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Different predictors of steatosis and fibrosis severity among lean, overweight and obese patients with nonalcoholic fatty liver disease

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ABSTRACT

Backgrounds: Non-obese nonalcoholic fatty liver disease (NAFLD) is paradoxically associated with improved metabolic and pathological features at diagnosis but worse prognosis relative to obese NAFLD.
Aim: To compare predictors of disease severity in NAFLD with different body mass index (BMI) categories.
Methods: All 1509 consecutive NAFLD patients were classified as lean (20.2%), overweight (23.1%) and obese (56.7%). Liver fat content (LFC) and fibrosis were estimated with magnetic resonance imaging-based proton density fat fraction and shear wave elastography respectively.
Results: Lipid profiles and uric acid (UA) were significantly increased in parallel with BMI categories (pairwise comparison $P < 0.001$), but insulin resistance (IR) was significantly different between the non-obese and obese groups. For LFC ≥ 10%, increased waist circumference (WC) was an independent predictor in all groups, while UA elevation ($P = 0.02$) was predictive in the overweight patients, but BMI ≥ 28 kg/m^2 ($P = 0.029$) and IR ($P = 0.026$) were significant in the obese patients. For fibrosis, alanine aminotransferase (ALT) > 40 U/L ($P = 0.031$), increased WC ($P = 0.012$) and BMI ≥ 28 kg/m^2 ($P < 0.001$) plus ALT > 40 U/L ($P = 0.007$) were predictors in the lean, overweight and obese patients, respectively.
Conclusions: WC was strongly predictive of disease severity in all NAFLD, while UA and BMI plus IR were additional predictors in the overweight and obese NAFLD respectively. Individualized screening strategies should be established for NAFLD according to different BMIs.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, with a prevalence over 25% worldwide [1]. Although the association between NAFLD and increased body mass index (BMI) has been verified, NAFLD also occurs in patients with normal BMI, referred to as lean or non-obese/non-overweight NAFLD [2]. This phenomenon in patients with NAFLD is more prevalent in Asia (15–21%) than in Western countries (7–16.7%) [3–5], which may suggest that ethnic differences in clinical features may exist in lean NAFLD.

Several population-based studies have reported that the disease course of lean patients with NAFLD is less serious compared with that of obese patients. In two meta-analyses by Sookoian et al. [6,7], lean patients with NAFLD (BMI <25 kg/m^2) had lower levels of histological parameters (steatosis, inflammation and fibrosis) and metabolic indices, such as triglyceride (TG), total cholesterol (Chol), fasting blood glucose (FBG), and alanine aminotransferase (ALT), relative to those with obese NAFLD. However, a long-term prognosis study from a prospective cohort in Asians reported that, compared with overweight NAFLD patients, non-overweight patients had a higher risk of cardiovascular disease (CVD) [8]. Lean NAFLD patients presented less severe metabolic abnormities at diagnosis but worse long-term outcomes than obese patients, suggesting that different factors may be involved in the progression of NAFLD in these two populations. According to the guidelines of the World Health Organization (WHO) [2], a BMI ≥23 kg/m^2 and ≥25 kg/m^2 is the defining cut-off value for overweight in Asian countries and Western countries, respectively. Previous meta-analyses concerning NAFLD defined lean NAFLD as BMI <25 kg/m^2, which included both lean and overweight patients according to the WHO recommendations. The differences in BMI criteria between Asian and Western countries may lead to miscalculations of disease progression in lean NAFLD relative to overweight or obese

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NAFLD [6,7]. As the prevalence of lean NAFLD may be up to 21% in nonobese Asians, more effective makers are needed to identify the severity of NAFLD in the general population.

Magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) has been acknowledged as a novel non-invasive assessment of fat content in total liver and pancreas [9], while 2-dimentional shear wave elastography (2D-SWE) may have the highest diagnostic accuracy for staging fibrosis in NAFLD patients [10]. In this study, we aimed to identify the differences in metabolic indices, liver fat content (LFC) and pancreas fat content (PFC) determined by MRI-PDFF and in liver stiffness determined by 2D-SWE in lean, overweight and obese patients with NAFLD who were characterized using stricter criteria of BMI.

2. Patients and methods

2.1. Study population

This cross-sectional study was conducted at the First Affiliated Hospital of Sun Yat-sen University, China and involved consecutive patients with NAFLD diagnosed by ultrasound from January 2011 to October 2018. Fatty liver on ultrasound was defined as 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 local ethics committee approved the study and all patients provided written informed consent. All the enrollees were over 18 years, with complete anthropometry measurements and laboratory results. Patients with any of the following were excluded: daily alcohol consumption (≥10 g in women and ≥20 g in men); positive hepatitis B surface antigen or antibody against hepatitis C virus; autoimmune liver disease; pregnancy; endocrine disorders (e.g., hypothyroidism, hypogonadism, hypercortisolism); competing etiologies of liver disease resulting in steatosis (e.g., consumption of tamoxifen and amiodarone); being a trained athlete with a hypertrophic muscle mass.

2.2. Clinical assessment

Each participant was required to complete a questionnaire for self-reported alcohol consumption, smoking and past medical history. Anthropometric data were acquired by two specialized doctors and included weight, height, waist circumference (WC), hip circumference, systolic blood pressure and diastolic blood pressure.

BMI was calculated as weight divided by the height squared (kg/m^2). Overweight was defined as ≥23–<25 kg/m^2, and obese was considered ≥25 kg/m^2. Increased WC was defined as >90 cm for men and >80 cm for women [11,12]. Waist-to-hip ratio (WHR) was calculated as WC divided by hip circumference (cm/cm).

After fasting overnight ≥8 h, blood samples were taken for liver biochemistry, lipids, glucose, insulin and routine blood tests. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as FBG (mmol/L) × fasting insulin (FINS, μU/mL)/22.5. Insulin resistance (IR) was defined as HOMA-IR >2.69 in our previous study [13].

2.3. MR quantification of liver fat content

Upper-abdominal MRI with a 3.0-Tesla MRI scanner (Siemens 3.0T MAGNETOM Verio) was performed within two weeks after the serum measurements. The scanning protocol and imaging parameters were as our previous studies described: TE1 2.5 ms, TE2 3.7 ms, 5.47 ms for repetition; 5° flip angle; ±504.0 kHz per pixel receiver bandwidth and a slice thickness of 3.0 mm [14]. After fat-water separation images were acquired using a T1volumetric interpolated breath-hold examination (VIBE) IDEAL-IQ/Dixon sequence, data for LFC, PFC and abdominal subcutaneous fat thickness (ASFT) were analyzed. LFC was further classified by MRI-PDFF as mild (5–10%), moderate (10–25%) or severe (≥25%) [15,16].

2.4. Liver stiffness measurement by 2D-SWE

Liver stiffness was measured using 2D-SWE within 2 weeks after the blood examinations. The examination results were adopted only if ≥5 eligible acquisitions were successfully attained, with an interquartile range (IQR)-to-median ratio <0.3. A cutoff value of 6.1 kPa based on our center's criteria was applied to evaluate the total number of patients with fibrosis.

2.5. Assessment of the risk of cardiovascular diseases

The carotid intima-media thickness (CIMT) and carotid plaque was detected using high-resolution B-mode ultrasonography by two specialist sonographers with over 10 years' experience. The CIMT was measured three times and the average value was used for analysis. A preliminary study for 100 NAFLD patients in our center showed that the kappa statistic of interobserver and interobserver reliability for CIMT and carotid plaque between the two specialist sonographers were 0.91 and 0.93, respectively. Carotid intima-media thickening was diagnosed by a cutoff value of 1.0 mm. The presence of carotid plaques was defined as a focal thickening ≥1.5 mm of the carotid artery [17,18].

To evaluate the risk of cardiovascular and cerebrovascular diseases, the atherosclerosis index (AI) was used [19]. AI was calculated as the difference between Chol and high-density lipoprotein cholesterol (HDL-C), divided by HDL-C, each in mmol/L [20].

2.6. Statistical analysis

Statistical calculations were performed using SPSS version 23.0 software (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation or median with IQR, as required. One-way analysis of variance and the Kruskal-Wallis test were used to compare continuous variables. The chi-squared test was applied to compare categorical variables. Univariate and multivariate backward stepwise logistics regression was used to evaluate factors that may be independently associated with moderate-to-severe steatosis, liver fibrosis. The statistically significant variables in univariate analysis would be included in the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was conducted for predictive factors. A two-sided P value <0.05 was regarded as statistically significant.

3. Results

3.1. Prevalence and metabolic profiles of lean NAFLD

The study population comprised 1509 patients with NAFLD diagnosed by ultrasonography (Table 1). There were 305 (20.2%), 348 (23.1%) and 856 (56.7%) classified as lean, overweight and obese, respectively. The ages and the proportion of men were statistically comparable among the three groups.

Compared with lean NAFLD, the overweight and the obese had higher ALT levels, with the highest in obese patients (median [IQR] 24 (19–35) vs. 30 (21–48) vs. 38 (25–61)U/L; P < 0.001). Similar trends were observed for aspartate aminotransferase (AST), FINS, HOMA-IR, uric acid (UA), hemoglobin and AI (all, P < 0.001; Table 1). There were also significant differences among the three groups regarding the rates of IR and AI >4: lean (13.9%; 19.8%), overweight (23.9%; 34.3%), and obese (43.9%, 41.4%; Table 1). The lean had the highest level of HDL-C but the lowest level of FBG compared with the overweight and the obese. In the post hoc analysis, there

Table 1
Anthropometrical and metabolic characteristics of lean, overweight and obese NAFLD patients.

Characteristics	Lean NAFLD (n = 305)	Overweight NAFLD (n = 348)	Obese NAFLD (n = 856)	*P*	Post-hoc		
					L vs OW	L vs OB	OW vs OB
Age (year)	44.7 ± 11.9	43.6 ± 11.7	42.4 ± 11.7	0.23	–	–	–
Male, n (%)	165 (54.2%)	221 (63.5%)	521 (60.9%)	0.19	–	–	–
BMI (kg/m^2)	21.6 ± 1.2	23.9 ± 0.6	28.3 ± 2.7	<0.001	<0.001	<0.001	<0.001
WC (cm)	79.1 ± 5.4	84.6 ± 5.2	94.3 ± 8.1	<0.001	<0.001	<0.001	<0.001
WHR	0.86 ± 0.06	0.88 ± 0.05	0.91 ± 0.06	<0.001	<0.001	<0.001	<0.001
SBP (mmHg)	124.7 ± 17.2	129.1 ± 17.1	132.1 ± 17.9	<0.001	0.003	<0.001	0.009
DBP (mmHg)	80.7 ± 12.6	82.5 ± 12.8	85.8 ± 12.8	<0.001	0.101	<0.001	<0.001
ALT (U/L)[a]	24 (19–35)	30 (21–48)	38 (25-60)	<0.001	<0.001	<0.001	<0.001
AST (U/L)[a]	25 (20–32)	27 (22–39)	31 (24–41)	<0.001	0.002	<0.001	<0.001
Total cholesterol (mmol/L)	5.2 ± 1.1	5.3 ± 1.1	5.4 ± 1.1	0.22	–	–	–
Triglycerides (mmol/L)	1.9 ± 1.4	2.1 ± 1.5	2.2 ± 1.6	0.08	–	–	–
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.5	1.1 ± 0.3	<0.001	0.22	<0.001	0.01
LDL-cholesterol (mmol/L)	3.2 ± 0.9	3.3 ± 1.0	3.3 ± 0.9	0.10	–	–	–
Free fatty acid (mmol/L)[a]	548 (404–750)	522 (422–646)	575 (451–739)	0.07	–	–	–
Fasting blood glucose (mmol/L)	5.1 ± 0.9	5.2 ± 1.0	5.4 ± 1.3	0.001	0.42	0.001	0.006
FINS (μU/mL)[a]	7.0 (4.8–9.5)	8.3 (6.3–11.3)	10.5 (7.7–14.3)	<0.001	<0.001	<0.001	<0.001
HOMA-IR[a]	1.6 (1.1–2.3)	1.9 (1.3–2.7)	2.5 (1.7–3.5)	<0.001	<0.001	<0.001	<0.001
HOMA-IR > 2.69, (%)	42 (13.9%)	83 (23.9%)	376 (43.9%)	<0.001	0.19	<0.001	<0.001
Uric acid (μmol/L)[a]	377 (296–433)	383 (322–442)	411 (344–484)	<0.001	0.20	<0.001	<0.001
AI[a]	3.3 ± 1.2	3.6 ± 1.4	3.9 ± 2.1	<0.001	0.019	<0.001	0.011
AI > 4, (%)	60 (19.8%)	119 (34.3%)	354 (41.4%)	<0.001	0.02	<0.001	0.09

Abbreviation: L, lean NAFLD; OW, overweight NAFLD; OB, obese NAFLD; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; AI, atherosclerosis index.

[a] Continuous variables are expressed as median with IQR for non-Gaussian distribution.

were significant differences between the lean and the overweight patients with regard to ALT, AST, FINS, HOMA-IR and AI (all, $P < 0.05$; Table 1).

3.2. Liver fat content, liver stiffness and subclinical atherosclerosis in lean NAFLD

Among 1509 NAFLD patients diagnosed by ultrasound, 556 patients received MRI-PDFF examination. However, 26 patients were with the LFC less than 5% by MRI-PDFF and excluded. Finally, 530 patients were in the further analysis (Table 2). No statistic differences of anthropometrical and metabolic characteristics were found between the overall cohort and those with MRI-PDFF examinations (Supplementary Table 1). The median (IQR) LFC of the lean, overweight and obese groups were 8.2% (6.4–13.7%), 10.2% (7.4–16.1%) and 15.1% (10.1–20.8%; $P < 0.001$), respectively. In the lean, overweight and obese groups, there were also significant differences in the percentage of patients with moderate-severe fatty liver (38.7, 51.4 and 76.4%; $P < 0.001$) and ASFT (19.3 ± 5.8; 21.6 ± 7.2 and 24.8 ± 8.9 mm; $P < 0.001$). The median (IQR) PFC of the lean, overweight and obese groups was 1.4% (0.9–2.1%), 1.7% (1.1–2.5%) and 2.0% (1.3–3.1%; $P < 0.001$). Furthermore, a significant difference was found in the percentage of patients with PFC >5% among the three groups (1.9, 8.1 and 12.6%; $P = 0.014$). 2D-SWE examination was performed in 481 patients (Table 2). The obese group had the highest level of liver stiffness and the highest rate of fibrosis compared with the lean and the overweight groups ($P < 0.001$). The CIMT was significantly lower in the lean group. However, no significant difference was found regarding the rates of CIMT ≥1.0 mm or carotid plaque among the three groups (Table 2).

3.3. Factors associated with imaging features among lean, overweight and obese patients with NAFLD

In the lean patients, increased WC was associated with moderate-to-severe steatosis by univariate logistic analysis (odds ratio [OR] 1.29; 95% confidence interval [CI]: 1.14–1.45; $P = 0.001$, Table 3). Only one variable (increased WC) was found significantly associated with moderate-to-severe steatosis. Therefore, the multivariate logistic analysis was not conducted in the lean patients. In the overweight patients, increased WC and UA elevation were associated with moderate-to-severe steatosis by univariate analysis (Table 3). The variables that were found significantly associated with moderate-to-severe steatosis in univariate analysis were entered in the multivariate model. Increased WC (OR 2.96; 95% CI: 1.27–6.91, $P = 0.012$) and UA elevation (OR 2.70; 95% CI: 1.17–6.26, $P = 0.020$) remained significant for moderate-to-severe steatosis (Table 5). For the obese patients, BMI ≥28 kg/m^2, increased WC, ALT >40 U/L, IR and UA elevation were associated with moderate-to-severe steatosis (Table 3). Multivariate analysis showed that BMI ≥28 kg/m^2 (OR 1.92; 95% CI: 1.07–3.46, $P = 0.029$), increased WC (OR 2.33; 95% CI: 1.11–4.89, $P = 0.026$), IR (OR 2.01; 95% CI: 1.09–3.27, $P = 0.026$) were independent predictors of moderate-to-severe steatosis (Table 5).

Among the lean patients, univariate analysis demonstrated that ALT >40 U/L (OR 5.39; 95% CI: 1.17–24.93, $P = 0.031$) was an independent predictor of fibrosis (Table 4). Since only one variable (ALT >40 U/L) was associated with fibrosis in univariate logistic analysis, the multivariate logistic analysis was not conducted. For the overweight patients, BMI ≥24 kg/m^2, increased WC, IR and LFC ≥10% were associated with fibrosis, and multivariate analysis included these significant variables showed that only increased WC (OR 1.18; 95% CI: 1.04–1.35; $P = 0.012$) remained a significant predictor of fibrosis (Tables 4 and 5). By univariate analysis, BMI ≥28 kg/m^2, increased WC and ALT >40 U/L were found to be significantly associated with fibrosis in obese patients (Table 4). Multivariate analysis demonstrated that BMI ≥28 kg/m^2 (OR 2.86; 95% CI: 1.66–4.92; $P < 0.001$) and ALT >40 U/L (OR 2.07; 95% CI: 1.22–3.49; $P = 0.007$) were predictors of fibrosis (Table 5).

3.4. Predictive factors of moderate-to-severe steatosis and fibrosis

Obesity-related indices, BMI and WC were used to construct ROC curves for predicting imaging features. We also combined the significant variables in logistic model to test their predicting value for moderate-to-severe steatosis or fibrosis (Fig. 1). For moderate-

Table 2
Imaging features of liver fat content, liver stiffness and subclinical atherosclerosis in lean, overweight and obese NAFLD patients.

Radiology	Lean NAFLD	Overweight NAFLD	Obese NAFLD	*P*	Post-hoc		
					L vs OW	L vs OB	OW vs OB
MRI	n = 106	n = 128	n = 296				
LFC (%)[a]	8.2 (6.4–13.7)	10.2 (7.4–16.1)	15.1 (10.1–20.8)	<0.001	0.01	<0.001	<0.001
Classification of LFC, (n, %)				<0.001	0.17	<0.001	<0.001
Mild (5–10%)	65 (61.3%)	62 (48.6%)	70 (23.6%)				
Moderate (10–25%)	37 (35.0%)	55 (43.1%)	181 (61.1%)				
Severe (≥25%)	4 (3.7%)	11 (8.3%)	45 (15.3%)				
PFC (%)[a]	1.4 (0.9–2.1)	1.7 (1.1–2.5)	2.0 (1.3–3.1)	<0.001	0.04	<0.001	0.04
PFC > 5, (%)	2 (1.9%)	10 (8.1%)	37 (12.6%)	0.014	0.049	0.005	0.24
ASFT (mm)	19.3 ± 5.8	21.6 ± 7.2	24.8 ± 8.9	<0.001	0.07	<0.001	0.01
2D-SWE	n = 102	n = 115	n = 264				
liver stiffness (kPa)[a]	4.9 (4.6–5.4)	5.3 (4.7–6.0)	6.6 (5.7–7.3)	<0.001	0.02	<0.001	<0.001
liver stiffness ≥ 6.1 kPa, (%)	11 (10.8%)	23 (20.0%)	86 (32.6%)	<0.001	0.03	<0.001	<0.001
Carotid Artery Ultrasound	n = 102	n = 115	n = 264				
CIMT (mm)[a]	0.6 (0.6–0.7)	0.6 (0.6–0.8)	0.8 (0.6–0.9)	0.02	0.12	<0.001	<0.001
CIMT ≥ 1.0 mm, (%)	10 (9.2%)	23 (20.0%)	40 (15.1%)	0.10	–	–	–
Detection of carotid plaque (%)	14 (13.3%)	24 (20.9%)	65 (24.6%)	0.09	–	–	–

Abbreviation: L, lean NAFLD; OW, overweight NAFLD; OB, obese NAFLD; LFC, liver fat content; PFC, pancreas fat content; ASFT, abdominal subcutaneous fat thickness; 2D-SWE, 2-dimensional shear wave elastography; CIMT, carotid intima-media thickness.
[a] Continuous variables are expressed as median with IQR for non-Gaussian distribution.

Table 3
Univariate logistic analysis for factors associated with moderate-to-severe steatosis (liver fat content ≥ 10%).

Factors	Lean NAFLD[a] OR (95%CI)	*P*	Overweight NAFLD OR (95%CI)	*P*	Obese NAFLD OR (95%CI)	*P*
Male	1.48 (0.59–3.74)	0.41	0.78 (0.35–1.74)	0.54	0.81 (0.42–1.54)	0.52
Age≥ 40 year	0.97 (0.38–2.48)	0.97	1.19 (0.56–2.53)	0.65	0.98 (0.96–1.01)	0.08
BMI[b]	1.15 (0.81–1.65)	0.44	1.40 (0.70–2.81)	0.35	2.68 (1.55–4.65)	0.001
Increased WC[c]	1.29 (1.14–1.45)	0.001	2.67 (1.18–6.04)	0.019	3.45 (1.74–6.86)	0.001
Hypertension	1.03 (0.98–1.06)	0.06	2.32 (0.93–5.76)	0.07	0.99 (0.56–1.76)	0.98
ALT > 40 U/L	1.47 (0.54–3.97)	0.45	1.79 (0.83–3.86)	0.14	2.02 (1.16–3.52)	0.013
Total cholesterol > 5.7 mmol/L	0.74 (0.25–2.23)	0.59	1.01 (0.44–2.33)	0.98	1.35 (0.74–2.47)	0.33
Triglycerides > 1.7 mmol/L	1.69 (0.64–4.53)	0.29	1.76 (0.76–4.05)	0.19	1.65 (0.92–2.94)	0.09
LDL-cholesterol > 3.4 mmol/L	1.38 (0.53–3.60)	0.52	2.05 (0.95–4.40)	0.07	1.26 (0.73–2.19)	0.41
Free fatty acid > 769 mmol/L	1.75 (0.55–5.91)	0.35	0.79 (0.25–2.52)	0.69	1.51 (0.68–3.35)	0.31
HOMA-IR > 2.69	1.21 (0.25–5.79)	0.82	1.87 (0.77–4.57)	0.17	2.73 (1.53–4.88)	0.001
Uric acid elevation[d]	1.77 (0.71–4.42)	0.23	2.42 (1.08–5.40)	0.032	1.92 (1.11–3.31)	0.02
Liver stiffness ≥ 6.1 kPa	0.94 (0.21–4.26)	0.94	1.29 (0.98–1.70)	0.07	1.26 (0.73–2.20)	0.41
CIMT > 1.0 mm	1.67 (0.39–7.22)	0.49	0.93 (0.37–2.38)	0.89	0.95 (0.45-1.99)	0.89

Abbreviation: WC, waist circumference; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; CIMT, carotid intima-media thickness.
[a] Only one factor was found significant, therefore multivariate analysis wouldn't be conducted.
[b] BMI: 18–23 kg/m^2 for lean NAFLD patients, 24–25 kg/m^2 for overweight NAFLD patients and ≥28 kg/m^2 for obese NAFLD patients. BMI was considered as continuous variable.
[c] Increased WC: >90 cm for men and >80 cm for women.
[d] Uric acid elevation: >420 μmol/L for men and >360 μmol/L for women.

to-severe steatosis (LFC ≥10%) in lean patients, the WC of 78.5 cm achieved an area under the ROC curve (AUC; 0.81, $P < 0.001$). Furthermore, the WC of 79.5 cm and the UA of 365 μmol/L achieved an AUC (0.75, $P < 0.001$, 0.73, $P < 0.001$, respectively) for predicting moderate-to-severe steatosis in overweight patients. The combination of WC and UA attained a higher AUC (0.80, $P < 0.001$). For obese patients, the HOMA-IR of 2.54 achieved the highest AUROC (0.73, $P < 0.001$) to predict the presence of moderate-to-severe steatosis, followed by the BMI of 27.34 kg/m^2 (0.72, $P < 0.001$) and the WC of 86 cm (0.67, $P < 0.001$). Furthermore, the combination of HOMA-IR, BMI and WC had a higher AUC of 0.82.

Only the ALT of 78 U/L was significant for predicting the presence of fibrosis in the lean patients. With regard to overweight patients, the BMI of 24.66 kg/m^2 and the WC of 87 cm achieved a statistically significant AUC (0.67, $P < 0.01$; 0.64, $P = 0.041$, respectively). The combination of BMI and WC attained a higher AUC (0.70, $P = 0.005$). For the obese patients, the BMI of 28.73 kg/m^2 achieved the highest AUROC (0.74, $P < 0.001$) to predict the presence of fibrosis followed by the ALT of 54 U/L (0.72, $P < 0.001$) and the WC of 102.5 cm (0.65, $P < 0.001$). The combination of BMI and ALT was found to be significant in predicting fibrosis with a statistically significant AUC of 0.76.

4. Discussion

This study investigated the predictors of liver injuries and their effects in lean, overweight and obese patients with NAFLD, as classified by BMI. For factors associated with moderate-to-severe steatosis, only increased WC was identified as a predictor, while increased WC and UA elevation were identified in overweight patients, and BMI ≥28 kg/m^2, increased WC and IR were identified in obese NAFLD patients, respectively. For factors associated with liver fibrosis, ALT >40 U/L and increased WC was found in the lean and overweight NAFLD respectively, while BMI ≥28 kg/m^2 and ALT >40 U/L were independent factors in obese NAFLD.

To the best of our knowledge, this study is the first to apply the WHO's stricter criteria for BMI for Asians to differentiate the metabolic features of lean, overweight and obese patients with NAFLD. We found that the lean patients had lower LFC, PFC and ASFT compared with the obese patients. The lean patients also had

Table 4
Univariate logistic analysis for factors associated with fibrosis (liver stiffness ≥ 6.1 kPa).

Factors	Lean NAFLD[a] OR (95%CI)	*P*	Overweight NAFLD OR (95%CI)	*P*	Obese NAFLD OR (95%CI)	*P*
Male	1.19 (0.26–5.37)	0.82	1.26 (0.47–3.38)	0.65	1.01 (0.99–1.03)	0.33
Age ≥ 40 year	0.89 (0.20–4.02)	0.88	1.86 (0.72–4.82)	0.20	1.58 (0.97–2.55)	0.08
BMI[b]	1.58 (0.73–3.43)	0.25	3.33 (1.24–8.95)	0.017	3.32 (2.00–5.50)	<0.001
Increased WC[c]	1.02 (0.91–1.15)	0.70	1.19 (1.07–1.33)	0.002	2.27 (1.18–4.36)	0.014
Hypertension	0.34 (0.45–9.75)	0.34	1.74 (0.65–4.68)	0.28	1.57 (0.92–2.66)	0.10
ALT > 40 U/L	5.39 (1.17–24.93)	0.031	1.86 (0.75–4.64)	0.18	2.47 (1.49–4.08)	<0.001
Total cholesterol > 5.7 mmol/L	1.02 (0.98–1.06)	0.07	1.72 (0.66–4.48)	0.27	1.08 (0.64–1.81)	0.79
Triglycerides > 1.7 mmol/L	0.81 (0.15–4.34)	0.81	1.24 (0.49–3.13)	0.64	1.18 (0.73–1.93)	0.49
LDL-cholesterol > 3.4 mmol/L	0.29 (0.03–2.46)	0.25	2.27 (0.89–5.76)	0.09	1.11 (0.69–1.81)	0.66
Free fatty acid > 769 mmol/L	0.65 (0.07–5.73)	0.70	1.69 (0.47–6.05)	0.42	0.80 (0.44–1.45)	0.47
HOMA-IR > 2.69	4.47 (0.71–28.14)	0.11	1.61 (1.09–2.40)	0.018	0.93 (0.57–1.50)	0.76
Uric acid elevation[d]	1.57 (0.36–6.80)	0.55	0.73 (0.29–1.83)	0.50	1.23 (0.75–1.99)	0.42
LFC ≥ 10%	0.94 (0.21–4.25)	0.94	2.86 (1.08–7.62)	0.035	1.26 (0.73–2.20)	0.41
CIMT > 1.0 mm	1.33(0.14–12.41)	0.80	1.01 (0.98–1.05)	0.51	0.84 (0.44–1.63)	0.61

Abbreviation: WC, waist circumference; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; LFC, liver fat content; CIMT, carotid intima-media thickness.

[a] Only one factor was found significant, therefore multivariate analysis wouldn't be conducted.

[b] BMI: 18–23 kg/m^2 for lean NAFLD patients, 24–25 kg/m^2 for overweight NAFLD patients and ≥28 kg/m^2 for obese NAFLD patients. BMI was considered as continuous variable.

[c] Increased WC: >90 cm for men and > 80 cm for women.

[d] Uric acid elevation: >420 μmol/L for men and >360 μmol/L for women.

Table 5
Multivariate logistic analysis for factors associated with moderate-to-severe steatosis (liver fat content ≥ 10%) and fibrosis (liver stiffness ≥ 6.1 kPa).

	Overweight NAFLD OR (95%CI)	*P*	Obese NAFLD OR (95%CI)	*P*
Factors for LFC ≥ 10%				
BMI[a]	–	–	1.92 (1.07–3.46)	0.029
Increased WC[b]	2.96 (1.27–6.91)	0.012	2.33 (1.11–4.89)	0.026
ALT > 40 U/L	–	–	1.61 (0.89–2.92)	0.12
HOMA-IR > 2.69	–	–	2.01 (1.09–3.72)	0.026
Uric acid elevation[c]	2.70 (1.17–6.26)	0.020	1.64 (0.92–2.93)	0.09
Factors for fibrosis				
BMI[a]	2.43 (0.84–7.04)	0.11	2.86 (1.66–4.92)	<0.001
Increased WC[b]	1.18 (1.04–1.35)	0.012	1.18 (0.58–2.43)	0.65
ALT > 40 U/L	–	–	2.07 (1.22–3.49)	0.007
HOMA-IR > 2.69	1.44 (0.91–2.26)	0.12	–	–
LFC ≥ 10%	1.26 (0.37–4.35)	0.72	–	–

Abbreviation: WC, waist circumference; ALT, alanine aminotransferase; HOMA-IR, Homeostasis model assessment of insulin resistance; LFC, liver fat content.

[a] BMI: 24–25 kg/m^2 for overweight NAFLD patients and ≥28 kg/m^2 for obese NAFLD patients. BMI was considered as continuous variable.

[b] Increased WC: >90 cm for men and >80 cm for women. BMI was considered as continuous variable.

[c] Uric acid elevation: >420 μmol/L for men and >360 μmol/L for women.

lower levels of metabolic indices (ALT, AST, FINS, HOMA-IR) than either the overweight or the obese groups. Our study also showed that AI and CIMT of the lean patients were the lowest among three groups. However, no significant difference was found in the rates of carotid intima-media thickening or carotid plaque among the three groups, which was different from the results from Yoshitaka et al. [8] that non-overweight NAFLD patients had a higher risk of incident CVD compared with the overweight patients after 10 years' follow-up. These may be limited to our cross-sectional study design, which could not reflect potential changes by NAFLD over time, especially for the chronic progression to carotid atherosclerosis. Further prospective studies with long-term follow-up periods would be needed on the incidence of CVD in NAFLD patients with different categories of BMIs.

The acknowledged prognostic factors in NAFLD are the severity of steatosis, inflammation and fibrosis [21,22]. However, the current histological scoring systems based on liver biopsy are limited to subjective visual judgement and sampling errors [23]. Although proton magnetic resonance spectroscopy is the golden standard to quantify liver fat noninvasively, it is also prone to sampling error, since only a single voxel and region of interest was detected [24]. Wei et al. [25] conducted a study involving 262 Chinese patients with NAFLD and found that the LFC levels of the obese and non-obese patients were comparable. However, according to a study of 55 Caucasian patients with NAFLD, the LFC of the non-obese patients was significantly less than that of the obese patients [26]. Unlike the two studies above, the present study utilized MRI-PDFF, which quantifies the fat content across the entire liver to determine the fat fraction distribution of the liver. Our study confirmed that lean patients with NAFLD had less steatosis compared with the overweight or obese patients.

Our study utilized 2D-SWE, which provides images of liver stiffness in real time. The results showed significant differences in liver stiffness among the three groups. This finding is in accordance with the results of another study from Hong Kong [27], in which the evaluation of 307 patients with NAFLD using FibroScan showed that liver stiffness was lower in the non-obese patients. Feldman et al. [26] also found that lean NAFLD patients had comparable FIB4 index but better NAFLD fibrosis score than the obese ones in Caucasians. FibroScan has been recommended for evaluating liver fibrosis [28], since it has a relatively higher diagnostic performance and convenience of operation. However, the validity of FibroScan can be influenced by several factors, especially obesity. Staging fibrosis in patients with NAFLD may be compromised by abdominal obesity [29–31]. It has been demonstrated that the diagnostic accuracy of 2D-SWE is better than that of FibroScan and FIB4 score in NAFLD

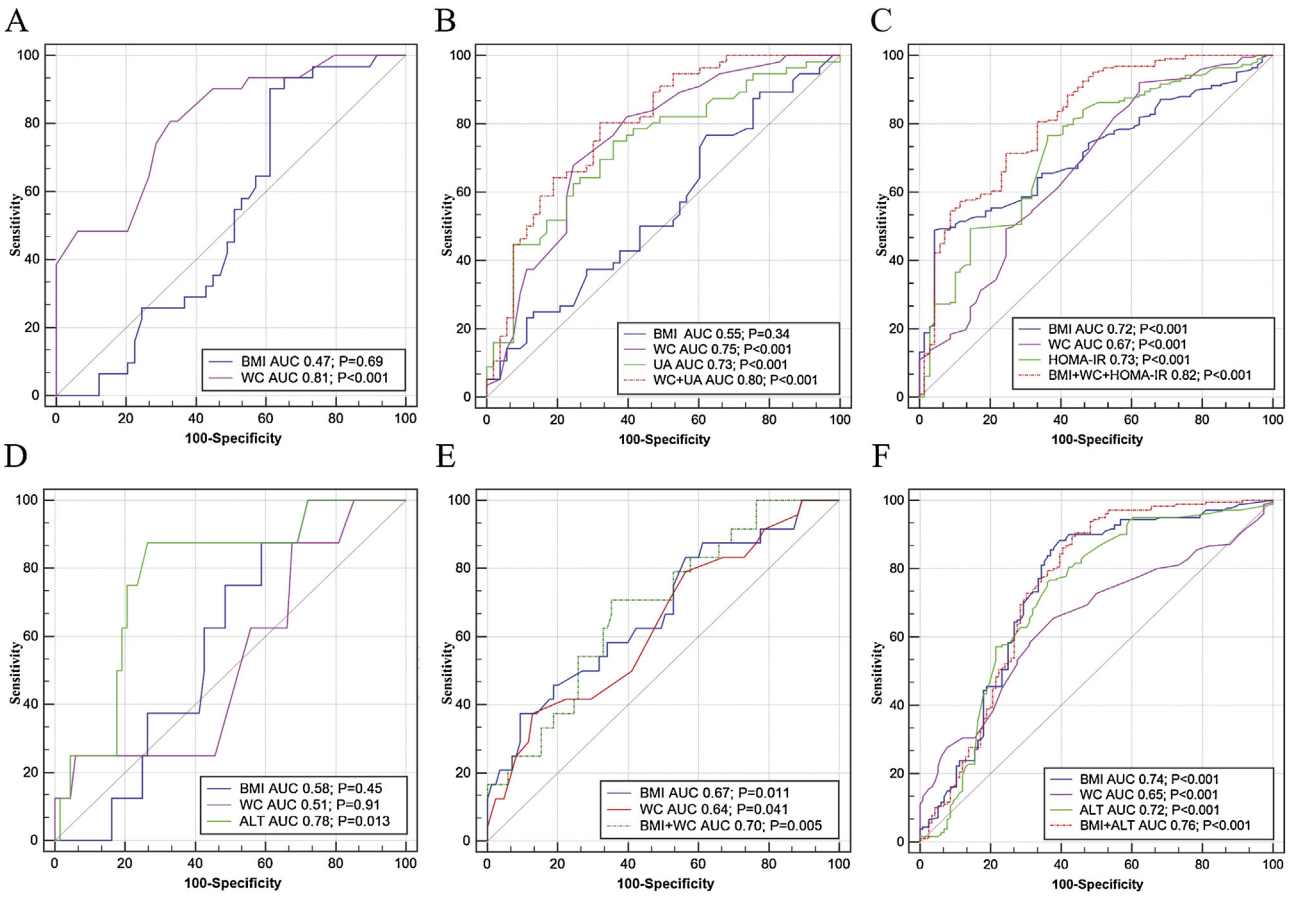

Fig. 1. Receiver operator characteristic (ROC) curve of factors that predict moderate-severe steatosis for lean NAFLD (A), overweight NAFLD (B), obese NAFLD (C) and the presence of fibrosis for lean NAFLD (D), overweight NAFLD (E), and obese NAFLD (F).

[10]. Therefore, we used the more accurate method to assess liver stiffness and these results demonstrated that lean patients did have advantages over the overweight and the obese patients with regard to progression of histological features, which was in consistent with a former study conducted by Kim et al., which consisted of 542 biopsy-proven NAFLD patients [32]. The results showed that compared with the obese patients, the non-obese patients had lower fibrosis stage and lower NAFLD activity scores [32].

In the present study, the lean, overweight, and obese patients were first compared for PFC levels. Excessive fat accumulation in the pancreas is putatively negatively associated with insulin secretion and leads to β-cell dysfunction, high blood glucose levels and diabetes [33,34]. The present study found that both overweight and obese patients had higher insulin secretion and HOMA-IR compared with the lean patients.

It has been reported that lean patients with NAFLD had more visceral adiposity compared with a healthy lean control group, as determined by WC [35]. The accumulation of visceral adiposity exposes the liver to high concentrations of free fatty acids, which exacerbates the accumulation of TG in the liver. In the setting of severe steatosis, the disruption of hepatic metabolism may lead to elevated levels of inflammatory cytokines that promote fibrosis, such as interleukin-6 and tumor necrosis factor [36].

Such parameters as WC and BMI have been used as the traditional indices for obesity in NAFLD. However, it should be noted that in the present study, in the lean patients and the overweight patients, it was WC but not BMI, that was strongly associated with moderate-to-severe steatosis and fibrosis. WC is the simplest and most common anthropometric index of central obesity and should be measured when evaluating obesity and related comorbidities [37]. Several studies revealed that central obesity was associated with development and progression of NAFLD [38,39]. A study conducted by Janssen et al. [40] involving 14,924 adults showed that WC, but not BMI, was an obesity-related health risk. Ishibashi et al. [41] also reported that WC correlates with hepatic fat accumulation, as evaluated by computed tomography. WHR and WC are regarded as surrogate markers of visceral obesity. However, Borruel et al. [42] found that WC was more accurate than WHR as an index of visceral adiposity, based on ROC analysis. In this study, among three groups, 35 (11.5%) lean patients, 101 (29.0%) overweight patients and 593 (69.3%) obese patients presented increased WC, respectively. The present data showed that abdominal obesity, as defined by WC, positively correlated with steatosis and liver stiffness, unlike general obesity suggested by BMI.

Lonardo et al. [43] also revealed that FINS and UA were the independent predictors of NAFLD. Ballestri et al. [44] conducted the study involving 118 consecutive biopsy-proven NAFLD patients further disclosed that HOMA-IR, UA, metabolic syndrome, ALT and Chol were the independent predictors of nonalcoholic steatohepatitis and the histological damage. Compared with the studies mentioned above, our data further expanded upon the knowledge that UA was associated with moderate-to-severe steatosis in overweight NAFLD paitents, while HOMA-IR was the predictor of moderate-to-severe steatosis in obese NAFLD patients.

The present study is limited, in that the sonographic steatosis was qualitative diagnosis and no semi-quantitative indices of ultrasound was adopted. Moreover, NAFLD is currently believed to be a sexually dimorphic disease [45]. However, the statistic power may be not sufficient to conduct the logistics analysis since the limited sample size in the subgroup of lean NAFLD for re-running the

data separately by sex. To minimize the limitation, we performed another multivariate logistics analysis model adjusting for the gender and age. The results showed that the factors associated with moderate-to-severe steatosis and fibrosis among three groups in previous logistic model remained significant (Supplementary Table 2). Furthermore, as inadequate potential confounding factors was identified in lean NAFLD, the increased WC has not been confirmed in multivariate analysis. Finally, this study focused solely on the metabolic and imaging features of the three groups without investigating gene polymorphisms or other metabolites that predispose non-obese individuals to NAFLD.

In conclusion, among our patients with NAFLD, the lean patients had lower metabolic disorders, liver stiffness, carotid atherosclerotic damage, LFC and PFC compared with the overweight and the obese patients. WC was strongly predictive of disease severity in all NAFLD, while UA and BMI plus IR were additional predictors in the overweight and obese NAFLD, respectively. Our findings highlight that individualized screening strategies should be established for NAFLD according to different BMIs.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.02.019.

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