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ORIGINAL RESEARCH

Markers Of Insulin Resistance and Their Clinical Implications In Patients with Type 2 Diabetes and Metabolic Dysfunction-Associated Steatotic Liver Disease

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Background: Insulin resistance, type 2 diabetes (T2D), and metabolic dysfunction-associated steatotic liver disease (MASLD) are pathogenically interconnected conditions, being part of a dysfunctional metabolic continuum that explains the high frequency of MASLD in patients with T2D.

Purpose: The present study evaluated the prevalence of MASLD in patients with T2D and identified key risk factors. We correlated MASLD with insulin resistance and other cardiovascular risk factors to determine cutoff values for increased hepatic steatosis risk.

Methods: We cross-sectionally evaluated 256 T2D patients (median age 63.5 years, 54.3% female) admitted to a regional diabetes center. MASLD diagnosis was based on FibroScan Echosens and standard clinical criteria. We recorded comorbidities and metabolic parameters, and calculated insulin resistance indexes, including TyG and METS-IR scores. We correlated MASLD with insulin resistance and other cardiovascular risk factors to determine cutoff values for increased hepatic steatosis risk.

Results: MASLD was present in 87.5% (95% CI: 76.4–99.7) of patients. TyG index and METS-IR showed statistically significant associations with MASLD presence, and ROC analysis indicated moderate discrimination (AUC values 0.80–0.86). ROC analysis identified HbA1c >7.2% as a discriminative threshold for MASLD, but predictive accuracy was modest (AUC 0.696).

Conclusion: In patients with T2D, suboptimal glycemic control and insulin resistance are associated with MASLD and fibrosis. Insulin resistance markers, TyG and METS-IR, were significantly associated with MASLD and showed moderate discriminative capacity in ROC analysis, suggesting potential value for screening. Incorporating these indices into routine assessment may improve identification of high-risk patients and guide timely interventions to prevent disease progression.

Keywords: metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steato-hepatitis, type 2 diabetes, insulin resistance

Introduction

Diabetes mellitus is a chronic condition that generates high costs and a high mortality rate, and that is associated with numerous complications and comorbidities, being considered the equivalent of a cardiovascular (CV) disease. New estimates predict that the number of people with diabetes will increase to at least 853 million in 2050.[1,2]

Metabolic dysfunction-associated steatotic liver disease (MASLD), and type 2 diabetes (T2D) are two interconnected metabolic dysfunctions that share similar risk factors, such as obesity, sedentary lifestyle, and unhealthy diet. MASLD is considered the hepatic manifestation of insulin resistance, the main pathophysiological mechanism in T2D.[3,4]

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MASLD includes a broad spectrum of liver diseases, from simple steatosis (fat loading of liver cells) to steatohepatitis and advanced liver fibrosis or liver cirrhosis in the absence of significant alcohol consumption.[5,6] It represents the main chronic liver disease in various geographical areas and especially in developed countries (it generally affects 20–30% of the adult population and 10% of children). It is associated with the modern lifestyle, characterized by reduced physical activity and unhealthy eating patterns, such as the Western diet high in saturated fats, simple sugars, and ultra-processed foods, with low fiber intake. The prevalence of MAFLD is higher (>50%) in patients with diabetes, obesity, or dyslipidemia.[7–9]

Metabolically-dysfunction-associated steatohepatitis (MASH), is the most severe form of MASLD. It typically occurs due to a metabolic disorder, resulting in a toxic accumulation of fat in the liver.[10]

Several mechanisms have been identified that cause liver damage in patients with diabetes. The primary causes of inflammation and fibrosis may include hyperinsulinemia secondary to insulin resistance, abnormalities in the PPAR gamma receptor, and mitochondrial dysfunction. Insulin resistance and the development of hyperglycemia, along with compensatory hyperinsulinemia, are the primary triggers. Disturbances in carbohydrate, protein, and lipid metabolism increase oxidative stress, triggering the inflammatory cascade.[11–13] Diabetes causes mitochondrial changes, characterized by reduced mitochondrial cristae density, pyknotic nuclei, and damaged nuclear membranes.

Additionally, there is increased lipid accumulation and decreased liver glycogen. The increased production of free radicals triggers hepatocyte apoptosis by releasing inflammatory cytokines, which, in turn, leads to increased expression of adhesion molecules and leukocyte infiltration. The liver is equipped with powerful antioxidants, including superoxide dismutase (SOD), catalase (CAT), and the glutathione (GSH) family of enzymes, such as glutathione-S-transferases (GST) and glutathione peroxidases (GPX). These neutralize free radicals and protect liver cells from oxidative damage. Hyperglycemia leads to decreased SOD and CAT levels, accompanied by increased free radicals, which contribute to liver damage through oxidative stress.[14–17]

Increased triglyceride values and small and dense LDL-c particles are common features of dyslipidemia in patients with diabetes and hepatic steatosis. These are due to lipolysis, leading to increased circulating fatty acid levels. The accumulation of circulating fatty acids disrupts mitochondrial β-oxidation, leading to fatty infiltration of the liver. The strong association between insulin resistance and hepatic steatosis makes diabetes an independent risk factor for cirrhosis and hepatocarcinoma in these patients.[18–20]

Chronic inflammation, through the release of pro-inflammatory cytokines TNF-α, interleukin (IL)-1β, and IL-6, causes liver tissue destruction, fibrosis, and loss of cellular function.[11,21]

MASH is a dynamic liver disease associated with obesity, insulin resistance, and dyslipidemia. It involves fat loading of hepatocytes, inflammation, and progression to advanced cirrhosis with increased morbidity and mortality. The key seems to be insulin resistance, which increases the influx of free fatty acids, and persistent hyperglycemia further accentuates lipotoxicity and glucotoxicity.[22–25]

Beyond the overlap of classical risk factors, the relationship between MASLD and T2D is mediated by subtle alterations in hepatic signaling pathways, including SREBP-1c, AMPK, and ChREBP, which regulate fatty acid synthesis and oxidation. Despite insulin resistance, there is selective hepatic lipogenesis, in which insulin fails to suppress gluconeogenesis but continues to stimulate de novo lipogenesis and hepatic triglyceride accumulation.[26,27]

Recent data highlight the central role of intestinal dysbiosis in linking glycemic control to MASLD activity by altering barrier permeability, translocating lipopolysaccharide (LPS) and microbial metabolites into the liver, and modifying bile acid supply, thereby impacting FXR/TGR5 signaling. Dysregulation of branched-chain amino acid (BCAA) metabolism, mediated in part by the microbiota, is associated with increased circulating BCAA levels, chronic low-grade inflammation, and concomitant worsening of insulin resistance and MASLD severity.[28,29]

In addition, the socio-metabolic context of our region is characterized by a high prevalence of metabolic syndrome and obesity, driven by dietary patterns rich in saturated fats, red meat, and sugary drinks, as well as by low intake of vegetables and fruits and low levels of physical activity. Romanian population studies have highlighted a combination of behavioral and socio-demographic factors (low educational level, rural environment, sedentary lifestyle) that favor metabolic dysfunction. Thus, our results on the T2D–MASLD link should be interpreted in this high-risk setting.[30,31]

The primary objective of our study was to determine the prevalence of MASLD in patients with T2D and to identify key risk factors. We correlated MASLD with insulin resistance and other cardiovascular risk factors to determine cutoff values for increased hepatic steatosis risk.

Materials and Methods

The Study Design and Patients

The study group consisted of 749 people admitted to the Diabetes, Nutrition and Metabolic Diseases Clinic of the "Pius Brînzeu" County Emergency Clinical Hospital in Timișoara between December 2024 and May 2025. According to the selection criteria (previously confirmed T2D, HbA1c > 6.5%, age> 18 years), 256 patients with T2D were included and analyzed in a cross-sectional design. The median age of participants was 63.5 years (range: 40–84 years), and the median duration of diabetes was 10.5 years (range: 1–31 years).

Those selected for the study already had a diagnosis of T2D and underwent periodic evaluations at the Diabetes Center, according to local standard care protocols, at 3 or 6-month intervals, depending on the severity of the case. The investigations were conducted in accordance with the principles set out in the Declaration of Helsinki, version 2013. The participants provided written consent to participate in the research, and the study protocol received approval from the Ethics Committee of the Timișoara County Emergency Clinical Hospital (number 518/30.12.2024). The writing of this manuscript was carried out in compliance with the STROBE recommendations for observational studies.

Patients under 18 years of age, those with a body mass index (BMI) below 18.5 kg/m^2 (where malnutrition and secondary etiologies of liver disease could alter the metabolic assessment and mechanisms of MASLD), and individuals with severe anemia (hemoglobin ≤ 7 g/dL) were excluded from the study. Individuals with a history of viral hepatitis, autoimmune hepatitis, liver tumors, drug-induced liver disease (such as those induced by amiodarone, corticosteroids, tamoxifen, methotrexate, antiepileptics, antiretrovirals, oral contraceptives, statins, or supplements with potential hepatotoxic effects), hepatolenticular degeneration, excessive alcohol consumption, severe hepatic or renal insufficiency, or relevant neurological or psychiatric diseases were also excluded.

Antidiabetic therapeutic regimens were recorded at the time of the index assessment. Patients included in the study were receiving metformin plus at least one other molecule from different therapeutic classes: GLP-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, sulfonylureas, or insulin. Due to the diversity of therapeutic regimens (combining 2, 3, or even 4 molecules), the study group was divided into four subgroups, depending on the molecule administered for the longest period at the time of inclusion: GLP-1 agonists (115/256; 45%), SGLT2 inhibitors (50/256; 19.5%), sulfonylureas or DPP-4 inhibitors (50/256; 19.5%), and insulin (41/256; 16.0%).

The primary objective was to assess the frequency of MASLD (metabolic steatotic liver disease) and its correlation with insulin resistance– related parameters: body mass index, HbA1c, TyG, and METS-IR. Secondary analyses examined the relationship between MASLD and diabetes complications, liver fibrosis, and various laboratory values.

Medical Assessments

In the study, demographic data such as gender, age, duration of diabetes, and anthropometric indicators (weight, height, BMI) were collected. Patients were questioned regarding alcohol consumption, smoking, and physical activity. Lipid profiles and renal function (estimated glomerular filtration rate, eGFR, and urinary albumin/creatinine ratio, UACr) were also analyzed. Glycemic control was assessed by determining blood glucose (fasting and postprandial) and glycated hemoglobin (HbA1c).

Diabetes complications were screened for micro- and macroangiopathy. Both laboratory analyses and specific imaging investigations were performed to assess liver status. The biochemical assessment also included alanine aminotransferase – ALT, aspartate aminotransferase – AST, C-reactive protein, CRP, fibrinogen, erythrocyte sedimentation rate, ESR, cholinesterase, albumin, gamma-glutamyltransferase, GGT, total bilirubin, TB, alkaline phosphatase, ALP.

Abdominal ultrasound and transient elastography (FibroScan Echosens, France) were performed by an experienced operator, with manufacturer-certified training, with patients in a fasting state, obtaining a minimum of 10 valid measurements, with an IQR/median ratio <30%, in accordance with current recommendations, to ensure the reliability of CAP and liver stiffness values. We categorized fibrosis into four stages: F0-F1, no fibrosis (≤ 8.2 kPa), F2, mild fibrosis (8.3–9.7 kPa), F3, moderate fibrosis (9.8–13.6 kPa), and F4, severe fibrosis, cirrhosis, permanent scarring, and irreversible damage (>13.6 kPa).[32] Additionally, using FibroScan, we quantified steatosis using the non-invasive controlled attenuation parameter (CAP) method, expressed in decibels per meter (dB/m). Liver steatosis was defined as CAP ≥ 248 dB/m; mild steatosis, CAP 248–268 dB/m, moderate 268–280 dB/m, and severe steatosis is defined as CAP ≥ 280 dB/m.[33]

The diagnostic criteria for MASLD consisted of identifying hepatic steatosis associated with the presence of at least one of the following five elements:

a) BMI ≥ 25 kg/m^2 or abdominal circumference > 94 cm in men and > 80 cm in women
b) Fasting blood glucose values (FPG) ≥ 100 mg/dL or 2-hour postprandial blood glucose ≥ 140 mg/dL or HbA1c ≥ 5.7%, or specific hypoglycemic drug treatment.
c) Systolic or diastolic blood pressure ≥ 130/85 mmHg, or use of antihypertensive treatment.
d) Serum triglycerides ≥ 150 mg/dL or specific treatment for hypertriglyceridemia.
e) HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women or specific treatment for dyslipidemia.[34]

The following markers were used to quantify insulin resistance:

1. Triglyceride–glucose (TyG) index = ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2];
2. Triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-c) = TG (mg/dl)/HDL-c (mg/dl);
3. Metabolic score for insulin resistance (METS-IR) = ln[(2 × FBG (mg/dL)) + TG (mg/dL)] × BMI (kg/m2))/(ln [HDL-C (mg/dL)][35–37]

Statistical Analysis

The statistical analysis was conducted using MedCalc Statistical Software version 20.211 (MedCalc Software Ltd., Ostend, Belgium, 2023, https://www.medcalc.org). The minimum sample size required for the ROC analysis was calculated using MedCalc, based on an expected AUROC of 0.75, alpha (α)=0.05, and 80% power, with the actual group structure and the following assumptions: normal distribution, approximately equal variances, and α level of 0.05. Continuous variables were presented as mean ± standard deviation or median (IQR), and categorical variables as numbers and percentages. For comparisons between two groups, the t or Mann–Whitney test was used, depending on the distribution. The Kruskal–Wallis test was used for more than two nonparametric groups. Pearson correlation analysis, logistic regression, and linear multivariate regression with stepwise selection were used to assess associations among variables. Multicollinearity was checked using variance inflation factors (VIF), and no significant collinearity was detected (all VIFs < 2). Optimal biomarker thresholds were determined by ROC analyses and the Youden index, with statistical significance at $p < 0.05$ and 95% confidence interval.

Results

Following the inclusion criteria, the study included 256 T2DM patients with a median age of 63.5 (40–84) years and a median diabetes duration of 10.5 (1–31) years, comprising 45.7% men (117/256) and 54.3% women (139/256). Glycemic control was suboptimal, as indicated by a median HbA1c of 8.4% (6.0; 12.3). Men had a statistically significantly higher weight than women, and women had a statistically significantly lower eGFR compared to men ($p < 0.001$) (Table 1).

The prevalence of MASLD was 87.50% (95% CI, 76.42–99.74%), diagnosed in 224 patients from the studied group, of whom 51.7% (116/224) were women ($p = 0.03$). Analyzing degrees of steatosis according to the CAP, we found that 136 patients (53.1%) had severe steatosis, 47 patients (18.4%) had moderate steatosis, 41 patients (16.0%) had mild steatosis, and 32 patients (12.5%) had no steatosis. Regarding fibrosis, it was present in 56.3% of patients. Specifically,

Table 1 Baseline Clinical and Biochemical Characteristics of the Study Population, Compared by Gender

Variable	Overall	Men (n=117)	Women (n=139)	p-value
Age (years) [a]	63.5 (40; 84)	62.0 (123.4)	65.0 (132.7)	NS
DM duration (years) [a]	10.5 (1; 31)	10.0 (125.1)	11.0 (131.2)	NS
Weight (kg) [a]	91.7 (51; 121)	95.5 (138.6)	88.0 (98.9)	p<0.0001
BMI (kg/m^2) [a]	32.1 (20; 42.8)	31.9 (128.0)	32.3 (128.9)	NS
HbA1c (%)[a]	8.4 (6.5; 12.3)	8.3 (134.6)	8.5 (122.3)	NS
FG (mg/dL) [a]	162.0 (107; 245)	163.0 (133.3)	161.0 (124.4)	NS
PPG (mg/dL) [a]	186.5 (101; 257)	187.0 (133.7)	186.0 (124.0)	NS
AST (U/L) [a]	51.0 (10; 128)	52.0 (134.3)	50.0 (123.6)	NS
ALT (U/L) [a]	53.5 (12; 143)	55.0 (135.7)	52.0 (122.4)	NS
TB (mg/dL) [a]	1.0 (0.2; 2.3)	1.1 (127.4)	1.08 (129.3)	NS
GGT (mg/dL) [a]	57.5 (8; 273)	59.0 (132.0)	56.0 (125.4)	NS
ALP (mg/dl) [a]	79.0 (29; 198)	82.0 (135.1)	76.0 (122.4)	NS
Cholinesterase (u/L) [a]	4776.5 (299; 9872)	4871.0 (130.7)	4621.0 (126.6)	NS
ESR (mm/h) [a]	20.0 (3; 83)	21.4 (127.4)	18.6 (126.7)	NS
CRP (mg/L) [a]	10.6 (2; 76)	10.3 (130.0)	11.0 (127.2)	NS
Fibrinogen (mg/dL) [a]	318.5 (104; 788)	317.0 (130.0)	321.0 (127.1)	NS
LDL (mg/dL) [a]	131.5 (12; 310)	131.0 (130.4)	132.0 (126.8)	NS
TG (mg/dL) [a]	197.5 (78; 497)	202.4 (138.7)	192.6 (134.6)	NS
HDL (mg/dL) [a]	38.0 (20; 64)	37.3 (120.7)	38.7 (135.0)	NS
Non-HDL cholesterol (mg/dL) [a]	191.0 (45; 382)	193.0 (130.7)	190.0 (126.6)	NS
Serum creatinine (mg/dL) [a]	1.0 (0,5; 2,9)	1.0 (131.7)	1.0 (125.7)	NS
eGFR (mL/min) [a]	68.0 (17; 127)	78.0 (154.6)	58.0 (106.5)	p<0.0001
UAC (mg/g) [a]	41.1 (2; 399)	39.0 (125.8)	43.3 (130.7)	NS
TG/HDLc [a]	5.5 (3.9; 7.7)	6.0 (142.2)	5.2 (116.9)	p= 0.006
TyG [b]	9.7±0.4	9.7±0.4	9.6±0.3	p= 0.02
METS-IR [b]	55.2±8.8	56.1±8.1	54.4±9.2	NS
SBP (mmHg) [b]	152.1± 21.9	153.9±22.3	151.3±21.5	NS
CAP (dB/m) [a]	281.0 (264.0;298.5)	285.0 (137.0)	279.0 (121.3)	NS
FibroScan (kPa) [a]	8.6 (7.3;10.2)	9.0 (134.6)	8.4 (123.2)	NS

Notes: [a] Mann–Whitney test; [b] t-Student test for sex differences. $p < 0.05$, statistically significant. Continuous variables with non-Gaussian distribution are described by their median (interquartile range in men and women columns, or 25–75 percentiles in the overall column) while those with Gaussian distribution are described by their mean and standard deviation.

Abbreviations: NS, not significant if $p > 0.05$, DM, diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; FG, fasting glycemia; PPG, postprandial glycemia; AST, Aspartate transaminase; ALT, Alanine transaminase; TB, Total bilirubin; GGT, Gamma-glutamyl transferase; ALP, Alkaline phosphatase; ESR, Erythrocyte sedimentation rate; CRP, C-Reactive Protein; LDLc, low-density lipoprotein cholesterol; TG, triglycerides; HDLc, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACr, urinary albumin/creatinine ratio; TyG, triglyceride–glucose index; METS-IR, metabolic score for insulin resistance, SBP, systolic blood pressure; CAP, controlled attenuation parameter.

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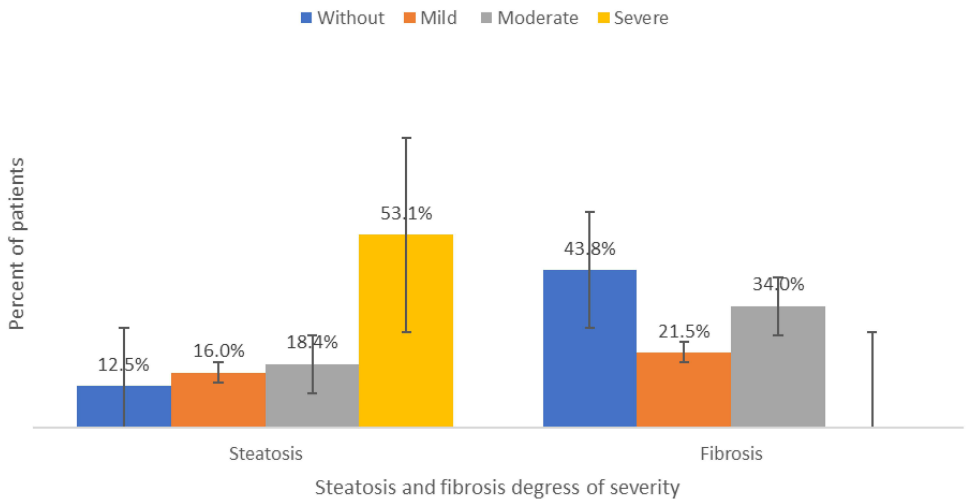

Figure 1 Distribution of steatosis and fibrosis by degrees in the studied group.

55 patients (21.5%) had mild fibrosis (F2), while 87 patients (34%) had moderate fibrosis (F3). Only two patients (0.8%) had severe fibrosis (F4) (Figure 1).

We compared patients' main parameters according to MASLD and found significant differences in most parameters. A post-hoc power analysis was conducted for the comparison of means between two independent groups using the *t*-test (two-tailed, two-sided), with a significance level of α=0.05. Calculations were performed using MedCalc (online calculator: https://www.medcalc.org/en/calc/post-hoc-power-analysis.php). For the main variables (BMI, HbA1c, TyG, METS-IR), we used the actual group sizes (MASLD: n=224; non-MASLD: n=32) and the observed means and standard deviations. All significant group differences observed confirm that the achieved power was sufficient. The patient profile with MASLD was characterized by higher body weight and BMI (mostly with obesity), poorer glycemic control (median HbA1c of 8%, with higher glycemic values in both fasting and postprandial conditions), elevated liver enzymes, ESR, altered lipid profile, and increased UACr (Table 2).

Analyzing insulin resistance markers, we found that they were statistically significantly higher in patients with MAFLD compared to those without MAFLD ($p < 0.001$), except for the coronary heart disease (CHD). We investigated the main diabetes-related complications in the study group. 30.5% (78/256) of patients had heart failure (HF), 42.5% (108/256) had CHD, 74.2% (190/256) had arterial hypertension (AHT), and 44.5% (114/256) had diabetic neuropathy (DN). The frequency was statistically significantly higher in patients with MASLD (Table 3).

Table 2 Comparison of the Studied Patients` Parameters by the Presence of MASLD

Variable	with MASLD (n= 224)	without MASLD (n= 32)	p[a]
Age (years) [a]	64.0 (132.5)	58.0 (99.9)	p= 0.01
Diabetes duration (years) [a]	11.0 (133.2)	8.0 (95.5)	p= 0.007
Weight (kg) [a]	91.0 (137.0)	79.5 (68.8)	p<0.0001
BMI (kg/m^2) [a]	32.5 (138.2)	27.8 (60.2)	p<0.0001
HbA1c (%)[a]	8.0 (134.0)	7.2 (84.0)	p< 0.0001
FG (mg/dL) [a]	163.0 (137.6)	137.5 (64.5)	p<0.0001
PPG (mg/dL) [a]	189.0 (141.7)	145.0 (35.6)	p<0.0001

(*Continued*)

Table 2 (Continued).

Variable	with MASLD (n= 224)	without MASLD (n= 32)	p[a]
AST (U/L) [a]	54.0 (139.5)	26.0 (50.8)	p<0.0001
ALT (U/L) [a]	55.5 (140.2)	26.5 (46.0)	p<0.0001
TB (mg/dL) [a]	1.1 (136.4)	0.8 (72.9)	p<0.0001
GGT (mg/dL) [a]	58.0 (131.7)	50.0 (105.6)	NS
ALP (mg/dl) [a]	78.0 (130.7)	72.5 (112.5)	NS
Cholinesterase (u/L) [a]	4826.5 (134.6)	3495.5 (85.7)	p<0.001
ESR (mm/h) [a]	20.5 (132.9)	14.0 (97.6)	p= 0.01
CRP (mg/L) [a]	11.0 (130.3)	7.0 (115.5)	NS
Fibrinogen (mg/dL) [a]	317.0 (127.8)	331.0 (132.9)	NS
LDL (mg/dL) [a]	136.5 (138.5)	87.0 (58.0)	p<0.001
TG (mg/dL) [a]	205.5 (138.1)	145.0 (60.8)	p<0.001
HDL (mg/dL) [a]	38.0 (119.4)	47.0 (191.5)	p<0.001
Non-HDL cholesterol (mg/dL) [a]	202.0 (142.3)	104.5 (31.6)	p<0.001
Serum creatinine (mg/dL) [a]	1.0 (132.3)	0.9 (101.2)	p= 0.02
eGFR (mL/min) [a]	63.0 (126.8)	75.5 (140.0)	NS
UACr (mg/g) [a]	43.1 (132.8)	30.7 (97.8)	p= 0.01
TG/HDLc [a]	5.8 (138.8)	3.0 (56.1)	p<0.001
TyG [b]	9.7±0.3	9.3±0.5	p<0.001
METS-IR [b]	56.6±8.1	45.3±6.3	p<0.001
FibroScan (kPa) [a]	9.0 (139.6)	6.3 (50.7)	p<0.001
CAP (dB/m) [a]	286.5 (144.5)	197.5 (16.5)	p<0.001

Notes: [a] Mann–Whitney test. [b] t-Student test. $p < 0.05$, statistically significant. Continuous variables with a non-Gaussian distribution are described by their median (interquartile range), while those with a Gaussian distribution are described by their mean and standard deviation.

Abbreviations: NS, not significant if $p > 0.05$, BMI, body mass index; HbA1c, glycated hemoglobin; FG, fasting glycemia; PPG, postprandial glycemia; AST, Aspartate transaminase; ALT, Alanine transaminase; TB, Total bilirubin; GGT, Gamma-glutamyl transferase; ALP, Alkaline phosphatase; ESR, Erythrocyte sedimentation rate; CRP, C-Reactive Protein; LDLc, low-density lipoprotein cholesterol; TG, triglycerides; HDLc, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACr, urinary albumin/creatinine ratio; TyG, triglyceride–glucose index; METS-IR, metabolic score for insulin resistance; SBP, systolic blood pressure; CAP, controlled attenuation parameter.

Table 3 Diabetes Complications Compared with the Presence of MASLD

Variable	without MASLD	with MASLD	Chi-squared value	p
CHD (%)	57.5	42.5	10.793	p= 0.001
AHT (%)	25.8	74.2	58.576	p<0.001
HF (%)	30.5	69.5	10.085	p= 0.001
PAD (%)	20.7	79.3	6.856	p<0.001

(*Continued*)

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Table 3 (Continued).

Variable	without MASLD	with MASLD	Chi-squared value	p
DR (%)	48	52	13.203	p<0.001
DN (%)	44.5	55.5	5.626	p= 0.01

Abbreviations: CHD, coronary heart disease; AHT, arterial hypertension; HF, heart failure; PAD, peripheral arterial disease; DR, diabetic retinopathy; DN, diabetic neuropathy.

In a correlation analysis, liver steatosis (CAP) was directly and significantly associated with TyG, METS-IR, and PPG (r = 0.4 for all). The liver fibrosis (FibroScan) was directly and moderately associated with TG/HDL, TyG, and PPG (r = 0.4 for all). Table 4 presents the correlations between liver steatosis (as assessed by CAP) and liver fibrosis (as measured by FibroScan), as well as the metabolic markers studied.

In univariate regression analysis, HbA1c was associated with liver fibrosis (FibroScan, r = 0.5, p < 0.001) and liver steatosis (CAP, r = 0.3, p = 0.03). We further conducted a multiple regression analysis to investigate the relationship between liver steatosis (as assessed by CAP), liver fibrosis (as measured by FibroScan), and metabolic biomarkers. The results are presented in Table 5. Both liver steatosis and liver fibrosis were directly associated with insulin resistance indexes (TyG and METS-IR) and HbA1c. Glycemic values, as evaluated by HbA1c, FG, and PPG, were associated with liver steatosis in a regression model.

To better understand the patient profile with liver fibrosis, we performed a stepwise logistic regression analysis, including the most significant variables as independent factors (HbA1c, TyG, METS-IR) and liver fibrosis as the dependent factor. For every one-unit increase in HbA1c, the risk of liver fibrosis nearly doubled, independent of other factors. A higher TyG score increased the risk of liver fibrosis by more than fourfold. In this analysis, METS-IR had a smaller, but statistically significant, effect on the risk of liver fibrosis. 31% of the variation in liver fibrosis among patients was explained by this statistical regression model, suggesting that other factors influence the risk of fibrosis. The results of the logistic regression analysis for predicting liver fibrosis are presented in Table 6.

Table 4 Correlations of Liver Steatosis (CAP) and Liver Fibrosis (FibroScan) with the Studied Metabolic Markers

Variable	r-value		p-value	
	CAP	FibroScan	CAP	FibroScan
FibroScan (kPa)	0.4	1	p< 0.001	p< 0.001
CAP (dB/m)	1	0.4	p< 0.001	p< 0.001
TG/HDL	0.3	0.4	p< 0.001	p< 0.001
TyG	0.4	0.4	p< 0.001	p< 0.001
METS-IR	0.4	0.3	p< 0.001	p< 0.001
Age (years)	0.1	0.1	p< 0.001	p< 0.001
Diabetes duration (years)	0.1	0.2	p< 0.001	p< 0.001
HbA1c (%)	0.3	0.5	p< 0.001	p< 0.001
FG (mg/dL)	0.3	0.3	p< 0.001	p< 0.001
PPG (mg/dL)	0.4	0.4	p< 0.001	p< 0.001
BMI (kg/m^2)	0.3	0.1	p< 0.001	p= 0.01

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; FG, fasting glycemia; PPG, postprandial glycemia; TG, triglycerides; HDLc, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACr, urinary albumin/creatinine ratio; TyG, triglyceride–glucose index; METS-IR, metabolic score for insulin resistance; CAP, controlled attenuation parameter.

Table 5 Multiple Linear Regression Analysis of the Relationship Between Liver Steatosis (CAP), Liver Fibrosis (FibroScan), and Metabolic Biomarkers

Independent Variables	Coefficient	Std. Error	t	p	$r_{partial}$	$r_{semipartial}$
Model: Liver steatosis (CAP) and insulin resistance						
(Constant)	−144.2					
TyG	34.7	6.4	5.4	p< 0.001	0.3	0.2
METS-IR	1.5	0.2	5.1	p< 0.001	0.3	0.2
Model: Liver steatosis (CAP) and glycemic control						
(Constant)	51.4					
HbA1c	12.6	3.2	3.8	p< 0.001	0.2	0.2
FG	0.3	0.1	2.1	p= 0.03	0.1	0.1
GPP	0.4	0.0	4.2	p< 0.001	0.2	0.2
Model: Liver fibrosis (FibroScan) and glycemic control						
(Constant)	−1.6					
HbA1c	1.2	0.1	9.4	p< 0.001	0.5	0.5
Model: Liver fibrosis (FibroScan) and insulin resistance						
(Constant)	−13.9					
TyG	2.1	0.3	6.9	p< 0.001	0.4	0.3
METS-IR	0.0	0.0	2.2	p= 0.02	0.1	0.1

Notes: Method stepwise, R^2-adjusted 0.27, multiple correlation coefficient 0.52, TG/HDL not included in the model, statistical significance for the model p<0.001. Method stepwise, R^2-Adjusted 0.24, multiple correlation coefficient 0.49. BMI, age, and diabetes duration were not included in the model. The model was statistically significant ($p < 0.001$). Method stepwise, R^2-Adjusted 0.25, multiple correlation coefficient 0.50. BMI, FG, PPG, age, and diabetes duration were not included in the model. The model was statistically significant ($p < 0.001$). Method stepwise, R^2-adjusted= 0.25, multiple correlation coefficient 0.49, TG/HDL not included in the model, statistical significance for the model p<0.001. If $p > 0.05$.
Abbreviation: NS, not significant.

Table 6 Logistic Regression Analysis for Predicting Liver Fibrosis

Variable	Coefficient	Std. Error	Wald	Odds Ratio	p
Constant	−22.5	4.0	31.5		p< 0.001
HbA1c	0.6	0.2	9.8	1.9	p= 0.001
TyG	1.5	0.4	11.1	4.5	p< 0.001
MetSIR	0.0	0.0	6.1	1.0	p= 0.01

Notes: Nagelkerke R^2= 0.31, p< 0.001.

We constructed ROC curve models to evaluate the main risk factors for developing MASLD. According to the ROC curve (AUROC=0.696, p = 0.002), HbA1c > 7.2% represents a statistically modest predictive factor of MASLD with a sensitivity of 93.3% and a specificity of 51.6% (Figure 2). Additionally, an HbA1c level greater than 7.7% is a statistically significant risk factor for fibrosis, with a sensitivity of 81.9% and a specificity of 55%, as indicated by the ROC curve (AUROC = 0.740, $p < 0.001$) (Figure 3).

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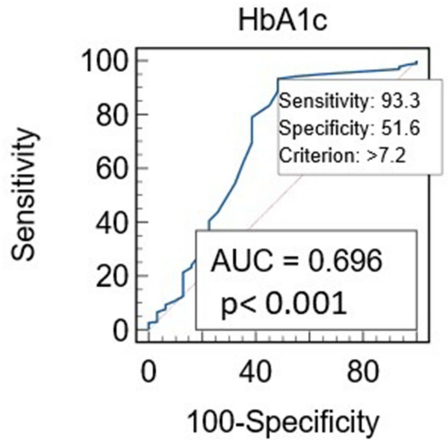

Figure 2 Graphical representation of the ROC curve of the HbA1c for MASLD.

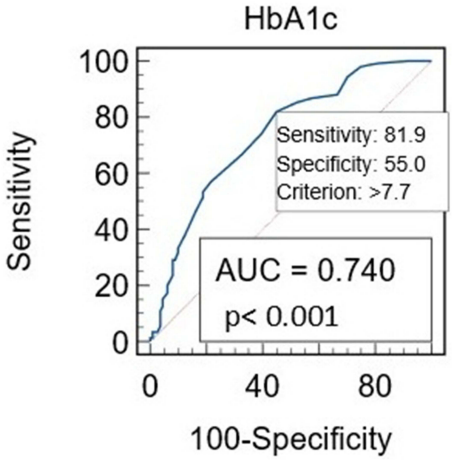

Figure 3 Graphical representation of the ROC curve of the HbA1c for liver fibrosis.

Analyzing the importance of insulin resistance markers in the occurrence and progression of MASLD, we found that the TyG index >9.26 represents a statistically significant predictive factor of MASLD, with a sensitivity of 93.7% and specificity of 71.9%, according to the ROC curve (AUROC = 0.805, p <0.001) presented in Figure 4. Another statistically significant predictive factor for MASLD was the METS-IR index greater than 48.12, with a sensitivity of 88.4% and specificity of 78.1%, as indicated by the ROC curve (AUROC = 0.860, p < 0.001) (Figure 5).

Discussion

Obesity, especially central obesity, is the main risk factor for MASLD. A meta-analysis investigating the role of central obesity in the occurrence of MASLD found odds ratios of 2.3 (95% CI, 1.8–3.0) for waist circumference and 2.85 (95% CI, 1.6–5.0) for BMI.[38]

A meta-analysis that included 80 studies from 20 countries conducted in patients with T2D to estimate the prevalence of MASLD, MASH, and advanced fibrosis evidenced the following: the prevalence of MASLD in patients with T2D was 55.5% (95% CI, 47.3 to 63.7), and the overall prevalence of MASH was 37.3% (95% CI, 24.7 to 50.0).[39]

The present study demonstrates that patients with MASLD had a significantly altered metabolic and clinical profile compared to those without MASLD. The MASLD subgroup exhibited higher body weight and BMI (91.0 vs 79.5 kg, p <

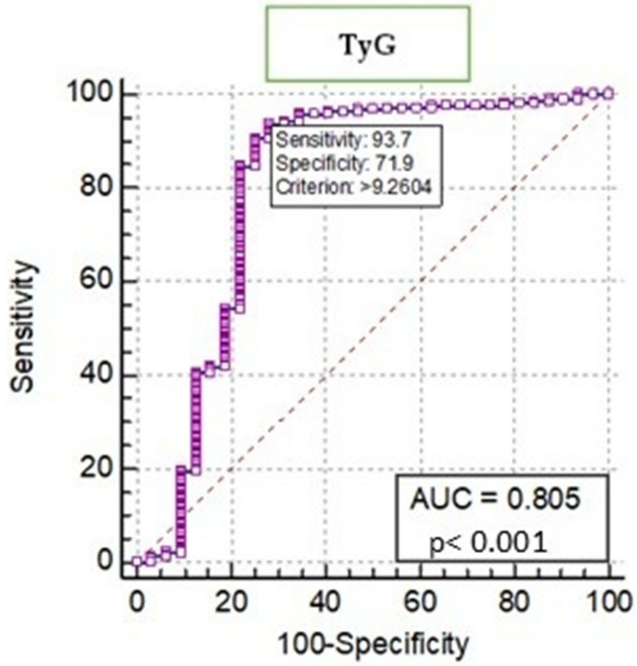

Figure 4 Graphical representation of the ROC curve of the TyG for MASLD.

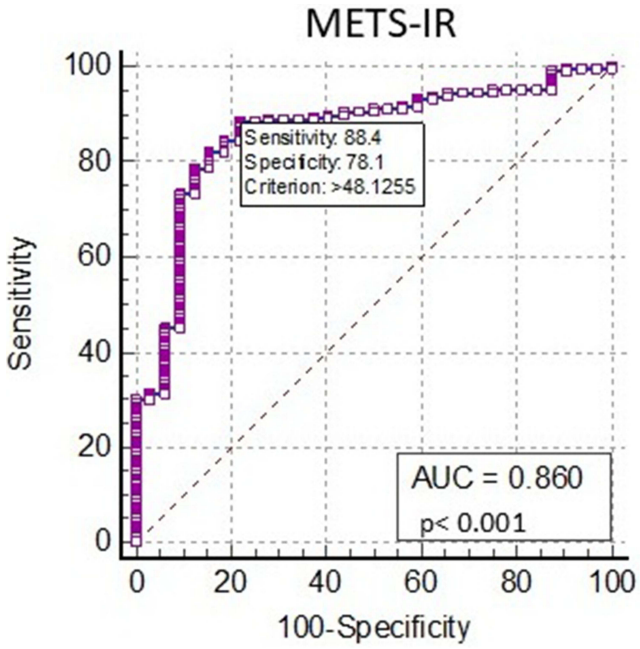

Figure 5 Graphical representation of the ROC curve of the MetSIR for MASLD.

0.001; 32.5 vs 27.8 kg/m^2, $p < 0.001$), reflecting a predominant association with obesity. Glycemic control was impaired, with higher HbA1c levels (8.0% vs 7.2%, $p < 0.001$), fasting glucose (163.0 vs 137.5 mg/dL, $p < 0.001$), and postprandial glucose (189.0 vs 145.0 mg/dL, $p < 0.001$), reinforcing the link between MASLD and diabetes-related dysglycemia.

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Free fatty acids (FFAs) contribute to insulin resistance by impairing the anti-lipolytic function and increasing hepatic TG synthesis. Saturated fatty acids generate intermediate lipotoxic products, such as diacylglycerols. This causes endoplasmic reticulum stress, leading to the production of reactive oxygen species (ROS), which play a major role in the pathogenesis of MASH. By binding to Toll-like receptor 4, saturated fatty acids induce increased mitochondrial dysfunction and activation of pro-inflammatory nuclear factor-kappa B (NF-κB).[19,40–43]

Liver biopsy remains the gold standard for diagnosing and staging MAFLD; however, it is less commonly used due to its invasive nature. Diagnostic methods such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used for screening and diagnosing MAFLD; however, they are expensive. Since insulin resistance plays an important role in the development of MAFLD and is linked to the progression of liver fibrosis, identifying markers of insulin resistance may represent the first step toward early diagnosis.[44]

Liver-related biomarkers were substantially elevated in MASLD, with AST and ALT more than doubling compared to controls ($p < 0.001$ for both), indicating hepatic injury. Bilirubin levels were also higher ($p < 0.001$), while inflammatory activity was indicated by an increased ESR ($p = 0.01$).

Fedchuk et al reported significant diagnostic accuracy of TyG in predicting steatosis, with an AUC of 0.902.[45] Zhang et al analyzed 6809 Chinese subjects with BMI < 25 kg/m^2 and found that TyG-BMI was more accurate in identifying MAFLD than the TyG index, with an AUC of 0.835.[46] In a study of 826 people with T2D, TyG-BMI (AUC = 0.727) was a better predictor of MAFLD than TyG, HOMA-IR, or the TG/HDL-c ratio. The predictive value of TyG-BMI for MAFLD was higher in persons with obesity than in those without obesity.[47]

In our research, the lipid profile of MASLD patients revealed atherogenic dyslipidemia, characterized by higher levels of LDL, triglycerides, and non-HDL cholesterol, and lower HDL levels (all $p < 0.001$). Insulin resistance markers, including the TG/HDL ratio, TyG, and METS-IR, were significantly elevated ($p < 0.001$), supporting the concept of MASLD as a hepatic manifestation of systemic insulin resistance. Additionally, renal impairment was more prevalent, as shown by higher UACr values ($p = 0.01$).

Correlation analyses further demonstrated significant associations between liver steatosis (as assessed by CAP) and fibrosis (as measured by FibroScan) with insulin resistance indices, glycemic control (as indicated by HbA1c, FG, and PPG), and BMI ($p < 0.001$ for all). HbA1c showed a moderate correlation with liver fibrosis ($r = 0.5$, $p < 0.001$), supporting a possible link between glycemic control and hepatic disease progression in this study population.

Complication rates were significantly higher in the MASLD group, including coronary disease, arterial hypertension, heart failure, peripheral arterial disease, retinopathy, and neuropathy (all $p \leq 0.01$). These findings emphasize the strong association between MASLD and both macrovascular and microvascular complications.

The logistic regression analysis identified three independent predictors of liver fibrosis: HbA1c, TyG index, and METS-IR. HbA1c was positively associated with fibrosis, with a coefficient of 0.6 ($p = 0.001$), corresponding to an odds ratio of 1.9. This indicates that each one-unit increase in HbA1c nearly doubles the risk of fibrosis. Similarly, the TyG index showed a strong association, with a coefficient of 1.5 and an odds ratio of 4.5 ($p < 0.001$), indicating that elevated TyG substantially increases the odds of fibrosis. METS-IR also contributed significantly ($p = 0.01$), although with a smaller effect size (odds ratio 1.0), reflecting its role as a broader marker of insulin resistance. The overall model demonstrated good explanatory power, with a Nagelkerke R^2 of 0.31 ($p < 0.001$).

ROC curve analysis provided further insights into the predictive value of these markers. For MASLD diagnosis, an HbA1c level greater than 7.2% was a significant cutoff (AUROC = 0.696, $p < 0.001$), with high sensitivity (93.3%) but modest specificity (51.6%). This highlights HbA1c as an effective screening tool, though with limited discriminatory capacity. When analyzing progression to fibrosis, a higher HbA1c threshold (>7.7%) achieved better predictive accuracy (AUROC = 0.740, $p < 0.001$), with sensitivity of 81.9% and specificity of 55%. These findings underscore the role of chronic hyperglycemia as a determinant not only for MASLD development but also for progression to advanced liver injury.

Insulin resistance markers, especially TyG and METS-IR, showed greater discrimination than HbA1c for MASLD detection in ROC analysis, suggesting that these indices may offer additional value for risk stratification. The TyG index >9.26 significantly predicted MASLD, with an AUROC of 0.805 ($p < 0.001$), a sensitivity of 93.7%, and a specificity of 71.9%. This suggests that TyG is both highly sensitive and clinically useful for identifying patients at risk. The METS-IR index with a value greater than 48.1 performed best, with an AUROC of 0.860 ($p < 0.001$), a sensitivity of 88.4%, and

a specificity of 78.1%, confirming its robustness as a predictive tool. Together, these indices reflect the critical role of insulin resistance in the pathogenesis of MASLD and its progression toward fibrosis. The observed differences, while notable, should be validated in future studies, including larger and more diverse populations.

Overall, these findings demonstrate that both HbA1c and insulin resistance indices (TyG, METS-IR) are significant predictors of MASLD and liver fibrosis. HbA1c remains a practical marker for clinical use, while TyG and METS-IR provide better accuracy for risk stratification. The integration of these markers may therefore enhance early detection and guide more personalized interventions in patients at risk for progression to MASLD.

In the Romanian study group investigated by Efrem et al,[48] TG > 184 mg/dL, AIP > 0.6, non-HDL/HDL ratio > 3.9, and HOMA-IR > 2.01 were identified as optimal cutoffs for MAFLD prediction in T2D patients. Our investigation extends these findings by evaluating novel, easy-to-calculate insulin resistance scores (METS-IR and TyG) and demonstrates moderate diagnostic performance in an independent population from Western Romania.

The molecular mechanisms by which hyperglycemia and insulin resistance, characteristic of T2D, activate inflammation and hepatic fibrosis can be explained by the interaction between Advanced Glycation End-products (AGEs) and the Receptor for Advanced Glycation End-products (RAGE). RAGE is a receptor present on the surface of many cells (hepatocytes, immune cells, hepatic stellate cells). Excess fatty acids and glucose promote protein glycation and the generation of AGEs, which, through activation of the RAGE receptor, intensify hepatic oxidative stress and trigger pro-inflammatory signals, oxidative stress, cellular dysfunction, and fibrotic proliferation.[49,50] The AGEs-RAGE axis perpetuates a vicious cycle of insulin resistance, chronic inflammation, and hepatic fibrosis, which is also correlated with the severity of steatosis, as indicated by the association between metabolic scores and the inflammatory phenotype observed in our study.

Study Limitations

One limitation of our study warrants discussion. Although the present study did not include the primary analysis of thyroid dysfunction, the literature demonstrates that hypothyroidism (both clinical and subclinical forms) represents an independent risk factor for the occurrence and progression of MASLD. The mechanisms involved include reduced basal metabolic rate, impaired fatty acid oxidation, increased adipocyte lipolysis, and insulin resistance, all of which favor hepatic lipid accumulation and stimulate oxidative stress. Elevated thyroid-stimulating hormone may induce steatosis by activating SREBP-1c transcription and dysregulating hepatic gluconeogenesis.[51,52] Given the increased frequency of hypothyroidism in the population with metabolic syndrome and T2D, screening and correction of thyroid dysfunction may have major therapeutic implications in the management of MASLD. Thus, to better understand the direct impact of thyroid function on the pathogenesis and progression of MASLD, it would be advisable to routinely assess thyroid function in patients with T2D and MASLD.

Recent literature highlights that pituitary axis deficiency – especially growth hormone (GH) and IGF-1 – has a significant impact on the progression of MASLD. GH deficiency is associated with central obesity, insulin resistance, and metabolic dysfunction, all of which are determinants of hepatic steatosis. GH and IGF-1 directly regulate hepatic metabolism, limiting lipid accumulation, oxidative stress, and promoting hepatocyte regeneration.[53] In most patients in our study, frank GH deficiency is unlikely; however, the phenotype of these patients partially overlaps with that of patients with GH deficiency—that is, both present with metabolic dysfunction, visceral adiposity, insulin resistance, and hepatic steatosis. In our study, the function of the GH/IGF-1 axis was not systematically evaluated; however, we believe these aspects warrant mention as possible secondary causes or cofactors in the progression of MASLD, especially in patients with known endocrine comorbidities.

A limitation of this study is the small number of patients without MASLD, which may limit the statistical power and validity of comparisons between groups. However, the study was not powered to robustly assess interaction or subgroup effects. The results regarding differences between patients with and without MASLD should be interpreted with caution, and further studies with more balanced samples are needed to confirm them. Post-hoc power analysis showed that the study has >80% power (α=0.05) to detect moderate differences between groups for the main markers assessed: BMI (~5 kg/m^2, SD=6.2), HbA1c (0.8%, SD≈1.5, power= 18.5%), TyG (0.4 units, SD≈0.5), and METS-IR (~11 points, SD≈8.5). The ROC power was ensured for variables with moderate-to-large effects and sufficient groups. However, for

variables with small groups (eg, HbA1c), it remained underpowered, and results should be interpreted with extra caution. The odds ratio values should be interpreted with caution, as the models were not internally validated and may be subject to some degree of overfitting.

An important limitation of the study is that we could not separately evaluate the influence of each class of antidiabetic drugs on metabolic and hepatic outcomes. Such an approach would have required a much larger number of patients for each therapeutic subgroup and for each additional variable analyzed. However, given the rigorous control over biological and clinical measurements, the results are valuable for generating hypotheses and guiding future studies with larger samples.

Another limitation of our study is the absence of liquid biopsy evaluation, a modern, non-invasive method based on the analysis of circulating molecular biomarkers (such as free DNA, RNA, and specific proteins), which would have enabled dynamic characterization of liver status without the risks associated with traditional invasive procedures. FibroScan and CAP were used to evaluate liver fibrosis and steatosis. While validated and widely accepted, they are not as precise as a liver biopsy, which remains the gold standard.

Although ESR and CRP were measured, more specific markers of systemic and hepatic inflammation (eg, IL-6, TNF-α) were not included, which might have provided a deeper understanding of MASLD progression.

The research was conducted at a single center, and the results may reflect local patient characteristics, healthcare access, and treatment strategies. Although the number of patients included in our study is regionally representative, it limits the generalizability of the results. To validate and extend our conclusions on the prevalence and risk factors of MASLD on a national and international scale, multicenter, multi-ethnic studies are needed.

Another important limitation is the absence of mediation or path analyses that simultaneously integrate insulin resistance, comorbidities (eg, hypertension, microvascular and macrovascular complications), and liver injury. Consequently, attributing the high prevalence of MASLD primarily to hyperglycemia and obesity should be viewed with caution, as our results are exploratory and hypothesis-generating rather than causally demonstrative. However, the purpose of cross-sectional studies is to estimate disease prevalence and to explore associations between potential risk factors and health status at a given point in time.

Conclusion

In the studied population, MASLD was highly prevalent among adults with T2D. Most patients were obese and exhibited an adverse cardiometabolic profile characterized by poor glycemic control, atherogenic dyslipidemia, and the presence of both microvascular and macrovascular complications.

The insulin resistance indices TyG and METS-IR showed a moderate ability to identify MASLD and performed better than HbA1c. Elevated TyG, METS-IR, and HbA1c values were independently associated with both hepatic steatosis and liver fibrosis.

The identified cutoffs—HbA1c >7.2% for MASLD and >7.7% for liver fibrosis—together with increased TyG and METS-IR values, may be used as simple risk-stratification tools in routine clinical practice. However, the modest area under the curve (AUC) values and the relatively small number of patients without MASLD warrant cautious interpretation of their predictive performance.

Routine incorporation of insulin resistance indices into the clinical assessment of patients with T2D, combined with sustained improvement in overall metabolic control, may enable earlier identification of individuals at high risk of progression from simple steatosis to MASH and advanced fibrosis, and support more individualized treatment strategies.

Institutional Review Board Statement

The investigation was conducted in accordance with the Declaration of Helsinki and with the approval of the Ethical Committee of Emergency County Hospital Timisoara (No. 518/December 30, 2024).

Informed Consent Statement

Informed consent was obtained from each patient by having them sign the informed consent form.

Data Sharing Statement

Data are available from the corresponding author on reasonable request.

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Author Contributions

Conceptualization OA and RT; Methodology AB; Validation BT; Formal Analysis OA and RT; Investigation, OA, BT, SP; Resources AB, SL; Data Curation AB and SL; Writing—Original Draft Preparation all authors; Writing—Review and Editing all authors; Visualization all authors; Supervision OA and RT; Project Administration OA; Funding Acquisition OA. All authors have read and agreed to the published version of the manuscript. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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