P < 0.001$), and uric acid (AOR = 1.05 [1.004–1.09]; $P = 0.030$) [Table 6].

## Discussion

In this large population-based study, the prevalence of lean MAFLD was found to be 12.3% among the MAFLD patients. Compared to overweight/obese MAFLD patients, lean MAFLD patients were older and had higher percentages of females and DM. Among lean MAFLD patients, those with DM had a higher percentage of carotid plaques and higher levels of NFS compared to those without DM. Furthermore, logistic regression analysis revealed that the "lean with DM" group had the highest risk of atherosclerosis compared to the "lean without DM," "overweight/obese with DM," and "overweight/obese without DM" groups. These findings suggest that lean MAFLD patients with diabetes should receive special attention for the risk of atherosclerosis.

**Table 4: Clinical characteristics and outcomes between lean metabolic-associated fatty liver disease patients with diabetes mellitus and those without**

| | Lean MAFLD with DM (*n*=247) | Lean MAFLD without DM (*n*=718) | *P* |
|---|---|---|---|
| Male, *n* (%) | 76 (30.8) | 149 (20.8) | 0.001 |
| Age (year) | 62.31±7.18 | 57.63±9.02 | <0.001 |
| HBV, *n* (%) | 25 (10.1) | 51 (7.1) | 0.129 |
| HCV, *n* (%) | 6 (2.4) | 14 (1.9) | 0.648 |
| Alcohol, *n* (%) | 8 (3.2) | 41 (5.7) | 0.127 |
| BMI (kg/m$^2$) | 21.61±1.14 | 21.67±1.06 | 0.437 |
| Glucose (mg/dL) | 134.36±42.59 | 94.31±8.15 | <0.001 |
| HbA1c (%) | 7.54±1.39 | 5.76±0.32 | <0.001 |
| TG (mg/dL) | 144.63±82.28 | 154.74±109.34 | 0.128 |
| Cholesterol (mg/dL) | 187.50±41.08 | 207.13±38.33 | <0.001 |
| HDL (mg/dL) | 49.96±10.92 | 52.38±13.14 | 0.005 |
| LDL (mg/dL) | 112.23±34.02 | 127.11±33.34 | <0.001 |
| Uric acid (mg/dL) | 5.29±1.29 | 5.29±1.25 | 0.951 |
| AST (U/L) | 27.54±40.75 | 25.12±10.01 | 0.357 |
| ALT (U/L) | 29.16±68.00 | 24.34±24.31 | 0.277 |
| GGT (U/L) | 25.06±17.69 | 27.65±63.04 | 0.524 |
| FLI | 21.30±14.17 | 21.96±15.64 | 0.556 |
| NFS | −1.06±0.90 | −2.35±0.98 | <0.001 |
| Carotid plaque, *n* (%) | 134 (54.3) | 248 (34.5) | <0.001 |

MAFLD: Metabolic-associated fatty liver disease, DM: Diabetes mellitus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BMI: Body mass index, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, FLI: Fatty liver index, TG: Triglyceride, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, NFS: Nonalcoholic fatty liver disease fibrosis score

The definition of lean MAFLD varies between Asian (BMI <23 kg/m$^2$) and non-Asian (BMI <25 kg/m$^2$) countries, as defined by the World Health Organization and Asian-Pacific Recommendations [18,19]. In addition, the nonlean category includes overweight and obese individuals. However, the nonobese category includes overweight and lean individuals. A meta-analysis and systemic review of 45 studies found the overall prevalence of MAFLD to be 38.77% in the pooled analysis, with 5.37% and 29.78% of lean and nonobese individuals, respectively [20]. However, another systemic review reported the epidemiology of MAFLD in individuals of normal weight, but all the included studies were conducted before the publication of the disease name "MAFLD" [21]. Our study is the first to describe the risk of clinical outcomes for lean MAFLD patients, with the prevalence of lean MAFLD being 4.8% in the general population and 12.3% in MAFLD patients.

**Table 5: The risk of advanced liver fibrosis and atherosclerosis stratified by the status of lean and diabetes mellitus in metabolic-associated fatty liver disease patients using logistic regression**

| | AOR | 95% CI | *P* |
|---|---|---|---|
| NFS >0.675 | | | |
| Lean without DM (reference) | 1 | | |
| Overweight/obese without DM | 1.24 | 0.76–2.02 | 0.397 |
| Lean with DM | 10.17 | 5.61–18.42 | <0.001 |
| Overweight/obese with DM | 19.27 | 12.52–29.67 | <0.001 |
| Carotid plaque | | | |
| Lean without DM (reference) | 1 | | |
| Overweight/obese without DM | 1.31 | 1.22–1.40 | <0.001 |
| Lean with DM | 3.72 | 3.13–4.41 | <0.001 |
| Overweight/obese with DM | 3.00 | 2.70–3.32 | <0.001 |

DM: Diabetes mellitus, NFS: Nonalcoholic fatty liver disease fibrosis score, AOR: Adjusted odds ratio, CI: Confidence interval

**Table 6: Factors associated with carotid plaque in metabolic-associated fatty liver disease patients using binary logistic regression (*n*=7843)**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | AOR | 95% CI | *P* |
| Male | 1.34 | 1.22–1.47 | <0.001 | 1.62 | 1.44–1.82 | <0.001 |
| Age (year) | 1.11 | 1.099–1.112 | <0.001 | 1.11 | 1.099–1.12 | <0.001 |
| DM | 2.24 | 2.01–2.49 | <0.001 | 1.48 | 1.24–1.77 | <0.001 |
| HBV | 0.64 | 0.54–0.77 | <0.001 | 0.79 | 0.65–0.95 | 0.015 |
| HCV | 1.28 | 0.94–1.74 | 0.123 | | | |
| Persistent drinking | 1.29 | 1.10–1.52 | 0.002 | 1.34 | 1.11–1.61 | 0.003 |
| BMI (kg/m$^2$) | 0.97 | 0.96–0.99 | <0.001 | 0.99 | 0.98–1.01 | 0.414 |
| Glucose (mg/dL) | 1.01 | 1.007–1.011 | <0.001 | 1.002 | 0.998–1.01 | 0.336 |
| HbA1c (%) | 1.31 | 1.25–1.37 | <0.001 | 1.03 | 0.93–1.13 | 0.599 |
| TG (mg/dL) | 1.00 | 1.00–1.001 | 0.216 | | | |
| Cholesterol (mg/dL) | 0.999 | 0.998–1.00 | 0.051 | | | |
| HDL (mg/dL) | 0.995 | 0.991–0.999 | 0.015 | 0.993 | 0.988–0.999 | 0.012 |
| LDL (mg/dL) | 0.998 | 0.997–1.00 | 0.011 | 1.004 | 1.002–1.005 | <0.001 |
| Uric acid (mg/dL) | 1.05 | 1.02–1.09 | 0.002 | 1.05 | 1.004–1.09 | 0.030 |
| AST (U/L) | 1.004 | 1.001–1.007 | 0.015 | 1.002 | 0.998–1.01 | 0.305 |
| ALT (U/L) | 0.999 | 0.998–1.001 | 0.454 | | | |
| GGT (U/L) | 1.001 | 0.999–1.002 | 0.301 | | | |
| FLI | 1.001 | 0.999–1.003 | 0.409 | | | |
| NFS | 1.52 | 1.46–1.59 | <0.001 | 1.04 | 0.98–1.10 | 0.171 |

OR: Odds ratio, CI: Confidence interval, AOR: Adjusted OR, DM: Diabetes mellitus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, BMI: Body mass index, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, NFS: Nonalcoholic fatty liver disease fibrosis score, FLI: Fatty liver index, TG: Triglyceride

NAFLD is strongly associated with central obesity, DM, and hyperlipidemia. Furthermore, NAFLD patients have lower overall survival rates compared to healthy controls, with cardiovascular disease (CVD), nonliver cancer, and liver disease being the leading causes of death [22,23]. In addition, NAFLD patients had worse metabolic profiles and diseases than healthy controls. These findings were consistent in lean subjects. A study of 11,613 subjects in the United States revealed that nonobese NAFLD patients had a higher prevalence of insulin resistance, DM, hypercholesterolemia, and hypertension than lean healthy controls [24]. A large Korean cohort with a median follow-up of 4 years demonstrated that lean NAFLD was a stronger risk factor for incident DM than overweight/obese subjects without NAFLD [25]. In liver function tests and metabolic profiles, lean NAFLD patients consistently had a higher risk of abnormal liver function tests and poor glucose and lipid profiles than lean healthy controls [26,27]. In a cohort of 5373 lean subjects with a median follow-up duration of 229 months, lean NAFLD patients showed higher hazards of all-cause and cardiovascular-related mortalities than lean healthy controls [28]. In the large, population-based study, lean MAFLD patients had worse metabolic profiles, a higher percentage of DM, and greater risks of advanced liver fibrosis and atherosclerosis than lean healthy controls. Based on these results, it can be concluded that lean MAFLD patients have worse metabolic profiles and increased risk of clinical outcomes than lean healthy controls.

Compared to overweight/obese MAFLD patients, lean MAFLD patients tend to exhibit lower levels of liver inflammatory markers such as AST, ALT, and GGT. However, the results regarding metabolic profiles and the risk of clinical outcomes are inconsistent and controversial. For instance, a large-scale study from the United States found a lower prevalence of insulin resistance, DM, hypertension, and hypercholesterolemia in lean NAFLD patients. In contrast, another Korean study with a large sample size discovered a higher prevalence of high blood pressure, glucose intolerance, and hypertriglyceridemia in nonobese NAFLD patients [29]. A recent study indicated a similar prevalence of DM, metabolic syndrome, and metabolic comorbidities between obese and nonobese NAFLD patients [30]. Regarding histological outcomes, a study of 646 patients with biopsy-proven NAFLD revealed that lean patients had less prevalence of nonalcoholic steatohepatitis (NASH) and fibrotic stages than overweight/obese patients [31]. Another Hong Kong study revealed that nonobese NAFLD patients had a lower NAFLD activity score and fibrosis stage than obese NAFLD patients [32]. However, in a study of 465 NAFLD patients with biopsy data in 220 patients with ALT elevation, no difference in histological findings was noted between obese and nonobese NAFLD patients [33]. Using serum biomarkers of liver fibrosis such as fibrosis-4 (FIB-4) and NFS, a retrospective study of the 1999–2016 NHANES cohort displayed an increased prevalence of advanced liver fibrosis in nonobese NAFLD patients. Moreover, nonobese NAFLD patients had higher 15-year cumulative all-cause mortality than obese NAFLD patients. In contrast, a study of biopsy-proven MAFLD patients with long-term follow-up showed similar overall mortality between lean and nonlean NAFLD patients. Another Hong Kong study proved that severe clinical outcomes were only observed in obese NAFLD patients after a median follow-up of 49 months [32]. In our large sample-sized study, we found that lean MAFLD patients had lower levels of NFS but a higher percentage of carotid plaques than nonlean MAFLD patients.

DM and obesity have been established as risk factors for MAFLD. In the new diagnostic criteria of MAFLD for

metabolic dysfunction, lean MAFLD patients can be classified into two groups: one is DM and the other is more than two metabolic risk abnormalities in nondiabetic subjects. In our study, we found that one-fourth of lean MAFLD patients were comorbid with DM. Those with DM had poorer metabolic profiles and a higher risk of liver fibrosis and atherosclerosis than those without, indicating that DM status can aid in risk stratification for lean MAFLD patients. Furthermore, we categorized MAFLD patients into four groups based on their BMI and DM status: "lean with DM," "lean without DM," "overweight/obese with DM," and "overweight/obese without DM." We found that the "lean with DM" group had the highest risk of atherosclerosis and the second-highest risk of advanced liver fibrosis among the four groups. This suggests that DM is a crucial factor in determining clinical outcomes, especially in lean MAFLD patients.

Our study has several strengths. First, this large, population-based study investigates the prevalence and clinical outcomes of Asian lean MAFLD patients using the updated diagnostic name and criteria of MAFLD. Second, it is the first study to divide MAFLD patients into four groups for comparison of clinical outcomes by the status of lean and DM. However, some limitations need to be addressed. First, fatty liver was determined by ultrasound without histology, which is invasive and unsuitable for population-based studies. Second, the severity of liver fibrosis was determined using FIB-4 index and NFS rather than liver histology. Third, it is indeed acknowledged that there is a lack of data on insulin resistance and high sensitivity C-reactive protein, which may lead to an underestimation of metabolic dysfunction and the potential for diagnosing MAFLD. Finally, the risk of atherosclerotic CVD was assessed cross-sectionally, but not real CVD events.

## Conclusions

In summary, our population-based study revealed that the prevalence of lean MAFLD was 12.4% in the MAFLD patients. Among lean MAFLD patients, 25.6% had comorbid DM, which was associated with poor metabolic profiles and increased severity of liver fibrosis and atherosclerosis. Moreover, lean MAFLD patients concurrent with DM had the highest risk of atherosclerosis compared to the "lean without DM," "overweight/obese with DM," and "overweight/obese without DM" groups, suggesting to receive special attention for the risk of atherosclerosis.

### Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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### Conflicts of interest

There are no conflicts of interest.

## References

1. Eslam M, Sanyal AJ, George J, International Consensus Panel. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999-2014.e1.
2. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-9.
3. Pal P, Palui R, Ray S. Heterogeneity of non-alcoholic fatty liver disease: Implications for clinical practice and research activity. World J Hepatol 2021;13:1584-610.
4. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, 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.
5. Méndez-Sánchez N, Bugianesi E, Gish RG, Lammert F, Tilg H, Nguyen MH, et al. Global multi-stakeholder endorsement of the MAFLD definition. Lancet Gastroenterol Hepatol 2022;7:388-90.
6. Cheng YM, Wang CC, Kao JH. Metabolic associated fatty liver disease better identifying patients at risk of liver and cardiovascular complications. Hepatol Int 2023;17:350-6.
7. Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int 2020;40:3018-30.
8. Tsutsumi T, Eslam M, Kawaguchi T, Yamamura S, Kawaguchi A, Nakano D, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: Generalized estimating equation approach. Hepatol Res 2021;51:1115-28.
9. Ayada I, van Kleef LA, Alferink LJ, 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.
10. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: Biochemical, metabolic, and clinical implications. Hepatology 2010;51:679-89.
11. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Rep 2019;1:329-41.
12. Fan CT, Lin JC, Lee CH. Taiwan biobank: A project aiming to aid Taiwan's transition into a biomedical Island. Pharmacogenomics 2008;9:235-46.
13. Timoteo VJ, Chiang KM, Pan WH. Positive or U-shaped association of elevated hemoglobin concentration levels with metabolic syndrome and metabolic components: Findings from Taiwan biobank and UK biobank. Nutrients 2022;14:4007.
14. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: A simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
15. Wang CC, Liu CH, Lin CL, Wang PC, Tseng TC, Lin HH, et al. Fibrosis index based on four factors better predicts advanced fibrosis or cirrhosis than aspartate aminotransferase/platelet ratio index in chronic hepatitis C patients. J Formos Med Assoc 2015;114:923-8.
16. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-54.
17. Kabłak-Ziembicka A, Przewłocki T. Clinical significance of carotid intima-media complex and carotid plaque assessment by ultrasound for the prediction of adverse cardiovascular events in primary and secondary care patients. J Clin Med 2021;10:4628.

18. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
19. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – A new worldwide definition. Lancet 2005;366:1059-62.
20. Chan KE, Koh TJ, Tang AS, Quek J, Yong JN, Tay P, et al. Global prevalence and clinical characteristics of metabolic-associated fatty liver disease: A meta-analysis and systematic review of 10 739 607 individuals. J Clin Endocrinol Metab 2022;107:2691-700.
21. Eslam M, El-Serag HB, Francque S, Sarin SK, Wei L, Bugianesi E, et al. Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight. Nat Rev Gastroenterol Hepatol 2022;19:638-51.
22. Brea A, Puzo J. Non-alcoholic fatty liver disease and cardiovascular risk. Int J Cardiol 2013;167:1109-17.
23. Brunner KT, Pedley A, Massaro JM, Hoffmann U, Benjamin EJ, Long MT. Increasing liver fat is associated with progression of cardiovascular risk factors. Liver Int 2020;40:1339-43.
24. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012;91:319-27.
25. Sinn DH, Kang D, Cho SJ, Paik SW, Guallar E, Cho J, et al. Lean non-alcoholic fatty liver disease and development of diabetes: A cohort study. Eur J Endocrinol 2019;181:185-92.
26. Chrysavgis L, Ztriva E, Protopapas A, Tziomalos K, Cholongitas E. Nonalcoholic fatty liver disease in lean subjects: Prognosis, outcomes and management. World J Gastroenterol 2020;26:6514-28.
27. Cheng YM, Kao JH, Wang CC. The metabolic profiles and body composition of lean metabolic associated fatty liver disease. Hepatol Int 2021;15:405-12.
28. Golabi P, Paik J, Fukui N, Locklear CT, de Avilla L, Younossi ZM. Patients with lean nonalcoholic fatty liver disease are metabolically abnormal and have a higher risk for mortality. Clin Diabetes 2019;37:65-72.
29. Kwon YM, Oh SW, Hwang SS, Lee C, Kwon H, Chung GE. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. Am J Gastroenterol 2012;107:1852-8.
30. Zou B, Yeo YH, Nguyen VH, Cheung R, Ingelsson E, Nguyen MH. Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999-2016. J Intern Med 2020;288:139-51.
31. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: A long-term follow-up study. Hepatol Commun 2018;2:48-57.
32. Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology 2017;65:54-64.
33. Alam S, Gupta UD, Alam M, Kabir J, Chowdhury ZR, Alam AK. Clinical, anthropometric, biochemical, and histological characteristics of nonobese nonalcoholic fatty liver disease patients of Bangladesh. Indian J Gastroenterol 2014;33:452-7.