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Original Article

Discrepancies between Nonalcoholic and Metabolic-associated Fatty Liver Disease by Multiple Steatosis Assessment

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Abstract

Background and Aims: The redefinition of metabolic-associated fatty liver disease (MAFLD) from nonalcoholic fatty liver disease (NAFLD) has caused a revolution in clinical practice, and the characteristics of patients with steatosis but not MAFLD remain unclear. The aims were to compare the diagnosis rate of MAFLD in NAFLD using different steatosis methods and explore the features of non-MAFLD–NAFLD and MAFLD–non-NAFLD. ***Methods:*** A cross-sectional study enrolling consecutive individuals was conducted at three medical centers in southern China from January 2015 to September 2020. Steatosis was evaluated by liver biopsy or magnetic resonance imaging-based proton density fat fraction (MRI-PDFF), ultrasound, controlled attenuation parameter (CAP), and fatty liver index (FLI). Fibrosis was assessed by the NAFLD fibrosis score, transient elastography, or shear wave elastography. ***Results:*** The study enrolled 14,985 Chinese adults. The agreement of MAFLD and NAFLD diagnoses were 83% for FLI, 95% for ultrasound, 94% for both CAP and MRI-PDFF, and 95% for liver biopsy. The body mass index, blood pressure and lipid levels among non-MAFLD–NAFLD patients were similar metabolic parameters ($p>0.05$ for all), but not the alanine aminotransferase and the proportion of patients with insulin resistance, which were significantly higher in non-MAFLD–NAFLD with significant fibrosis. ***Conclusions:*** The new MAFLD definition ruled out 5–17% of NAFLD cases. NAFLD and MAFLD–NAFLD involved more severe metabolic abnormalities than MAFLD and MAFLD–non-NAFLD. Non-MAFLD–NAFLD patients with significant fibrosis had more severe liver injury and increased glycemic dysregulation within the normal range. Attention should be paid to its progression.

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Introduction

With a prevalence of over 25%, nonalcoholic fatty liver disease (NAFLD) has been regarded as the predominant cause of chronic liver disease worldwide, triggering tremendous economic and health burdens on both individuals and health care systems.[1] NAFLD is associated with the presence of metabolic syndrome and cardiovascular disease (CVD), which is the leading cause of death among NAFLD patients.[2] The components of metabolic syndrome are the most severe morbidities, accounting for the pathophysiological links between NAFLD and CVD.

The definition of NAFLD, was first proposed by Schaffner *et al*. in the early 1980s, and was based on the evidence of liver fat deposition excluding other known causes of steatosis, including excessive alcohol intake, vital hepatitis, and autoimmune liver disease.[3–5] However, this diagnostic census of NAFLD was exclusive and did not focus on the pathophysiology that involved the internal links of metabolic dysfunction to CVD. In 2020, multiple international

Keywords: Controlled attenuation parameter; Fatty liver index; Liver biopsy; Metabolic-associated fatty liver disease; Magnetic resonance imaging-based proton density fat fraction.

Abbreviations: CAP, controlled attenuation parameter; CVD, cardiovascular disease; 2D-SWE, two-dimensional shear wave elastography; FLI, fatty liver index; 1HMRS, proton-magnetic resonance spectroscopy; HOMA-IR, homeostasis model assessment of insulin resistance; LFC, liver fat content; MAFLD, metabolic associated fatty liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, nonalcoholic fatty liver disease.

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expert panels reached agreed on a nomenclature change from NAFLD to metabolic-associated fatty liver disease (MAFLD).[6–10] MAFLD not only renames the condition but also establishes a novel diagnostic flow. Briefly, MAFLD no longer requires the exclusion of excessive alcohol intake or other liver disease. It is primarily based on evidence of liver steatosis from the fatty liver index (FLI); imaging including ultrasound, controlled attenuation parameter (CAP), proton-magnetic resonance spectroscopy (^{1}HMRS), and magnetic resonance imaging proton density fat fraction (MRI-PDFF). Liver histology, the presence of overweight/obesity, type 2 diabetes mellitus (T2DM) or normal weight/lean with metabolic dysfunction, defined as abdominal obesity and a dysregulated serum lipid or glycemic profile are considered.[6–9]

Although diagnostic criteria for MAFLD have been proposed, the impact of the renaming has not yet been well elucidated. A retrospective study conducted by Lin *et al.* reanalyzed 13,083 participants from the third National Health and Nutrition Examination Surveys of the United States and demonstrated that compared with NAFLD patients, MAFLD patients were significantly older, had a higher body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR), lipids, liver enzymes, and greater percentages of metabolic comorbidities and advanced fibrosis.[11] Thus, the MAFLD definition is more practical for identifying patients with fatty liver disease and a high risk of disease progression. A similar result was also found in a study of 765 Japanese participants, in whom liver stiffness was greater in MAFLD than in NAFLD (7.7 vs. 6.8 kPa, p=0.0010).[12] However, a recent prospective study of 922 patients in Hong Kong using proton-magnetic resonance spectroscopy to found that applying the new diagnostic criteria for MAFLD did not significantly change the prevalence of disease or liver stiffness measurements compared with NAFLD in patients who fulfilled the MAFLD but not NAFLD criteria.[13] This raised considerable debate on NAFLD patients who do not meet the MAFLD criteria, even those with severe hepatic steatosis or fibrosis. Whether the metabolic dysfunction defined in these MAFLD criteria underestimates the impact of steatosis (i.e. hepatic metabolic dysfunction) remains unclear.

According to the new criteria, there are five methods for detecting liver steatosis in clinical practice, namely liver biopsy, ^{1}HMRS or MRI-PDFF, ultrasound, CAP, and FLI. The aim of this study was to compare the diagnostic rates of MAFLD in a cohort of Chinese patients previously diagnosed with NAFLD using five different methods. We also evaluated the characteristics of non-MAFLD–NAFLD patients and the proportions with moderate-to-severe steatosis or fibrosis.

Methods

Study design

This cross-sectional study was conducted at three medical centers in southern China, the First Affiliated Hospital, Sun Yat-Sen University; the First Affiliated Hospital, Guangzhou Medical University; and the Affiliated Dongguan People's Hospital, Southern Medical University (Dongguan People's Hospital), from January 2015 to December 2020. The patients were consecutively enrolled. The study protocol was approved by the institutional and regional medical ethics committees (approval number: 2014, no. 112), and was conducted following the ethical standards of the 1964 Declaration of Helsinki. All patients provided written informed consent. Fatty liver was diagnosed by at least one of the following: FLI, ultrasound, MRI-PDFF, CAP, or histology. Patients with any of the following were classified as non-NAFLD: daily alcohol consumption ≥20 g in men and ≥10 g in women, positive hepatitis B surface antigen or antibody against hepatitis C virus, autoimmune liver disease, pregnancy, endocrine disorders (e.g., hypothyroidism); other etiologies of liver disease resulting in steatosis (e.g., consumption of tamoxifen), or malignancies.[14] The diagnosis criteria for MAFLD were evidence of liver fat accumulation by histology, imaging, or blood biomarker in addition to overweight/obesity, diabetes, or metabolic dysregulation following the Asian Pacific guidelines for MAFLD management.[7]

Clinical assessment

Patients completed a standardized questionnaire self-reporting alcohol consumption, smoking, past medical history, and family history. Anthropometric data were obtained by specialized doctors. Blood samples were taken for liver biochemistry, lipids, glucose, insulin, uric acid, and hypersensitive-c-reactive-protein (hs-CRP) after fasting overnight. The homeostasis model of assessment for HOMA-IR was calculated as fasting blood glucose (FBG) mmol/L × fasting blood insulin (FINS), μU/mL) / 22.5.[15] A cutoff value of 2.5 was used to define insulin resistance (IR).[7] The FLI was calculated as $(e^{0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745}) / (1+e^{0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745}) \times 100$. The cutoff values of <30 and ≥60 were used to rule out or rule in hepatic steatosis, respectively.[16] The NAFLD fibrosis score (NFS), was calculated as −1.675+0.037 × age, (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes=1, no=0) + 0.99 × AST/ALT ratio −0.013 × platelet count (×10^9/L) −0.66 × albumin (g/dL). A score lower than −1.445 predicted the absence of advanced fibrosis (F3-F4).[17]

Ultrasonography

Ultrasonography was performed within 2 weeks after serum assays and physical examination. Typical ultrasonography features of fatty liver include the presence of liver and kidney echo discrepancy, with or without the presence of posterior attenuation of ultrasound beam, vessel blurring as well as difficult visualization of the gallbladder wall or the diaphragm. The degree of steatosis can be subjectively scored as (1) mild, defined by the manifestation of diffusely increased echogenicity or hepatorenal contrast or (2) moderate-to-severe, judged by the visualization of bright echoes and increased hepatorenal contrast concurrently or ultrasound beam attenuation.

CAP and liver stiffness measurement

CAP and liver stiffness measurements were conducted via transient elastography (FibroScan 402, Echosens, France) with either an M- or an XL-probe along with the instructions within 2 weeks after serum assays. Patients were placed in a supine position with the right arm elevated above the head and extended to the maximum. A success rate of >60% and ≥10 eligible acquisitions were adopted as a valid measurement. As a lack of uniform reference values of CAP has been reported, cutoff values of 244, 265, and 292 dB/m were chosen for discriminating non-, mild, moderate, and severe steatosis, and 7.3 kPa was used to define significant fibrosis.[18]

Liver stiffness measurement by shear wave elastography

Two-dimensional shear wave elastography (2D-SWE) was used to measure liver stiffness within 2 weeks of blood assays. A valid result included ≥5 eligible acquisitions with an interquartile range (IQR)-to-median ratio of <0.3. A cutoff

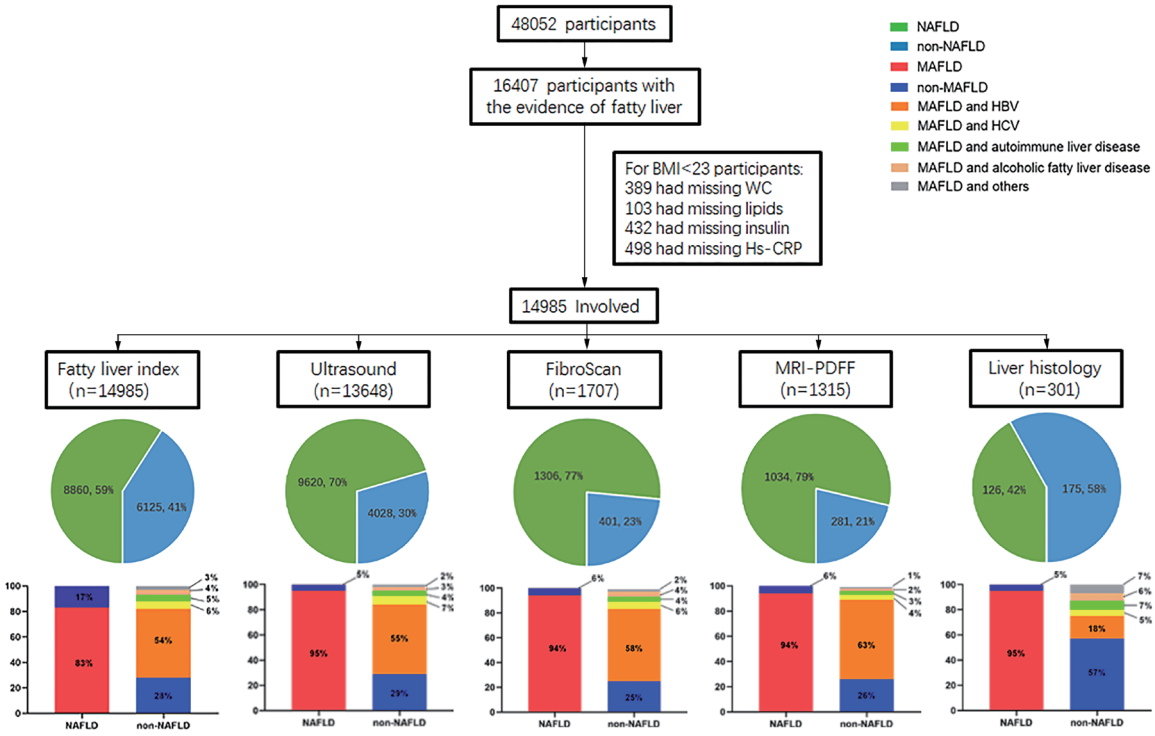

Fig. 1. Flow diagram of participant recruitment, screening, and the proportions of different liver diseases. Hs-CRP, hypersensitive-c-reactive-protein; MRI-PDFF, magnetic resonance imaging proton density fat fraction; WC, waist circumference.

value of 7.1 kPa was used to define significant fibrosis.[19]

Histological assessment

Liver biopsy was performed using 18 G Temno needles to get two 15 mm samples within 2 weeks of the initial clinical assessment. Tissues were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin or Masson's trichrome. The histological characteristics were evaluated and scored using the NASH clinical research network system. Fibrosis was staged using the Kleiner NAFLD fibrosis score. Two pathologists who blinded to the clinical data evaluated the liver specimens separately. Inconsistencies in scoring, were resolved by discussion with a third pathologist.

MRI quantification of liver fat content

Liver fat content (LFC) was measured by upper-abdominal MRI with a 3.0-Tesla MRI scanner (Siemens 3.0T Magnetom Verio) within 2 weeks of the serum assays. The liver fat-water separation images were obtained via a T1 volumetric interpolated breath-hold examination IDEAL-IQ/Dixon sequence, and the scanning protocol and imaging parameter settings were the same as previously described.[20] After attaining the fat-water separation images, data for LFC was further analyzed. Fatty liver was reported as mild (5.36–15.36%), moderate (15.36–20.35%), and severe (>20.35%) based on the LFC.[21]

Sample size calculation

Previously reported ultrasound diagnosis rates of MAFLD and NAFLD were 31.24% and 33.23%, respectively.[22] Using those percentages, PASS software (NCSS, Kaysville, USA) estimated a sample size of at least 3980 was needed to achieve a power of 90% with an alpha of 0.05.

Statistical analysis

The statistical analysis was performed with SPSS software version 25.0, (IBM Corp., Armonk., NY, USA). The results were reported as means ± standard deviation for variables with a normal distribution; others were reported as medians and interquartile range (IQR). One-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables. Categorical variables were compared with chi-squared tests. A two-tailed p-value <0.05 was considered statistically significant.

Results

Prevalence of NAFLD and MAFLD with different steatosis detection methods

Data from 48,052 patients were extracted, and 16,407 patients met the criteria for the diagnosis of steatosis. After excluding 1422 patients with missing data, a total of 14,985 with complete laboratory and/or ultrasonography, (13,648 91.1%) with CAP, (1707, 11.4%) with MRI-PDFF, (1315, 8.8%), and (301, 2.0%) with histology measurements were enrolled in the study (Fig. 1). Using the FLI to detect steatosis, NAFLD was diagnosed in 8860/14,985 (59.1%) patients, with MAFLD identified in 83% of patients (7320) with NAFLD, MAFLD–NAFLD, and the prevalence

of NAFLD without MAFLD (non-MAFLD–NAFLD) was 17%. For ultrasound, 9620/13648 (70.5%) patients were found to have NAFLD, while 5% of patients with NAFLD did not meet the criteria for MAFLD. A similar trend was also found when using CAP and MRI-PDFF; 1306/1701 (76.7%) and 1034/1315 (78.6%) patients were diagnosed with NAFLD, of whom 94.0% and 94.4% were diagnosed with MAFLD, respectively. For liver biopsy, 126/301 (41.9%) patients had NAFLD, and 4.8% of patients with NAFLD did not meet the criteria for MAFLD. Non-NAFLD was classified as non-MAFLD-non-NAFLD, and MAFLD–non-NAFLD (MAFLD co-existing with other liver diseases). A similar proportion of non-NAFLD cases was shown with different steatosis detection methods (Fig. 1).

Clinical characteristics of patients with steatosis determined by the FLI

Overall, 11,730 and 8860 patients were diagnosed with MAFLD and NAFLD by FLI, respectively, 7320 with MAFLD–NAFLD, 4410 MAFLD–non-NAFLD, and 1540 non-MAFLD–NAFLD. Compared with patients diagnosed with NAFLD, patients with MAFLD had higher BMI, waist circumference (WC), blood pressure and alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) levels (all, $p<0.05$; Table 1). Similar trends were also found in lipids (CHOL, TG, HDL-C, LDL-C), uric acid (UA) and FLI. Age, sex, alkaline phosphatase (ALP) and glucose metabolism indices, including FBG, FINS, and insulin resistance (IR) were comparable (Table 1). Compared with patients who had MAFLD–non-NAFLD, patients who had MAFLD–NAFLD had lower levels of blood pressure, ALT, AST, and HDL-C but higher levels of BMI, GGT, TG, LDL-C, FBG, FINS, HOMA-IR, UA, and FLI. Furthermore, patients who had non-MAFLD–NAFLD were divided into two groups by the NFS cutoff of −1.445. Compared with the ≥1.445 group (F3-F4), patients in the NFS ≤.445 (F0-F2) group had a higher BMIs (20.4±1.7 vs. 19.8±1.7, $p<0.001$), WC (20.4±1.7 vs. 19.8±1.7, $p=0.001$) and systolic blood pressure (113±13 vs. 110±14, $p=0.023$). In addition, ALT, FBG, hs-CRP levels, the FLI, and the proportions of patients with IR increased stepwise, while HDL-C and UA decreased from the F0-F2 to the F3-F4 group (Table 1). Also, the non-MAFLD–NAFLD group had the lowest HOMA-IR [1.9 (1.8–2.1)] and the smallest percentage of insulin resistance (28.1%). The highest HOMA-IR was in the NAFLD group, and the greatest proportion of insulin resistance was in the NAFLD, MAFLD, MAFLD–NAFLD, MAFLD–non-NAFLD, and non-MAFLD–NAFLD groups (Fig. 2A, F). Similarly, the FLI and the proportion of NFS ≥1.445 were the lowest in the non-MAFLD–NAFLD group and highest in the NAFLD group (Fig. 2K, P).

Clinical characteristics of steatosis patients based on ultrasound

Overall, there were 9620 NAFLD and 11,965 patients and MAFLD patients, of whom 9105 were diagnosed with MAFLD–NAFLD 2860 with MAFLD–non-NAFLD, and 515 with non-MAFLD–NAFLD. Compared with patients diagnosed with NAFLD, those with MAFLD had higher BMIs, WC, and blood pressure. Similarly, patients with MAFLD had higher liver enzymes (ALT, AST and GGT), lipids (CHOL, TG and LDL), and HOMA-IR (Table 2). Compared with MAFLD–NAFLD patients, those diagnosed with MAFLD–non-NAFLD had significantly lower BMIs, WC, WHR, CHOL, LDL-C, FBG, FINS, and UA, and higher levels of liver enzymes. We further divided non-MAFLD–NAFLD into mild fatty liver (77.3%) and moderate-to-severe fatty liver (22.7%) as determined by ultrasonography. Patients with moderate-to-severe fatty liver had a larger WC (67.2±6.1 vs. 65.9±6.2, $p=0.043$), larger WHR (0.86±0.02 vs. 0.83±0.03, $p=0.045$), and higher UA (376±89 vs. 352±87, $p=0.01$). In addition, patients with F3-F4 determined by the NFS had significantly higher ALT and AST levels, and a larger proportion of patients with IR than those with F0-F2 (Table 2). A significant difference in HOMA-IR was found among the five groups (Fig. 2B), and the non-MAFLD–NAFLD group had the smallest proportion of patients with IR (5.2%; Fig. 2G). The proportion of patients with moderate-to-severe steatosis and NFS ≥1.445 were both smallest in the non-MAFLD–NAFLD group (Fig. 2L, Q).

Clinical characteristics of patients with steatosis based on CAP and transient elastography

In total, 1306 patients with NAFLD and 1528 patients with MAFLD were assessed by CAP. Different from FLI and ultrasound, the MAFLD group had only a greater proportion of patients with IR than the NAFLD group (41.9% vs. 40.8%, $p<0.001$; Table 3). The MAFLD–NAFLD group included 1227 patients, and the MAFLD–non-NAFLD group included 301 patients. Compared with the MAFLD–NAFLD group, the MAFLD–non-NAFLD group had lower BMI, WC, WHR, FBG, FINS, HOMA-IR, UA, and CAP, and ALT, HDL-C and liver stiffness were higher (Table 3). We used cutoff values of CAP to classify non-MAFLD–NAFLD as mild (22.8%), moderate (59.5%), and severe fatty liver (17.7%). Among the three groups, mild non-MAFLD–NAFLD was predominantly observed in women and had the lowest BMI, WC, WHR, TG, CAP, and liver stiffness. A cutoff value of 7.3 kPa by transient elastography was used to define significant fibrosis. The non-fibrosis group had significantly lower levels of ALT [28 (22–38) vs. 48 (38–63), $p=0.002$], and ALP [72 (63–86) vs. 92 (85–114), $p=0.001$] and a smaller proportion of patients with IR (6.3% vs. 25.0%, $p=0.027$; Table 3). There was a significant difference in HOMA-IR, CAP and liver stiffness among the five groups (Fig. 2C, M, and R). Similarly, only 10.1% of patients presented with IR in the non-MAFLD–NAFLD group, while the greatest proportion of insulin resistance was found in the MAFLD–NAFLD group (Fig. 2H).

Clinical characteristics of patients with steatosis based on MRI-PDFF

Of the 1,315 patients undergoing MRI-PDFF, a total of 1034 were had NAFLD and 1184 had MAFLD. There was no difference between NAFLD and MAFLD with regard to anthropometric data, metabolic, or imaging indices (Table 4). Patients in the MAFLD group were further divided into MAFLD–NAFLD and MAFLD–non-NAFLD groups. Only HDL-C was higher in the MAFLD–non-NAFLD than in the MAFLD–NAFLD group (1.24±0.39 vs.1.14±0.28, $p<0.001$), and BMI, WC, WHR, GGT, LDL-C, FINS, HOMA-IR, UA and LFC were all lower in the MAFLD–non-NAFLD patients (Table 4). In the non-MAFLD–NAFLD group, 6.9% of patients were found to have severe fatty liver with increased WC, WHR, and LFC compared with those having mild or moderate steatosis. In addition, no difference between patients with fibrosis and those without fibrosis was found by 2D-SWE, except for the proportions of patients with IR (Table 4). HOMA-IR, LFC, and liver stiffness were the lowest in the non-MAFLD–NAFLD group (Fig. 2D, N, S). The MAFLD–NAFLD patients had the greatest proportion of IR (44.8%), followed by the NAFLD (42.9%), MAFLD (42.2%), MAFLD–non-NAFLD (30.3%) and non-MAFLD–NAFLD groups (8.6%; Fig. 2I).

Table 1. Comparison of clinical characteristics of MAFLD and NAFLD patients with hepatic steatosis and diagnosed by fatty liver index

Characteristics	All NAFLD	All MAFLD	*p*	MAFLD–NAFLD	MAFLD-non-NAFLD	*p*	NAFLD-non-MAFLD		*p*
							NFS ≤ −1.445	NFS > −1.445	
	(*n*=8,860)	(*n*=11,730)		(*n*=7,320)	(*n*=4,410)		(*n*=1,383)	(*n*=157)	
Age (year)	43.6±14.6	43.7±15.1	0.18	43.8±14.3	43.2±14.1	0.13	42.5±10.4	42.9±8.1	0.64
Male, *n* (%)	5,800 (65.5)	7,589 (64.7)	0.25	4,740 (64.8)	2,875 (65.23)	0.86	950 (68.7)	110 (70.1)	0.73
Body mass index (kg/m^2)	25.1±3.8	25.8±4.0	<0.001	26.0±4.1	25.1±3.7	<0.001	20.4±1.7	20.5±1.8	0.68
Waist circumference (cm)	83.8±11.8	86.0±11.0	<0.001	86.0±10.8	86.1±10.6	0.74	64.1±5.3	64.5±4.8	0.59
Systolic blood pressure (mmHg)	127±17	129±16	<0.001	127±16	130±18	<0.001	113±13	114±15	0.74
Diastolic blood pressure (mmHg)	80±14	83±13	<0.001	81±11	84±13	<0.001	67±10	67±13	0.76
Alanine aminotransferase (U/L)†	30 (18–53)	36 (21–63)	<0.001	33 (18–59)	48 (29–82)	<0.001	25 (20–37)	28 (21–42)	0.018
Aspartate aminotransferase (U/L)†	25 (20–37)	27 (20–40)	<0.001	25 (18–37)	34 (24–48)	<0.001	30 (18–53)	38 (22–67)	0.75
γ-Glutamyl transpeptidase (U/L)†	35 (23–60)	41 (26–72)	<0.001	43 (26–73)	40 (26–62)	0.002	35 (23–60)	40 (26–70)	0.74
Alkaline phosphatase (U/L)†	76 (64–90)	77 (64–90)	0.24	78 (63–91)	76 (64–86)	0.35	76 (64–90)	77 (64–89)	0.69
Total cholesterol (mmol/L)	5.18±1.08	5.26±1.13	<0.001	5.27±1.10	5.22±1.28	0.11	4.73±0.89	4.69±0.91	0.59
Triglycerides (mmol/L)	1.88±0.36	1.99±0.45	<0.001	2.04±0.59	1.73±0.43	<0.001	1.11±0.53	1.17±0.82	0.20
HDL-C (mmol/L)	1.29±0.40	1.23±0.44	<0.001	1.22±0.38	1.30±0.66	<0.001	1.65±0.35	1.58±0.35	0.012
LDL-C (mmol/L)	3.15±0.90	3.29±0.91	<0.001	3.31±0.99	3.19±0.90	0.003	2.66±0.82	2.55±0.72	0.12
Fasting blood glucose (mmol/L)	5.40±1.09	5.41±1.00	0.52	5.48±1.01	5.06±0.96	<0.001	4.99±0.30	4.95±0.31	0.26
Fasting insulin (μU/mL)†	10.9 (8.7–15.1)	11.6 (9.0–16.3)	0.07	11.6 (9.0–16.3)	9.1 (6.4–12.3)	<0.001	9.05 (8.49–10.2)	8.30 (7.96–9.12)	0.10
HOMA-IR†	2.6 (2.0–3.6)	2.8 (2.1–4.0)	0.08	2.7 (2.0–3.8)	1.9 (1.4–2.9)	0.001	2.37 (2.29–2.60)	2.36 (2.29–3.0)	0.56
HOMA-IR >2.5, (%)	4,687 (52.9)	6,135 (52.3)	0.39	4,255 (58.1)	1,777 (40.3)	<0.001	370 (26.8)	62 (39.5)	0.001
Uric acid (μmol/L)†	399±106	405±108	<0.001	408±111	389±92	<0.001	358±84	335±67	0.001
Hs-CRP (mg/L)	-	-		-	-	-	3.81±1.59	4.11±1.84	0.039
Fatty liver index†	43 (34–59)	47 (36–63)	<0.001	47 (36–47)	46 (36–61)	0.002	41 (34–41)	41 (36–51)	0.008
NFS >-1.445, *n* (%)	2,109 (23.8)	2,874 (24.5)	0.25	1,610 (22.0)	1,0235 (23.2)	0.13	-	-	-

Data are means ± standard deviation or †medians and IQR for continuous variables with non-Gaussian distribution. HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, hypersensitive-c-reactive-protein; LDL-cholesterol, low-density lipoprotein cholesterol.

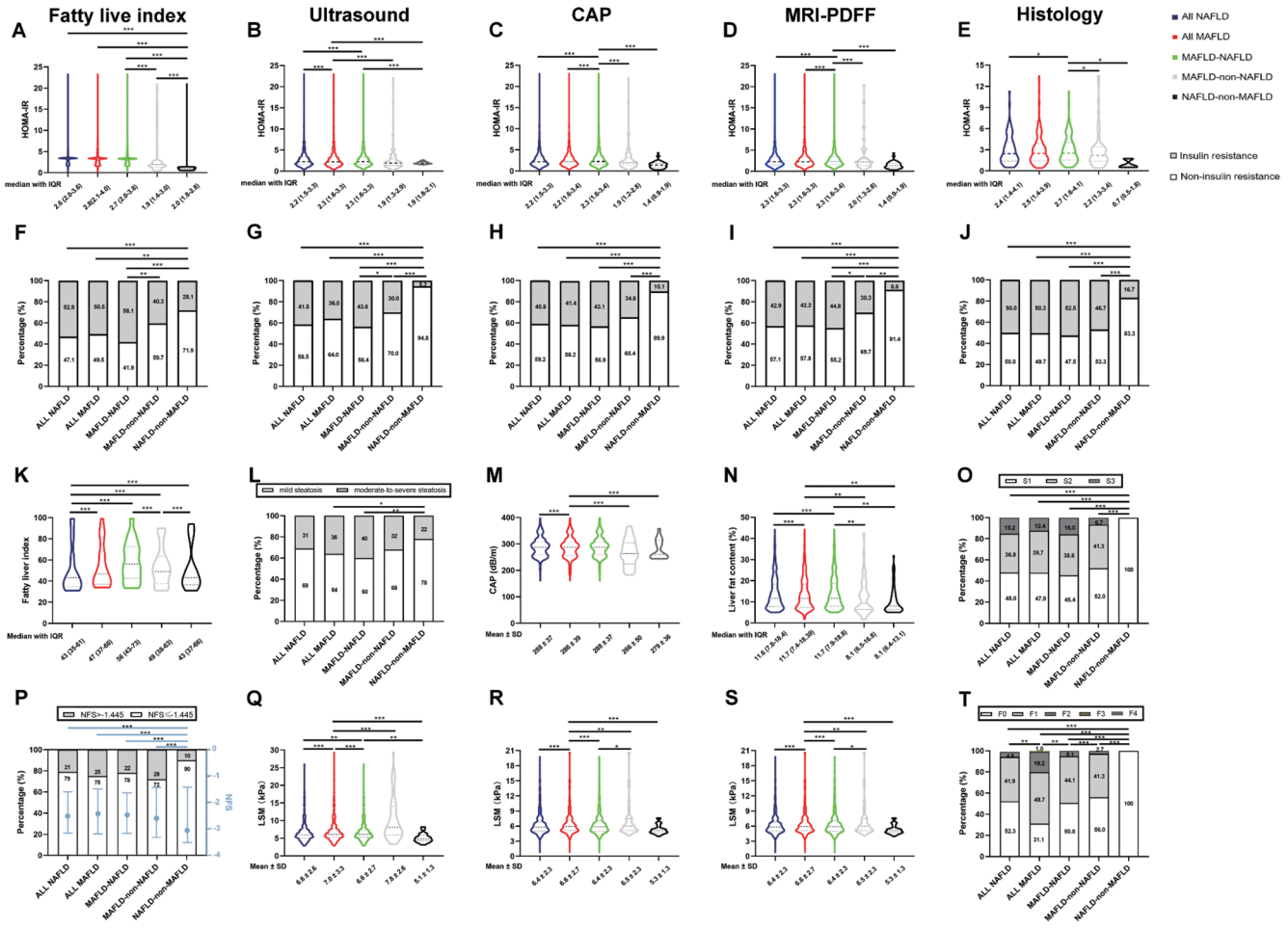

Fig. 2. Comparison of HOMA-IR. (A–E) The proportion of patients with insulin resistance; (F–J) steatosis; (K–O) liver stiffness; and (P–T) fibrosis in NAFLD, all MAFLD, MAFLD, and NAFLD, MAFLD-non-NAFLD and NAFLD-non-MAFLD diagnosed by different steatosis assessment methods: Fatty liver index (A, F, K, P); Ultrasound (B, G, L, Q); CAP (C, H, M, R); MRI-PDFF (D, I, N, S); Histology (E, J, O, T). CAP, controlled attenuation parameter; HOMA-IR, homeostasis model assessment of insulin resistance; LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NFS, NAFLD fibrosis score.

Clinical characteristics of patients based on histology-diagnosed hepatic steatosis

Of the 301 patients with liver biopsies, 126 were diagnosed with NAFLD and 195 patients were diagnosed with MAFLD. Patients with MAFLD had higher levels of ALT, HDL-C, and UA. Those with MAFLD had a higher stage of fibrosis [1 (0–1) vs. 0 (0–1), $p<0.001$] and higher steatosis activity fibrosis (SAF) score [4 (3–6) vs. 4 (3–5), $p=0.006$; Table 5)]. The MAFLD–NAFLD group included 120 patients and the MAFLD–non-NAFLD group included 75 patients with histology evaluations. Blood pressure, HDL-C, FBG, and liver stiffness were significantly higher in the MAFLD–non-NAFLD group, and BMI, ALT, AST, GGT, ALP, CHOL, TG, LDL-C, UA, and LFC were significantly lower than in the MAFLD–NAFLD group (Table 5). Six patients were categorized as non-MAFLD–NAFLD, all of whom had mild steatosis and were at the F0 stage (Table 5). One patient (16.7%) in the non-MAFLD–NAFLD group had IR, and the proportions in the other four groups were comparable (Fig.2 E, J). Six patients in the non-MAFLD–NAFLD group had grade 1 steatosis and stage 4 fibrosis. The MAFLD–NAFLD group had the greatest proportion of S3, and the MAFLD group had the highest proportion of F2 and F3 (Fig. 2O, T). Representative images of liver steatosis and fibrosis are shown in Supplementary Figure 1.

Factors associated with moderate-to-severe steatosis and/or fibrosis in non-MAFLD–NAFLD diagnosed by different steatosis assessment methods

Non-MAFLD–NAFLD patients were diagnosed by FLI, ultrasound, CAP, MRI-PDFF, and histology. For patients diagnosed with FLI, age, BMI, WC and HOMA-IR were associated with moderate-to-severe steatosis and/or fibrosis by univariate logistic analysis (Supplementary Table 1). The variables that were found significantly associated with moderate-to-severe steatosis and/or fibrosis in univariate analysis were entered in the multivariate model. Age (odds ratio [OR] 1.10; 95% confidence interval [CI]: 1.08–1.13; $p<0.001$) and HOMA-IR (OR 1.46; 95% CI: 1.21–1.75; $p<0.001$) remained significant for moderate-to-severe steatosis and/or fibrosis (Supplementary Table 2). For patients with non-MAFLD–NAFLD detected by ultrasound, univariate analysis found that WC, HDL-C, LDL-C, HOMA-IR, and UA were independent predictors of moderate-to-severe steatosis and/or fibrosis (Supplementary Table 1). Multivariate analysis including those variables found that

Table 2. Comparison of clinical parameters in MAFLD–NAFLD, NAFLD–non-MAFLD, and MAFLD–non-NAFLD patients with steatosis diagnosed by ultrasound

Characteristics	All NAFLD	All MAFLD	*p*	MAFLD–NAFLD	MAFLD-non-NAFLD	*p*	NAFLD-non-MAFLD		*p*	NAFLD-non-MAFLD		*p*
							Mild steatosis	Moderate-to-sever steatosis		NFS		
										≤-1.445	> −1.445	
	(*n*=9,620)	(*n*=11,965)		(*n*=9,105)	(*n*=2,860)		(*n*=398)	(*n*=117)		(*n*=488)	(*n*=27)	
Age (year)	41.2±12.4	41.3±12.0	0.96	41.6±10.4	41.2±12.5	0.09	34.7±10.5	35.5±10.7	0.43	34.8±9.3	43.8±12.0	0.37
Male, *n* (%)	6,253 (65.0)	7,897 (66.0)	0.12	6,191 (68.0)	812 (69.5)	0.13	153 (38.4)	53 (45.3)	0.18	198 (40.6)	8 (29.6)	0.26
Body mass index (kg/m^2)	26.6±3.6	26.5±3.4	0.93	27.0±3.4	25.5±3.5	<0.001	20.4±1.7	20.3±1.7	0.58	20.4±1.7	20.4±1.5	0.87
Waist circumstance (cm)	89.4±10.1	90.0±8.7	<0.001	90.7±8.5	87.8±8.7	<0.001	65.9±6.2	67.2±6.1	0.043	66.1±6.1	66.2±7.3	0.94
Systolic blood pressure (mmHg)	130±16	132±16	<0.001	132±16	132±18	0.99	110±11	118±15	0.17	112±12	112±16	0.99
Diastolic blood pressure (mmHg)	86±12	86±13	<0.001	87±11	87±12	0.99	69±9	70±12	0.25	67±10	68±13	0.49
Alanine aminotransferase (U/L)†	38 (23–63)	42 (23–43)	<0.001	40 (24–65)	50 (31–79)	<0.001	13 (9–19)	12 (9–18)	0.26	15 (10–21)	19 (12–23)	<0.001
Aspartate aminotransferase (U/L)†	29 (22–40)	31 (23–43)	<0.001	31 (23–41)	35 (26–49)	<0.001	18 (15–20)	19 (15–21)	0.10	18 (15–21)	18 (17–21)	0.039
γ-Glutamyl transpeptidase (U/L)†	43 (26–69)	44 (27–70)	0.008	41 (27–71)	45 (27–66)	0.04	21 (15–28)	25 (18–29)	0.09	22 (16–29)	24 (15–29)	0.51
Alkaline phosphatase (U/L)†	77 (67–87)	77 (67–87)	0.39	77 (67–87)	77 (65–89)	0.47	60 (51–77)	60 (54–73)	0.95	60 (54–77)	63 (52–73)	0.42
Total cholesterol (mmol/L)	5.14±1.05	5.31±1.59	<0.001	5.27±1.15	5.16±1.06	<0.001	4.72±0.87	4.74±1.07	0.85	4.76±0.91	4.98±1.10	0.23
Triglycerides (mmol/L)	1.83±0.24	1.88±0.43	0.013	1.89±1.34	1.86±1.25	0.29	1.03±0.39	1.09±0.73	0.25	1.13±0.59	1.33±1.10	0.32
HDL-C (mmol/L)	1.17±0.30	1.27±0.31	0.10	1.14±0.28	1.29±0.69	<0.001	1.67±0.31	1.52±0.38	0.31	1.63±0.32	1.59±0.41	0.11
LDL-C (mmol/L)	3.22±0.80	3.27±0.81	<0.001	3.36±0.97	3.25±0.80	<0.001	2.63±0.83	2.75±0.91	0.18	2.69±0.84	2.77±0.91	0.52
Fasting blood glucose (mmol/L)	5.13±1.07	5.14±1.09	0.52	5.15±1.11	5.03±0.95	0.004	5.07±0.27	5.07±0.31	0.94	5.01±0.31	4.93±0.29	0.11
Fasting insulin (μU/mL)†	9.9 (7.3–14.1)	9.8 (7.2–14.1)	0.036	9.9 (7.3–14.1)	8.8 (6.4–12.3)	<0.001	9.2 (8.4–10.2)	9.5 (8.3–10.4)	0.51	8.3 (7.5–9.2)	8.3 (7.9–9.1)	0.42
HOMA-IR†	2.3 (1.6–3.3)	2.2 (1.5–3.3)	0.012	2.3 (1.6–3.3)	1.9 (1.3–2.9)	<0.001	1.9 (1.8–2.1)	2.1 (1.8–2.4)	0.07	1.9 (1.8–2.1)	1.9 (1.8–2.5)	0.99
HOMA-IR >2.5, *n* (%)	4,194 (43.6)	5,181 (43.3)	0.68	3,970 (43.6)	340 (30.0)	<0.001	17 (4.3)	10 (8.6)	0.31	23 (4.7)	4 (14.3)	0.027
Uric acid (μmol/L)†	411±103	409±102	0.27	414±104	393±93	<0.001	352±87	376±89	0.01	359±89	340±76	0.30
Hs-CRP (mg/L)	-	-	-	-	-	-	4.68±2.11	4.83±2.24	0.75	3.78±1.58	3.96±1.91	0.57
NFS >-1.445, *n* (%)	755 (7.8)	1,071 (9.0)	0.004	728 (8.0)	343 (12.0)	<0.001	16 (4.0)	11 (9.4)	0.02	-	-	-

Data are means ± standard deviation or †medians and IQR for continuous variables with non-Gaussian distribution. HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, hypersensitive-c-reactive-protein LDL-cholesterol, low-density lipoprotein cholesterol.

Table 3. Comparison of clinical parameters in MAFLD–NAFLD, NAFLD–non-MAFLD, and MAFLD–non-NAFLD patients with steatosis and fibrosis diagnosed by controlled attenuation parameter

Characteristics	All NAFLD	All MAFLD	*p*	MAFLD–NAFLD	MAFLD-non-NAFLD	*p*	NAFLD-non-MAFLD			*p*	NAFLD-non-MAFLD		*p*
							Mild	Moderate	Severe		F0-F1	F2-F4	
	(*n*= 1,306)	(*n*= 1,528)		(*n*= 1,227)	(*n*=301)		(*n*=18)	(*n*=47)	(*n*=14)		(*n*=63)	(*n*=16)	
Age (year)	41.2± 12.3	41.0± 12.1	0.65	41.4± 11.1	40.5± 10.2	0.20	42.3± 13.1	39.4± 10.3	33.3± 4.1	0.86	40.9± 11.6	43.3± 13.8	0.59
Male, *n* (%)	985 (75.4)	1,164 (76.2)	0.64	931 (75.9)	236 (78.4)	0.36	8 (44.4)	32 (68.1)	10 (71.4)	0.16	40 (63.5)	10 (62.5)	0.94
Body mass index (kg/m^2)	26.5± 3.5	26.6± 3.5	0.54	26.8± 3.4	25.3± 3.1	<0.001	21.5± 1.4	22.0± 0.8	21.9± 1.1	0.045	21.4± 1.5	22.2± 0.6	0.13
Waist circumstance (cm)	89.5± 8.9	89.8± 8.6	0.25	90.3± 8.5	87.9± 8.1	0.007	75.1± 5.6	80.0± 4.4	78.5± 4.1	0.001	76.3± 6.0	79.2± 4.3	0.17
Systolic blood pressure (mmHg)	131± 16	131± 16	0.23	131± 16	129± 21	0.07	121± 18	120± 18	123± 15	0.46	121± 19	121± 12	0.92
Diastolic blood pressure (mmHg)	86± 12	87± 12	0.26	86± 12	83± 13	0.08	80± 12	76± 11	78± 19	0.87	80± 12	79± 11	0.87
Alanine aminotransferase (U/L)†	42 (25–71)	43 (26–75)	0.13	42 (25–72)	46 (31–71)	0.15	39 (22–94)	29 (20–57)	43 (26–47)	0.35	28 (22–38)	48 (38–63)	0.002
Aspartate aminotransferase (U/L)†	31 (23–43)	31 (23–45)	0.14	31 (23–43)	33 (26–47)	0.04	37 (28–55)	27 (22–38)	28 (25–41)	0.15	29 (22–62)	44 (40–97)	0.09
γ-Glutamyl transpeptidase (U/L)†	43 (27–72)	43 (27–72)	0.83	44 (28–73)	39 (26–58)	0.07	30 (22–37)	31 (22–59)	29 (19–49)	0.72	28 (20–49)	43 (33–51)	0.06
Alkaline phosphatase (U/L)†	78 (67–88)	78 (67–89)	0.92	78 (67–89)	77 (67–87)	0.72	82 (71–107)	73 (56–82)	84 (71–99)	0.01	72 (63–86)	92 (85–114)	0.001
Total cholesterol (mmol/L)	5.14± 1.03	5.27± 1.59	0.28	5.15± 1.03	5.14± 1.02	0.88	4.98± 0.76	5.10± 1.36	4.99± 0.48	0.90	5.08± 1.16	4.78± 0.72	0.47
Triglycerides (mmol/L)	1.82± 0.61	2.02± 0.85	0.20	1.83± 1.20	1.86± 1.22	0.70	0.91± 0.26	1.10± 0.14	1.36± 0.55	0.002	1.22± 0.51	1.12± 0.16	0.56
HDL-C (mmol/L)	1.15± 0.28	1.23± 0.33	0.23	1.14± 0.26	1.33± 0.73	<0.001	1.45± 0.32	1.36± 0.41	1.14± 0.11	0.06	1.36± 0.37	1.22± 0.19	0.32
LDL-C (mmol/L)	3.25± 0.79	3.33± 1.49	0.27	3.25± 0.79	3.30± 0.81	0.33	2.99± 0.68	3.16± 0.96	3.16± 0.29	0.75	3.14± 0.84	2.98± 0.54	0.59
Fasting blood glucose (mmol/L)	5.11± 1.04	5.06± 0.96	0.43	5.11± 1.01	4.84± 0.67	<0.001	4.76± 0.51	4.59± 0.63	4.50± 0.92	0.53	4.56± 0.62	4.86± 0.78	0.10
Fasting insulin (μU/mL)†	9.7 (7.2–14.1)	9.9 (7.3–14.5)	0.44	9.9 (7.3–14.5)	9.1 (5.9–11.4)	0.005	7.0 (3.7–7.3)	6.5 (4.6–9.5)	5.6 (8.0–9.7)	0.23	4.61 (6.98–9.49)	6.70 (3.51–8.47)	0.72
HOMA-IR†	2.2 (1.5–3.3)	2.2 (1.6–3.4)	0.41	2.3 (1.6–3.4)	1.9 (1.2–2.8)	0.001	1.6 (0.7–1.8)	1.4 (0.9–2.0)	1.6 (0.5–3.2)	0.75	1.20 (0.85–1.84)	1.72 (1.42–2.03)	0.14

(continued)

Table 3. *(continued)*

Characteristics	All NAFLD (*n*= 1,306)	All MAFLD (*n*= 1,528)	*p*	MAFLD–NAFLD (*n*= 1,227)	MAFLD-non-NAFLD (*n*=301)	*p*	NAFLD-non-MAFLD			NAFLD-non-MAFLD		
							Mild (*n*=18)	Moderate (*n*=47)	Severe (*n*=14)	*p*	F0-F1 (*n*=63)	F2-F4 (*n*=16)	*p*
HOMA-IR >2.5, *n* (%)	533 (40.8)	640 (41.9)	<0.001	529 (43.1)	104 (34.6)	0.007	2 (11.1)	3 (6.4)	3 (21.4)	0.26	4 (6.3)	4 (25.0)	0.027
Uric acid (μmol/L)†	414± 104	413± 103	0.80	416± 105	393± 96	<0.001	348± 57	371± 93	405± 106	0.21	367± 86	409± 117	0.23
Hs-CRP (mg/L)	-	-	-	-	-	-	3.6± 1.7	3.6± 1.5	4.6± 1.2	0.11	3.79± 1.56	3.75± 1.67	0.94
CAP (dB/m)†	288± 37	286± 39	0.54	288± 37	266± 50	<0.001	249± 6	278± 15	321± 20	<0.001	279± 23	282± 41	0.74
Liver stiffness by FibroScan (kPa)	6.6± 2.6	7.0± 3.3	0.012	6.6± 2.7	7.8± 2.6	<0.001	4.8± 1.4	4.8± 0.9	5.6± 1.3	0.22	4.9± 0.6	7.1± 0.9	<0.001
Liver stiffness >7.3 kPa	116 (8.9)	136 (8.9)	0.99	100 (8.1)	36 (12.0)	0.037	1 (5.6)	9 (19.1)	6 (42.9)	0.032	-	-	-

Data are means ± standard deviation or †medians and IQR for continuous variables with non-Gaussian distribution. CAP, controlled attenuation parameter; HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, hypersensitive-c-reactive-protein; LDL-cholesterol, low-density lipoprotein cholesterol.

HOMA-IR (OR 3.87; 95% CI: 2.38–6.32; $p<0.001$), WC (OR 1.04; 95% CI: 1.02–1.06; $p<0.001$) and HDL-C (OR 0.42; 95 %CI: 0.20–0.90; $p=0.025$) remained significant predictors (Supplementary Table 2). When CAP was used to detect steatosis, univariate analysis showed that BMI, WC, HDL-C, and HOMA-IR were significantly associated with moderate-to-severe steatosis and/or fibrosis (Supplementary Table 1). Multivariate analysis found that WC (OR 1.17; 95% CI: 1.01–1.36; $p=0.041$) and HOMA-IR (OR 2.87; 95% CI: 1.09–7.51; $p=0.032$) were significantly associated with moderate-to-severe steatosis and/or fibrosis (Supplementary Table 2). Among patients diagnosed via MRI-PDFF, BMI, WC, HOMA-IR, and UA were associated with moderate-to-severe steatosis and/or fibrosis (Supplementary Table 1). After multivariate analysis, WC (OR 1.22; 95% CI: 1.01–1.46; $p=0.037$) and HOMA-IR (OR 4.97; 95% CI: 2.09–8.45; $p=0.003$) remained significant (Supplementary Table 2). There were only six patients with non-MAFLD–NAFLD who had liver biopsies. Therefore, the sample size was not enough to conduct logistic analysis.

Discussion

We found that although different steatosis detection methods were used, diagnosis switching to MAFLD occurred in 83–95% of NAFLD patients. Compared with NAFLD patients, MAFLD patients had significantly increased anthropometric parameters and worse metabolic profiles. The comparison of clinical characteristics among MAFLD–non-NAFLD, MAFLD–NAFLD and non-MAFLD–NAFLD groups by five different steatosis assessment methods is summarized in Figure 3. After stratifying non MAFLD–NAFLD patients by the severity of steatosis or fibrosis, we found that most clinical characteristics other than glucose metabolism-related indexes were comparable, even though steatosis was assessed by different tools. To the best of our knowledge, this is the first study using real-world data from China to fully compare MAFLD and NAFLD by different steatosis assessment methods.

The influence of the novel MAFLD concept and diagnostic flow to liver clinics remained validated. The study found that 5–17% of NAFLD patients without metabolic dysregulation were ruled out by the MAFLD criteria, which is consistent with a study that reanalyzed data from the National Health and Nutrition Examination Surveys of the United States and showed that 620/13,083 (4.74%) cases satisfied the NAFLD but not the MAFLD criteria.[11] In a study conducted in Hong Kong, proton-magnetic resonance spectroscopy found that 14 of 277 newly diagnosed NAFLD patients (5.1%) did not meet the metabolic criteria for MAFLD during a median interval of 47 months.[13] This study found that that MAFLD impacted 5–17% of previously established NAFLD cases, even when using different methods of evaluation in clinical settings.

The agreement of NAFLD and MAFLD diagnoses varied with the steatosis assessment method. The percentage agreements were 83% for FLI, 95% for ultrasound, 94% for CAP and MRI-PDFF, and 95% for liver biopsy. The agreement rate for FLI was lower than that for other assessment methods, but there were no significant differences among the other four imaging modalities. The explanation for the differences in rate might be that the calculation of FLI includes of BMI, WC, TG, and GGT, and, patients with autoimmune liver disease, alcohol abuse, drug-induced liver injury, or bile duct obstruction might have higher GGT levels, which would also result in a higher FLI. These conditions would not rule out a diagnosis of MAFLD.[16–20] Therefore, the effect of GGT could account for the discordance.

MAFLD patients had increased metabolic indices and liver enzymes compared with NAFLD patients, which is in line with a study by Lin *et al*,[11] but Sakura *et al.* reported that liver stiffness was greater in MAFLD than in NAFLD (7.7 vs. 6.8 kPa,

Table 4. Comparison of clinical parameters in MAFLD–NAFLD, NAFLD–non-MAFLD, and MAFLD–non-NAFLD patients with fibrosis diagnosed by MRI-PDFF and fibrosis diagnosed by two-dimensional shear wave elastography

Characteristics	All NAFLD	All MAFLD	*p*	MAFLD–NAFLD	MAFLD-non-NAFLD	*p*	NAFLD-non-MAFLD			*p*	NAFLD-non-MAFLD		*p*
							Mild	Moderate	Severe		F0-F1	F2-F4	
	(*n*= 1,034)	(*n*= 1,184)		(*n*=976)	(*n*=208)		(*n*=37)	(*n*=17)	(*n*=4)		(*n*=46)	(*n*=12)	
Age (year)	41.4± 12.4	41.2± 12.2	0.74	41.4± 12.4	39.6± 10.2	0.19	42.3± 13.1	39.4± 10.3	33.3± 4.1	0.32	41.1± 11.8	37.0± 15.5	0.47
Male, *n* (%)	770 (74.5)	897 (75.8)	0.48	730 (74.8)	165 (79.3)	0.17	23 (62.2)	13 (76.5)	4 (100)	0.22	33 (71.7)	7 (58.3)	0.37
Body mass index (kg/m^2)	26.8± 3.6	27.0± 3.6	0.14	27.1± 3.4	25.8± 3.9	0.001	21.1± 1.5	22.0± 0.8	21.9± 1.1	0.06	21.4± 1.4	21.7± 0.7	0.57
Waist circumstance (cm)	90.1± 8.9	90.6± 8.8	0.16	90.8± 8.4	88.7± 9.2	0.001	75.1± 5.6	80.0± 4.4	78.5± 4.1	0.01	76.4± 5.7	79.8± 4.0	0.20
Systolic blood pressure (mmHg)	131± 16	131± 16	0.91	131± 16	130± 18	0.42	121± 18	120± 18	123± 15	0.97	121± 17	122± 22	0.91
Diastolic blood pressure (mmHg)	86± 12	86± 12	0.61	86± 11	86± 12	0.99	80± 12	76± 11	78± 19	0.61	79± 12	78± 9	0.86
Alanine aminotransferase (U/L)†	41 (25–68)	43 (25–71)	0.29	42 (25–70)	47 (28–67)	0.53	26 (21–62)	40 (25–55)	50 (42–70)	0.27	35 (22–57)	46 (30–108)	0.15
Aspartate aminotransferase (U/L)†	31 (23–42)	31 (23–43)	0.23	31 (23–43)	33 (25–42)	0.33	28 (22–40)	28 (23–38)	35 (29–59)	0.34	28 (22–38)	38 (25–107)	0.17
γ-Glutamyl transpeptidase (U/L)†	44 (27–71)	44 (27–71)	0.99	36 (23–52)	45 (28–72)	0.011	28 (20–54)	32 (23–47)	38 (31–64)	0.43	29 (22–50)	32 (23–250)	0.59
Alkaline phosphatase (U/L)†	78 (67–88)	77 (66–87)	0.67	78 (67–88)	75 (64–83)	0.07	74 (64–88)	74 (56–80)	83 (78–95)	0.21	74 (63–84)	84 (62–97)	0.47
Total cholesterol (mmol/L)	5.15± 1.05	5.17± 1.07	0.62	5.31± 1.18	5.15± 1.05	0.07	5.06± 1.27	4.99± 0.99	4.80± 0.96	0.91	5.05± 1.14	4.72± 1.46	0.54
Triglycerides (mmol/L)	1.84± 0.36	1.89± 0.85	0.39	1.89± 0.81	1.78± 0.91	0.08	1.23± 0.52	1.24± 0.49	1.23± 0.32	0.99	1.25± 0.51	1.19± 0.39	0.55
HDL-C (mmol/L)	1.15± 0.29	1.15± 0.27	0.68	1.14± 0.28	1.24± 0.39	<0.001	1.39± 0.44	1.29± 0.23	1.07± 0.03	0.23	1.35± 0.39	1.18± 0.11	0.33
LDL-C (mmol/L)	3.25± 0.79	3.26± 0.82	0.65	3.43± 0.97	3.26± 0.79	0.018	3.10± 0.84	3.17± 0.81	3.16± 0.70	0.95	3.14± 0.80	3.01± 1.03	0.74
Fasting blood glucose (mmol/L)	5.11± 1.08	5.11± 1.07	0.98	5.14± 1.09	5.07± 0.76	0.38	4.65± 0.54	4.51± 0.85	4.63± 0.85	0.76	4.59± 0.69	4.67± 0.51	0.72
Fasting insulin (μU/mL)†	9.93 (7.28–14.13)	10.35 (7.31–14.32)	0.38	10.2 (7.5–14.5)	9.1 (6.4–12.0)	0.038	6.6 (4.1–8.4)	7.8 (5.4–9.8)	7.0 (3.1–13.8)	0.37	6.62 (4.50–9.50)	8.02 (5.74–10.67)	0.43
HOMA-IR†	2.3 (1.6–3.3)	2.3 (1.6–3.3)	0.48	2.3 (1.6–3.4)	2.0 (1.3–2.8)	0.017	1.4 (0.9–1.9)	1.5 (1.1–2.0)	1.6 (0.5–3.2)	0.66	1.36 (0.88–2.00)	1.78 (1.24–2.53)	0.35

(continued)

Table 4. *(continued)*

Characteristics	All NAFLD (*n*= 1,034)	All MAFLD (*n*= 1,184)	*p*	MAFLD–NAFLD (*n*=976)	MAFLD-non-NAFLD (*n*=208)	*p*	NAFLD-non-MAFLD			NAFLD-non-MAFLD		
							Mild (*n*=37)	Moderate (*n*=17)	Severe (*n*=4)	*p*	F0-F1 (*n*=46)	F2-F4 (*n*=12)	*p*
HOMA-IR >2.5, *n* (%)	440 (46.9)	498 (53.1)	0.82	437 (44.8)	63 (30.3)	<0.001	1 (2.7)	3 (17.6)	1 (25.0)	0.10	2 (4.3)	3 (25.0)	0.023
Uric acid (μmol/L)†	414± 104	411± 100	0.46	416± 104	377± 74	<0.001	361± 79	383± 108	462± 135	0.11	373± 91	387± 134	0.75
Hs-CRP (mg/L)	-	-	-	-	-	-	3.54± 1.64	4.00± 1.52	4.75± 0.52	0.26	3.71± 1.61	4.20± 1.10	0.52
LFC (%)†	11.6 (7.8–18.4)	11.7 (7.4–18.3)	0.52	11.7 (7.9–18.8)	8.1 (6.5–16.8)	0.017	6.5 (5.8–7.9)	14.1 (11.5–17.3)	26.0 (25.3–30.1)	0.001	8.10 (6.14–13.63)	9.24 (6.90–11.65)	0.65
Liver stiffness by 2D-SWE (kPa)	6.5± 1.7	6.7± 2.5	0.06	4.9± 2.3	5.0± 2.3	0.84	4.3± 0.9	4.5± 1.0	4.4± 1.3	0.36	5.9± 1.0	6.9± 1.3	0.005
Liver stiffness >7.1 kPa	106 (10.3)	117 (9.9)	0.77	94 (9.6)	23 (11.1)	0.51	4 (10.8)	6 (35.3)	2 (50.0)	0.039	-	-	

Data are means ± standard deviation or †medians and IQR for continuous variables with non-Gaussian distribution. 2D-SWE, two-dimensional shear wave elastography; HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, hypersensitive-c-reactive-protein; LFC, liver fat content; LDL-cholesterol, low-density lipoprotein cholesterol.

p=0.001), and MAFLD (OR 4.401; 95% CI: 2.144–10.629; *p*<0.001), alcohol intake (OR 1.761; 95% CI: 1.081–2.853; *p*=0.023), and NAFLD (OR 1.721; 95% CI: 1.009–2.951; *p*=0.046) were independently associated with significant fibrosis.[12] This study did not find significant differences liver stiffness in patients evaluated by TE, 2D-SWE, or histology. Also, because MAFLD was changed from an exclusive diagnosis to a positive diagnosis, the criteria for MAFLD do not exclude the excessive intake of alcohol or other liver disease.[6,23] Collectively, the criteria for MAFLD are beneficial to the comprehensive and effective treatment of patients with various chronic liver diseases and metabolic dysregulation.

The proportion of patients with IR were significantly higher in the MAFLD–NAFLD group than in MAFLD–non-NAFLD group using FLI, ultrasound, CAP, and MRI-PDFF to detect hepatic steatosis. Compared with the diagnostic criteria of NAFLD, MAFLD emphasizes not only the presence of hepatic steatosis but also on metabolic dysfunction, especially in those with normal BMIs. Therefore, MAFLD–NAFLD presented with higher proportions of IR. Also, the MAFLD–non-NAFLD group included patients with hepatic steatosis that coexisted with excessive alcohol intake or other liver disease (e.g., viral hepatitis, autoimmune liver disease and others), which contributed more to liver fibrosis than MAFLD. No consensus has been reached with regard to liver stiffness in the two groups. MAFLD–non-NAFLD had higher proportions of patients with stage 2 or higher fibrosis in all five steatosis assessments methods.

A distinction between MAFLD and NAFLD was that only lean NAFLD (BMI <23kg/m^2) Asian patients with metabolic dysregulation were diagnosed as MAFLD. However, the metabolic characteristics of non-MAFLD–NAFLD patients with severe steatosis or fibrosis have not been reported. This is of particular importance for steatosis management, as both steatosis and fibrosis severity have been acknowledged as key impactors of prognosis.[24,25] Our results revealed that moderate-to-severe steatosis was detected by ultrasound in 22.7%, by CAP in 77.2%, and by MRI-PDFF in 36.2% of non-MAFLD–NAFLD patients. while NFS, TE, and SWE found significant fibrosis in 2.1%, 18.4%, and 18.5% of those patients, respectively. In this study, most parameters of the metabolic profile among non-MAFLD–NAFLD subjects were similar in those with and without moderate-to-severe steatosis or in those with and without significant fibrosis. However, we found that glycemia-related parameters, including fasting serum glucose or HOMA-IR, were significantly increased, but remained within the normal range as fibrosis severity increased. Notably, the non-MAFLD–NAFLD patients had a lower risk of metabolic abnormalities with the current MAFLD criteria. We still need to pay attention to those who meet the criteria for NAFLD but not MAFLD, especially those with higher stages of fibrosis. That alerts us that even if a MAFLD diagnosis has not been established, there is a potential for glycemic dysregulation progression over time, even below the threshold of the glycemic indexes that indicate metabolic dysfunction as evidence of hepatic fibrosis. Routine monitoring of lipid and glucose metabolism is recommended to assess non-MAFLD–NAFLD with increased fibrosis severity.

The major strength of this study is comprehensive measurement using multiple steatosis assessments, namely, liver biopsy, MRI-PDFF, CAP, ultrasound, and FLI, and the impact on changing the diagnosis from NAFLD to MAFLD. The study also has limitations. First, the sample of individual patients with liver biopsies was small, which may have impaired the comparison of the clinical characteristics of MAFLD and NAFLD. Second, because of the limited number of patients with F3–F4 fibrosis we could not include a comparison of different fibrosis stages. Third, the cross-sectional study design used data acquired before the MAFLD consensus was complete.

In conclusion, the new MAFLD definition ruled out 5–17% of NAFLD, and MAFLD patients had higher level of metabolic

Table 5. Comparison of clinical parameters of MAFLD–NAFLD, NAFLD–non-MAFLD, and MAFLD–non-NAFLD patients with hepatic steatosis and fibrosis diagnosed by histology

Characteristics	All NAFLD	All MAFLD	*p*	MAFLD–NAFLD	MAFLD-non-NAFLD	*p*	NAFLD-non-MAFLD	
							Mild steatosis	Fibrosis stage (F0)
	(*n*=126)	(*n*=195)		(*n*=120)	(*n*=75)		(*n*=6)	(*n*=6)
Age (year)	37.7±12.8	38.8±11.6	0.43	38.0±12.8	40.1±9.4	0.22	32.3±11.8	32.3±11.8
Male, *n* (%)	88 (69.8)	143 (73.3)	0.50	84 (58.7)	71 (41.3)	0.98	4 (66.7)	4 (66.7)
Body mass index (kg/m^2)	26.4±4.2	26.1±4.1	0.44	26.7±4.2	24.9±3.6	0.006	21.8±0.9	21.8±0.9
Waist circumstance (cm)	88.8±10.0	88.7±9.9	0.87	89.4±9.8	87.1±9.6	0.15	77.7±0.6	77.7±0.6
Systolic blood pressure (mmHg)	127±17	129±16	0.20	129±18	136±17	0.016	126±9	126±9
Diastolic blood pressure (mmHg)	85±13	87±13	0.18	86±13	86±13	0.032	77±12	77±12
Alanine aminotransferase (U/L)†	53 (30–101)	75 (44–125)	0.005	30 (21–47)	76 (46–125)	<0.001	34 (22–57)	34 (22–57)
Aspartate aminotransferase (U/L)†	44 (30–66)	38 (28–59)	0.18	33 (25–45)	44 (31–67)	<0.001	22 (18–29)	22 (18–29)
γ-Glutamyl transpeptidase (U/L)†	65 (40–108)	60 (36–90)	0.16	41 (26–70)	67 (44–112)	<0.001	35 (17–73)	35 (17–73)
Alkaline phosphatase (U/L)†	82 (72–90)	81 (67–93)	0.38	75 (60–99)	82 (72–90)	<0.001	82 (82–84)	82 (82–84)
Total cholesterol (mmol/L)	5.03±1.01	4.99±0.99	0.73	5.10±0.98	4.77±0.98	0.038	3.70±0.50	3.70±0.50
Triglycerides (mmol/L)	2.13±0.86	1.96±0.63	0.40	2.20±0.88	1.46±0.73	0.005	0.73±0.14	0.73±0.14
HDL-C (mmol/L)	1.14±0.56	1.32±0.78	0.032	1.14±0.58	1.68±1.00	<0.001	1.14±0.10	1.14±0.10
LDL-C (mmol/L)	3.21±0.79	3.00±0.98	0.06	3.26±0.77	2.46±1.14	<0.001	2.17±0.33	2.17±0.33
Fasting blood glucose (mmol/L)	5.07±1.22	5.39±2.07	0.13	5.93±1.08	5.12±1.23	<0.013	4.20±0.32	4.20±0.32
Fasting insulin (μU/mL)†	10.9 (7.5–17.3)	10.5 (6.8–15.4)	0.73	11.2 (7.6–17.6)	9.6 (5.8–12.6)	0.80	4.0 (2.8–8.6)	4.0 (2.8–8.6)
HOMA-IR†	2.4 (1.4–4.1)	2.5 (1.4–3.9)	0.99	2.7 (1.6–4.1)	2.2 (1.3–3.4)	0.81	0.7 (0.5–1.8)	0.7 (0.5–1.8)
HOMA-IR >2.5, *n* (%)	66 (52.4)	98 (50.3)	0.71	63 (52.5)	35 (46.7)	0.43	1 (16.7)	1 (16.7)
Uric acid (μmol/L)†	414±118	444±123	0.03	447±124	358±82	<0.001	440±136	440±136
Hs-CRP (mg/L)	-	-	-	-	-	-	4.38±0.34	4.38±0.34
Steatosis (0–3)	2 (1–2)	2 (1–2)	0.81	2 (1–2)	1 (1–2)	0.17	1 (1–1)	1 (1–1)
Lobular inflammation (0–3)	1 (1–1)	1 (1–1)	0.29	1 (1–1)	1 (1–1)	0.17	1 (0–1)	1 (0–1)
Ballooning (0–2)	1 (0–1)	1 (0–1)	0.59	1 (0–1)	1 (0–1)	0.20	1 (0–1)	1 (0–1)
Fibrosis (0–4)	0 (0–1)	1 (0–1)	<0.001	0 (0–1)	1 (1–2)	<0.001	0 ()0–0	0 ()0–0
NAS	3 (2–4)	3 (3–4)	0.56	3 (2–4)	3 (3–4)	0.59	3 (1–3)	3 (1–3)
SAF	4 (3–5)	4 (3–5)	0.006	4 (3–5)	5 (4–6)	<0.001	3 (1–3)	3 (1–3)

Data are means ± standard deviation or †medians and IQR for continuous variables with non-Gaussian distribution. HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, hypersensitive-c-reactive-protein; LDL-cholesterol, low-density lipoprotein cholesterol.

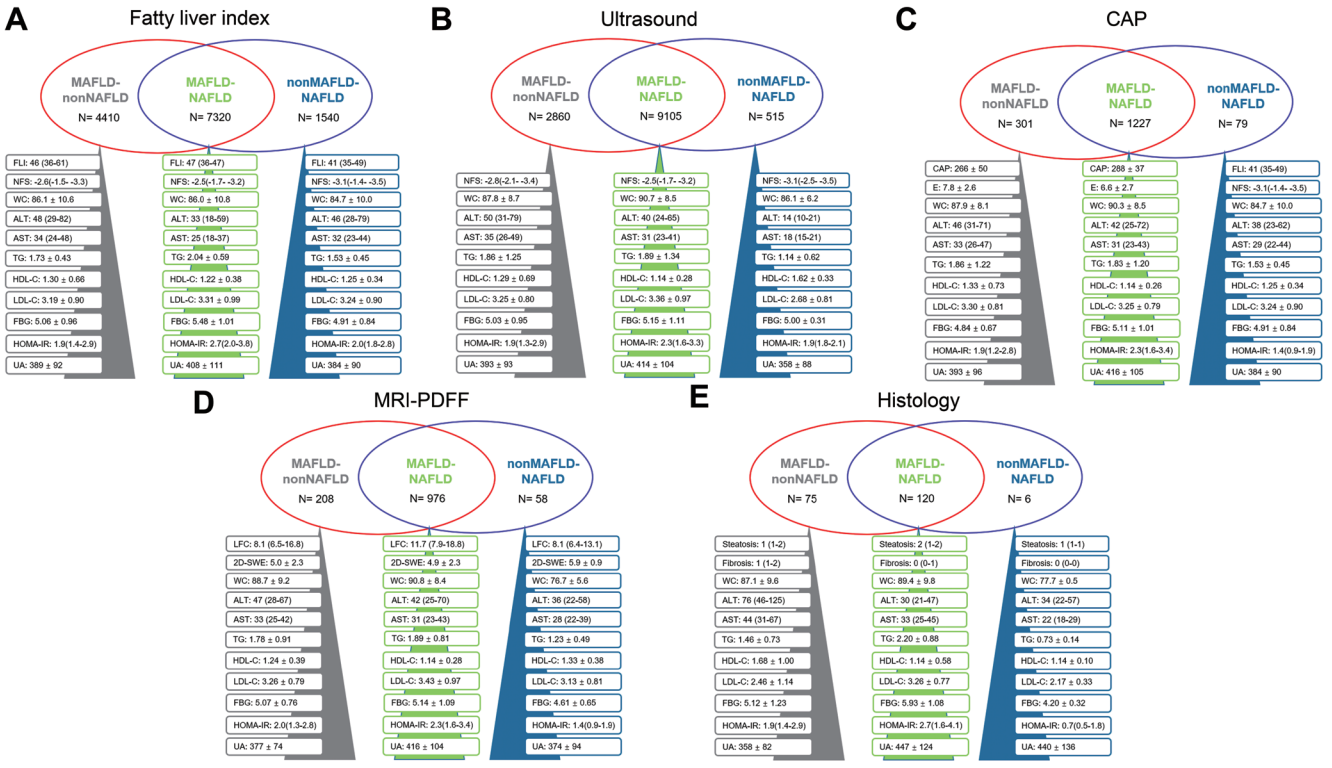

Fig. 3. Comparison of the clinical characteristics of MAFLD–non NAFLD, MAFLD–NAFLD and non-MAFLD–NAFLD groups by five different steatosis assessment methods. (A) FLI; (B) ultrasound; (C) CAP; (D) MRI-PDFF; and (E) Histology. ALT, alanine aminotransferase; CAP, controlled attenuation parameter; FBG, fasting blood glucose; FLI, fatty liver index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NFS, NAFLD fibrosis score; UA, uric acid; WC, waist circumference.

dysfunction. All NAFLD and MAFLD–NAFLD patients had more severe metabolic abnormalities than the MAFLD and MAFLD–non-NAFLD patients. The non-MAFLD–NAFLD patients had more severe liver injury and a deteriorating transition from normal glycemic control that occurred within the normal cut-off values. Individualized screening and treatment of non-MAFLD–NAFLD patients with fibrosis is recommended in clinical practice.

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Conflict of interest

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

Author contributions

Conception, design, and critical revision of the manuscript for important intellectual content (BZ, XG), data analysis, interpretation of results, and manuscript drafting (CS, JY), data collection (CS, JY, XL, YL), histological assessment (BL) and imaging data collection (SF).

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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