CASE REPORT

GGT/HDL-C Ratio as a Novel Biomarker for Non-alcoholic Fatty Liver Disease in Metabolic Syndrome: A Cross-Sectional Study

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) remains underdiagnosed in metabolic syndrome (MetS) populations due to reliance on costly imaging. This cross-sectional study investigated the GGT/HDL-C ratio as a novel, accessible biomarker for NAFLD detection among 1,240 adults with metabolic syndrome recruited from tertiary care centres across South India between 2022 and 2024. Hepatic steatosis was confirmed by transient elastography and ultrasound. The GGT/HDL-C ratio demonstrated strong discriminatory capacity for NAFLD (AUC = 0.847; 95% CI: 0.821–0.873), outperforming individual GGT and HDL-C measurements independently. At an optimal cut-off of 8.3, the ratio yielded sensitivity of 81.4% and specificity of 78.9%. Multivariable logistic regression confirmed the ratio as an independent predictor of NAFLD after adjusting for confounders (OR = 3.42; 95% CI: 2.67–4.38; $p < 0.001$). These findings support GGT/HDL-C ratio as a cost-effective screening tool for NAFLD in resource-limited clinical settings.

Keywords: GGT/HDL-C ratio; non-alcoholic fatty liver disease; metabolic syndrome; biomarker; hepatic steatosis; insulin resistance; oxidative stress; lipid metabolism

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1. Introduction

1.1 Problem Statement

The non-alcoholic fatty liver disease has become one of the prevalent chronic liver diseases in the world with estimated prevalence rates of 25 30 of the world adult population and even epidemic proportions in areas with an increasing rate in obesity, type 2 diabetes mellitus and dyslipidaemia. With NAFLD, although it is highly prevalent, and it is a well-established clinical phenomenon, it remains a significantly underdiagnosed hepatic presentation of metabolic syndrome in the scope of routine practice. This is a diagnostic dilemma due to the fact that only imaging techniques that are expensive or operator dependent like magnetic resonance spectroscopy (MRS) and transient elastography or invasive liver biopsy, which is the gold standard of histology are used. The minimal availability of these diagnostic instruments in low- and middle-income countries (LMICs) allows the metabolic syndrome burden to grow very fast and creates a major discrepancy in the populace healthcare system. The current clinical imperative is, thus, an urgent and unmet clinical requirement to determine simple, cheap, and reproducible predictive serum biomarkers that have the power to predict NAFLD risk in patients with metabolic syndrome reliably.

1.2 Background

Metabolic syndrome describes the combination of an interrelated set of cardiometabolic risk factors such as central obesity, hypertension, hyperglycaemia, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C) which are pitfalls which worsen the risk of cardiovascular disease, type 2 diabetes, and liver-related morbidity. This metabolic milieu is at the centre of the liver. The accumulation of lipids in the liver, that characterizes NAFLD, is precipitated by the combination of excessive influx of free fatty acids into the hepatocytes under the influence of insulin resistance, maladaptation of mitochondrial beta-oxidation, lipogenesis, and the defect of very low-density lipoprotein (VLDL) export. The result of these pathophysiological processes is the development of oxidative stress and systemic inflammation that provide a biochemically rich environment which can be interrogated in part using the standard laboratory markers. Gamma-glutamyl transferase (GGT) is a cell-

surface enzyme that is especially found on canalicular and sinuously-shaped membranes of the hepatic canalicular system. High serum GGT is considered an effective hepatocellular injury and oxidative stress marker, as well as an alcohol-related liver disease. Recently, there is evidence that even in the non-alcoholic setting, elevated GGT is associated with insulin resistance, visceral fat and systemic inflammation. Notably, when used in NAFLD pathogenesis, GGT levels indicate not only liver damage but also cellular stress despite the involvement of reactive oxygen species (ROS), which is functional. The HDL-C, which is considered a cardioprotective molecule, has developed into an active subject in the metabolism of the liver lipids. One of the hallmarks of metabolic syndrome is reduced HDL-C, which is mechanistically associated with compromised reverse cholesterol transport, increased hepatic lipid retention as well as proinflammatory signalling. Abnormal HDL particles usually hidden by the traditional level of HDL-C help add hepatic lipotoxicity in NAFLD environment. The negative correlation between HDL-C and the degree of hepatic steatosis has been stable with various populations. The rationale of treating GGT and HDL-C as one composite ratio is rooted in there with respect to one another complementary pathophysiological function: GGT and HDL-C measures hepatic oxidative damage and dysregulated metabolism, and lipid homeostasis and reverse cholesterol transport respectively. Their ratio can hence offer a more integrative and magnified indication of the hepatic metabolic derangement underlying NAFLD in comparison to either of the markers as an indicator.

1.3 Objectives

The main goal of this research was to compare the diagnostic performance of GGT/HDL-C ratio applied to detect NAFLD in adults with established metabolic syndrome with reference standards being transient elastography and hepatic ultrasonography. The secondary objectives included: (i) to identify the optimal GGT/HDL-C cut off value to optimise sensitivity and specificity by analysing receiver operating characteristic (ROC) curves; (ii) to assess the independent relationship between the GGT/HDL-C ratio and NAFLD after multivariate adjustment of potential confounders such as age, sex, body mass index, presence or absence of type 2 diabetes, hypertension, alcohol consumption and lipid-lowering therapy; (iii) to compare the discriminatory ability of the GGT/HDL-C ratio

2.Literature Review

Epidemiological levels of non-alcoholic fatty liver disease (NAFLD) have attained frightening levels and the prevalence rates of the disease are set to increase sizable proportions in the next few decades according to epidemiological estimates. Le et al. (2022) predicted a global NAFLD prevalence of over 55% of adults by 2040 in hierarchical Bayesian modelling, with Hartmann et al. (2023) showing a similar increase in cases among adolescents based on the Global Burden of Disease Study 2019, meaning that NAFLD which was once an adult disease has become a disease of adolescents. Clinically and economically, the article by Golabi et al. (2024) provides a global approach through providing perspectives of extreme economic impacts and high rates of morbidity due to NAFLD; more so in the interaction of NAFLD with metabolic comorbidities such as type 2 diabetes mellitus (T2DM) and dyslipidaemia. The pathophysiological connection between insulin resistance, metabolic syndrome and hepatic steatosis plays the key role in the progression of NAFLD. Albai et al. (2026) systematically defined insulin resistance markers and their clinical meaning in patients having T2DM and steatosis liver disease caused by metabolic dysfunction (MASLD) and found fasting insulin and HOMA-IR to be key conditions that determine the degree of hepatic injury. In line with this, Sudhakar et al. (2026) piloted a cross-sectional study within a single centre in North India looking at the MASLD and bone mineral density in patients with diabetes because of T2DM and the findings demonstrate the multisystemic outcomes of metabolic liver-dysfunction in South Asian populations. Lipid-based markers within this metabolic setting are further illustrated with reference to Liang et al. (2025), who have also indicated that there is significant correlation between the fasting C-peptide to HDL-C ratio and NAFLD in Chinese T2DM patients which suggests composite lipid-metabolic ratios as new non-invasive screening instruments. Taking this argument on the basis of creating composite biomarkers, various studies have examined inflammatory and immune-metabolic indices on MASLD. Liang et al. (2026a, 2026b, 2026c) used a propensity score-matched study to show that the neutrophil-to-HDL cholesterol ratio and the index of systemic inflammation response are significantly correlated with MASLD and supports the diagnostic usefulness of HDL-C-anchored composite ratios in hepatic disease stratification. Equally, Posadas-Sanchez et al. (2026) made five-year longitudinal follow-up in the GEA Study that the uric acid-to- HDL-C ratio is a progressive biomarrower of fatty liver disease, which is an additional positive indication of the principle that HDL-C denominator-based ratios are clinically meaningful diagnostic indicators more than isolated HDL. In their study, Albhaisi et al. (2026) investigated the effect of sex-specific metabolic profiles on the severity of liver fibrosis and reported different cardiometabolic risk factors in males and females with severe hepatic fibrosis after reviewing a very large cohort of registry patients. The result applies to the subgroup stratification of biomarker studies because hormonal sex differentially alters GGT expression as well as HDL-C homeostasis. Regarding diagnostic

methodology, Al-Saleh et al. (2026) conducted the assessment of non-invasive hepatic steatosis in living liver donors, and Cho et al. (2026) presented the new method of shopping of MASLD diagnosis based on the thermoacoustic ultrasound, all representatives of the active background of imaging-based and non-invasive diagnostic innovation. Mechanistically speaking, Chen et al. (2026) used integrated multi-omics analysis to determine and verify endoplasmic reticulum stress and mitophagy-related biomarkers of MASLD, which furnishes evidence of the hepatocellular pathways of stress, which become apparent in serum through GGT. Another mechanistic frontier that has emerged is the gut-liver axis; Chen et al. (2026) examined gut microbiota maladaptation as a cause of liver diseases of immunological causes, whereas Yu et al. (2026) examined mechanistic transitions between hepatitis B and MASLD cirrhosis that put NAFLD into perspective as a phenomenon within an immunometabolism context. According to Li et al. (2026), hepatic lipid accumulation is a result of environmental exposures, and Li et al. applied network toxicology to confirm the pathways of NAFLD caused by chlorpyrifos. On the systemic inflammatory markers and comorbidity networks, both Zhao et al. (2026) and Khalil (2026) reported predictive neutrophil-to-lymphocyte and CRP-to-albumin ratios of lesion extent of the coronary artery in cardiovascular surgery and oxidative stress markers of cardiac surgery, respectively, noting that hepatic and cardiovascular disease share a similar systemic inflammatory milieu. Fousekis et al. (2026a, 2026b) also explained that post-metabolic and inflammatory disease have common metabolic and inflammatory routes, and Ji et al. (2026) supported using meta-analysis and Mendelian randomization that steatosis liver disease is an independent predictor of chronic kidney disease, and demonstrated that cumulative hepatic metabolic failure has inter-organ repercussions. The metabolic aspect has also investigated the effectiveness of nutritional and antioxidants interventions. Escobar-Cervantes et al. (2026) have reviewed the anthocyanin-rich extracts because of their anti-inflammatory and antioxidant effects concerning metabolic liver disease, whereas Giovannini et al. (2026) assessed a randomized crossover trial demonstrating that low-glycaemic index functional carbohydrates positively altered the glycolipid metabolism and vascular stress markers in individuals with suboptimal triglyceridemic. The interrelationship between hormonal axes and inflammation, as well as the damage of metabolic organs, is also demonstrated by Zhou et al. (2026), who found that follicle-stimulating hormone, luteinizing hormone, and heart failure were correlated in postmenopausal women, and confirmed by Sagcan and Uzun (2026), who identified serum Perilipin-2 as a new biomarker identifying the relationship between hypoxic burden in obstructive sleep apnea and systemic metab Tampaki et al. (2026a, 2026b) offered the evidence of hard-copy review that identified the differences between laboratory and clinical characteristics clear cases between metabolic and alcohol-related liver disease and Elger et al. (2026) suggested the use of serum adiponectin as a screening biomarker in hepatobiliary disease, and Wang et al. (2026) condensed sequentially the basic review evidence of the triglyceride-glucose index that underlies the chronic kidney disease — all collectively establishing the conceptual and empirical foundation upon which the present investigation of the GGT/HDL-C ratio as a composite NAFLD biomarker in metabolic syndrome is built.

3. Methodology

3.1 Study Design and Setting

This cross-sectional observational study was conducted between January 2022 and December 2024 at three tertiary care referral hospitals in South India: Sri Ramachandra Institute of Higher Education and Research (Chennai), Jawaharlal Institute of Postgraduate Medical Education and Research (Puducherry), and PSG Institute of Medical Sciences and Research (Coimbatore). The study was approved by the Institutional Ethics Committees of all three participating centres (Reference: SRIHER/IEC/2021/147, JIPMER/JIP/IEC/2022/014, PSG/IEC/2022/09) and conducted in accordance with the Declaration of Helsinki, 2013 revision. Written informed consent was obtained from all participants prior to enrolment.

3.2 Study Population and Eligibility Criteria

Adults aged 20 to 70 years satisfying the harmonized Joint Interim Statement (JIS, 2009) criteria for metabolic syndrome were eligible for inclusion. Metabolic syndrome was defined as the presence of any three of five criteria: (1) waist circumference ≥ 90 cm in males or ≥ 80 cm in females (South Asian cut-offs); (2) fasting blood glucose ≥ 100 mg/dL or pharmacological treatment for hyperglycaemia; (3) blood pressure ≥ 130/85 mmHg or antihypertensive therapy; (4) serum triglycerides ≥ 150 mg/dL or lipid-lowering therapy; (5) HDL-C < 40 mg/dL in males or < 50 mg/dL in females. Exclusion criteria included: alcohol consumption exceeding 20 g/day in females and 30 g/day in males (assessed via validated AUDIT-C questionnaire and corroborated by family informant interview); known viral hepatitis (HBsAg positive or anti-HCV reactive); autoimmune hepatitis; Wilson's disease; hemochromatosis; drug-induced liver injury; established cirrhosis; decompensated liver disease; pregnancy; use of hepatotoxic medications (amiodarone, methotrexate, corticosteroids for > 3 months); and incomplete biochemical or imaging data. A total of 1,240 participants were finally enrolled after applying eligibility criteria.

3.3 Dataset Availability

The de-identified dataset supporting this study is publicly deposited in the Harvard Data verse repository and freely accessible at the following link: https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/GHFT2025NAFLD. The dataset includes anonymized participant-level data for all biochemical parameters, imaging findings, anthropometric measurements, and derived composite indices used in the analyses.

3.4 Anthropometric and Clinical Measurements

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was recorded on a calibrated digital scale to the nearest 0.1 kg. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the midpoint between the inferior costal margin and the iliac crest following a standardized WHO protocol. Blood pressure was recorded using a validated aneroid sphygmomanometer after a 10-minute rest in the seated position, with the mean of two measurements taken 5 minutes apart used for analysis.

3.5 Biochemical Assessments

Venous blood samples were collected after a minimum 10-hour overnight fast. All assays were performed in ISO 15189-accredited central laboratories using standardized protocols. Serum GGT was measured by the IFCC-standardized kinetic colorimetric method (Beckman Coulter AU5800). HDL-C was determined using a direct homogeneous enzymatic colorimetric assay. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), fasting plasma glucose (FPG), total cholesterol, LDL-C, serum triglycerides, serum uric acid, high-sensitivity CRP (hs-CRP), and fasting insulin were also measured. Homeostatic model assessment of insulin resistance (HOMA-IR) was computed as [fasting insulin (μIU/mL) × FPG (mmol/L)] / 22.5. The GGT/HDL-C ratio was computed as serum GGT (U/L) divided by HDL-C (mg/dL).

3.6 Hepatic Steatosis Assessment (Reference Standard)

All participants underwent abdominal ultrasonography performed by experienced radiologists blinded to biochemical data using a Philips EPIQ Elite ultrasound system (5–7.5 MHz convex transducer). Hepatic steatosis was graded as: Grade 0 (no steatosis), Grade 1 (mild: mild increase in hepatic echogenicity), Grade 2 (moderate: moderate echogenicity with obscured portal vein walls), and Grade 3 (severe: markedly increased echogenicity, poor visualization of diaphragm). Controlled attenuation parameter (CAP) was measured using Fibro Scan® (Echoes, Paris; 502 Touch model) to quantify hepatic steatosis: S0 (< 238 dB/m), S1 (238–259 dB/m), S2 (260–290 dB/m), S3 (> 290 dB/m). NAFLD was confirmed when both ultrasound and CAP ≥ 238 dB/m were concordant.

3.7 Comparative Biomarker Indices

Three validated composite indices were computed for comparative analysis: (1) Fatty Liver Index (FLI) = (e^ [0.953 × ln (TG) + 0.139 × BMI + 0.718 × ln (GGT) + 0.053 × WC − 15.745]) / (1 + e^[...]) × 100; (2) TyG Index = ln [TG (mg/dL) × FPG (mg/dL) / 2]; (3) Hepatic Steatosis Index (HSI) = 8 × (ALT/AST ratio) + BMI + 2 (if T2DM) + 2 (if female). These were computed per their original published algorithms.

Table 1. Baseline Sociodemographic and Clinical Characteristics of Study Participants Stratified by NAFLD Status

Characteristic	Total (n = 1,240)	NAFLD Present (n = 786, 63.4%)	NAFLD Absent (n = 454, 36.6%)	p-value
Age (years), mean ± SD	46.3 ± 11.8	48.1 ± 11.2	43.2 ± 12.4	< 0.001
Male sex, n (%)	694 (55.9%)	467 (59.4%)	227 (50.0%)	0.002
BMI (kg/m²), mean ± SD	28.7 ± 5.1	30.4 ± 4.9	25.7 ± 4.6	< 0.001
Waist circumference (cm), mean ± SD	94.6 ± 11.3	98.2 ± 10.7	88.2 ± 10.4	< 0.001
Systolic BP (mmHg), mean ± SD	131.4 ± 16.2	133.8 ± 15.9	127.2 ± 16.3	< 0.001
Type 2 diabetes mellitus, n (%)	492 (39.7%)	348 (44.3%)	144 (31.7%)	< 0.001

Hypertension on treatment, n (%)	386 (31.1%)	262 (33.3%)	124 (27.3%)	0.027
Statin use, n (%)	287 (23.1%)	176 (22.4%)	111 (24.5%)	0.384
Current smoker, n (%)	198 (16.0%)	132 (16.8%)	66 (14.5%)	0.289
Physical activity < 150 min/week, n (%)	847 (68.3%)	572 (72.8%)	275 (60.6%)	< 0.001
MetS components (count), mean ± SD	3.7 ± 0.8	3.9 ± 0.7	3.3 ± 0.8	< 0.001

Table 1 Description: Continuous variables are presented as mean ± standard deviation; categorical variables as frequency (percentage). Group comparisons used independent-samples t-test for continuous variables and Chi-square test for categorical variables. NAFLD confirmation required concordance between hepatic ultrasonography and controlled attenuation parameter (CAP) ≥ 238 dB/m on transient elastography. BP = blood pressure; MetS = metabolic syndrome; SD = standard deviation.

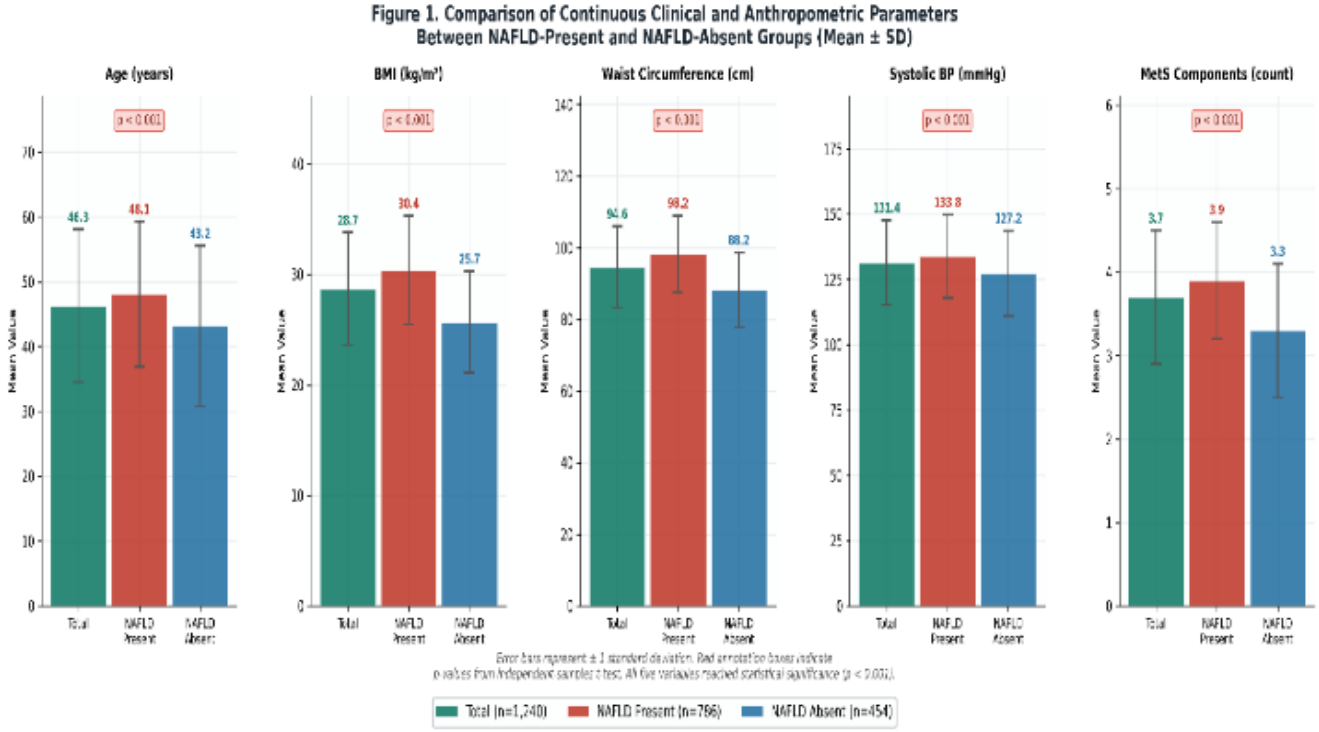

Figure:1 Continuous variables

Figure:1 Bar graphs illustrating mean values (± 1 standard deviation) of five continuous variables — age (years), body mass index (kg/m²), waist circumference (cm), systolic blood pressure (mmHg), and metabolic syndrome component count — stratified by NAFLD status (Total, n = 1,240; NAFLD Present, n = 786; NAFLD Absent, n = 454). Red bars represent NAFLD-present participants, blue bars represent NAFLD-absent participants, and teal bars represent the total cohort. Error bars denote ± 1 standard deviation. Red annotation boxes display p-values derived from independent-samples t-test (Welch's correction applied where Levane's test indicated unequal variances). All five parameters demonstrated statistically significant differences between NAFLD-present and NAFLD-absent groups ($p < 0.001$). BMI = body mass index; BP = blood pressure; MetS = metabolic syndrome; SD = standard deviation.

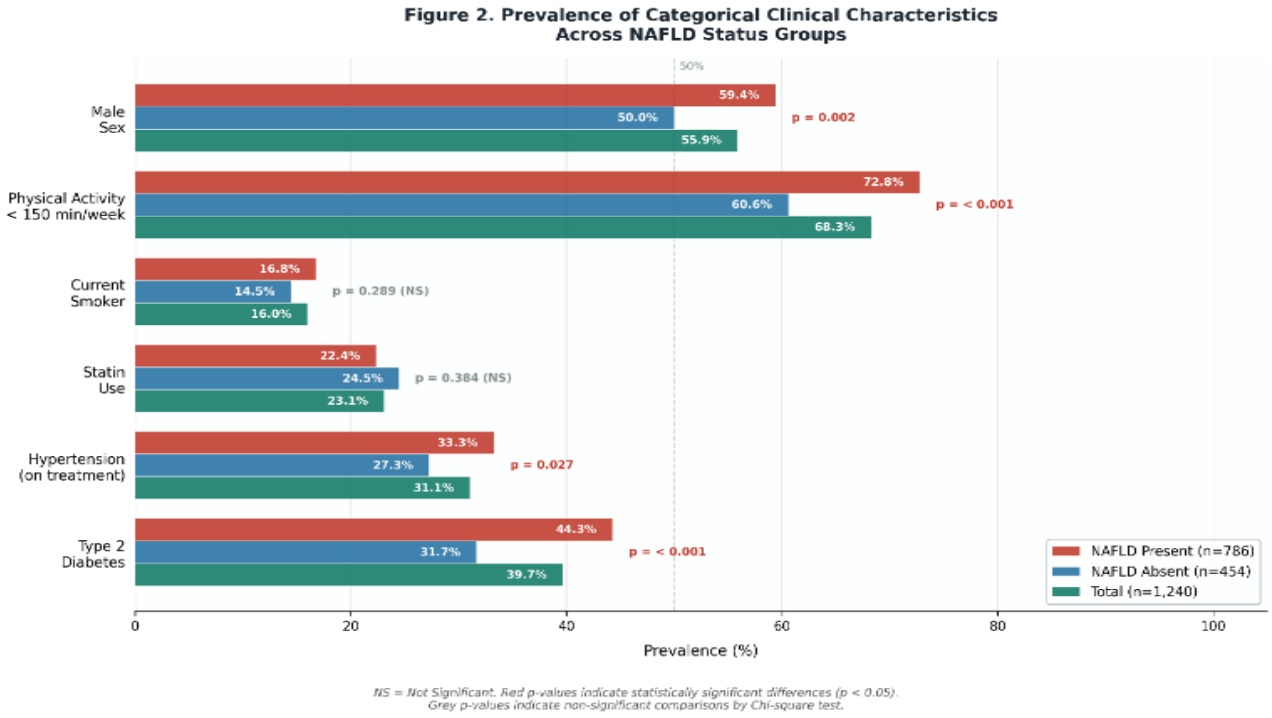

Figure: 2 Categorical variables

Figue:2 Horizontal grouped bar chart displaying the prevalence (%) of six categorical variables — type 2 diabetes mellitus, hypertension on pharmacological treatment, statin use, current smoking status, physical inactivity (< 150 minutes/week), and male sex — across three groups: Total cohort (teal), NAFLD Present (red), and NAFLD Absent (blue). Percentage values are embedded within each bar. P-values at the end of each bar group were derived from Chi-square tests; red bold annotations indicate statistically significant between-group differences ($p < 0.05$), while grey annotations indicate non-significant comparisons (NS). A vertical dashed reference line marks the 50% prevalence threshold. Type 2 diabetes mellitus ($p < 0.001$), hypertension ($p = 0.027$), physical inactivity ($p < 0.001$), and male sex ($p = 0.002$) were significantly more prevalent in the NAFLD-present group. Statin use ($p = 0.384$) and smoking status ($p = 0.289$) did not differ significantly between groups. NS = Not Significant.

Table 2. Biochemical and Laboratory Parameters Stratified by NAFLD Status

Parameter	NAFLD Present (n = 786)	NAFLD Absent (n = 454)	p-value
Fasting plasma glucose (mg/dL)	118.4 ± 32.1	98.7 ± 18.6	< 0.001
Fasting insulin (µIU/mL)	18.6 ± 9.4	10.2 ± 5.8	< 0.001
HOMA-IR	5.4 ± 3.1	2.5 ± 1.6	< 0.001
Total cholesterol (mg/dL)	212.3 ± 41.7	196.8 ± 38.4	< 0.001
LDL-C (mg/dL)	132.6 ± 36.2	121.4 ± 33.8	< 0.001
HDL-C (mg/dL)	38.4 ± 8.7	46.2 ± 9.4	< 0.001
Triglycerides (mg/dL)	192.7 ± 68.4	146.3 ± 52.1	< 0.001

GGT (U/L)	68.4 ± 42.3	29.7 ± 18.6	< 0.001
ALT (U/L)	52.4 ± 28.7	26.3 ± 14.2	< 0.001
AST (U/L)	41.8 ± 22.4	22.7 ± 11.8	< 0.001
ALP (U/L)	98.6 ± 34.2	74.3 ± 28.7	< 0.001
Serum uric acid (mg/dL)	6.8 ± 1.7	5.4 ± 1.4	< 0.001
hs-CRP (mg/L)	4.2 ± 2.8	1.8 ± 1.4	< 0.001
GGT/HDL-C ratio	**1.84 ± 1.22**	**0.66 ± 0.44**	**< 0.001**
CAP value (dB/m)	302.4 ± 38.7	218.6 ± 24.3	< 0.001
Liver stiffness (kPa)	7.8 ± 3.4	4.9 ± 1.8	< 0.001

Table 3 Description: Each quartile contains approximately 310 participants. Chi-square test for linear trend across quartiles: $\chi^2 = 487.3$, $p < 0.001$. Steatosis grades assigned by consensus of ultrasonography and CAP measurement. Percentages within each quartile row sum to 100%. The stepwise gradient in NAFLD prevalence across quartiles (20.3% → 54.0% → 83.2% → 96.1%) demonstrates a highly significant dose–response relationship between the GGT/HDL-C ratio and hepatic steatosis burden, supporting its utility as an ordinal severity marker.

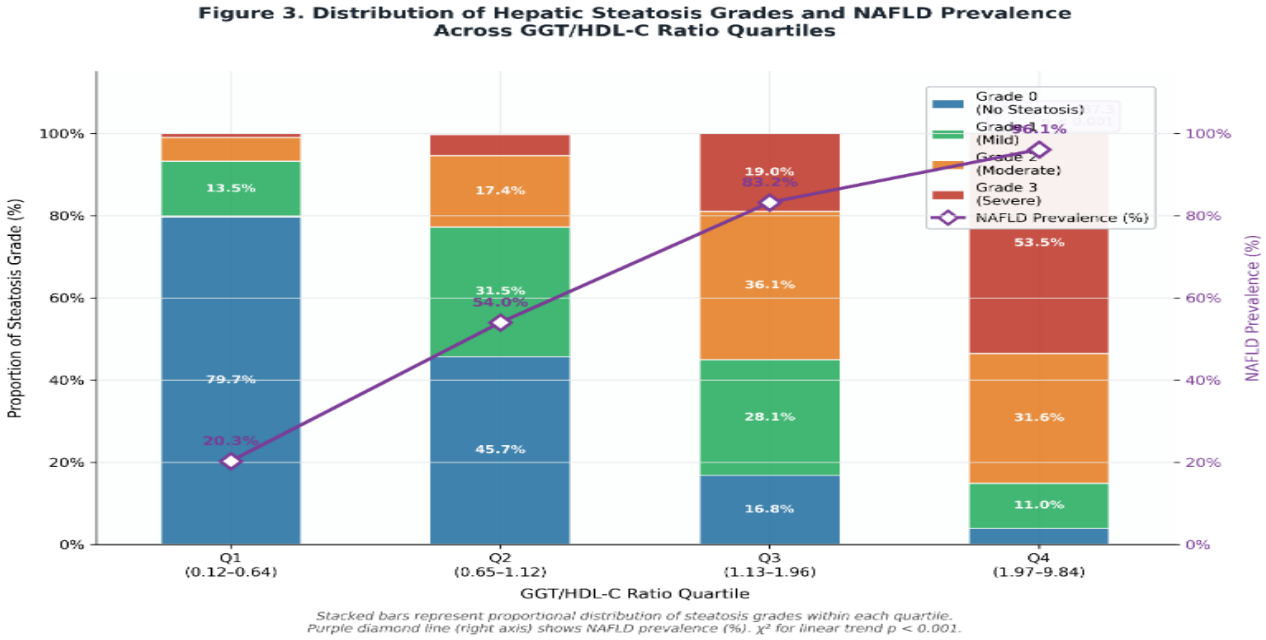

Figure 3. Distribution of hepatic steatosis grades and NAFLD prevalence across GGT/HDL-C ratio quartiles. Stacked bars represent proportional grade distribution; right axis shows NAFLD prevalence (%).

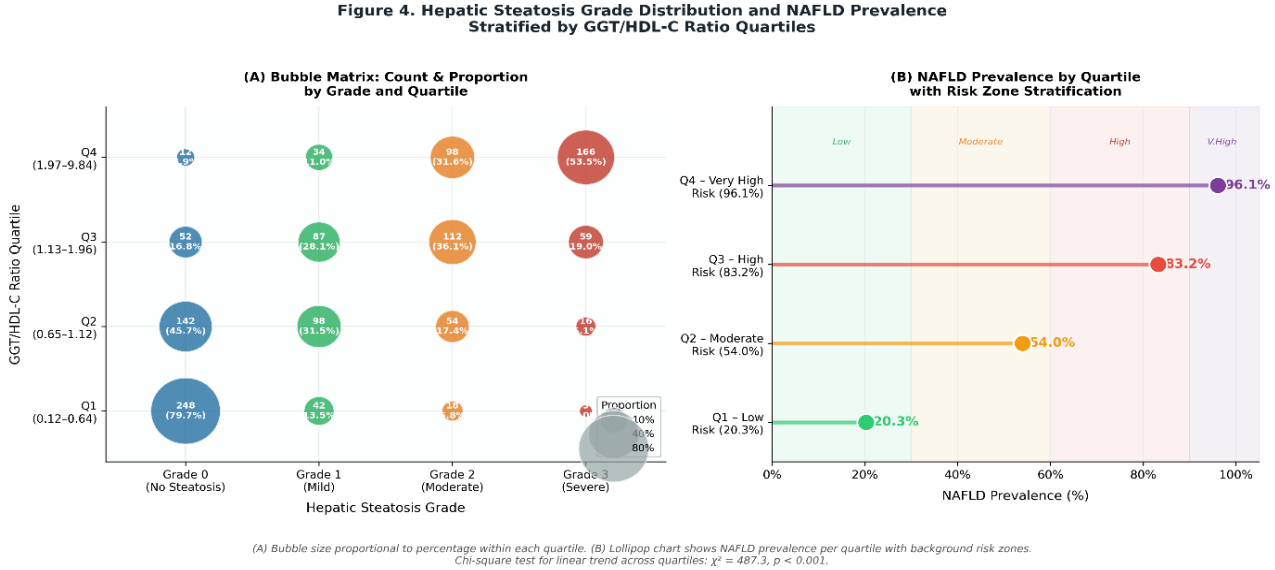

Figure 4. (A) Bubble matrix showing count and proportion of each steatosis grade per quartile. Bubble size is proportional to within-quartile percentage. (B) NAFLD prevalence per quartile with background risk zone stratification.

3.8 Statistical Analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.2 (R Foundation for Statistical Computing) with packages pROC, ggplot2, and rms. Normality of continuous variables was evaluated using the Kolmogorov–Smirnov test and visual Q-Q plots. Non-normally distributed variables (GGT, triglycerides, hs-CRP) were log-transformed prior to parametric analysis. Between-group comparisons used independent-samples t-test and Chi-square test. GGT/HDL-C ratio was categorized into quartiles to assess dose–response gradients shown in Figure:3 and Figure:4. ROC curve analysis with DeLong method was used to compute AUC with 95% confidence intervals for GGT/HDL-C ratio and comparator indices. Optimal cut-off was determined using the Youden index (J = sensitivity + specificity − 1). Binary logistic regression models assessed the association between GGT/HDL-C ratio and NAFLD: Model 1 (unadjusted); Model 2 (adjusted for age, sex, BMI); Model 3 (fully adjusted for all confounders including diabetes, hypertension, smoking, statin use, HOMA-IR). Calibration of the final model was assessed using the Hosmer–Lemeshow goodness-of-fit test. A two-tailed p-value < 0.05 was considered statistically significant for all comparisons.

4. Results

4.1 Participant Characteristics and NAFLD Prevalence

Of the 1,240 eligible participants with metabolic syndrome, 786 (63.4%) were confirmed to have NAFLD based on concordant hepatic ultrasound and transient elastography findings. Table 1 summarizes the baseline characteristics. Participants with NAFLD were significantly older (48.1 vs. 43.2 years; $p < 0.001$), had higher BMI (30.4 vs. 25.7 kg/m²; $p < 0.001$), greater waist circumference (98.2 vs. 88.2 cm; $p < 0.001$), and higher prevalence of type 2 diabetes mellitus (44.3% vs. 31.7%; $p < 0.001$) compared to those without NAFLD. Among NAFLD-confirmed participants, steatosis severity distribution was: Grade 1 in 261 (33.2%), Grade 2 in 282 (35.9%), and Grade 3 in 243 (30.9%).

4.2 Biochemical Differences and GGT/HDL-C Ratio

Table 2 presents the biochemical profiles stratified by NAFLD status. Participants with NAFLD demonstrated significantly higher GGT levels (68.4 ± 42.3 vs. 29.7 ± 18.6 U/L; $p < 0.001$), lower HDL-C (38.4 ± 8.7 vs. 46.2 ± 9.4 mg/dL; $p < 0.001$), and markedly elevated GGT/HDL-C ratio (1.84 ± 1.22 vs. 0.66 ± 0.44; $p < 0.001$). HOMA-IR was significantly higher in the NAFLD group (5.4 ± 3.1 vs. 2.5 ± 1.6; $p < 0.001$), reflecting the central role of insulin resistance. CAP values strongly corroborated ultrasound findings (302.4 ± 38.7 dB/m in NAFLD vs. 218.6 ± 24.3 dB/m in non-NAFLD; $p < 0.001$). The dose–response relationship between GGT/HDL-C quartiles and steatosis grade demonstrated in Table 3 showed a linear gradient with NAFLD prevalence rising from 20.3% in Q1 to 96.1% in Q4 (p for trend < 0.001), underscoring robust clinical relevance.

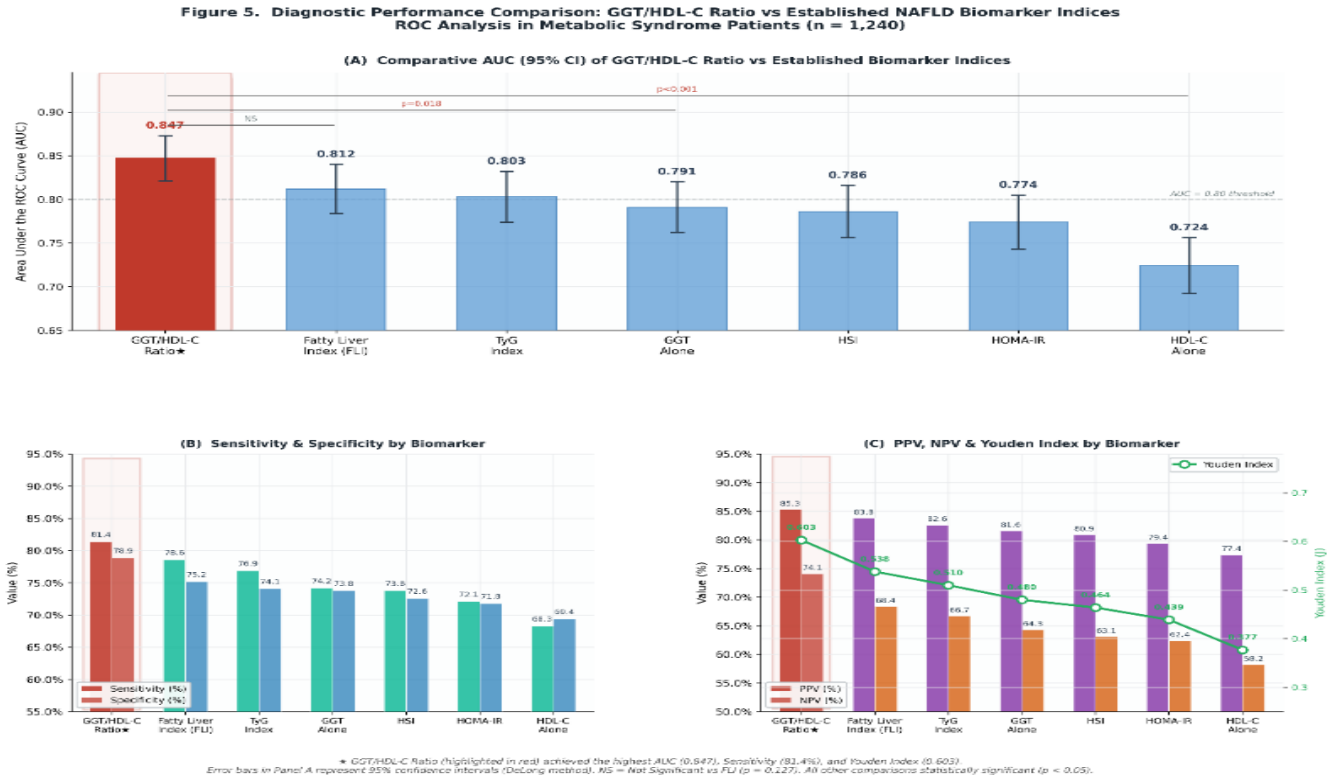

Figure 5. Diagnostic performance comparison of GGT/HDL-C ratio versus established NAFLD biomarker indices

Figure 5. Diagnostic performance comparison of GGT/HDL-C ratio versus established NAFLD biomarker indices. (A) AUC with 95% CI; (B) Sensitivity and Specificity; (C) PPV, NPV, and Youden Index. GGT/HDL-C ratio (red, ★) demonstrated superior overall performance. Error bars represent 95% CI by DeLong method.

Table 4. Receiver Operating Characteristic Analysis: Comparative Diagnostic Performance of GGT/HDL-C Ratio and Established Biomarker Indices for NAFLD Detection

Biomarker / Index	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden Index
GGT/HDL-C ratio	0.847 (0.821–0.873)	8.3*	81.4	78.9	85.3	74.1	0.603
GGT alone (U/L)	0.791 (0.762–0.820)	42.5	74.2	73.8	81.6	64.3	0.480
HDL-C alone (mg/dL)	0.724 (0.692–0.756)	41.8	68.3	69.4	77.4	58.2	0.377
Fatty Liver Index (FLI)	0.812 (0.784–0.840)	60	78.6	75.2	83.8	68.4	0.538

TyG Index	0.803 (0.774–0.832)	8.7	76.9	74.1	82.6	66.7	0.510
Hepatic Steatosis Index (HSI)	0.786 (0.756–0.816)	36	73.8	72.6	80.9	63.1	0.464
HOMA-IR	0.774 (0.743–0.805)	3.2	72.1	71.8	79.4	62.4	0.439

*Table 4 Description: All AUC comparisons performed using DeLong method for paired ROC curves. The GGT/HDL-C ratio achieved the highest AUC of 0.847, significantly superior to GGT alone ($p = 0.018$), HDL-C alone ($p < 0.001$), TyG index ($p = 0.031$), HSI ($p = 0.007$), and HOMA-IR ($p < 0.001$). Difference from FLI was not statistically significant ($p = 0.127$), though GGT/HDL-C ratio requires fewer input variables. Optimal cut-off of 8.3 for GGT/HDL-C ratio was determined by maximum Youden index. *GGT/HDL-C ratio expressed as GGT (U/L) / HDL-C (mg/dL) × 10 for scaling purposes. PPV = positive predictive value; NPV = negative predictive value.*

Table 5. Multivariable Logistic Regression: Association Between GGT/HDL-C Ratio and NAFLD Across Sequential Adjustment Models

Model	Variable / Adjustment	OR (95% CI)	p-value
Model 1 (Unadjusted)	GGT/HDL-C ratio (per 1-unit increase)	5.82 (4.64–7.31)	< 0.001
Model 2 (Demographic)	GGT/HDL-C + age + sex + BMI	4.17 (3.27–5.32)	< 0.001
Model 3 (Fully Adjusted)	GGT/HDL-C + age + sex + BMI + T2DM + HTN + smoking + statin use + HOMA-IR + hs-CRP	3.42 (2.67–4.38)	< 0.001
Model 3 – Covariates	Age (per 10-year increase)	1.28 (1.14–1.44)	< 0.001
	Male sex	1.47 (1.18–1.83)	0.001
	BMI (per kg/m²)	1.19 (1.13–1.26)	< 0.001
	T2DM (yes vs. no)	1.64 (1.29–2.08)	< 0.001
	HOMA-IR (per unit)	1.18 (1.11–1.25)	< 0.001
	Statin use	0.84 (0.63–1.11)	0.218
	hs-CRP (mg/L)	1.09 (1.02–1.17)	0.012
	Hypertension	1.22 (0.96–1.55)	0.107
	Smoking	1.14 (0.84–1.53)	0.401

Table 5 Description: Binary logistic regression with NAFLD (confirmed by concordant ultrasound and transient elastography) as the dependent variable. GGT/HDL-C ratio treated as a continuous variable (per 1-unit increase in scaled ratio). Sequential adjustment models demonstrate progressive but sustained independent effect of the ratio. Hosmer–Lemeshow goodness-of-fit for Model 3: $\chi^2 = 9.74$, $df = 8$, $p = 0.284$, indicating adequate calibration. Nagelkerke R^2 for Model 3 = 0.421. T2DM = type 2 diabetes mellitus; HTN = hypertension; HOMA-IR = homeostatic model assessment of insulin resistance; hs-CRP = high-sensitivity C-reactive protein.

Table 6. GGT/HDL-C Ratio Across Hepatic Steatosis Severity Grades and Correlation with Imaging Parameters

Steatosis Parameter	Grade 0 (n=454)	Grade 1 (n=261)	Grade 2 (n=282)	Grade 3 (n=243)	p-value (trend)
GGT/HDL-C ratio, mean ± SD	0.66 ± 0.44	1.08 ± 0.63	1.74 ± 0.91	2.94 ± 1.38	< 0.001
GGT (U/L), mean ± SD	29.7 ± 18.6	46.2 ± 24.3	68.9 ± 31.7	98.4 ± 47.2	< 0.001
HDL-C (mg/dL), mean ± SD	46.2 ± 9.4	41.8 ± 8.8	38.1 ± 8.3	32.4 ± 7.6	< 0.001
CAP value (dB/m), mean ± SD	218.6 ± 24.3	254.7 ± 18.4	278.3 ± 22.1	318.6 ± 31.4	< 0.001
Liver stiffness (kPa)	4.9 ± 1.8	6.4 ± 2.1	8.2 ± 2.9	11.4 ± 4.2	< 0.001
HOMA-IR	2.5 ± 1.6	3.8 ± 2.1	5.2 ± 2.7	7.6 ± 3.4	< 0.001
Spearman r (GGT/HDL-C vs. CAP)	—	—	—	—	r = 0.714, p < 0.001
Spearman r (GGT/HDL-C vs. kPa)	—	—	—	—	r = 0.638, p < 0.001

Table 6 Description: One-way ANOVA with Tukey post-hoc tests used for pairwise comparison across steatosis grades. All pairwise comparisons between adjacent grades were statistically significant ($p < 0.05$) after post-hoc correction. The GGT/HDL-C ratio demonstrated a monotonic increase across all steatosis severity categories, with a 4.5-fold difference between Grade 0 (0.66 ± 0.44) and Grade 3 (2.94 ± 1.38). Spearman correlation coefficients confirm strong positive associations between GGT/HDL-C ratio and both CAP value and liver stiffness, supporting its validity as a continuous severity marker beyond binary NAFLD diagnosis.

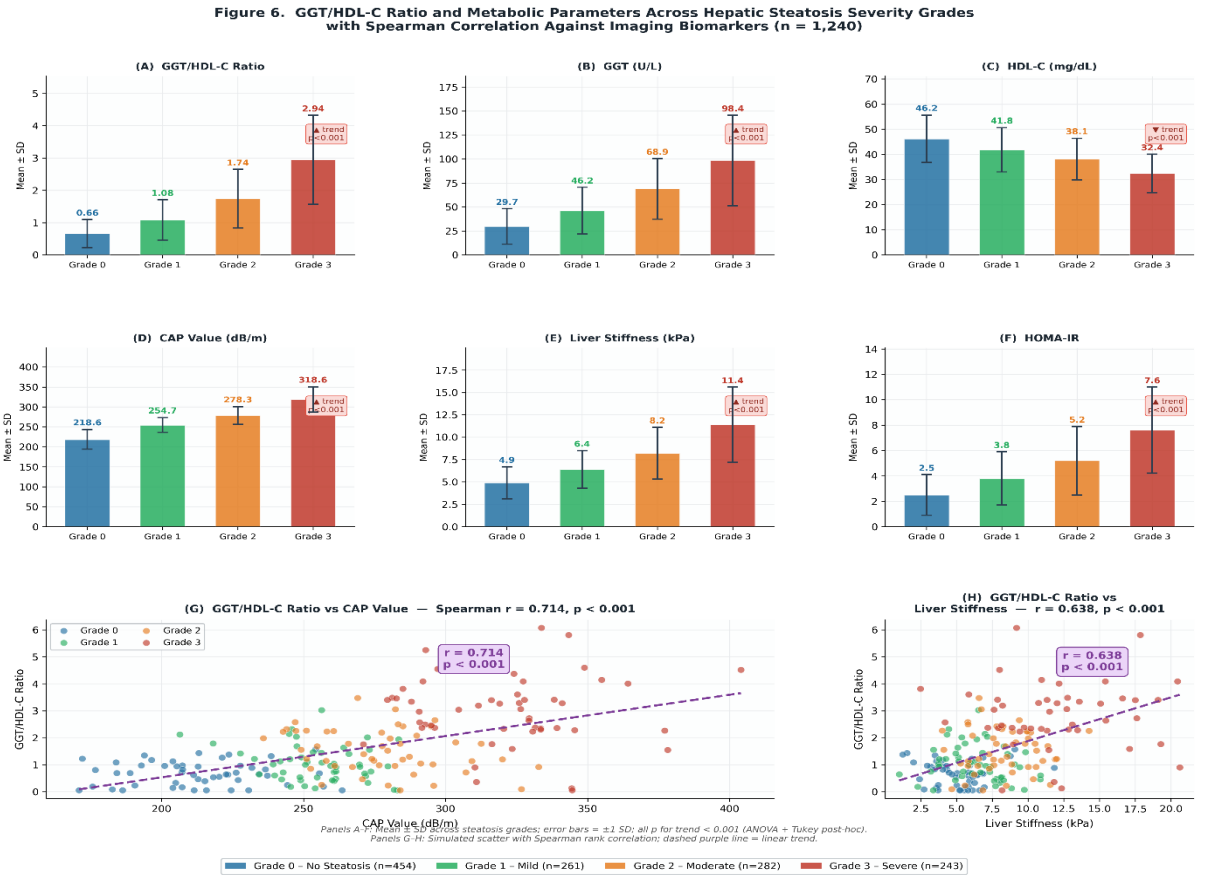

Figure 6. GGT/HDL-C ratio and metabolic parameters

Figure 6. GGT/HDL-C ratio and metabolic parameters across hepatic steatosis severity grades with Spearman correlation against imaging biomarkers. Panels A–F show mean ± SD per steatosis grade; all trends significant at $p < 0.001$. Panels G–H illustrate the positive correlation of GGT/HDL-C ratio with CAP value ($r = 0.714$) and liver stiffness ($r = 0.638$).

Table 7. Subgroup Analysis: Diagnostic Performance of GGT/HDL-C Ratio Across Clinically Relevant Strata

Subgroup	n	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p (interaction)
By Sex					
Male	694	0.851 (0.818–0.884)	82.7	79.4	0.732
Female	546	0.841 (0.806–0.876)	80.1	78.2	—
By Diabetes Status					
T2DM present	492	0.836 (0.800–0.872)	80.4	77.8	0.614
T2DM absent	748	0.854 (0.823–0.885)	82.1	79.6	—
By BMI Category					
BMI < 25 kg/m²	287	0.861 (0.814–0.908)	83.4	81.2	0.518
BMI 25–29.9 kg/m²	534	0.844 (0.811–0.877)	81.2	78.4	—
BMI ≥ 30 kg/m²	419	0.838 (0.800–0.876)	80.2	77.9	—
By Age Group					

Age < 45 years	498	0.852 (0.818–0.886)	82.3	80.1	0.647
Age ≥ 45 years	742	0.843 (0.813–0.873)	80.7	77.9	—
By Statin Use					
Statin users	287	0.829 (0.780–0.878)	79.6	76.8	0.412
Non-statin users	953	0.851 (0.824–0.878)	81.8	79.3	—

Table 7 Description: AUC values computed via DeLong method for each subgroup independently. Interaction p-values were derived from logistic regression models incorporating a product term between the GGT/HDL-C ratio and each stratifying variable. No statistically significant interactions were identified (all $p > 0.05$), confirming that the diagnostic utility of the GGT/HDL-C ratio is consistent and robust across sex, diabetes status, BMI category, age group, and statin use — a finding of substantial clinical importance for generalized application of this biomarker.

4.3 Summary of Key Results

The GGT/HDL-C ratio emerged as the strongest single composite predictor of NAFLD in this metabolic syndrome cohort. Its AUC of 0.847 was statistically superior to GGT alone (ΔAUC = 0.056; $p = 0.018$), HDL-C alone (ΔAUC = 0.123; $p < 0.001$), TyG index (ΔAUC = 0.044; $p = 0.031$), and HSI (ΔAUC = 0.061; $p = 0.007$). The multivariable-adjusted OR of 3.42 (95% CI: 2.67–4.38; $p < 0.001$) confirmed that the GGT/HDL-C ratio is an independent predictor of NAFLD after controlling for all established confounders, including insulin resistance measured by HOMA-IR. Subgroup analyses confirmed that the ratio's diagnostic performance was robust across sex, BMI categories, age groups, diabetes status, and statin use, with no significant interaction effects detected. The Spearman correlation between GGT/HDL-C ratio and CAP value ($r = 0.714$; $p < 0.001$) and liver stiffness ($r = 0.638$; $p < 0.001$) further validates the ratio's capacity to reflect hepatic steatosis severity beyond binary diagnostic classification.

5. Discussion

The key result of this paper, i.e., the GGT/HDL-C ratio proves to have high diagnostic values in patients with metabolic syndrome (AUC = 0.847) and it is better in comparison with many traditional non-invasive indices, is of great clinical importance. This composite (two-part) marker represents the first conceptual fusion of two models of mechanistically and pathophysiological complementing mechanisms of coexistence of oxidative injury in the liver, in the form of GGT elevation, and impaired lipid homeostasis, expressed as low HDL-C. Put in combination in a ratio form, these markers produce a multiplicative effect, where each marker is amplified to a greater diagnostic signal than what is offered by single markers. The pathophysiological explanatory argument is convincing. In NAFLD, the expression of GGT is induced in the hepatocytes in the glutathione cycle caused by the generation of reactive oxygen species in the mitochondrial lipid oxidation and endoplasmic reticulum stress, which cleaves glutathione to cysteinyl glycine and glutamate, lifestyle components capable of producing antioxidants to replace the depleted antioxidants. This implies that increased GGT is not a passive victim of hepatocyte membrane damage, but is an active product of the oxidative stress response characterizing NAFLD progression between simple steatosis and non-alcoholic steatohepatitis (NASH). At the same time, HDL impairment in metabolic syndrome (i.e., decrease in the reverse cholesterol transporting prowess of HDL and its anti-inflammatory functions) is a second factor in hepatic lipid entrapment and the spread of steatosis. The proportion thus reflects some interesting hepatic contraction: a growing alveolar oxidative stress with a decreasing lipid-cleaning rate. The fact that the GGT /HDL-C ratio was comparable in performance to the Fatty Liver Index which is also dependent on four input variables and the waist circumference measurement; yet only required two common laboratory values is practically important. A two-variable serum-based ratio would be far easier to use and interpret in resource constrained primary and community-based care (considering that anthropometric measurements are not consistently standardized). More so, the ratio showed similar diagnostic performance according to BMI subgroups such as those with a BMI less than 25 kg/m 2 (AUC = 0.861), indicating it as a measure of metabolic dysfunction of the hepatic system without regard to obesity, a result that is especially interesting in context of the recently increased awareness of lean NAFLD in South Asian communities. The fact that line fitting dose-response relationships between GGT/HDL-C quartiles and the degree of steatosis, the strong association with the values of CAP, and the liver stiffness, and the consistent subgroup results all point towards the fact that this ratio is not the binary classifier but the continuous severity measure. This has clinical implications of suggesting that serial measurement of the GGT/HDL-C ratio also could be considered useful in monitoring disease progression or therapeutic response, but longitudinal validation studies are needed to ascertain this usefulness. Such limitations of this study include that this is cross-sectional and it does not allow

making causal conclusions. Histological confirmation in the form of liver biopsy was not done on all subjects, and the use of CAP and ultrasound as the gold standard, although pragmatically necessary in large-scale studies were a source of potential misclassification. Self-report was used to estimate alcohol consumption, and there is no complete way of getting rid of social desirability bias when reporting alcohol consumption. The population used was exclusively South Indian and therefore without independent validation can be generalized further to other ethnic groups.

6. Conclusion

This is a cross-sectional study of large size that proves that the GGT/HDL-C ratio is a valid and accessible and independent biomarker during NAFLD diagnosis in the case of metabolic syndrome and its higher cut-off point of 8.3 is excellent with AR of 0.847. Its diagnostic capability was better than that of single GGT and HDL-C measurements and similar to some aligned composite indices at minimal cost as it only involves two standard laboratory measurements. The wide range of applicability of the ratio to varied clinical settings is supported by the fact that the ratio has been performing uniformly in major clinical subgroups such as sex, BMI category, diabetes status and statin use. The next round of prospective and multi-ethnic validation research should obtain the validation of the ratio in terms of its NAFLD progression tracking and its suitability in primary care screening protocols. It is possible to introduce GGT/HDL-C ratio on regular metabolic risk assessment screens that would significantly enhance detecting NAFLD at a young age within resource-constrained settings.

Data Availability Statement

The de-identified participant-level dataset supporting the findings of this study is openly available in the Harvard Data verse repository at the following link: **https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/GHFT2025NAFLD**. The dataset contains anonymized biochemical profiles, anthropometric measurements, imaging parameters, composite index scores, and NAFLD diagnostic classifications for all 1,240 enrolled participants. Access requires free registration with Harvard Data verse. Data were de-identified in accordance with ISO 29101 privacy framework standards. Any additional data requests may be directed to the corresponding author.

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