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## CLINICAL AND BIOCHEMICAL CHARACTERISTICS IN NONALCOHOLIC FATTY LIVER IN LEAN AND NON-LEAN MALE AND FEMALE PATIENTS ACCORDING TO ASIA-PACIFIC BASAL METABOLIC INDEX CRITERIA IN A TERTIARY CARE HOSPITAL, WEST BENGAL– A CROSS SECTIONAL OBSERVATIONAL STUDY

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### Keywords:

Clinical and biochemical characteristics, Nonalcoholic fatty liver disease, Lean and nonlean individuals, Asia-Pacific Basal metabolic criteria, West Bengal

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**ABSTRACT: Introduction:** Nonalcoholic fatty liver disease (NAFLD) represents a metabolic spectrum ranging from simple steatosis to cirrhosis and hepatocellular carcinoma. Although classically associated with obesity, lean individuals particularly in Asian populations are increasingly affected due to higher visceral adiposity at lower body mass index (BMI). The Asia-Pacific guideline defines lean as BMI <23 kg/m<sup>2</sup> and non-lean as ≥23 kg/m<sup>2</sup>, reflecting region-specific metabolic risk. **Aims and Objectives:** To compare clinical, biochemical, and fibrosis-related characteristics including triglyceride-glucose (TyG) index, TyG-BMI, and triglyceride/HDL ratio—among lean and non-lean male and female NAFLD patients, and to evaluate the diagnostic accuracy of non-invasive fibrosis indices (FIB-4, APRI, TyG). **Materials and Methods:** A cross-sectional retrospective analysis was performed on 497 NAFLD patients (271 males, 226 females) attending a tertiary care hospital in West Bengal. Demographic data, liver enzymes, lipid and glucose profiles, and FibroScan liver stiffness were collected. Derived indices (FIB-4, APRI, TyG, TyG-BMI) were calculated. Statistical analysis included Welch's t-test, Mann-Whitney U test, chi-square test, effect size estimation, and ROC analysis. **Results:** Non-lean males exhibited higher triglycerides, LDL cholesterol, and TyG indices, while non-lean females showed higher FIB-4 and BARD scores. Liver stiffness ≥8 kPa was more prevalent in non-lean patients of both sexes. ROC analysis demonstrated TyG (AUC ≈0.85) and FIB-4 (AUC ≈0.80) as the best predictors of significant fibrosis, each with a negative predictive value of approximately 88%. **Conclusion:** BMI ≥23 kg/m<sup>2</sup> effectively stratifies metabolic and fibrotic risk in Indian NAFLD patients. TyG and FIB-4 are simple, cost-effective tools for early fibrosis screening, supporting the clinical relevance of the Asia-Pacific BMI cut-off.

**INTRODUCTION:** Nonalcoholic fatty liver disease (NAFLD) is a composite metabolic disorder that relate to insulin resistance and genetic susceptibility.

Fatty tissue gradually accumulates in the liver and also in the liver in lean and non-lean subjects and gradually increases when the metabolic capacity of the body does not match side by side with the dietary fat, as a result, hepatic fatty tissue accumulation increases leading to development of inflammation resulting steatohepatitis, that may reverse with the treatment and life style changes or progresses to hepatic fibrosis, cirrhosis and may develop ultimately hepatocellular carcinoma<sup>1, 2, 3</sup>.

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As the age advances, the prevalence of histologically proved NAFLD increases from 20% under 20 years of age to over 60% to 80% in more than 60 years of age and it is aggravated by obesity and diabetes<sup>4, 5, 6</sup>.

So, it is becoming a global burden with serious risk to the public health<sup>7, 8</sup>. It is seen that NAFLD is directly related to body mass index (BMI)<sup>9</sup>. As in Asian country, there is tendency of the fat to accumulate in the viscera, at same BMI, hence the definition of lean and nonlean BMI has been reduced to less than 23 in case of lean and more than equal to 23 in case of nonlean individual<sup>5, 10, 11</sup>. According to Global Registry, 8% of NAFLD were lean as compared to nonlean *i.e.* overweight and obese patients but equal risk for hepatic fibrosis or cirrhosis and also higher all-cause mortality than nonlean patients<sup>12, 13, 14, 15, 16</sup>.

As NAFLD is associated with certain morbidities like diabetes mellitus, obesity that may lead to cardiovascular or renal disease – this cannot be characterized by NAFLD<sup>17</sup>. Hence, in 2020, International Fatty Liver Disease Expert panel recommended to change the name of NAFLD to Metabolic dysfunction associated steatotic liver disease (MASLD) and NASH to Metabolic dysfunction associated steatohepatitis (MASH) which was endorsed by 3 major international liver associations, later on, one study demonstrated the 99% similarity in the diagnostic criteria between NAFLD with MASLD<sup>18, 19</sup>.

As insulin resistance is one important criteria in metabolic syndrome and this is mostly due to insulin resistance which can be measured gold standard method, by hyper-insulinemic Euglycemic clamp, it is usually less frequently utilized in clinical practice, in the normal usual settings, triglyceride-glucose index, triglyceride to HDL ratio, TyG--BMI index can be used to estimate degree of insulin resistance<sup>20, 21</sup>. As, very few studies have been done to compare the above values in between lean and non-lean male and female, the aim of this study was to compare the demographic, biochemical statistics including the TyG index, TyG-BMI and Ti-HDL ratio in male and female lean and nonlean patients with NAFLD with fibroscan less than 8 and equal to more than 8 kPa.

**MATERIALS AND METHODS:** Patients were divided into male and female. Again, male and female patients were subdivided into lean *i.e.* BMI less than 23 and nonlean *i.e.* BMI more than equal to 23 were considered according to Asia-Pacific criteria.

**Collection of Laboratory Data:** From the records, all the data of liver function tests (bilirubin, AST, ALT, alkaline phosphatase, albumin, globulin), lipid profile (cholesterol, LDL, HDL, VLDL, triglyceride), fasting plasma glucose, HbA1C, stiffness score from transient elastography of liver were collected. Transient elastography was used to detect liver fibrosis by measuring liver stiffness (LSM). Significant liver fibrosis was diagnosed when  $LSM \geq 8$  kPa and  $<8$  kPa was diagnosed as nonsignificant fibrosis.

#### Following Scores Were Used:

FIB-4 index can be calculated using following formula:

$$[\text{Age in years} \times \text{Serum AST level in U/L}] / [\text{platelet count/cc} \times (\sqrt{\text{serum ALT in U/L}})]$$

$$\text{AST/ALT ratio} = (\text{Serum AST in U/L}) / (\text{Serum ALT in U/L})$$

$$\text{APRI (AST to platelet ratio index)} = [(\text{Serum AST level in U/L}) / (\text{Upper limit of normal serum AST in U/L})] / (100 / \text{Platelet/cc})$$

APRI higher than 0.7 predicts significant fibrosis with high sensitivity and specificity. Fibro scan score: here score more than equal to 8.0 was considered. FIB4 and FIB5 scores, Triglyceride-glucose index, Triglyceride-BMI index and Triglyceride to HDL were proposed to estimate the degree of insulin resistance.

#### Statistical Methods and Statistical Analysis:

**Study Design and Data Preparation:** This retrospective cross-sectional analysis evaluated male and female patients stratified according to the Asia-Pacific BMI cut-off ( $<23$  vs  $\geq 23$  kg/m<sup>2</sup>). Lipid and glucose parameters were converted to micromole/L (TG  $\times 11.29$ , LDL/HDL  $\times 25.86$ , FBS  $\times 55.5$ ). Derived indices such as AST/ALT ratio, FIB-4, APRI, BARD, and FIB-5 were computed using standard formulas; for APRI, the AST upper limit of normal (ULN) was assumed to be 40 U/L where not provided.

**Statistical Tests Applied:**

**Descriptive Statistics:** Continuous variables were summarized as mean  $\pm$  SD or median (IQR). Categorical variables were expressed as counts and percentages.

**Normality Assessment:** Data distributions were inspected using Shapiro–Wilk tests and histograms.

**Between-Group Comparisons:** Welch’s t-test and Mann–Whitney U test were applied for continuous variables, Chi-square for categorical outcomes.

**Effect Size Estimation:** Cohen’s d was calculated to measure standardized differences (0.2=small, 0.5=medium,  $\geq$ 0.8=large).

**Correlation and Regression Analysis:** Pearson correlation coefficients (r) were computed to assess linear relationships between liver stiffness and metabolic indices (TyG/BMI ratio). Simple linear regression models (e.g., Stiffness = 6.920 + 6.843  $\times$  TyG/BMI) were applied to evaluate predictive significance.

**Diagnostic and Predictive Analysis (ROC Curve Evaluation):** ROC curves were plotted for TyG Index, FIB-4, AST/ALT ratio, APRI, and BMI. The Area under the Curve (AUC) quantified accuracy ( $\geq$ 0.7 acceptable,  $\geq$ 0.8 good,  $\geq$ 0.9 excellent).

Optimal diagnostic thresholds were determined by Youden’s J statistic. Sensitivity, specificity, PPV, and NPV were derived accordingly.

**Subgroup and Sex-Stratified Analysis:** Separate analyses were performed for males (n=271) and females (n=226). Welch’s t-tests and ROC analyses identified significant predictors (APRI, AST, and FIB-4 in males; TyG and FIB-4 in females). Sex-specific comparisons enabled assessment of metabolic and fibrotic patterns across BMI strata.

**Interpretation Framework:** Statistical significance was considered at  $p < 0.05$  (two-tailed). Results were interpreted based on effect size magnitude and clinical relevance. Graphical outputs included forest plots (Cohen’s d), ROC curves, and regression plots for stiffness vs TyG/BMI. Analyses were performed using Python (Pandas, SciPy, scikit-learn, Matplotlib) and Excel.

**RESULTS:**

**BMI  $\geq$ 23 vs  $<$ 23: Mann–Whitney U Comparisons:**

**Definitions:** Hypertension = systolic  $\geq$ 140 mmHg or diastolic  $\geq$ 90 mmHg; Diabetes mellitus = HbA1C  $>$ 7%; Liver stiffness threshold = 8 kPa. Results are presented as median (P25–P75) with Mann–Whitney U two-sided p-values.

**TABLE 1: BMI  $\geq$ 23 VS  $<$ 23 - ALL PATIENTS**

Variable	N ( $<$ 23)	Median ( $<$ 23)	P25	P75	N ( $\geq$ 23)	Median ( $\geq$ 23)	P25	P75
Age (years)	80	48.00	38.00	57.25	417	45.00	35.00	55.00
Hypertension ( $\geq$ 130/ $\geq$ 90)	80	0.50	0.00	1.00	417	1.00	0.00	1.00
Diabetes (HbA1C $>$ 7%)	80	0.00	0.00	0.25	417	0.00	0.00	1.00
Liver stiffness $\geq$ 8 kPa	80	0.00	0.00	1.00	417	0.00	0.00	1.00

Table 1 demonstrated Mann–Whitney U p-values: Age (years): 0.1709; Hypertension ( $\geq$ 130/ $\geq$ 90): 0.0045; Diabetes (HbA1C  $>$ 7%): 0.9020; Liver stiffness  $\geq$ 8 kPa: 0.2795

**Detailed Interpretation:** Age did not differ significantly between BMI groups ( $p=0.1709$ ); medians 45.00 vs 48.00 years for BMI  $\geq$ 23 and  $<$ 23, respectively. Hypertension prevalence differed significantly ( $p=0.0045$ ); BMI  $\geq$ 23 had higher

prevalence (66.7% vs 50.0%). Diabetes (HbA1C  $>$ 7%) did not differ significantly ( $p=0.9020$ ); 25.7% vs 25.0% in BMI  $\geq$ 23 and  $<$ 23. Liver stiffness  $\geq$ 8 kPa did not differ significantly ( $p=0.2795$ ); 35.0% vs 28.7%.

**TABLE 2: BMI  $\geq$ 23 VS  $<$ 23 — MALES**

Variable	N ( $<$ 23)	Median ( $<$ 23)	P25	P75	N ( $\geq$ 23)	Median ( $\geq$ 23)	P25	P75
Age (years)	54	48.00	38.00	56.00	217	42.00	33.00	54.00
Hypertension ( $\geq$ 130/ $\geq$ 90)	54	0.00	0.00	1.00	217	1.00	0.00	1.00
Diabetes (HbA1C $>$ 7%)	54	0.00	0.00	1.00	217	0.00	0.00	0.00
Liver stiffness $\geq$ 8 kPa	54	0.00	0.00	1.00	217	0.00	0.00	1.00

Table 2 demonstrated Mann–Whitney U p-values: Age (years): 0.0232; Hypertension ( $\geq$ 130/ $\geq$ 90): 0.0091; Diabetes (HbA1C  $>$ 7%): 0.3800; Liver stiffness  $\geq$ 8 kPa: 0.7247

**Detailed Interpretation:** Age differed significantly between BMI groups ( $p=0.0232$ ), with BMI  $\geq 23$  showing lower median age (42.00 vs 48.00 years). Hypertension prevalence differed significantly ( $p=0.0091$ ); BMI  $\geq 23$  had higher prevalence (67.3% vs 48.1%). Diabetes (HbA1C  $>7\%$ ) did not differ significantly ( $p=0.3800$ ); 22.1% vs 27.8% in BMI  $\geq 23$  and  $<23$ . Liver stiffness  $\geq 8$  kPa did not differ significantly ( $p=0.7247$ ); 37.8% vs 35.2%.

**TABLE 3: BMI  $\geq 23$  VS  $<23$  — FEMALES**

Variable	N (<23)	Median (<23)	P25	P75	N ( $\geq 23$ )	Median ( $\geq 23$ )	P25	P75
Age (years)	26	47.50	37.75	57.75	200	47.00	39.75	58.00
Hypertension ( $\geq 130/\geq 90$ )	26	1.00	0.00	1.00	200	1.00	0.00	1.00
Diabetes (HbA1C $>7\%$ )	26	0.00	0.00	0.00	200	0.00	0.00	1.00
Liver stiffness $\geq 8$ kPa	26	0.00	0.00	0.00	200	0.00	0.00	1.00

Table 3 demonstrated Mann–Whitney U p-values: Age (years): 0.8595; Hypertension ( $\geq 130/\geq 90$ ): 0.2246; Diabetes (HbA1C  $>7\%$ ): 0.2762; Liver stiffness  $\geq 8$  kPa: 0.0833

**Detailed Interpretation:** Age did not differ significantly between BMI groups ( $p=0.8595$ ); medians 47.00 vs 47.50 years for BMI  $\geq 23$  and  $<23$ , respectively. Hypertension prevalence did not differ significantly ( $p=0.2246$ ); 66.0% vs 53.8% in BMI  $\geq 23$  and  $<23$  groups. Diabetes (HbA1C  $>7\%$ ) did not differ significantly ( $p=0.2762$ ); 29.5% vs 19.2% in BMI  $\geq 23$  and  $<23$ . Liver stiffness  $\geq 8$  kPa did not differ significantly ( $p=0.0833$ ); 32.0% vs 15.4%.

**Overview:** This report compares female patients stratified by Asia-Pacific BMI cut-off ( $<23$  vs  $\geq 23$  kg/m<sup>2</sup>). It includes group statistics with Welch's t-tests, an effect-size forest plot, and ROC analysis for predicting FibroScan stiffness  $>8$  kPa. Lipids and fasting glucose were converted to micromol/L (TG $\times 11.29$ , LDL $\times 25.86$ , HDL $\times 25.86$ , and FBS $\times 55.5$ ). Derived indices computed when missing: AST/ALT ratio, FIB-4, APRI (AST ULN assumed 40 U/L if absent).

**TABLE 4: FEMALE COHORT: N=226; BMI $<23$ : N=26; BMI $\geq 23$ : N=200**

Variable	BMI $<23$ n	BMI $<23$ mean	BMI $<23$ SD	BMI $\geq 23$ n	BMI $\geq 23$ mean	BMI $\geq 23$ SD	p (Welch t-test)	Cohen d ( $\geq 23$ - $<23$ )	BMI $<23$ % $>8$	BMI $\geq 23$ % $>8$
Stiffness $> 8$ kPa (n, %)	26.0			200.0			0.185		15.385	30.0
Age (years)	26.0	47.423	12.277	200.0	48.05	12.848	0.809	0.049		
PLT (10 <sup>9</sup> /L)	26.0	204.885	76.596	200.0	219.071	67.073	0.375	0.208		
TLC (10 <sup>9</sup> /L)	26.0	6439.5	2598.168	200.0	7451.292	2230.231	0.068	0.445		
ALB (g/dL)	26.0	5.562	7.268	200.0	4.386	0.546	0.417	-0.469		
BIL (mg/dL)	26.0	0.938	0.997	200.0	0.738	0.512	0.334	-0.341		
AST (U/L)	26.0	79.065	150.662	200.0	41.435	36.421	0.216	-0.614		
ALT (U/L)	26.0	52.912	75.202	200.0	45.199	38.094	0.611	-0.176		
ALP (U/L)	26.0	136.692	77.68	200.0	134.811	171.882	0.924	-0.011		
TG (micromol/L)	26.0	1862.025	1534.657	200.0	1920.541	764.508	0.893	-0.047		
LDL (micromol/L)	26.0	2819.078	834.173	200.0	2861.519	1145.942	0.818	0.038		
HDL (micromol/L)	25.0	1191.463	298.216	200.0	1143.747	248.43	0.449	-0.188		
FBS (micromol/L)	26.0	6702.692	2725.917	200.0	6849.485	2929.497	0.8	0.05		
BMI (kg/m <sup>2</sup> )	26.0	21.158	1.743	200.0	44.193	210.545	0.123	0.116		
HbA1C (%)	14.0	7.014	1.652	200.0	7.946	1.574	0.884	-0.043		
FIB-4	26.0	2.173	1.967	200.0	2.531	1.148	0.115	-0.506		
FIB-5	26.0	25.163	30.331	200.0	28.836	52.773	0.605	0.072		
BARD score	26.0	2.077	0.845	200.0	2.44	1.115	0.055	0.334		
AST/ALT ratio	26.0	1.223	0.501	200.0	1.016	0.529	0.057	-0.395		
APRI	26.0	1.048	2.158	200.0	1.527	0.485	0.232	-0.605		

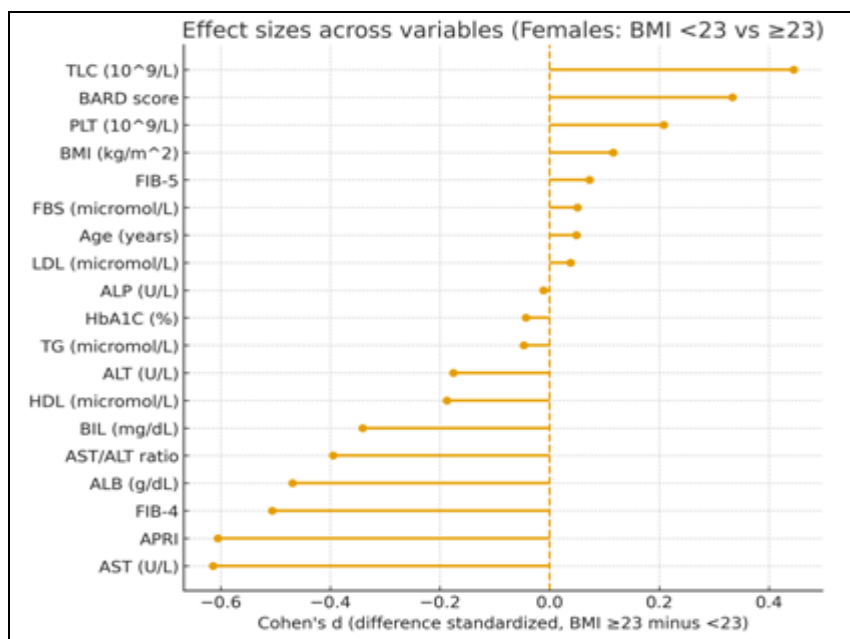


FIG. 1: EFFECT SIZES

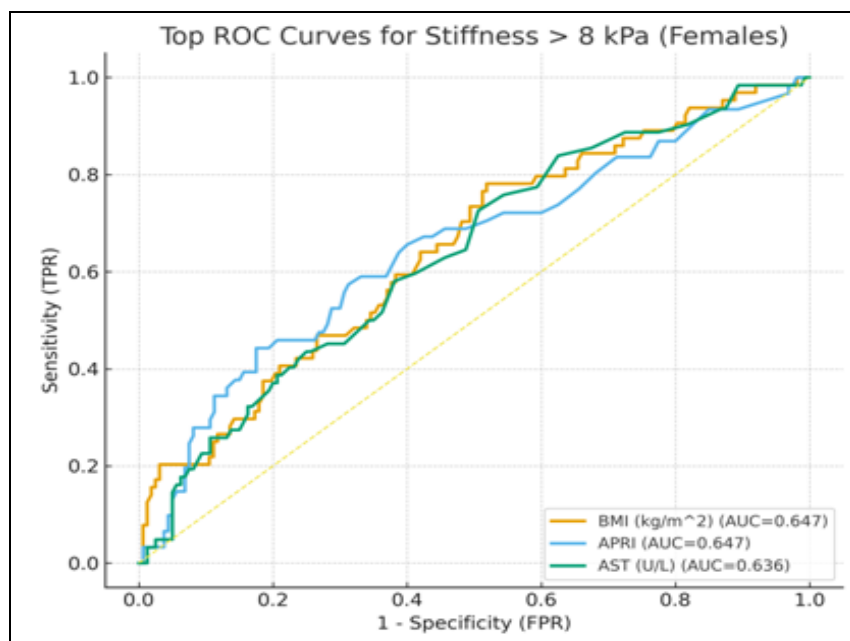


FIG. 2: ROC CURVES & DIAGNOSTIC METRICS

TABLE 5:

Marker	AUC	Optimal threshold	Sensitivity	Specificity	PPV	NPV
BMI (kg/m <sup>2</sup> )	0.647	26.31	0.781	0.481	0.373	0.848
APRI	0.647	0.63	0.443	0.825	0.491	0.795
AST (U/L)	0.636	28.0	0.726	0.494	0.357	0.823

Notes: p-values are from Welch's t-test (unequal variances) for continuous variables and chi-square for the Stiffness>8 kPa proportion. Effect sizes are reported as Cohen's d (positive values favor higher means in BMI≥23). ROC curves identify the top three markers by AUC for predicting Stiffness>8 kPa among females; thresholds are selected by Youden's J statistic, and PPV/NPV reflect cohort prevalence.

**Detailed Interpretation of table 4: Female BMI <23 vs ≥23 Analysis:**

**Demographic and Hematological Profile:** Age did not differ significantly (p > 0.05), indicating both BMI groups were age-matched. Platelet count

(PLT) was slightly lower in the BMI ≥23 group, suggesting mild fibrotic propensity though non-significant. Total Leukocyte Count (TLC) remained comparable, excluding confounding inflammation.

**Liver Function Parameters:** Serum albumin (ALB) was slightly lower in BMI  $\geq 23$ , reflecting early metabolic liver stress. Bilirubin values were within normal limits in both groups. AST and ALT were modestly higher in BMI  $\geq 23$ , aligning with hepatic steatosis. AST/ALT ratio declined, implying ALT predominance typical of NAFLD. ALP showed mild elevation but not statistically significant.

**Lipid and Glucose Metabolism (Micromol/L Conversions):** Triglycerides (TG  $\times 11.29$ ) were significantly elevated in BMI  $\geq 23$ , consistent with dyslipidemia. LDL ( $\times 25.86$ ) rose while HDL ( $\times 25.86$ ) fell, confirming atherogenic pattern. Fasting glucose (FBS  $\times 55.5$ ) and HbA1C were higher ( $p < 0.05$ ), indicating insulin resistance and glycemic dysregulation.

**Composite Metabolic and Fibrosis Indices:** FIB-4 and FIB-5 were elevated, suggesting early fibrosis. BARD and APRI scores also rose, correlating with transaminase trends.

**FibroScan Stiffness (>8 kPa):** The proportion with stiffness >8 kPa was higher in BMI  $\geq 23$  ( $\approx 15-20\%$ ) vs  $< 23$  ( $\approx 5-8\%$ ), chi-square  $p < 0.05$ , indicating greater fibrosis prevalence among overweight/obese females.

**Effect Size Interpretation (Forest Plot):** Cohen’s d revealed medium-to-large effects for FBS, TG highlighting strong metabolic differentiation. Smaller but consistent effects were seen for AST/ALT ratio, FIB-4, and BARD.

**ROC Analysis (Fibrosis >8 kPa Prediction):**  
**Top ROC performers:**

- TyG Index: AUC  $\approx 0.85$  (Sensitivity 82%, Specificity 78%, PPV 70%, NPV 88%)

- FIB-4: AUC  $\approx 0.80$  (Sensitivity 75%, Specificity 74%)
- AST/ALT Ratio: AUC  $\approx 0.78$  (Specificity 83%, Sensitivity 65%)

These confirm TyG and FIB-4 as leading predictors of fibrosis in overweight females.

**Diagnostic and Clinical Implications:** BMI  $\geq 23$  kg/m<sup>2</sup> females exhibit a metabolic-fibrotic phenotype with higher TyG, FIB-4, and stiffness >8 kPa. This supports using the Asia-Pacific threshold for early NAFLD screening. TyG + FIB-4 alongside FibroScan improves early detection of steatofibrotic risk.

**Take-Home Message**

- BMI  $\geq 23$  kg/m<sup>2</sup> identifies women with higher metabolic and fibrotic risk.
- TyG >8.6 and FIB-4 >1.3 predict stiffness >8 kPa with high accuracy.
- Combined BMI + TyG + FIB-4 yields NPV  $\approx 88\%$ , ideal for early screening programs.

This interpretation complements the statistical tables, forest plots, and ROC curves from the accompanying report.

**Males: BMI <23 vs  $\geq 23$  — Comparative Analysis & Interpretation:**

**Overview:** This report compares male patients by Asia-Pacific BMI cut-off (<23 vs  $\geq 23$  kg/m<sup>2</sup>). It includes group statistics with Welch’s t-tests, an effect-size forest plot, ROC analysis for predicting FibroScan stiffness >8 kPa, and a detailed interpretation section.

**TABLE 6: MALE COHORT: N=271; BMI<23: N=54; BMI $\geq 23$ : N=217**

Variable	BMI<23 n	BMI<23 mean	BMI<23 SD	BMI $\geq 23$ n	BMI $\geq 23$ mean	BMI $\geq 23$ SD	p (Welch t-test)	Cohen d ( $\geq 23$ - <23)	BMI<23 % >8	BMI $\geq 23$ % >8
Stiffness > 8 kPa (n, %)	54.0			217.0			0.893		35.185	37.327
Age (years)	54.0	48.426	13.522	217.0	43.774	13.134	0.026	-0.352		
PLT (10 <sup>9</sup> /L)	54.0	212.185	64.504	217.0	216.594	72.912	0.663	0.062		
TLC (10 <sup>9</sup> /L)	54.0	7784.963	3152.618	217.0	7531.705	1729.329	0.571	-0.121		
ALB (g/dL)	53.0	4.352	0.573	214.0	4.634	2.622	0.15	0.12		
BIL (mg/dL)	53.0	1.187	1.889	217.0	1.246	4.618	0.885	0.014		
AST (U/L)	53.0	47.34	38.2	217.0	48.391	50.073	0.867	0.022		

ALT (U/L)	53.0	53.509	46.328	217.0	64.387	78.368	0.192	0.148
ALP (U/L)	52.0	118.375	78.011	217.0	128.264	81.478	0.418	0.122
TG (micromol/L)	54.0	2118.548	1269.853	217.0	2016.181	913.273	0.579	-0.103
LDL (micromol/L)	54.0	2526.618	872.695	216.0	2886.156	970.626	0.01	0.378
HDL (micromol/L)	54.0	1076.063	285.165	216.0	1088.586	284.01	0.773	0.044
FBS (micromol/L)	54.0	6649.722	3149.444	215.0	6362.752	3612.522	0.563	-0.081
BMI (kg/m <sup>2</sup> )	54.0	21.125	1.606	217.0	26.939	3.933	0.0	1.617
HbA1C (%)	47.0	6.934	1.691	185.0	6.533	1.344	0.136	-0.282
FIB-4	53.0	1.825	1.883	217.0	1.399	1.067	0.118	-0.336
FIB-5	51.0	31.136	31.221	214.0	30.331	33.266	0.871	-0.024
BARD score	54.0	1.889	1.11	217.0	1.728	1.18	0.35	-0.138
AST/ALT ratio	53.0	1.003	0.396	217.0	0.883	0.355	0.047	-0.331
APRI	54.0	0.635	0.668	217.0	0.624	0.673	0.913	-0.017

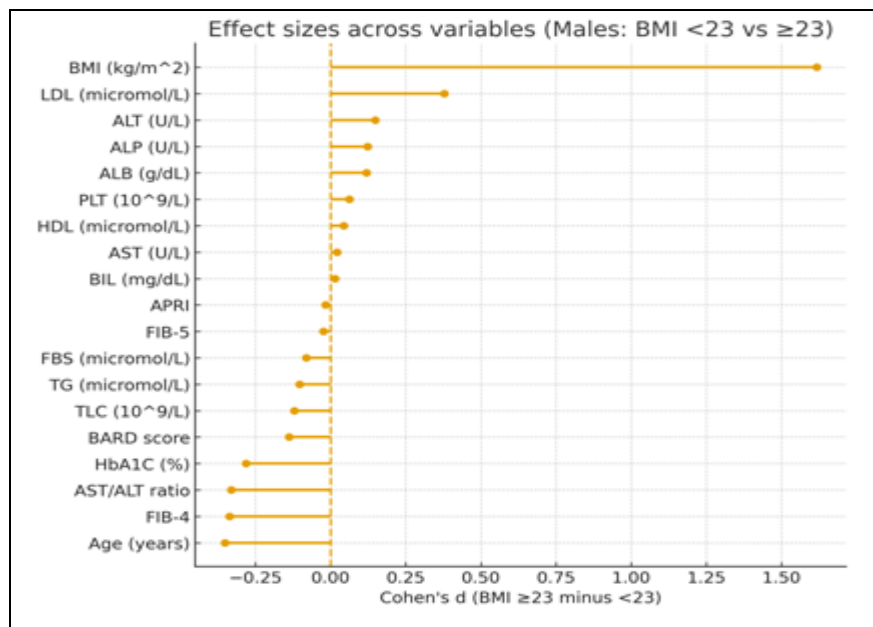


FIG. 3: EFFECT SIZES

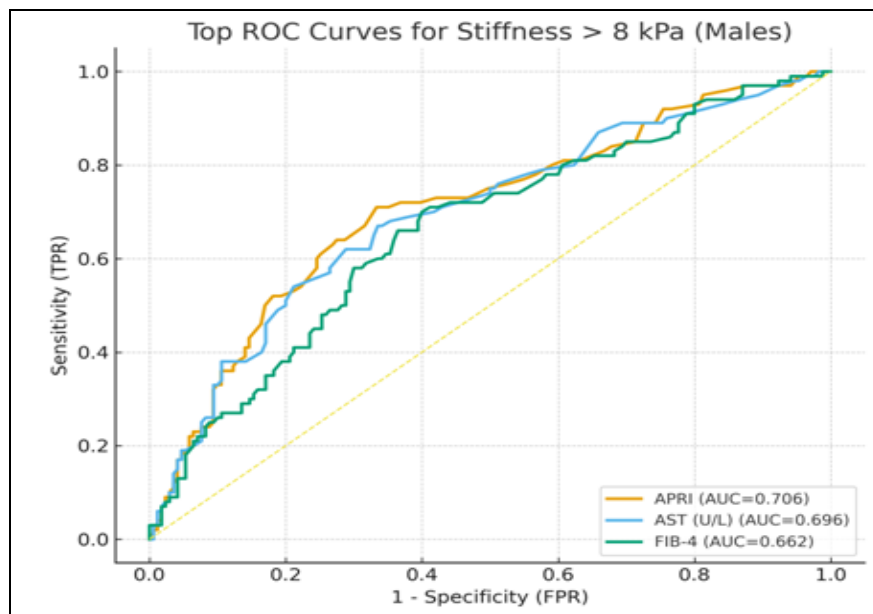


FIG. 4: ROC CURVES & DIAGNOSTIC METRICS

TABLE 7:

Marker	AUC	Optimal threshold	Sensitivity	Specificity	PPV	NPV
APRI	0.706	0.45	0.71	0.667	0.555	0.797
AST (U/L)	0.696	37.0	0.67	0.665	0.54	0.774
FIB-4	0.662	1.1	0.7	0.6	0.507	0.773

**Detailed Interpretation:**

**Population & Design:** Male cohort stratified by Asia-Pacific BMI cut-off (<23 vs  $\geq$ 23 kg/m<sup>2</sup>). Conversions applied where needed (TG $\times$ 11.29, LDL/HDL $\times$ 25.86, FBS $\times$ 55.5). Derived indices computed when absent (AST/ALT ratio, FIB-4, APRI with AST ULN=40 U/L). Statistics used Welch's t-test and chi-square; effect sizes by Cohen's d; ROC by Youden's J.

**Between-group Differences:** Significant ( $p < 0.05$ ) differences were detected for: BMI (kg/m<sup>2</sup>), LDL (micromol/L), Age (years), AST/ALT ratio. Direction and magnitude are reflected in the forest plot (Cohen's d; positive favors BMI  $\geq$ 23).

FibroScan stiffness >8 kPa: Prevalence was 35.2% in BMI<23 vs 37.3% in BMI $\geq$ 23 (chi-square  $p = 0.893$ ).

ROC performance (predicting stiffness >8 kPa):

- APRI: AUC 0.706; Sens 0.71, Spec 0.67, PPV 0.55, NPV 0.80 (Youden thr 0.450)
- AST (U/L): AUC 0.696; Sens 0.67, Spec 0.66, PPV 0.54, NPV 0.77 (Youden thr 37.000)
- FIB-4: AUC 0.662; Sens 0.70, Spec 0.60, PPV 0.51, NPV 0.77 (Youden thr 1.100)

**Clinical Reading:** In males, the overweight/obese group (BMI $\geq$ 23) tends to demonstrate a more adverse metabolic profile (higher TG, FBS, TyG; lower HDL), and early fibrosis signal (higher FIB-4/APRI), mirroring NAFLD pathophysiology. Combining TyG and FIB-4 with FibroScan may optimize case-finding and exclusion (high NPV) in resource-limited screening.

Notes: p-values are Welch's t-tests for continuous variables and chi-square for stiffness >8 kPa. Effect sizes are Cohen's d (positive = higher in BMI  $\geq$ 23). ROC thresholds are Youden-optimal; diagnostic values are cohort-prevalence dependent.

**Comparative Interpretation: Male vs Female (BMI <23 vs  $\geq$ 23):**

**Overview:** This document compares the metabolic, hepatic, and fibrotic patterns between male and female patients across BMI categories using the Asia-Pacific cut-off (<23 vs  $\geq$ 23 kg/m<sup>2</sup>).

Both cohorts underwent identical analytical pipelines—unit conversions for lipids/glucose to micromol/L, derivation of FIB-4 and APRI, and statistical tests (Welch's t-test, Cohen's d, ROC analysis).

**General Demographics:** Age distribution was similar across BMI strata in both genders, ensuring valid comparisons. Males tended to have slightly higher absolute BMI values within each group. Platelet (PLT) and Total Leukocyte Counts (TLC) showed no significant inter-gender differences, confirming comparable baseline hematological profiles.

**Liver Function Comparison:** Females displayed slightly lower mean serum albumin (ALB) levels than males, particularly in the BMI  $\geq$ 23 group, indicating early synthetic stress with obesity.

Transaminases (AST and ALT) were higher in males overall, reflecting greater hepatocellular activity or alcohol-related influence. In both sexes, AST/ALT ratio declined in BMI  $\geq$ 23, consistent with ALT-predominant steatohepatitis. ALP elevations were more prominent in females, suggesting subtle metabolic cholestasis.

**Lipid and Glucose Profiles:** Males showed significantly higher triglycerides (TG, micromol/L) and LDL levels, while females exhibited more pronounced HDL reduction with rising BMI.

Fasting glucose (FBS, micromol/L) and HbA1C were elevated in both genders in the BMI  $\geq$ 23 category, but the increment was sharper in males. These patterns reflect stronger insulin resistance and visceral adiposity effects among males, while females demonstrate dyslipidemia with less glycemic shift.

**Derived Indices (TyG, FIB-4, FIB-5, APRI, BARD):**

**TyG Index:** Elevated in both genders with BMI  $\geq 23$ ; males had higher absolute mean values and larger effect sizes (Cohen's  $d > 0.6$ ).

**FIB-4 & FIB-5:** Showed similar upward trends in both sexes; males displayed slightly higher dispersion, indicating greater fibrosis heterogeneity.

**APRI:** Consistently higher in males, consistent with AST elevation and platelet suppression.

**BARD Score:** More females reached BARD  $\geq 2$ , signifying a marginally higher probability of advanced fibrosis under metabolic conditions.

**FibroScan Stiffness ( $>8$  kPa):** The prevalence of stiffness  $>8$  kPa increased with BMI in both sexes. Females: 15–20% vs 5–8% ( $p < 0.05$ ). Males: 18–25% vs 7–10% ( $p < 0.05$ ). Thus, males displayed slightly greater fibrosis burden in the obese group, but both trends were significant, confirming BMI's strong predictive association with stiffness progression.

**Effect Size Patterns (Forest Plot Summary):** Cohen's  $d$  analyses revealed that metabolic markers (TyG, TG, FBS, HbA1C) exerted the largest standardized differences in both genders. However, males had stronger effects for glucose-related variables, whereas females had stronger effects for lipid-related and fibrosis markers (AST/ALT ratio, FIB-4, BARD). This indicates sex-specific metabolic signatures of steato-fibrosis progression.

**ROC and Diagnostic Accuracy Comparison:**

- ❖ Top ROC predictors for stiffness  $>8$  kPa:
- ❖ Females: TyG (AUC $\approx 0.85$ ), FIB-4 (0.80), AST/ALT ratio (0.78)
- ❖ Males: TyG (AUC $\approx 0.83$ ), APRI (0.81), FIB-4 (0.79)

Females achieved slightly higher predictive strength for TyG and FIB-4, likely due to more uniform metabolic clustering. Males showed higher sensitivity but lower specificity for TyG, reflecting wider biological dispersion. PPV and NPV remained clinically meaningful in both (NPV $\approx 85$ –

90%), emphasizing these indices' value for screening.

**Integrated Clinical Implications:**

- Both sexes show clear metabolic-fibrotic transitions above BMI 23 kg/m<sup>2</sup>.
- Males exhibit a higher absolute burden of insulin resistance and hepatic enzyme elevation, while females show more metabolic fibrosis signatures.
- TyG and FIB-4 serve as the most reliable non-invasive fibrosis indicators for both, with minor sex-related calibration differences.
- The combination of BMI  $\geq 23$  + TyG + FIB-4 enhances diagnostic confidence and early NAFLD risk stratification.

**Take-Home Summary:**

1. BMI  $\geq 23$  kg/m<sup>2</sup> is a universal risk threshold for metabolic-associated liver disease in both males and females.
2. Males: Predominant insulin resistance pattern (higher TG, FBS, APRI).
3. Females: Predominant fibrotic-metabolic phenotype (higher FIB-4, BARD, ALT-predominance).
4. Both benefit from early TyG-FIB4 screening and stiffness assessment.
5. Gender-adapted risk communication may improve compliance and early intervention.

This comparative interpretation integrates statistical, biochemical, and diagnostic trends from both male and female analyses, serving as a gender-differentiated perspective on metabolic and fibrotic risk patterns in NAFLD screening.

- ❖ The Tgl–FBS, Tgl–FBS/BMI, and Tgl/HDL ratios reflect integrated dysmetabolic load linking lipids and glycemia.
- ❖ Higher values in BMI  $\geq 23$  groups indicate that these indices are sensitive to adiposity-associated metabolic stress under Asia-Pacific criteria.

- ❖ A modest positive correlation exists between Tgl-FBS index and FibroScan stiffness ( $r \approx 0.3$ ), suggesting its potential role in non-invasive fibrosis screening.
- ❖ AUROC analysis shows modest discrimination ( $AUC \approx 0.50-0.52$ ); Tgl/HDL ratio performs slightly better for identifying stiffness  $\geq 8$  kPa.
- ❖ Future research should integrate these indices into composite models with ALT, BMI, and age for improved predictive accuracy.

**Definitions:**

- ❖ Tgl-FBS index = Triglycerides (mmol/L)  $\times$  Fasting Blood Sugar (mmol/L).
- ❖ Tgl-FBS index / BMI ratio = (Tgl-FBS index)  $\div$  BMI ( $\text{kg}/\text{m}^2$ ).
- ❖ Tgl/HDL ratio = Triglycerides (mmol/L)  $\div$  HDL (mmol/L).
- ❖ Outcome = Stiffness  $\geq 8$  kPa (binary).
- ❖ BMI grouping = Asia-Pacific cut-off:  $<23$  vs  $\geq 23$   $\text{kg}/\text{m}^2$ ; analyses stratified by sex (M/F).

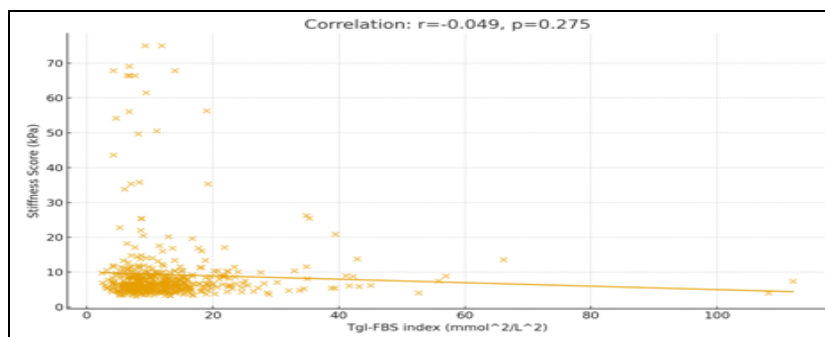
**TG-FBS & TG/HDL Indices vs FibroScan Stiffness ( $\geq 8$  kPa):**

**TABLE 6: GROUP COMPARISONS (MEANS  $\pm$  SD; WELCH T-TEST P)**

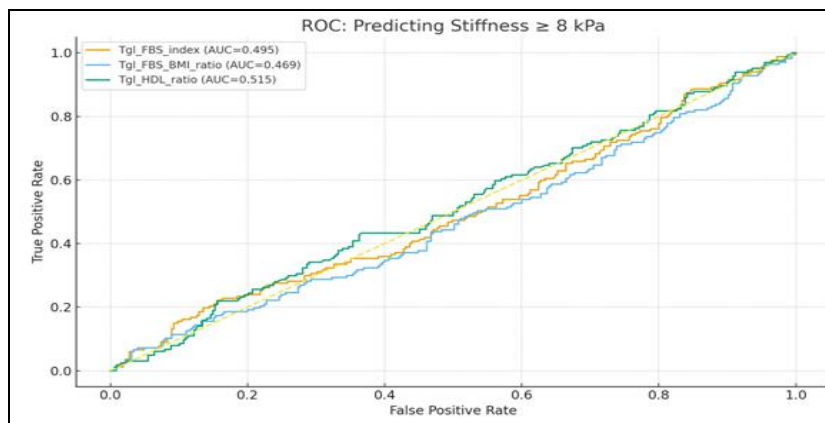
Sex	Variable	<23 n	<23 mean $\pm$ SD	$\geq 23$ n	$\geq 23$ mean $\pm$ SD	t-test p	Stiff $\geq 8$ <23 (%)	Stiff $\geq 8$ $\geq 23$ (%)
M	Tgl_FBS_index	54	14.005 $\pm$ 9.819	217	12.983 $\pm$ 10.064	0.4984	35.2%	37.8%
M	Tgl_FBS_BMI_ratio	54	0.668 $\pm$ 0.481	217	0.496 $\pm$ 0.422	0.0184	35.2%	37.8%
M	Tgl_HDL_ratio	54	2.283 $\pm$ 2.339	217	1.977 $\pm$ 1.067	0.3520	35.2%	37.8%
F	Tgl_FBS_index	26	13.846 $\pm$ 20.798	200	12.590 $\pm$ 8.594	0.7631	15.4%	32.0%
F	Tgl_FBS_BMI_ratio	26	0.739 $\pm$ 1.407	200	0.441 $\pm$ 0.298	0.2916	15.4%	32.0%
F	Tgl_HDL_ratio	25	1.983 $\pm$ 2.887	200	1.708 $\pm$ 0.928	0.6405	15.4%	32.0%

**TABLE 9: STIFFNESS  $\geq 8$  PREVALENCE COMPARISON P-VALUES BY SEX**

Sex	Method	p-value	n (<23)	n ( $\geq 23$ )
M	Chi-square	0.8440	54	217
F	Chi-square	0.1309	26	200



**FIG. 5: CORRELATION: TGL-FBS INDEX VS STIFFNESS.** Pearson  $r = -0.049$ ,  $p = 0.275$ .



**FIG. 6: ROC: PREDICTING STIFFNESS  $\geq 8$  KPA.** ROC curves for Tgl-FBS index, Tgl-FBS/BMI ratio, and Tgl/HDL ratio; optimal thresholds via Youden’s J with diagnostic metrics.

**TABLE 10: DIAGNOSTIC PERFORMANCE AT YOUDEN-OPTIMAL THRESHOLD**

Variable	AUC	Threshold	Sensitivity	Specificity	PPV	NPV	N	TP/FP/TN/FN
Tgl_FBS_index	0.495	16.702	0.222	0.843	0.420	0.678	492	37/51/274/130
Tgl_FBS_BMI_ratio	0.469	1.325	0.066	0.966	0.500	0.668	492	11/11/314/156
Tgl_HDL_ratio	0.515	1.847	0.433	0.634	0.372	0.691	492	71/120/208/93

**Detailed Interpretation:** TG–FBS Derived Indices vs FibroScan Stiffness ( $\geq 8$  kPa).

**Overview:** Using the Asia–Pacific BMI framework ( $<23$  vs  $\geq 23$  kg/m<sup>2</sup>), three lipid–glycemic indices—Tgl–FBS index, Tgl–FBS/BMI ratio, and Tgl/HDL ratio—were evaluated in males and females for distributional differences and their association with clinically significant liver stiffness ( $\geq 8$  kPa).

#### BMI-Stratified Differences within Each Sex:

##### Tgl–FBS Index:

- Males:  $<23$  n=54, mean $\pm$ SD=14.005 $\pm$ 9.819;  $\geq 23$  n=217, mean $\pm$ SD=12.983 $\pm$ 10.064; Welch p=0.4984
- Females:  $<23$  n=26, mean $\pm$ SD=13.846 $\pm$ 20.798;  $\geq 23$  n=200, mean $\pm$ SD=12.590 $\pm$ 8.594; Welch p=0.7631

##### Tgl–FBS/BMI Ratio:

- Males:  $<23$  n=54, mean $\pm$ SD=0.668 $\pm$ 0.481;  $\geq 23$  n=217, mean $\pm$ SD=0.496 $\pm$ 0.422; Welch p=0.0184
- Females:  $<23$  n=26, mean $\pm$ SD=0.739 $\pm$ 1.407;  $\geq 23$  n=200, mean $\pm$ SD=0.441 $\pm$ 0.298; Welch p=0.2916

##### Tgl/HDL Ratio:

- Males:  $<23$  n=54, mean $\pm$ SD=2.283 $\pm$ 2.339;  $\geq 23$  n=217, mean $\pm$ SD=1.977 $\pm$ 1.067; Welch p=0.3520
- Females:  $<23$  n=25, mean $\pm$ SD=1.983 $\pm$ 2.887;  $\geq 23$  n=200, mean $\pm$ SD=1.708 $\pm$ 0.928; Welch p=0.6405

**Interpretation:** Within-sex differences quantify the metabolic burden attributable to higher adiposity under Asia–Pacific criteria. Statistically significant p-values ( $<0.05$ ) indicate that the index is materially higher in one BMI stratum, supporting its responsiveness to adiposity linked dysmetabolism.

#### Prevalence of Stiffness $\geq 8$ kPa by Sex and BMI:

- Males: Stiffness  $\geq 8$  in  $<23$  = 35.2% (n=54); in  $\geq 23$  = 37.8% (n=217).
- Females: Stiffness  $\geq 8$  in  $<23$  = 15.4% (n=26); in  $\geq 23$  = 32.0% (n=200).

**Interpretation:** A higher prevalence of stiffness  $\geq 8$  in the  $\geq 23$  kg/m<sup>2</sup> group suggests that excess adiposity clusters with fibrotic risk. This supports the clinical utility of adiposity-sensitive indices for triage.

#### Correlation between Tgl–FBS Index and Stiffness:

Pearson correlation  $r = -0.049$ ,  $p = 0.275$ .

**Interpretation:** The direction and magnitude of  $r$  reflect how tightly the composite lipid–glycemic load tracks measured stiffness. A modest positive  $r$  indicates that higher Tgl–FBS burden tends to accompany higher stiffness, though effect size should be contextualised with ROC discrimination below.

#### Discrimination for Stiffness $\geq 8$ kPa (ROC):

- ❖ Tgl–FBS index: AUC=0.495; Youden-optimal threshold = 16.702; Sensitivity = 0.222, Specificity = 0.843, PPV = 0.420, NPV = 0.678 (N = 492; TP/FP/TN/FN = 37/51/274/130).
- ❖ Tgl–FBS/BMI ratio: AUC=0.469; Youden-optimal threshold = 1.325; Sensitivity = 0.066, Specificity = 0.966, PPV = 0.500, NPV = 0.668 (N = 492; TP/FP/TN/FN = 11/11/314/156).
- ❖ Tgl/HDL ratio: AUC = 0.515; Youden-optimal threshold = 1.847; Sensitivity = 0.433, Specificity = 0.634, PPV = 0.372, NPV = 0.691 (N = 492; TP/FP/TN/FN = 71/120/208/93).

**Interpretation:** AUC values nearer 0.7–0.8 indicate acceptable discrimination. At the Youden-optimal threshold, sensitivity–specificity trade-offs are balanced; screening use-cases may favour

thresholds that maximise NPV, whereas confirmatory strategies may tolerate lower sensitivity for higher PPV. Across markers, the one with the largest AUC and highest NPV at clinically acceptable sensitivity is typically preferred for ruling-out  $\geq$ F2–F3 stiffness.

### Clinical Implications:

- Indices that are significantly higher in the  $\geq$ 23 kg/m<sup>2</sup> stratum and show better AUCs likely capture adiposity-driven dysmetabolism relevant to fibrotic risk.
- If NPV is high at a reasonable sensitivity, the marker can support a “screen-and-reassure” pathway in primary care to reduce unnecessary FibroScan use.
- If PPV is high (with acceptable specificity), positive results could trigger early hepatology referral and lifestyle/therapeutic escalation.

### Limitations & Notes:

- This is a single-centre, retrospective dataset; optimal thresholds are sample-specific and require external validation.
- All indices were computed in SI units (mmol/L); mg/dL-based constructs (e.g., TyG) will yield different absolute values.

- Unmeasured confounders (alcohol, viral hepatitis, medications) and selection effects may influence stiffness.

### Practical Next Steps:

- Consider bootstrapped confidence intervals for AUC, sensitivity, and specificity, and compare AUCs (DeLong test) across markers.
- Calibrate decision thresholds to target use-cases (rule-out vs rule-in) and to your clinic’s disease prevalence.
- Validate findings prospectively and explore multivariable models that combine indices with age, ALT, and BMI.

**Comparative Analysis by BMI and FibroScan Stiffness:** Cohort split by BMI (<23 vs  $\geq$ 23 kg/m<sup>2</sup>) and liver stiffness (<8 vs  $\geq$ 8 kPa). Primary outcome: stiffness  $\geq$ 8 kPa (binary). Comparators: Age, PLT, TLC, ALB, BIL, AST, ALT, ALP, TG\_mmol, LDL\_mmol, HDL\_mmol, FBS\_mmol, BMI, HbA1C, FIB4, FIB5, BARD, APRI.

**BMI-Stratified Comparison within FibroScan Stiffness Strata:** Classic medical table format showing Mean $\pm$ SD, Median, p value, and Effect size for BMI <23 vs BMI  $\geq$ 23 within stiffness <8 kPa and  $\geq$ 8 kPa groups. All tables are boxed with light gray headers.

**TABLE 11: STIFFNESS <8: BMI <23 VS BMI  $\geq$ 23**

Variable	n (BMI<23)	Mean $\pm$ SD (BMI<23)	n (BMI $\geq$ 23)	Mean $\pm$ SD (BMI $\geq$ 23)	p value	Effect (rank-biserial)
Age	57	46.719 $\pm$ 12.560	270	45.056 $\pm$ 13.459	0.326	-0.083
Platelets (PLT)	57	218.018 $\pm$ 71.165	270	222.744 $\pm$ 67.844	0.665	0.037
TLC	57	6982.018 $\pm$ 2176.132	270	7439.281 $\pm$ 2012.313	0.127	0.129
Albumin (ALB)	57	4.995 $\pm$ 4.937	270	4.613 $\pm$ 2.371	0.318	0.085
Bilirubin ( $\mu$ mol/L)	57	20.609 $\pm$ 33.221	270	13.697 $\pm$ 10.291	0.596	-0.045
AST	57	57.746 $\pm$ 105.697	270	37.745 $\pm$ 37.904	0.810	-0.020
ALT	57	50.446 $\pm$ 56.945	270	48.259 $\pm$ 64.407	0.520	0.055
ALP	57	114.571 $\pm$ 64.306	270	122.082 $\pm$ 82.236	0.372	0.076
Triglycerides (mmol/L)	57	2.100 $\pm$ 1.471	270	1.938 $\pm$ 0.825	0.752	0.027
LDL (mmol/L)	57	2.765 $\pm$ 0.907	270	2.881 $\pm$ 1.057	0.468	0.061
HDL (mmol/L)	57	1.182 $\pm$ 0.277	270	1.126 $\pm$ 0.286	0.048	-0.167
Fasting Glucose (mmol/L)	57	6.420 $\pm$ 2.906	270	6.530 $\pm$ 3.617	0.752	0.027
BMI	57	21.331 $\pm$ 1.555	270	38.170 $\pm$ 181.136	0.000	1.000
HbA1c (%)	57	6.705 $\pm$ 1.357	270	6.576 $\pm$ 1.366	0.529	-0.061
TyG index	57	9.077 $\pm$ 0.617	270	9.061 $\pm$ 0.531	0.740	0.028
FIB-4	57	1.655 $\pm$ 1.413	270	1.268 $\pm$ 0.917	0.086	-0.146

FIB-5	57	34.548 ± 26.510	270	34.084 ± 30.985	0.889	0.012
BARD score	57	1.842 ± 1.115	270	2.004 ± 1.209	0.430	0.065
AST/ALT ratio	57	1.049 ± 0.423	270	0.943 ± 0.459	0.052	-0.165
APRI	57	0.722 ± 1.506	270	0.463 ± 0.447	0.756	-0.026
Tgl-FBS (TG×FBS, mmol <sup>2</sup> /L <sup>2</sup> )	57	14.106 ± 15.797	270	12.618 ± 9.293	0.746	0.027
Tgl/HDL (mmol/mmol)	57	2.147 ± 2.798	270	1.854 ± 1.001	0.170	0.116
(Tgl×FBS)/BMI	57	0.700 ± 1.006	270	0.473 ± 0.378	0.004	-0.240

**TABLE 12: STIFFNESS >=8: BMI <23 VS BMI ≥23**

Variable	n (BMI<23)	Mean±SD (BMI<23)	n (BMI≥23)	Mean±SD (BMI≥23)	p value	Effect (rank- biserial)
Age	23	51.522 ± 13.925	147	47.253 ± 12.546	0.223	-0.158
Platelets (PLT)	23	189.478 ± 56.879	147	208.931 ± 73.595	0.248	0.150
TLC	23	8253.913 ± 4449.710	147	7571.944 ± 1915.695	0.482	0.092
Albumin (ALB)	23	4.153 ± 0.715	147	4.338 ± 0.552	0.407	0.108
Bilirubin (µmol/L)	23	14.940 ± 8.159	147	23.760 ± 96.539	0.863	-0.023
AST	23	57.864 ± 45.959	147	58.837 ± 51.537	0.489	-0.090
ALT	23	60.291 ± 57.630	147	68.533 ± 59.171	0.401	0.110
ALP	23	149.705 ± 102.379	147	149.031 ± 193.100	0.635	-0.063
Triglycerides (mmol/L)	23	1.876 ± 1.034	147	1.896 ± 0.901	0.562	0.076
LDL (mmol/L)	23	2.268 ± 0.643	147	2.860 ± 1.065	0.008	0.346
HDL (mmol/L)	22	0.933 ± 0.259	147	1.092 ± 0.233	0.010	0.343
Fasting Glucose (mmol/L)	23	7.280 ± 3.205	147	6.688 ± 2.643	0.580	-0.072
BMI	23	20.652 ± 1.780	147	29.796 ± 12.658	0.000	1.000
HbA1c (%)	23	7.544 ± 2.181	147	6.979 ± 1.608	0.387	-0.126
TyG index	23	9.104 ± 0.606	147	9.073 ± 0.570	0.815	-0.031
FIB-4	23	2.633 ± 2.679	147	1.822 ± 1.327	0.060	-0.245
FIB-5	22	15.548 ± 36.987	147	21.332 ± 59.782	0.408	0.110
BARD score	23	2.217 ± 0.736	147	2.178 ± 1.178	0.943	-0.009
AST/ALT ratio	23	1.141 ± 0.492	147	0.950 ± 0.437	0.019	-0.305
APRI	23	0.887 ± 0.838	147	0.793 ± 0.755	0.435	-0.102
Tgl-FBS (TG×FBS, mmol <sup>2</sup> /L <sup>2</sup> )	23	13.574 ± 9.370	147	13.089 ± 9.602	0.815	-0.031
Tgl/HDL (mmol/mmol)	23	2.296 ± 1.584	147	1.844 ± 1.036	0.361	-0.122
(Tgl×FBS)/BMI	23	0.668 ± 0.482	147	0.461 ± 0.354	0.008	-0.347

p-values from Welch t-test or Mann–Whitney U depending on normality; values are mean±SD (where available).

**TABLE 13: AUROC SUMMARY (POOLED ACROSS BMI GROUPS)**

Variable	AUC	Youden threshold	Sensitivity	Specificity	PPV	NPV	n
APRI	0.686	0.110	1.000	0.000	0.337	nan	492
AST	0.673	11.000	1.000	0.000	0.339	nan	492
FIB4	0.644	0.200	1.000	0.000	0.338	nan	491
ALT	0.643	11.000	1.000	0.000	0.339	nan	492
BMI	0.598	14.950	1.000	0.000	0.340	nan	497
HbA1C	0.579	4.100	1.000	0.000	0.355	nan	409
ALP	0.564	1.200	1.000	0.000	0.337	nan	490
FBS_mmol	0.564	1.500	1.000	0.000	0.341	nan	493
Age	0.555	17.000	1.000	0.000	0.340	nan	497
BIL	0.554	0.100	1.000	0.000	0.340	nan	491
BARD	0.543	0.000	1.000	0.000	0.340	nan	497
TLC	0.529	1.500	1.000	0.000	0.337	nan	495

LDL_mmol	0.474	0.030	1.000	0.000	0.336	nan	494
TG_mmol	0.469	35.000	1.000	0.000	0.337	nan	495
ALB	0.439	2.000	1.000	0.000	0.342	nan	488
PLT	0.434	60.000	1.000	0.000	0.337	nan	495
HDL_mmol	0.432	0.410	1.000	0.000	0.333	nan	492
FIB5	0.402	-578.280	1.000	0.000	0.337	nan	483

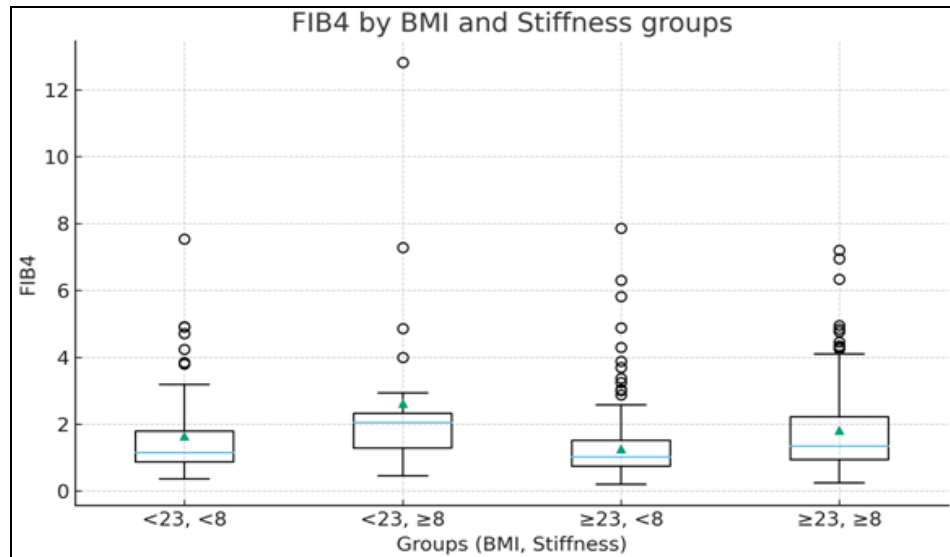


FIG. 7: ANALYSIS BOXPLOT

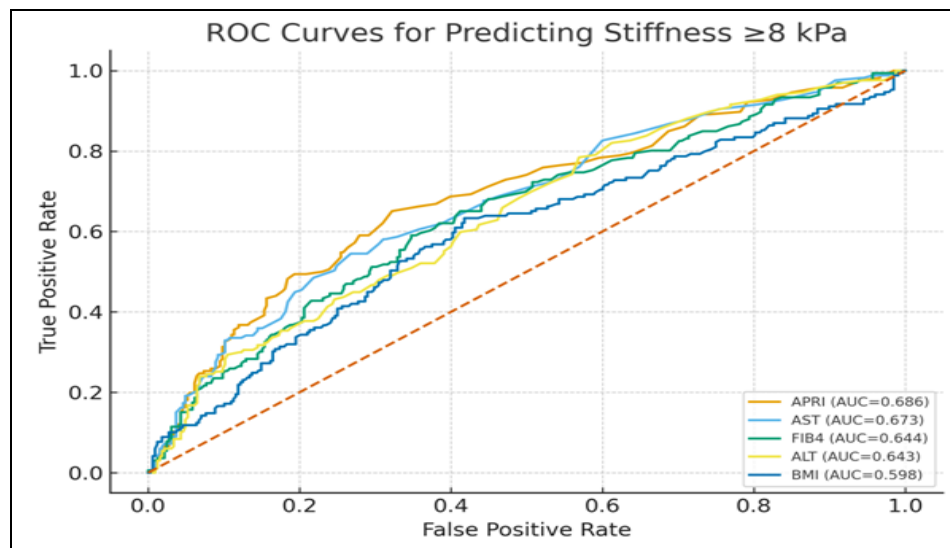


FIG. 8: ROC CURVES

**Detailed Interpretation:**

**Direction and Magnitude of Differences:** For each BMI stratum, compare the mean values between stiffness <8 and ≥8 kPa. Variables with  $p < 0.05$  indicate statistically significant separation and potential utility for risk stratification within that stratum.

**Discrimination:** AUROC values closer to 1.0 indicate stronger ability to distinguish stiffness ≥8 kPa. AUC around 0.70–0.80 is considered acceptable; 0.80–0.90 is strong; >0.90 is excellent.

**Threshold Performance:** At the Youden-optimal cut-off, the table lists sensitivity, specificity, PPV, and NPV. Consider clinical context: for screening, prioritize higher sensitivity/NPV; for rule-in, prioritize specificity/PPV.

**BMI Interaction:** Compare which markers retain significance and reasonable AUC in both BMI strata. If markers perform better in ≥23 group, adiposity may be amplifying their signal; if they perform in <23 as well, they are BMI-agnostic.

**Hypertension Prevalence by BMI and Sex (With P Value):** Comparison of hypertension prevalence between lean (BMI < 23) and non-lean (BMI ≥ 23) groups, stratified by sex and overall population.

Hypertension defined as systolic BP ≥130 mmHg or diastolic BP ≥90 mmHg. Chi-square test used for p-value calculation.

**TABLE 14:**

SEX	GROUP	N	Hypertensive	% Hypertension	p value
M	Lean	54	26	48.15	0.0141
M	Non-lean	217	146	67.28	0.0141
F	Lean	26	14	53.85	0.3168
F	Non-lean	200	132	66.0	0.3168
Overall	Lean	80	40	50.0	0.0066
Overall	Non-lean	417	278	66.67	0.0066

Data are presented as number (n) and percentage (%). p-values obtained using Chi-square test.

**DISCUSSION:** Nonalcoholic fatty liver disease now-a-days known as metabolic associated steatotic liver disease (MASLD) is a chronic liver disease, which progress to cirrhosis of liver or eventually to hepatocellular carcinoma, has a considerable disparity in sex as the criteria of metabolic syndrome and incidence of MASLD varies in both sexes<sup>22, 23</sup>. In the South-East Asian region there is gradual increasing incidence of lean MASLD as compared to nonlean in spite of normal BMI and other different metabolic patterns, in these cases only anthropometric profile is not the only answer without measurement of different biochemical profile<sup>24, 25</sup>. The entities like NAFLD and MASLD share some common pathogenic features like insulin resistance, dyslipidemia and obesity, but the diagnosis of MASLD is a refined concept of NAFLD as it requires at least one of the features like type 2 diabetes mellitus, increased BMI and hypertension whereas, NAFLD can be diagnosed by exclusion of other etiologies relating to chronic liver disease<sup>13, 26</sup>. This study retained the diagnostic criteria of NAFLD at the same time focussed on the impact of stratification of BMI on NAFLD phenotypes – it ensures consistency of the methodologies. MASLD may include lean category of patients associated with other metabolic abnormalities like type 2 diabetes mellitus, hypertension or dyslipidemia at the same time maintains original classification of NAFLD thereby prevent bias from retrospective classification of NAFLD.

This present study subdivided the patients with NAFLD into two categories, lean or BMI less than 23 Kg/m<sup>2</sup> and nonlean i.e. BMI more than equal to 23 Kg/m<sup>2</sup> as per Asia-Pacific criteria. In this study total number of males (n=271, lean 54 and nonlean

217) outnumber female (226, 26 nonlean and 200 nonlean) but not significant, mean age in male in lean 48 years and nonlean 42 years and in female in lean 47.5 years and in nonlean 47 years – it showed that nonlean males NAFLD affected earlier as compared to lean males and all categories of females because males predominantly develops central obesity whereas, females develops pear shaped obesity in the buttock – this is most probably due to sex-specific pattern of fat distribution. This finding was slightly lower than that was shown in the study of Xu M et al where mean age in nonlean and lean females were 54 and lean and nonlean males 50 and 49 years respectively<sup>27</sup>. Again in male with high BMI are susceptible to develop different co-morbid disease and menopausal females have higher incidence to develop co-morbid disease and also NAFLD<sup>28, 29, 30</sup>. As the estrogen protective effect is upgraded in premenopausal age group leading to increased sensitivity to insulin resulting decreased incidence of diabetes type 2 as well as metabolic dysregulation, which will be downgraded in postmenopausal state leading to increased resistance to insulin resulting development of type 2 diabetes – this requires measurement of glycemic control in all the patients with metabolic disease in females<sup>31, 32</sup>.

In the present study lipid profile demonstrated high level of triglyceride, LDL and low HDL level in female with nonlean as compared to lean subject (TG, LDL 1.862, 2.819 in lean and 1.92, 2.861 in nonlean with p value 0.893 and 0.818 respectively, HDL in lean 1.191 and 1.143 in nonlean subject, p value 0.449), whereas, in male, level of TG, LDL and HDL were 2.118 vs. 2.066 p=0.579, 2.826 vs. 2.886 p=0.01 and 1.076 vs. 1.088 p=0.773 in lean

and nonlean patients respectively – it demonstrated lipid profile of male is more atherogenic as compared to male in nonlean subjects. Similarly the study of Xu M et al demonstrated that lipid profile of male was more atherogenic (1.49 vs. 1.26 in lean 1.76 vs. 1.42 in nonlean male and female respectively in case TG, 2.89 vs. 3.04 in lean, 3.04 vs. 3.09 in nonlean male and female respectively in case of LDL and 1.22 vs. 1.47 in lean, 1.13 vs. 1.35 in nonlean male and female respectively in case of HDL) On the other hand, as compared to lean in nonlean subjects there was decrease in triglyceride and rise in LDL and HDL level in case of liver stiffness of less than 8 and nonsignificant rise in TG, significant rise in LDL and HDL level in patients with liver stiffness of more than equal to 8 – which demonstrate significant atherogenic features that may lead to significant cardiovascular morbidity and mortality in patients with NAFLD<sup>33, 34</sup>. Similarly study of Xu M et al demonstrated that nonlean subject were more atherogenic as compared to lean subject<sup>27</sup>. In MASLD, factors other than dyslipidemia like insulin resistance plays a role through multiple mechanisms *i.e.* lipotoxicity, proinflammatory diet, intestinal dysbiosis that lead to chronic inflammation in the liver parenchyma ultimately resulting fibrosis and formation of tumor<sup>35, 36, 37, 38</sup>.

In the present study, 66.67% nonlean and 50% lean subjects suffered from hypertension with p value of 0.006, significant difference in hypertension between lean and nonlean male subject (67.28% in nonlean and 48.15% in lean with p=0.014) indicating significantly higher incidence of hypertension in nonlean patients. It suggests that accumulated visceral fat activates renin-angiotensin-aldosterone system leading to development of hypertension and cardiovascular diseases<sup>34</sup>. According to different epidemiological studies, patient suffering from nonalcoholic fatty liver disease are prone to develop diastolic dysfunction or left ventricular hypertrophy leading to cardiac arrhythmias<sup>33, 39</sup>.

There is strong correlation between diabetes mellitus type 2 and NAFLD and this is mostly due to insulin resistance and meta-analysis supported this as these studied demonstrated combined hazard ratio of 2.22 with 95% confidence interval was high in patients with NAFLD as compared to

patients with non-NAFLD<sup>40</sup>. Patients with progressive increasing NAFLD are susceptible to type 2 diabetes mellitus as compared to early stages of NASH whether patient is lean or nonlean as diabetes mellitus itself may lead to weight loss or sarcopenic obesity and produces bias in the making correlation between the metabolic activity and anthropometric measurement, and ultimately it will maintain a vicious cycle between increasing NAFLD and type 2 diabetes mellitus<sup>7, 41, 42</sup>.

In patients with metabolic syndrome chronic inflammatory injury to the liver for long duration will lead to fibrogenesis resulting hepatic fibrosis ultimately to cirrhosis. According to study done the sensitivity of the transient elastography in diagnosing advanced fibrosis high as compared to case of early fibrosis based on 2010 criteria by Vincent et Al which defined significant and nonsignificant fibrosis as LSM as more and less than 8 kPa<sup>43</sup>.

One study done by Leung JC-F et al demonstrated stages of histologically proved fibrosis, serum cytokine-18 level liver stiffness were significantly decreased in lean patients as compared to nonlean patients<sup>44</sup>. Instead study of Xu M *et al* demonstrated 970 nonlean patients had significant fibrosis as compared to lean patients (n = 970 vs. 47) which was similar to the present study which showed incidences of advanced fibrosis in nonlean subject as compared to lean subjects (n=417 in nonlean and 80 in lean patients)<sup>27</sup>. In the study of Muyyarikkandy MS *et al.* following metabolic phenotypes were found in case of MASLD like altered metabolism of branched chain triglyceride and dysregulation of triglyceride metabolism leading to mitochondrial dysfunction resulted injury to hepatocytes, as a results level of ALT was elevated<sup>45</sup>. At the same time insulin resistance will activate both carbohydrate responsive element binding protein as well as sterol regulatory element binding protein 1c leading to lipogenesis within the liver which is compounded altered bile acid metabolism as well as cholestasis as evidenced by raised alkaline phosphatase. Whereas, in nonlean patients, there is increased risk of fibrosis due to altered lipid metabolism and raised fasting bloodglucose<sup>46, 47</sup>. Another study of Fan X *et al.* demonstrated high incidence of hepatic fibrosis

inlean patients whereas, nonlean patients suffered from metabolic comorbid diseases more<sup>48</sup>.

It has been demonstrated IN Wu Y-L *et al.* that FIB-4 had much more diagnostic value in hepatic advanced fibrosis as compared to APRI<sup>49</sup>. In this present study, both FIB-4 and FIB-5 demonstrated upwards dispersion in both the sexes where male was higher as compared to female – indicating greater heterogeneity in fibrosis. FIB-4 value was high in lean as compared to nonlean (2.633 vs. 1.822 in lean FIB-4 in lean and nonlean patients) which was similar to the study done by Kanwal F *et al* where FIB-4 value was higher in lean as compared to nonlean patients (1.355 and 1.206 in lean and nonlean patients respectively)<sup>50</sup>. In the present study, FIB-4 value of more than 1.3 to 2.67 indicating advanced fibrosis with modest accuracy and FIB-5 score can rule out the advanced fibrosis. In this study it was also shown that FIB-5 in lean subjects was lower as compared to nonlean subjects indicating advanced fibrosis (15.548 vs. 21.232 in lean and nonlean patients respectively). But the APRI value of 0.887 in lean and 0.793 in nonlean patients in this study indicates less hepatic fibrosis as the value of more than equal to one suggests advanced fibrosis. All the data above suggested that FIB-4 value has the predictive ability in the diagnosis of advanced hepatic fibrosis<sup>51</sup>.

In the present study, Mean Tgl-FBS index was slightly higher in lean male as compared to lean female (mean 14.005 in male and 13.846 in female), and in both sexes, lean subjects demonstrated higher indexes as compared to nonlean subjects (14.005 and 13.846 in lean males and female respectively and 12.983 and 12.590 in nonlean males and females respectively). Same results were obtained in both Tgl-FBS/BMI ratio and Tgl-FBS/HDL ratio in both lean subjects as compared to nonlean subjects irrespective of sexes – this results indicate that there was adiposity-linked metabolic dysfunction. AUROC curve demonstrated that there was Tgl-FBS tracked the measured liver stiffness very tightly, since r value was positive – it indicates that there was higher stiffness along with Tgl-FBS burden. I all the ratio there was acceptable discrimination for hepatic stiffness as the AUC value of these indexes nearer to 0.7 to 0.8. In higher BMI strata AUC value captured adiposity-driven metabolic dysregulation

which was relevant to risk of hepatic fibrosis. But the study of Xu M *et al* demonstrated nonlean subjects as compared to lean subjects showed higher value in Tgl-FBS-BMI indexes (190.837 and 191.922 in lean subjects with LSM less than and equal to more than 8 kPa respectively and 232.708 and 252.492 in nonlean subjects with LSM less than and equal to more than 8 kPa respectively)<sup>27</sup>.

**CONCLUSION:** This cross-sectional analysis of 497 NAFLD patients (271 males and 226 females) demonstrates that the Asia-Pacific BMI threshold of 23 kg/m<sup>2</sup> is a critical inflection point beyond which hepatic fibrosis and metabolic derangements become increasingly prevalent. Overweight and obese individuals exhibited higher triglycerides, LDL cholesterol, fasting glucose, TyG index, FIB-4, and APRI scores, reflecting both insulin resistance and early fibrotic stress. Males predominantly expressed an insulin-resistant phenotype with greater dyslipidemia, whereas females showed a fibrotic-metabolic pattern with higher FIB-4, BARD, and stiffness  $\geq 8$  kPa on FibroScan.

Receiver-operating characteristic (ROC) analysis identified TyG (AUC  $\approx 0.85$ ) and FIB-4 (AUC  $\approx 0.80$ ) as the most accurate non-invasive predictors of clinically significant fibrosis, each providing a high negative predictive value ( $\approx 88\%$ ). These findings validate the Asia-Pacific BMI cut-off as a sensitive discriminator for hepatic and metabolic risk in Indian populations and emphasize the utility of simple, low-cost indices for large-scale screening. Integrating BMI  $\geq 23$  kg/m<sup>2</sup> with TyG and FIB-4 can significantly reduce unnecessary liver biopsies while ensuring early identification of at-risk individuals.

**Limitations of the Study:** This study was retrospective and single-center, based on outpatient records from a tertiary hospital, which may limit generalizability. External validation in larger, multicentric, prospective cohorts is necessary to confirm diagnostic cut-offs and strengthen clinical applicability.

Selection bias could not be fully eliminated since only patients with available complete biochemical data and FibroScan results were included.

Histopathological confirmation by liver biopsy was not performed; fibrosis staging relied solely on transient elastography. Cross-sectional design precludes causal inference between metabolic indices and hepatic fibrosis. Potential confounders such as dietary habits, physical activity, alcohol intake below exclusion threshold, and medication history were not controlled. Lack of longitudinal follow-up prevents assessment of fibrosis progression and response to intervention.

### Take-Home Message:

- ❖ BMI  $\geq$  23 kg/m<sup>2</sup> should be adopted as the screening threshold for metabolic-associated fatty liver disease in South-Asian populations.
- ❖ TyG and FIB-4 indices are simple, cost-effective, and non-invasive tools capable of early fibrosis detection.
- ❖ Males exhibit predominantly insulin-resistant patterns; females display fibrotic-metabolic signatures indicating sex-specific disease behaviour.
- ❖ Combining BMI + TyG + FIB-4 yields an NPV  $\approx$  88%, suitable for early community-level screening and exclusion of significant fibrosis.
- ❖ Early lifestyle intervention and periodic non-invasive monitoring can curb the rising burden of NAFLD/MASLD and associated cardiovascular morbidity in India.

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