

CHARACTERISTICS OF CARDIOVASCULAR RISK IN PATIENTS WITH METABOLIC DYSFUNCTION–ASSOCIATED FATTY LIVER DISEASE ACCORDING TO OBESITY STATUS

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Annotation: This study compared cardiovascular risk profiles in 128 patients with metabolic dysfunction–associated fatty liver disease (MAFLD), stratified by obesity (BMI ≥ 30 kg/m², n = 68) or lean phenotype (BMI 18.5–24.9 kg/m², n = 60). All participants underwent anthropometric assessment, fasting biochemistry (HOMA-IR, lipid panel, hs-CRP, IL-6), endothelial markers (nitric oxide metabolites, endothelin-1), carotid intima-media thickness (CIMT) measurement, and 10-year risk estimation (FRS, SCORE, ASCVD). Obese MAFLD patients exhibited significantly higher insulin resistance, inflammation, endothelial dysfunction, CIMT, and elevated risk scores. However, 18 % of lean MAFLD individuals also had FRS ≥ 10 % and 23 % showed CIMT ≥ 0.9 mm, indicating “hidden” cardiovascular risk. Findings underscore the necessity of comprehensive risk assessment beyond BMI in all MAFLD patients.

Keywords: MAFLD; obesity; lean phenotype; cardiovascular risk; insulin resistance; systemic inflammation; endothelial dysfunction; carotid intima-media thickness

Metabolic dysfunction–associated fatty liver disease (MAFLD) represents a spectrum of hepatic pathology characterized by excessive triglyceride accumulation in hepatocytes within the context of systemic metabolic disturbances, most notably insulin resistance, dyslipidemia, and low-grade inflammation. Initially described as a “benign” hepatic condition, MAFLD is now recognized as a multisystem disorder with profound cardiovascular implications. Although obesity—particularly visceral adiposity—has long been viewed as the primary driver of both hepatic steatosis and atherogenesis, recent observations have identified a paradoxical “lean” MAFLD phenotype: individuals whose body mass index (BMI) remains within the normal range despite clear evidence of hepatic fat deposition. In light of this, our investigation sought to delineate the cardiovascular risk profiles of MAFLD patients stratified by obesity status, thereby highlighting how traditional risk stratification tools may fail to capture “hidden” risk in lean individuals.

Between May 2022 and March 2025, we prospectively enrolled 128 adult patients aged 32 to 67 years (mean age 49.6 ± 8.7 years) who were referred to a tertiary-care hepatology clinic with ultrasonographically or elastographically confirmed MAFLD. Inclusion criteria required evidence of hepatic steatosis—either on ultrasound (bright echotexture with increased attenuation) or controlled attenuation parameter (CAP ≥ 238 dB/m) on transient elastography—combined with metabolic dysregulation. Exclusion criteria encompassed significant alcohol consumption (> 20 g/day for women; > 30 g/day for men), viral hepatitis, autoimmune liver disease, medication-induced steatosis, known overt cardiovascular disease, decompensated cirrhosis (liver stiffness > 12.5 kPa), active infection or inflammatory illness within the preceding four weeks, and malignancy. Each participant

underwent a standardized assessment that included anthropometric measurements, detailed laboratory studies, noninvasive vascular imaging, and cardiovascular risk scoring.

Body mass index was calculated from measured weight and height, and patients were classified as obese if BMI ≥ 30 kg/m² (n = 68) or lean if BMI ranged from 18.5 to 24.9 kg/m² (n = 60). Waist circumference was measured midway between the lowest rib and iliac crest, hip circumference at the widest point of the hips, and waist-to-hip ratio (WHR) subsequently calculated. Blood pressure was recorded as the mean of two seated measurements after a five-minute rest. After overnight fasting (≥ 10 hours), venous blood draws provided data for fasting glucose, insulin (used to calculate HOMA-IR as [fasting insulin \times fasting glucose]/22.5), lipid panels (total cholesterol, LDL, HDL, triglycerides), liver function tests (ALT, AST, GGT), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and endothelial markers—namely nitric oxide metabolites (combined nitrite and nitrate measured by the Griess reaction) and endothelin-1 (ET-1) via enzyme-linked immunosorbent assay. Noninvasive imaging included hepatic ultrasonography for steatosis grading and transient elastography for fibrosis staging, along with bilateral common carotid artery scanning to determine carotid intima-media thickness (CIMT). A CIMT of 0.9 mm or greater was predefined as evidence of subclinical atherosclerosis. Ten-year cardiovascular risk estimates were generated using the Framingham Risk Score (FRS), SCORE calibrated for a low-risk European population, and ASCVD Pooled Cohort Equations. Patients were considered at elevated risk if FRS ≥ 10 percent, SCORE ≥ 5 percent, or ASCVD ≥ 7.5 percent. All statistical analyses were performed in SPSS version 26.0; normally distributed continuous variables are reported as mean \pm standard deviation and compared via independent t-tests, while nonparametric variables are expressed as median with interquartile range and compared using the Mann–Whitney U test. Categorical variables are shown as frequencies and percentages, analyzed by chi-square tests. Correlation coefficients (Pearson's or Spearman's as appropriate) assessed relationships between metabolic, inflammatory, and vascular parameters, with $p < 0.05$ denoting statistical significance.

Despite similar age (50.3 ± 8.4 years in obese versus 48.7 ± 9.0 years in lean; $p = 0.27$) and an identical sex distribution (40 percent female, 60 percent male in both cohorts), obese patients exhibited markedly different anthropometric and metabolic profiles. The obese group's mean BMI was 32.8 ± 2.5 kg/m², significantly higher than the lean group's 22.6 ± 1.8 kg/m² ($p < 0.001$). Waist circumference averaged 106.5 ± 8.0 cm in obese patients versus 83.9 ± 6.4 cm in lean ($p < 0.001$), and their waist-to-hip ratio was 0.98 ± 0.07 compared to 0.83 ± 0.06 ($p < 0.001$). Fasting glucose levels, although modestly elevated in obese individuals (5.8 ± 0.9 mmol/L versus 5.4 ± 0.7 mmol/L; $p = 0.02$), were overshadowed by pronounced differences in fasting insulin (15.2 ± 4.3 μ U/mL in obese vs. 8.7 ± 3.1 μ U/mL in lean; $p < 0.001$), leading to significantly higher insulin resistance (HOMA-IR of 3.8 ± 1.2 versus 2.2 ± 0.8 ; $p < 0.001$).

Dyslipidemia was more severe among obese participants: mean total cholesterol measured 5.8 ± 1.0 mmol/L compared to 5.2 ± 0.9 mmol/L in lean ($p = 0.003$), LDL-cholesterol 3.5 ± 0.7 mmol/L versus 3.0 ± 0.6 mmol/L ($p < 0.001$), HDL-cholesterol 1.0 ± 0.2 mmol/L versus 1.3 ± 0.3 mmol/L ($p < 0.001$), and triglycerides 2.3 ± 0.6 mmol/L versus 1.6 ± 0.5 mmol/L ($p < 0.001$). High-sensitivity C-reactive protein, reflecting systemic inflammation, was elevated in obese subjects (median 4.1 mg/L [IQR 2.9–5.4]) compared to lean (1.9 mg/L [IQR 1.0–2.7]; $p < 0.001$), and IL-6 levels averaged 5.5 ± 1.6 pg/mL in the obese group versus 3.3 ± 1.2 pg/mL in lean ($p < 0.001$). Markers of endothelial function corroborated this inflammatory milieu: nitric oxide metabolites (NOx) were lower among obese

patients ($17.8 \pm 5.9 \mu\text{mol/L}$) than lean counterparts ($24.2 \pm 6.5 \mu\text{mol/L}$; $p < 0.001$), whereas endothelin-1 was higher in obese ($2.7 \pm 0.7 \text{ pg/mL}$) compared to lean ($1.9 \pm 0.5 \text{ pg/mL}$; $p < 0.001$).

Carotid ultrasound revealed mean CIMT of $0.94 \pm 0.13 \text{ mm}$ in obese patients versus $0.84 \pm 0.11 \text{ mm}$ in lean ($p < 0.001$). A CIMT $\geq 0.9 \text{ mm}$ was present in 45 percent of obese individuals (31/68) but only 23 percent of lean (14/60; $\chi^2 = 7.0$, $p = 0.008$). Ten-year cardiovascular risk calculations similarly diverged: Framingham Risk Score ≥ 10 percent was observed in 38 percent of obese patients versus 17 percent of lean ($\chi^2 = 7.8$, $p = 0.005$); SCORE ≥ 5 percent occurred in 33 percent of obese versus 15 percent of lean ($\chi^2 = 6.3$, $p = 0.010$); and ASCVD ≥ 7.5 percent was found in 35 percent of obese compared to 18 percent of lean ($\chi^2 = 5.1$, $p = 0.024$). Correlation analyses highlighted the interdependence of these metabolic and vascular alterations: HOMA-IR correlated positively with CIMT ($r = 0.57$; $p < 0.001$), hs-CRP correlated with CIMT ($r = 0.60$; $p < 0.001$), endothelin-1 correlated with HOMA-IR ($r = 0.49$; $p < 0.001$), and NOx inversely correlated with CIMT ($r = -0.45$; $p < 0.001$).

Notably, among lean MAFLD patients, 18 percent (11/60) exhibited a Framingham Risk Score ≥ 10 percent despite having HOMA-IR values in the 2.0–2.5 range and hs-CRP between 1.5–2.3 mg/L. Of these eleven lean individuals with elevated calculated risk, seven (64 percent) also demonstrated CIMT $\geq 0.9 \text{ mm}$, underscoring a concordance between subclinical atherosclerosis and modestly raised metabolic markers even in the absence of obesity.

Taken together, these findings demonstrate that obese MAFLD patients harbor significantly more pronounced insulin resistance, dyslipidemia, low-grade inflammation, and endothelial dysfunction, which coincide with accelerated carotid intima-media thickening and higher predicted 10-year cardiovascular risk. However, lean MAFLD individuals—despite normal anthropometric profiles—also present with subclinical insulin resistance (mean HOMA-IR 2.2 ± 0.8), low-grade inflammation (median hs-CRP 1.9 mg/L), and endothelial impairment (mean ET-1 $1.9 \pm 0.5 \text{ pg/mL}$), resulting in one-fifth of lean patients meeting FRS criteria for elevated risk and nearly one-quarter showing CIMT $\geq 0.9 \text{ mm}$. This “hidden” risk in lean MAFLD is likely driven by visceral adiposity not captured by BMI, genetic predispositions (e.g., PNPLA3 or TM6SF2 polymorphisms), and gut microbiota alterations that collectively foster a proatherogenic environment despite normal weight.

Importantly, reliance solely on traditional risk calculators may underestimate cardiovascular vulnerability in lean MAFLD patients. While risk scores aligned more closely with subclinical markers in obese subjects, discordance was evident in lean individuals, where modest elevations in inflammatory and endothelial biomarkers revealed atherosclerotic changes that risk algorithms alone failed to detect. Consequently, a more nuanced, phenotype-driven approach to risk stratification is warranted for all MAFLD patients—one that integrates anthropometric measures with metabolic, inflammatory, endothelial, and imaging parameters.

Clinicians should therefore consider comprehensive cardiovascular evaluation for MAFLD patients regardless of BMI. This includes measurement of HOMA-IR and hs-CRP to gauge metabolic and inflammatory stress; noninvasive vascular imaging (e.g., CIMT) to identify subclinical atherosclerosis; and assessment of endothelial function through NO metabolite and ET-1 quantification. Early intervention—comprising lifestyle modifications (caloric restriction, structured aerobic and resistance exercise) and, where appropriate, insulin-sensitizing or anti-inflammatory pharmacotherapies (such as

pioglitazone or GLP-1 receptor agonists)—may effectively mitigate the progression of both hepatic steatosis and cardiovascular disease.

Future longitudinal studies following lean and obese MAFLD cohorts over time will be critical to understanding incident cardiovascular event rates and validating the predictive value of combined biomarker and imaging approaches. Genetic and epigenetic investigations may further elucidate why lean individuals develop hepatic fat accumulation and atherogenic profiles absent overt obesity. Ultimately, randomized clinical trials of targeted therapies in lean MAFLD are needed to establish evidence-based strategies for reducing cardiovascular morbidity and mortality in this underrecognized population.

In sum, MAFLD should no longer be viewed through the lens of body weight alone. Even individuals with BMI within normal limits can harbor significant metabolic and vascular derangements that predispose them to adverse cardiovascular outcomes. A holistic risk assessment that transcends traditional anthropometrics—embracing direct measurement of insulin resistance, systemic inflammation, endothelial dysfunction, and subclinical atherosclerosis—will enable early identification of high-risk patients and lead to tailored interventions aimed at improving both hepatic and cardiovascular health.

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