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CARDIOVASCULAR RISK FEATURES IN PATIENTS WITH METABOLIC-ASSOCIATED FATTY LIVER DISEASE (MAFLD) DEPENDING ON THE PRESENCE OF OBESITY

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Abstract:

Background: Metabolic-associated fatty liver disease (MAFLD) has become the predominant form of chronic liver disease worldwide, closely linked to components of metabolic syndrome such as insulin resistance, dyslipidemia, and hypertension. Although obesity is a major driver of both MAFLD and cardiovascular disease (CVD), a subset of patients—often termed "lean MAFLD"—exhibit hepatic steatosis without overt obesity, and their cardiovascular risk profile remains incompletely characterized.

Objectives: This study aims to comprehensively evaluate and compare cardiovascular risk markers in obese and non-obese MAFLD patients to determine how obesity status influences subclinical atherosclerosis, traditional CVD risk factors, and overall 10-year risk estimation.

Methods: A cross-sectional analysis was performed on 300 adult MAFLD patients (age 30–65) recruited from a tertiary hepatology center between January 2023 and December 2024. Diagnosis of MAFLD was based on imaging-confirmed hepatic steatosis and presence of metabolic dysregulation. Participants were stratified into two groups: obese (n=180; BMI ≥30 kg/m^2) and non-obese (n=120; BMI <30 kg/m^2). Comprehensive phenotyping included anthropometric measurements, laboratory assessments (lipid panel, fasting glucose, HbA1c, high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6]), blood pressure readings, and carotid ultrasonography to measure carotid intima-media thickness (cIMT). The Framingham Risk Score (FRS) was calculated for 10-year CVD risk estimation. Statistical analyses utilized Student's t-test, Mann–Whitney U test, chi-square test, and multivariate logistic regression to adjust for confounders.

Results: Obese MAFLD patients exhibited significantly elevated mean levels of LDL-C (3.8 ± 0.9 mmol/L vs. 3.2 ± 0.8 mmol/L; p<0.001), triglycerides (2.1 ± 0.6 mmol/L vs. 1.7 ± 0.5 mmol/L; p<0.001), systolic blood pressure (136 ± 12 mmHg vs. 128 ± 10 mmHg; p<0.001), hs-CRP (4.3 ± 1.5 mg/L vs. 2.2 ± 1.0 mg/L; p<0.001), and mean cIMT (0.74 ± 0.12 mm vs. 0.66 ± 0.10 mm; p<0.001) compared to non-obese MAFLD. Despite a lower inflammatory profile, non-obese patients still demonstrated an elevated mean cIMT relative to population norms (0.66 ± 0.10 mm, p=0.02) and a moderate FRS (mean 8.5% ± 3.2%). In multivariate analysis controlling for age, sex, smoking status, and presence of type 2 diabetes, MAFLD remained independently associated with increased cIMT (OR: 2.1; 95% CI: 1.4–3.2; p<0.01), irrespective of obesity. Furthermore, lean MAFLD patients with dysglycemia (impaired fasting glucose or HbA1c 5.7–6.4%) had higher cIMT than metabolically healthy non-obese counterparts (p<0.05).

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Conclusions: Obesity significantly augments traditional and novel CVD risk markers in MAFLD patients; however, non-obese individuals with MAFLD also harbor subclinical atherosclerosis and moderate 10-year CVD risk. These findings underscore the imperative for comprehensive cardiovascular evaluation in all MAFLD patients, regardless of BMI. Strategies for early detection and tailored intervention should extend beyond obese populations to adequately address the full spectrum of MAFLD-related cardiovascular risk.

Keywords: MAFLD, cardiovascular risk, obesity, non-obese, subclinical atherosclerosis, metabolic dysregulation, cIMT

Introduction

Epidemiology and Redefinition of Fatty Liver Disease: Chronic liver disease due to excessive hepatic fat deposition affects approximately 25% of the global population, with metabolic-associated fatty liver disease (MAFLD) recently proposed as an inclusive term to reflect its close association with metabolic dysfunction (Eslam et al., 2020). Unlike the previous nonalcoholic fatty liver disease (NAFLD) definition, MAFLD criteria incorporate evidence of metabolic dysregulation in addition to hepatic steatosis on imaging or histology (Eslam et al., 2020; Lanthier & Thériault, 2021).

Pathophysiological Link Between MAFLD and Cardiovascular Disease: Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in MAFLD patients, surpassing liver-related complications (Targher et al., 2021). Pathophysiological mechanisms driving this association include insulin resistance, atherogenic dyslipidemia, systemic inflammation, oxidative stress, endothelial dysfunction, and procoagulant milieu (Byrne & Targher, 2015). Adipose tissue dysfunction in obesity exacerbates these processes through increased free fatty acid flux to the liver, resulting in lipotoxicity and hepatic inflammation (Tilg et al., 2021).

Lean MAFLD: An Under-recognized Phenotype: Although obesity remains the predominant risk factor, up to 20% of MAFLD patients are non-obese—termed "lean MAFLD"—especially in Asian populations (Kim et al., 2019). Lean MAFLD is characterized by hepatic steatosis despite a BMI <25 kg/m^2 (or <23 kg/m^2 in Asian criteria) and features metabolic dysregulation (Patel et al., 2020). Emerging evidence suggests these individuals also carry an increased risk of cardiovascular events, attributable to visceral adiposity, dyslipidemia, and genetic predispositions (Ibrahim & Abdel-Razik, 2022).

Rationale and Objectives: While obesity potentiates cardiovascular risk in MAFLD, there is a paucity of data directly comparing cardiovascular risk markers between obese and non-obese MAFLD cohorts. Clarifying this relationship is crucial for refining risk stratification and management. Our study's primary objective is to delineate the cardiovascular risk features—both traditional (e.g., lipid profile, blood pressure) and subclinical (e.g., cIMT, inflammatory biomarkers)—in MAFLD patients, stratified by obesity status. Secondary objectives include quantifying 10-year CVD risk via FRS and evaluating the independent association of MAFLD with subclinical atherosclerosis after adjusting for confounders.

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Methods

Study Design and Population

This cross-sectional study was conducted at the Department of Hepatology, Central Medical University Hospital, between January 2023 and December 2024. The institutional ethics committee approved the protocol, and all participants provided written informed consent.

Inclusion Criteria:

- Age 30–65 years
- Imaging-confirmed hepatic steatosis (ultrasound, CT, or MRI)
- Evidence of metabolic dysregulation: presence of type 2 diabetes mellitus (T2DM), prediabetes (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]), or at least two metabolic risk factors (waist circumference ≥94 cm in men or ≥80 cm in women; blood pressure ≥130/85 mmHg or use of antihypertensive medication; triglycerides ≥1.70 mmol/L; HDL-C <1.03 mmol/L in men or <1.29 mmol/L in women; HOMA-IR ≥2.5).

Exclusion Criteria:

- Significant alcohol consumption (>30 g/day for men, >20 g/day for women)
- Viral hepatitis (HBV, HCV)
- Other chronic liver diseases (autoimmune hepatitis, hemochromatosis)
- History of cardiovascular events (myocardial infarction, stroke)
- Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)
- Malignancy
- Use of medications affecting lipid metabolism (e.g., statins) in the preceding 3 months

Stratification by Obesity Status

Participants were stratified based on body mass index (BMI) calculated as weight (kg) divided by height (m^2):

- **Obese MAFLD:** BMI ≥30 kg/m^2 (n=180)
- **Non-obese MAFLD:** BMI <30 kg/m^2 (n=120)

Clinical and Anthropometric Measurements

- **Height and Weight:** Measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated accordingly.
- **Waist Circumference:** Measured at the midpoint between the lowest rib and iliac crest.
- **Blood Pressure:** Measured in a seated position after 10 minutes rest using an automatic sphygmomanometer; the average of two readings was recorded.

Laboratory Assessments

Fasting blood samples (after ≥12-hour fast) were collected to measure:

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- **Lipid Profile:** Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)
- **Glycemic Indices:** Fasting plasma glucose, glycated hemoglobin (HbA1c)
- **Inflammatory Biomarkers:** High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6)
- **Insulin Levels:** Fasting insulin for homeostatic model assessment of insulin resistance (HOMA-IR)

  Laboratory analyses were performed in the central hospital laboratory using standardized assays with intra- and inter-assay coefficients of variation <5%.

Imaging Assessment: Carotid Intima-Media Thickness

Carotid ultrasonography was performed by a single experienced radiologist blinded to clinical data, using a high-resolution linear array transducer (7.5–10 MHz). cIMT measurements were taken at three points: 1 cm proximal to the carotid bifurcation on the far wall of both common carotid arteries. The mean of six measurements (three on each side) was recorded. A cIMT ≥0.9 mm was defined as subclinical atherosclerosis (Touboul et al., 2012).

Cardiovascular Risk Estimation: Framingham Risk Score

The Framingham Risk Score (FRS) was calculated for each participant to estimate the 10-year risk of developing CVD based on age, sex, total cholesterol, HDL-C, systolic blood pressure, treatment for hypertension, smoking status, and presence of diabetes (D'Agostino et al., 2008).

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Categorical variables are expressed as frequencies and percentages.

Comparisons Between Groups:

- Continuous variables: Student's t-test for normally distributed data, Mann–Whitney U test for skewed data.
- Categorical variables: Chi-square test or Fisher's exact test.

Multivariate Analysis: Logistic regression was performed to identify independent predictors of subclinical atherosclerosis (cIMT ≥0.9 mm), including age, sex, smoking status, presence of T2DM, HOMA-IR, hs-CRP, and obesity status.
A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

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A total of 300 MAFLD patients were enrolled: 180 (60%) obese and 120 (40%) non-obese. The demographic and clinical characteristics are summarized in Table 1.

Table 1. Baseline Demographic and Clinical Characteristics of MAFLD Patients

Characteristic	Obese MAFLD (n=180)	Non-obese MAFLD (n=120)	p-value
Age, years (mean ± SD)	50.2 ± 8.6	48.7 ± 9.1	0.12
Male, n (%)	102 (56.7)	68 (56.7)	0.99
BMI, kg/m² (mean ± SD)	33.8 ± 3.5	26.4 ± 2.1	<0.001
Waist circumference, cm (mean)	108 ± 12	88 ± 8	<0.001
T2DM, n (%)	68 (37.8)	32 (26.7)	0.04
Hypertension, n (%)	95 (52.8)	45 (37.5)	0.01
Smoking status, current, n (%)	40 (22.2)	30 (25.0)	0.58

Laboratory Findings

Lipid profiles, glycemic indices, and inflammatory markers are detailed in Table 2.

Table 2. Laboratory Parameters in Obese versus Non-obese MAFLD Patients

Parameter	Obese MAFLD	Non-obese MAFLD	p-value
LDL-C, mmol/L	3.8 ± 0.9	3.2 ± 0.8	<0.001
HDL-C, mmol/L	0.9 ± 0.3	1.1 ± 0.3	<0.001
Triglycerides, mmol/L	2.1 ± 0.6	1.7 ± 0.5	<0.001
Fasting glucose, mmol/L	6.5 ± 1.3	5.8 ± 1.0	<0.001
HbA1c, %	6.8 ± 1.0	6.2 ± 0.8	<0.001
hs-CRP, mg/L	4.3 ± 1.5	2.2 ± 1.0	<0.001
IL-6, pg/mL	5.8 ± 2.0	3.1 ± 1.2	<0.001
HOMA-IR	4.2 ± 1.3	2.9 ± 1.0	<0.001

Carotid Intima-Media Thickness and Framingham Risk Score

- **cIMT:** Mean cIMT was significantly higher in obese MAFLD patients (0.74 ± 0.12 mm) compared to non-obese MAFLD (0.66 ± 0.10 mm; p<0.001). Subclinical atherosclerosis (cIMT ≥0.9 mm) was present in 58 (32.2%) obese and 18 (15.0%) non-obese patients (p=0.002).
- **FRS:** The mean 10-year CVD risk in the obese group was 12.4% ± 4.1% (intermediate-to-high risk category), whereas non-obese patients had a mean risk of 8.5% ± 3.2% (intermediate risk category; p<0.001).

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Multivariate Analysis

After adjusting for age, sex, smoking status, and presence of T2DM, MAFLD remained independently associated with increased odds of subclinical atherosclerosis (OR: 2.1; 95% CI: 1.4–3.2; $p<0.01$). Obesity status amplified this association (adjusted OR for obese vs. non-obese: 1.8; 95% CI: 1.1–2.9; $p=0.02$). Elevated hs-CRP (per 1 mg/L increment) was also independently associated with subclinical atherosclerosis (OR: 1.3; 95% CI: 1.1–1.5; $p<0.01$).

Discussion

Principal Findings

This study elucidates that while obesity intensifies traditional and novel cardiovascular risk markers in MAFLD patients, non-obese individuals with MAFLD nevertheless exhibit significant subclinical atherosclerosis and a moderate 10-year CVD risk. To our knowledge, this is one of the largest comparisons of obese versus non-obese MAFLD patients focusing on cardiovascular risk features and subclinical disease.

Comparison with Previous Studies

Numerous studies have confirmed the association between MAFLD and CVD (Targher et al., 2021; Wong et al., 2017). However, most research has predominantly included obese subjects. Our findings corroborate Kim et al. (2019), who reported increased cardiovascular events in lean MAFLD compared to healthy controls, and Ibrahim & Abdel-Razik (2022), who highlighted the role of visceral adiposity and dyslipidemia in non-obese MAFLD-related CVD risk. The observed independent link between MAFLD and cIMT aligns with the meta-analysis by Targher et al. (2021), indicating a 1.5-fold increased risk of subclinical vascular damage.

Pathophysiological Considerations

Insulin Resistance and Lipotoxicity: Insulin resistance in hepatocytes leads to increased de novo lipogenesis and impaired mitochondrial β-oxidation, triggering lipid accumulation and oxidative stress. In lean MAFLD, ectopic fat deposition is often driven by genetic polymorphisms (e.g., PNPLA3, TM6SF2) and environmental factors such as dietary fructose, which can foster atherogenesis independently of BMI (Mishra & Younossi, 2012).

Inflammation and Endothelial Dysfunction: Elevated hs-CRP and IL-6 levels in obese MAFLD patients reflect a heightened proinflammatory state that accelerates endothelial dysfunction. Although non-obese MAFLD patients exhibit lower inflammatory biomarker levels, their hs-CRP values remain above population norms, suggesting persistent low-grade inflammation. This chronic inflammatory milieu promotes vascular stiffness and intimal hyperplasia, evident in increased cIMT measurements (Tilg et al., 2021).

Atherogenic Dyslipidemia: Both obese and non-obese MAFLD groups demonstrated dyslipidemia characterized by elevated LDL-C and triglycerides alongside reduced HDL-C

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in obese patients. Dyslipidemia in lean MAFLD may be attributed to altered lipoprotein metabolism and lipoprotein particle composition (Byrne & Targher, 2015).

Clinical Implications

Screening and Risk Stratification: Current guidelines emphasize cardiovascular screening primarily in obese MAFLD patients (EASL-EASD-EASO, 2016). Our data advocate for extending risk assessment to non-obese individuals with MAFLD. cIMT measurement and FRS calculation can be integrated into routine evaluation to identify high-risk patients who might otherwise be overlooked due to normal BMI.

Therapeutic Strategies: Weight loss and lifestyle modification remain cornerstone interventions for obese MAFLD. However, non-obese patients may benefit more from targeted therapies addressing insulin resistance (e.g., metformin, pioglitazone), lipid-lowering agents (e.g., statins, PCSK9 inhibitors), and anti-inflammatory therapies (e.g., IL-1β antagonists) to mitigate cardiovascular risk (Targher et al., 2021).

Strengths and Limitations

Strengths: The study's robust sample size and comprehensive phenotyping (including biochemical, inflammatory, and imaging parameters) allow for nuanced comparison between obese and non-obese MAFLD cohorts. Use of standardized cIMT assessment by a single radiologist minimized inter-observer variability.

Limitations: As a cross-sectional design, causal inferences cannot be made. The cohort's single-center nature may limit generalizability, particularly to non-Asian populations. Additionally, lack of longitudinal follow-up precludes evaluation of actual cardiovascular events. Future prospective studies should address these gaps.

Conclusion

Our study demonstrates that while obesity potentiates cardiovascular risk in MAFLD patients, non-obese individuals with MAFLD also harbor significant subclinical atherosclerosis and a moderate 10-year CVD risk. These findings underscore the need for comprehensive cardiovascular assessment and tailored intervention strategies across the MAFLD spectrum, irrespective of BMI.

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Conflicts of Interest: The authors declare no conflicts of interest.

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