Metabolic Associated Fatty Liver Disease Better Identifying Patients at Risk of Liver and Cardiovascular Complications

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Research Article

Keywords: metabolic associated fatty liver disease, non-alcoholic fatty liver disease, metabolic dysfunction, liver fibrosis, cardiovascular disease, fatty liver index, fibrosis-4 score, NAFLD fibrosis score, intima media thickness, carotid plaque

Posted Date: September 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2025707/v1

Abstract

Background/purpose:

A nomenclature of “metabolic associated fatty liver disease” (MAFLD) with new definition was proposed in 2020 instead of previous “non-alcoholic fatty liver disease” (NAFLD). However, which better fits the clinical demand remains controversial.

Methods

The participants with fatty liver on ultrasonography from Taiwan bio-bank cohort were included. MAFLD was defined as the presence of fatty liver, plus any of the following three conditions: overweight/obesity, type 2 diabetes mellitus (DM), or metabolic dysfunction. The severity of liver fibrosis was determined using fibrosis-4 (FIB-4) score and NAFLD fibrosis score (NFS). The risk of atherosclerosis was assessed using intima media thickness (IMT) or plaques of carotid duplex ultrasound.

Results

A total of 9719 subjects (age 55.9 ± 10.8; males 42.6%) were divided to four groups including “both fatty liver disease (FLD)”, “MAFLD only”, “NAFLD only”, and “neither FLD” with the percentages of 79.7%, 12%, 7.1%, and 1.2%, respectively. Compared with NAFLD patients, MAFLD patients had higher frequency of male gender, BMI, waist circumference, HbA1C, and triglyceride. On addition, they had higher levels of serum ALT, AST, GGT, fatty liver index (FLI), NFS and IMT, but no difference in FIB-4 index and the percentage of carotid plaques. Of note, the added population “MAFLD only group” had higher levels of AST, ALT, GGT, FLI, FIB-4, NFS, IMT and higher percentage of carotid plaques than the missed population “NAFLD only group”.

Conclusions

This large, population-based study showed MAFLD with new diagnostic criteria could identify more high-risk patients of metabolic, liver and cardiovascular disease complications in clinical practice.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the commonest cause of chronic liver disease in Western countries and its prevalence continues to increase in parallel with the epidemic of obesity and diabetes[1] It has a spectrum of histologic features ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) with varying stages of liver fibrosis, and can be complicated with cirrhosis, end-stage liver disease or even hepatocellular carcinoma.[2] NAFLD was clinically associated with metabolic

syndrome and metabolic components such as obesity, diabetes, and hyperlipidemia. Therefore, it was also considered as liver manifestation of metabolic syndrome.[3,4] Furthermore, NAFLD patients had increased overall mortality than general population and top three causes of death were cardiovascular disease, liver diseases and non-liver cancers.[5–7]Therefore, it is an important health issue worldwide.

NAFLD is a heterogenous disease with a “multiple-hit” pathogenesis.[8] Sine it is an exclusive diagnosis without pointing out the underlying causes in nomenclature, it was easily misunderstanding due to the term of “non alcohol” for patients and difficult to explain and educate in clinical practice. A meeting organized by European liver patient’s association (ELPA) and European commission in 2018 proposed to rename the nomenclature from NAFLD to metabolic (dysfunction) associated fatty liver disease (MAFLD).[9] In 2020, another international consortium of the 32 experts from 22 countries all over the world was convened to re-define the diagnostic criteria of MAFLD and its spectrum of heterogeneity.[10] The criteria are based on the evidence of hepatic steatosis by either imaging or liver histology, plus any of the following three criteria: overweight/obesity, type 2 diabetes mellitus (DM), or evidence of metabolic dysfunction. Obviously, the new disease name is an “inclusive” diagnosis mentioning the underlying cause of metabolic dysfunction. It has the benefit of easy understanding and education in clinical practice. However, the disease name was not fully accepted by major societies. A study of 1710 participants from a general United State (US) population using vibration-controlled transient elastography to assess the status of hepatic steatosis and liver fibrosis found the prevalence and the risk of advanced liver fibrosis was similar between NAFLD and MAFLD.[11] Due to the change of diagnostic criteria, some patients may be added (combined other causes of chronic liver diseases) or missed (no metabolic risk) after the change of nomenclature from NAFLD to MAFLD. Since whether MAFLD is better than NAFLD remains inconclusive, a study using a large cohort of Taiwan bio-bank, a representative sample of Taiwan general population was conducted to investigate the change of metabolic profiles, severity of liver fibrosis and cardiovascular (CV) risk after the change of disease name and diagnostic criteria from NAFLD to MAFLD

Materials And Methods

Patients and study design

The data were collected from Taiwan bio-bank. It is a general population-based research database comprised of > 20 year-old residents. The participants were enrolled through 43 recruitment stations in Taiwan since 2008. The methodologies of data collection from all participants were in standardized procedure and have been described in previous studies.[12,13] Briefly, after obtaining informed consent, a formal questionnaire including past history, smoking, drinking, diet, work and exercise was performed by an experienced studying nurse. The type (% of alcohol), the amount and frequency of alcohol were recorded. Furthermore, the demographic, clinical and laboratory data were collected. The samples of DNA, blood and urine were optionally obtained. All the participants were invited to receive follow-up at the interval of 2–4 years. At the first follow-up, the participants will receive additional examinations including

abdominal ultrasound, bone density measurement, and carotid duplex ultrasound. Till June 30, 2022, the number of participants increases to around 172,000.

In the present study, the participants without the data of liver ultrasound were excluded. NAFLD was defined as fatty liver in ultrasound examination without hepatitis B virus (HBV), hepatitis C virus infection, alcohol or other known causes of chronic liver disease. Participants with persistent alcohol intake > 210 g/week for men and > 140 g/week for women with a period of at least 3 months were excluded from the diagnosis of NAFLD. The diagnosis of MAFLD was based on the evidence of hepatic steatosis on liver ultrasound plus any of the following three criteria: overweight/obesity (body mass index (BMI) > 23 kg/m^2), type 2 DM, or metabolic dysfunction. DM is defined as having past history of diabetes mellitus or serum HbA1C > 6.5%.

Fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) were used as the markers of liver fibrosis. The FIB-4 was calculated based on the formula: FIB-4 = Age (years)×AST (U/L)/[PLT (10^9/L)×$ALT^{1/2}$(U/L)].[14] The formula of NFS was "−1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 ×impaired fasting glycemia/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl)".[15] The fatty liver index was used to predict the grade of hepatic steatosis and calculated by the formula: ($e^{0.953\times\log e(\text{triglycerides})+0.139\times\text{BMI}+0.718\times\log e(\text{GGT})+0.053\times\text{waist circumference}-15.745}$)/ (1 + $e^{0.953\times\log e(\text{triglycerides})+0.139\times\text{BMI}+0.718\times\log e(\text{GGT})+0.053\times\text{waist circumference}-15.745}$) × 100.[16] Using the data of carotid duplex ultrasound, carotid intima media thickness (IMT) and the presence of carotid plaques were used as the markers of atherosclerotic risk.[17] The IMT was the average of right and left common carotid arteries (CCA). In this large, population-based study, they were divided into four groups: "both fatty liver disease (FLD)", "MAFLD only group", "NAFLD only group", or "neither FLD" according to the status of NAFLD and MAFLD. The impact after the change of disease name and diagnostic criteria on metabolic profiles and the risk of liver and cardiovascular diseases was investigated.

Ethical considerations

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

Statistical Analyses

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). Data were analyzed by chi-square test and student's t test. A p value less than 0.05 was considered statistically significant.

Results

A total of 22,909 cases with the data of ultrasound abdominal ultrasonography were recruited from Taiwan bio-bank. Of them, 9735 (42.5%) participants had fatty liver in ultrasound. After excluding those without the data of hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), and alcohol consumption, 9719 subjects were included for final analysis. The percentages of “both FLD”, “MAFLD only group”, “NAFLD only group”, and “neither FLD” were 79.7%, 12%, 7.1%, and 1.2%, respectively. After the change of diagnostic criteria from NAFLD to MAFLD, the missed population was “NAFLD only group” and the added population was “MAFLD only group”, as shown on Fig. 1. The concordance of the two diseases diagnosis was 79.7% in our study population.

Comparison of clinical characteristics and metabolic profiles between NAFLD and MAFLD patients

Since NAFLD and MAFLD patients were selected based on different diagnostic criteria from the same population, more than 80 to 90% of patients in these two groups were duplicated. Therefore, it is relatively difficult to reach statistical difference. Compared with NAFLD patients, MAFLD patients had higher frequency of male gender, DM, and history of hypertension. Furthermore, several metabolic components including BMI, body fat, waist circumference (WC), glycated hemoglobin (HbA1C), triglyceride (TG), and uric acid were higher, but lower high-density lipoprotein (HDL) in MAFLD patients than NAFLD patients. The two groups of patients were comparable in age, history of hyperlipidemia, cholesterol (CHO), and low-density lipoprotein (LDL) (Table 1).

Comparison of liver and cardiovascular risk between NAFLD and MAFLD patients

MAFLD patients had higher serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST), gamma-glutamyl transferase) (GGT), fatty liver index, NFS, and IMT, but no difference in FIB-4 score and the percentage of carotid plaque (Table 1).

Comparison of clinical characteristics and metabolic profiles between “MAFLD only group” and “NAFLD only group”

These two groups of patients were new or missed population after the change of diagnostic criteria from NAFLD to MAFLD. Compared with “NAFLD only group”, “MAFLD only group” had higher percentage of male gender, DM, history of hypertension and hyperlipidemia. Furthermore, they had higher age, BMI, body fat, WC, HbA1C, TG, and uric acid, but lower CHO and HDL level. The serum LDL levels were comparable between two groups (Table 2).

Liver and cardiovascular risk between “NAFLD only group” and “MAFLD only group”

“MAFLD only group” had higher serum ALT/AST, GGT, fatty liver index, FIB-4 score, NFS, carotid IMT, and the percentage of carotid plaque than “NAFLD only group” (Table 2).

Discussion

In this study of 9719 fatty liver patients, 79.7% was “both FLD”, which fulfills both diagnostic criteria of NAFLD and MAFLD. The new population (MAFLD only group; 12%) has more people than the missed population (NAFLD only group; 7.1%) after the change of diagnostic criteria from NAFLD to MAFLD. Compared with NAFLD patients, MAFLD patients had higher frequency of male gender, DM, and hypertension. Furthermore, several metabolic components including BMI, uric acid, glucose and lipid profiles were higher in MAFLD patients than NAFLD patients even a high degree of overlap between the two groups of patients. In addition, the new population had higher frequency of metabolic diseases; poor metabolic profiles; increased severity of hepatic steatosis and liver fibrosis; and risk of atherosclerosis than the missed population. Therefore, the new diagnostic criteria of MAFLD not only include more patients, but also high-risk patients of metabolic, liver and cardiovascular (CV) diseases, suggesting MAFLD may be a better nomenclature than NAFLD in clinical practice.

Fatty liver patients with alcohol or other known etiologies of chronic liver disease were excluded from the diagnosis of NAFLD. In contrast, the diagnosis of MAFLD includes fatty liver plus metabolic risk and permits to have other concomitant liver diseases.[18] Two large population-based studies from Korea and China showed the added population had more people than the missed population after the change of disease name from NAFLD to MAFLD.[19,20] However, another population-based study from NHANES-III database, a representative sample of United State (US) general population had inconsistent findings. MAFLD patients were diagnosed in 31.24% participants, while NAFLD in 33.23% amongst the overall population.[21] Our large, population-based study from Taiwan showed the diagnostic criteria of MAFLD could include more patients than NAFLD.

The diagnostic criteria of MAFLD have two essential factors: fatty liver and metabolic dysfunction. The difference of diagnostic criteria between MAFLD and NAFLD is metabolic dysfunction and any of other concomitant liver diseases. A recent study from China showed MAFLD patients had greater proportions of DM and dyslipidemia, higher BMI, WC, blood glucose, and lipid levels than NAFLD patients.[19] Our study also found higher frequency of metabolic diseases and abnormal metabolic factors including BMI, glucose, lipid, and uric acid metabolism in MAFLD patients, suggesting the definition of MAFLD can diagnose fatty liver patients with higher degree of metabolic dysfunction than NAFLD.

The top three causes of death in NAFLD patients were CV disease, liver-related diseases, and non-liver cancers. Therefore, whether the new diagnostic criteria of MAFLD have the advantage of picking out high-risk patients of liver or CV diseases needs research to confirm. As we know, the severity of liver fibrosis was associated with overall mortality and the risk of HCC development.[22] The severity of atherosclerosis correlates with the risk of CVD.[23] A Taiwan study of 166 cases with pathologic diagnosis of hepatic steatosis or cryptogenic cirrhosis showed that “MAFLD alone group” patients had higher NAFLD activity score and percentage of advanced fibrosis than those with “NAFLD alone group”.[24] In another study of 765 Japanese fatty liver patients using shear wave elastography, they found liver stiffness was higher in MAFLD patients than those of NAFLD. In addition, the diagnostic criteria of MAFLD had higher sensitivity for detecting significant liver fibrosis than the previous NAFLD criteria.[25] In our study, MAFLD patients

had higher serum AST, ALT, GGT, fatty liver index and NFS than NAFLD patients. Furthermore, the “MAFLD only group’ had higher serum AST, ALT, GGT, fatty liver index, NFS, and FIB-4 score than “NAFLD only group”. Taking together, the new diagnostic criteria of MAFLD can help identifying those with a high degree of disease activity including hepatic steatosis, liver inflammatory and fibrosis than previous NAFLD criteria.

Regarding CVD risk, a nationwide health-screening database from Korea cohort followed by a median of 10.1 years revealed NAFLD and MAFLD patients had higher risk of CV events. In addition, when the “neither FLD” was used as reference, “both FLD” had highest hazard ratios for CV events, followed by MAFLD only and NAFLD only groups, suggesting the added patients (MAFLD only) had higher CV risk than the missed population (NAFLD only) after the change of diagnostic criteria from NAFLD to MAFLD.[26] Another study of 2985 subjects followed for 7 years found that although NAFLD and MAFLD had similar metabolic traits at baseline and similar outcome of CV events, “MAFLD only” patients had higher risk of adverse outcomes than “NAFLD only” patients.[28] Using the data of carotid duplex ultrasound, our study found MAFLD patients had higher IMTs than those with NAFLD. In addition, the new population after the change of disease name from NAFLD to MAFLD had higher IMT and percentage of carotid plaques than the missed population. Our data consistently confirmed the new terminology of MAFLD better identifies high-risk patients of CVD.

The missed population after the change of diagnostic criteria from NAFLD to MAFLD includes fatty liver patients who fulfilled the definition of NAFLD, but no metabolic risk (MR) (“NAFLD only group”; non-MR NAFLD). These subjects presented with fatty liver in imaging or histology without metabolic dysfunction, such as overweight/obese, DM, and metabolic dysregulation and without other etiologies of chronic liver disease. Since these patients had no metabolic diseases and other concomitant liver diseases, the risk of liver and CVD is expected to be minimal. Some previous studies confirmed the subjects with non-MR NAFLD without urgent diagnostic and therapeutic intervention needs due to a potentially favorable disease.[25] However, a recent brief report using NHANES III database noted “non-MR NAFLD only” patients with severe fatty liver in ultrasound might have significant liver injury and fibrosis and need more attention in clinical practice.[28] Since the definition of non-MR NAFLD in this study excluded only excessive alcohol consumption and metabolic risk, the results might be confounded by viral hepatitis or other causes of liver disease. In another study of 1217 cases with liver biopsy, there was no significant difference in the degree of liver inflammation and fibrosis among MAFLD, NAFLD, and “non-MR NAFLD” groups histologically. They suggested MAFLD criteria might overlook a subset of patients with steatohepatitis and significant fibrosis. However, since the majority of the cases were infected with HBV (93.26%), the confounding effect cannot be excluded.[29] Our study revealed that the missed population had lower risk of liver fibrosis and CVD compared with the new population after the change of disease name and diagnostic criteria from NAFLD to MAFLD.

Our study had some strengths. First, this is a large, population-based study from Taiwan bio-bank with simultaneous assessment of liver and CVD risk. Second, this was the first study to compare the risk of

CVD between NAFLD and MAFLD patient using the data of carotid duplex ultrasound. Third, since the database have detailed description about the type, amount, frequency and duration of alcohol drinking, the amount of alcohol consumed in a day can be accurately calculated to make the correct judge about the positive or negative diagnosis of NAFLD. However, some limitations should also be addressed. First, fatty liver was determined by ultrasound without histology in our study. However, liver biopsy is not well suited in population-based study. Furthermore, ultrasound-based studies remain poor diagnostic accuracy of fatty liver when hepatic steatosis is < 30%, for which ultrasound tends to underestimate the true prevalence of NAFLD and MAFLD. Second, this was a cross-sectional study and unable to demonstrate the causal relationship. Third, since the data of high-sensitivity C reactive protein and insulin resistance were not available in our study, the prevalence of MAFLD might be underestimated.

In summary, MAFLD is an “inclusive” diagnosis with the mention of underlying causes, which makes explanation and education more easily between physicians and patients. In addition, this large-scale, population-based study confirmed the change of nomenclature and diagnostic criteria from NAFLD to MAFLD could identify more patients at risk of metabolic, liver and CV complications for early intervention, suggesting MAFLD may be a better nomenclature than NAFLD in clinical practice. However, since MAFLD patients could have other concomitant liver diseases such as alcohol, viral hepatitis, or autoimmune liver diseases etc., the natural history and clinical outcomes of those patients need further investigations.[30]

Declarations

Funding statement:

This work was supported by grants from Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (TCRD-TPE-111-09) and the Taiwan Liver Disease Consortium, Ministry of Science and Technology, Taiwan (MOST 109-2314-B-002-091-MY3).

Conflict and Interest:

All authors declare no conflict and interest.

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Tables

Table 1: Comparison of clinical characteristics and outcomes between MAFLD and NAFLD

	MAFLD (n=8916)	NAFLD (n=8451)	P value
Age, years	56.12±10.04	56.05±10.13	0.647
Male, n (%)	3949 (44.3%)	3481 (41.2%)	< 0.001
DM, n (%)	2205 (24.7%)	1928 (22.8%)	0.003
HTN, n (%)	2264 (25.4%)	2010 (23.8%)	0.014
Hyperlipidemia, n (%)	1471 (16.5%)	1359 (16.1%)	0.457
BMI, Kg/m^2	26.53±3.57	26.05±3.76	< 0.001
Fatty liver index	43.09±24.66	40.05±25.39	< 0.001
Body fat %	31.54±7.48	31.13±7.56	0.001
WC, cm	89.72±9.27	88.45±9.83	< 0.001
Alcohol, n (%)	240 (2.7%)	0	0
HBsAg (+), n (%)	762 (8.5%)	0	0
Anti-HCV (+), n (%)	188 (2.1%)	0	0
Glucose, mg/dL	103.67±27.03	102.51±26.23	0.004
HbA1c, %	6.16±1.03	6.12±1.00	0.004
TG, mg/dL	157.66±97.57	152.15±94.80	0.001
CHO, mg/dL	199.24±37.61	200.03±37.48	0.166
HDL, mg/dL	48.88±11.08	50.02±11.80	< 0.001
LDL, mg/dL	124.41±33.50	124.80±33.37	0.442
Uric acid, mg/dL	5.93±1.42	5.82±1.43	< 0.001
AST, U/L	27.43±15.10	26.75±14.28	0.002
ALT, U/L	30.91±29.46	29.37±25.48	< 0.001
GGT, U/L	30.14±32.62	28.52±29.21	0.001
FIB-4 score	1.33±0.69	1.32±0.67	0.207
NFS	-1.87±1.23	-1.93±1.23	0.001
IMT, mm	0.64±0.15	0.63±0.15	0.025
Carotid plaque, n (%)	3127 (35.1%)	2906 (34.4%)	0.343

Abbreviation: MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; WC, waist circumference; HBsAg,

hepatitis B surface antigen; HbA1c, glycated hemoglobin; TG, triglycerides; CHO, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; FIB-4, fibrosis-4; NFS, NAFLD fibrosis score; IMT, intima media thickness.

Table 2: Comparison of clinical characteristics and outcomes between “MAFLD only” and “NAFLD only” groups

	Both FL disease (n = 7766)	MAFLD only (n = 1150)	NAFLD only (n = 685)	P value*
Age, years	56.3±10.09	54.92±9.61	53.14±10.16	< 0.001
Male, n (%)	3328 (42.9%)	621 (54%)	153 (22.3%)	< 0.001
DM, n (%)	1928 (24.8%)	277 (24.1%)	0	0
HTN, n (%)	1978 (25.5%)	286 (24.9%)	32 (4.7%)	< 0.001
Hyperlipidemia, n (%)	1305 (16.8%)	166 (14.4%)	54 (7.9%)	< 0.001
BMI, Kg/m^2	26.49±3.58	26.79±3.55	21.07±1.44	< 0.001
Fatty liver index	42.85±24.50	44.63±25.65	8.32±6.87	< 0.001
Body fat %	31.65±7.48	30.76±7.42	25.35±5.77	< 0.001
WC, cm	89.6±9.26	90.52±9.35	75.43±5.92	< 0.001
Alcohol, n (%)	0	240 (20.9%)	0	0
HBsAg (+), n (%)	0	762 (66.3%)	0	0
Anti-HCV (+), n (%)	0	188 (16.3%)	0	0
Glucose, mg/dL	103.58±27.03	104.25±27.08	90.42±6.66	< 0.001
HbA1c, %	6.17±1.02	6.13±1.08	5.57±0.28	< 0.001
TG, mg/dL	158.04±96.14	155.09±106.78	85.47±35.39	< 0.001
CHO, mg/dL	199.76±37.56	195.74±37.77	203.1±36.43	< 0.001
HDL, mg/dL	48.9±11.03	48.71±11.41	62.68±12.87	< 0.001
LDL, mg/dL	124.94±33.48	120.83±33.38	123.17±31.99	0.140
Uric acid, mg/dL	5.91±1.42	6.03±1.42	4.8±1.11	< 0.001
AST, U/L	27.04±1.45	30.07±18.41	23.41±11.15	< 0.001
ALT, U/L	30.25±26.18	35.37±45.59	19.38±11.42	< 0.001
GGT, U/L	29.37±29.03	35.31±50.27	18.81±29.48	< 0.001
FIB-4 score	1.31±0.67	1.44±0.78	1.35±0.62	0.008
NFS	-1.89±1.23	-1.74±1.21	-2.40±1.06	< 0.001
IMT, mm	0.64±0.15	0.63±0.13	0.56±0.12	< 0.001
Carotid plaque, n (%)	2759 (35.5%)	368 (32%)	147 (21.5%)	< 0.001

Abbreviation: FLD, fatty liver disease; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; WC, waist circumference; HBsAg, hepatitis B surface antigen; HbA1c, glycated hemoglobin; TG, triglycerides; CHO, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; FIB-4, fibrosis-4; NFS, NAFLD fibrosis score; IMT, intima media thickness.

*The statistical analysis and comparison were conducted between the MAFLD-only and NAFLD-only groups.

Figures

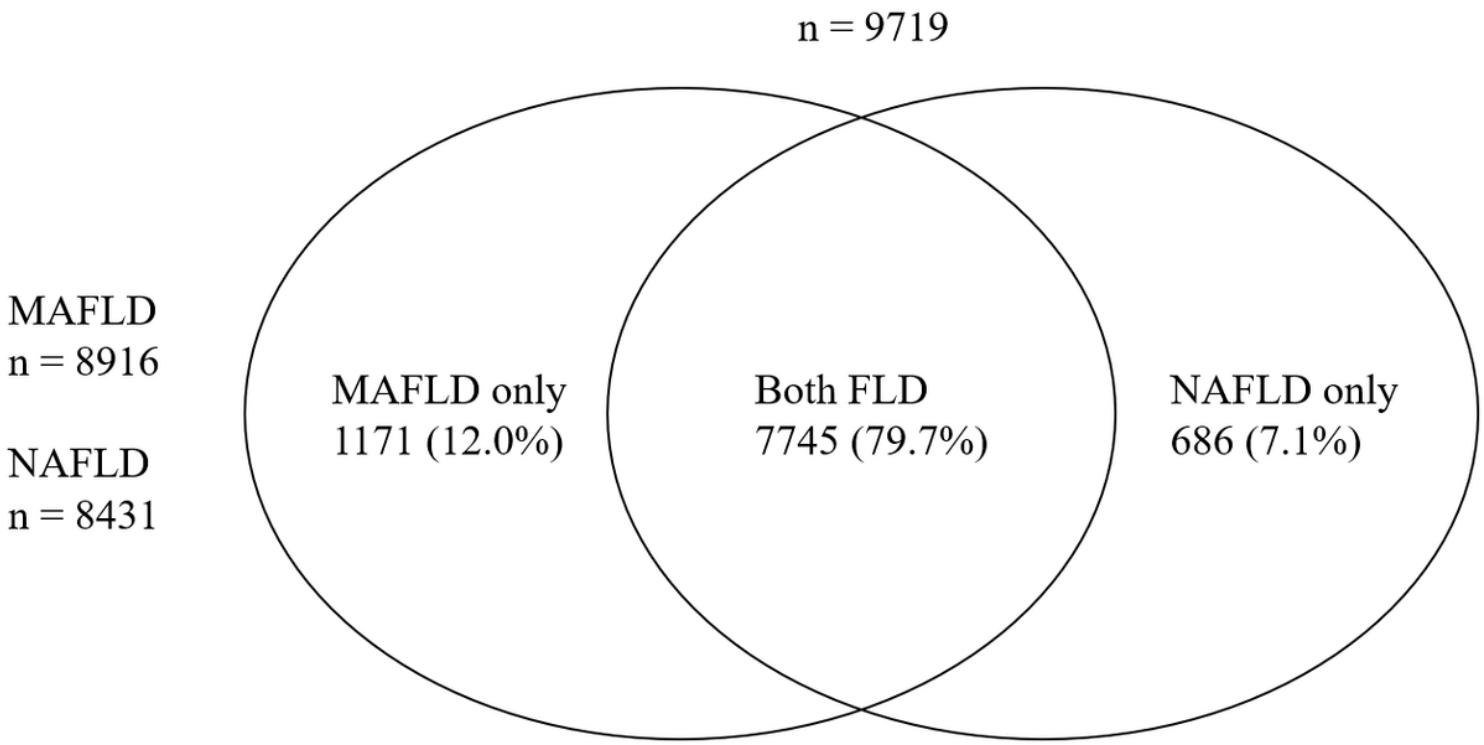

Figure 1

The percentage of different “fatty liver disease” based on NAFLD and MAFLD criteria

Abbreviation: MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease.