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RESEARCH ARTICLE

Association Between Non-Invasive Liver Fibrosis Scores (FIB-4 and APRI) and Estimated Cardiovascular Risk Among Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

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Abstract: ***Objective:*** To determine the association between non-invasive liver fibrosis scores (Fibrosis-4 [FIB-4] and Aspartate Aminotransferase-to-Platelet Ratio Index [APRI]) and estimated cardiovascular risk among adults with metabolic dysfunction-associated steatotic liver disease (MASLD) presenting to tertiary care hospitals in Pakistan.***Material & Methods:*** A descriptive cross-sectional study was conducted in the Departments of Gastroenterology and Cardiology of tertiary care hospitals in Pakistan after obtaining institutional ethical approval. Between February 2025 and July 2025, 348 adults with MASLD were enrolled using a consecutive non-probability sampling technique. Demographic, clinical, anthropometric, and laboratory data were collected using a structured proforma. Liver fibrosis was assessed using the FIB-4 index and APRI score, while the 10-year cardiovascular risk was estimated using the ACC/AHA ASCVD Risk Estimator.***Results:*** The mean age was 51.6 ± 11.8 years, and 206 (59.2%) participants were male. High FIB-4 scores were observed in 76 (21.8%) participants, while 94 (27.0%) had advanced fibrosis according to the APRI score. Intermediate-to-high estimated cardiovascular risk was identified in 147 (42.2%) participants. Individuals with high FIB-4 scores had a significantly greater prevalence of intermediate-to-high cardiovascular risk than those with low/intermediate FIB-4 scores (77.6% vs. 30.2%; p<0.001). On multivariable logistic regression, high FIB-4 (aOR=3.62, 95% CI: 2.04–6.43), advanced fibrosis by APRI (aOR=2.81, 95% CI: 1.61–4.91), diabetes mellitus, and hypertension were independent predictors of elevated cardiovascular risk.***Conclusion:*** Higher non-invasive liver fibrosis scores were independently associated with increased estimated cardiovascular risk among adults with MASLD. Routine assessment of FIB-4 and APRI may provide a simple and cost-effective approach for combined hepatic and cardiovascular risk stratification in clinical practice.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease; MASLD; Fibrosis-4 Index; FIB-4; Aspartate Aminotransferase-to-Platelet Ratio Index; APRI; Cardiovascular Risk; ASCVD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disease globally, and a significant burden on metabolic diseases worldwide (1). MASLD, which has a close association with obesity, type 2 diabetes mellitus, dyslipidemia, hypertension and insulin resistance, is increasingly recognised as a multisystem disease rather than one confined to the liver. Global estimates suggest that MASLD affects nearly one in three adults, and prevalence remains on the rise due to increasing obesity and diabetes rates. This finding is especially important because it shows that cardiovascular disease (CVD) — not liver-related complications — is the leading cause of death in patients with MASLD (2).

Each year, new patients with MASLD appear in older populations rapidly across South Asia, where urbanization, a sedentary lifestyle, and the catch-up with unhealthy dietary patterns are accelerated (3). Obesity, diabetes, and metabolic syndrome have also increased over the last decades in Pakistan, with an ever-increasing obesity and a large population leading to a more appropriate environment for MASLD. In local epidemiological studies, MASLD is diagnosed in 15%–35% of adults, with significantly higher prevalence among people with obesity and type 2 diabetes. Cardiovascular disease is also the major cause of morbidity and mortality in Pakistan, so a combined approach to hepatic and cardiovascular health is warranted (4).

The assessment of liver fibrosis is central to the management of MASLD because the stage of fibrosis is clearly one of the most important determinants of liver-related and overall mortality (5). However, liver biopsy – the reference standard is invasive, expensive, and infrequently done. Therefore, noninvasive fibrosis scores have now been widely accepted as legitimate, cost-effective, validated instruments for identifying patients at high risk for advanced fibrosis, particularly the Fibrosis-4 (FIB-4) index and the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI).

However, there is new evidence that these fibrosis scores may also mirror systemic inflammation and metabolic dysfunction, indicating increased cardiovascular risk beyond the severity of their hepatic disease (6).

Given the increasing prevalence of MASLD and the significant burden of cardiovascular disease in Pakistan, few studies have assessed whether low-cost non-invasive liver fibrosis scores can be correlated with estimated cardiovascular risk (7). The majority of published studies come from either Western or East Asian populations, whose demographics, metabolic parameters, and healthcare systems vary significantly from Pakistan. Whether the FIB-4 and APRI correlate with the estimated cardiovascular risk in Pakistani adults with MASLD could provide an easy, inexpensive method to perform concurrent hepatic and cardiovascular risk stratification based on clinical and laboratory parameters readily available. This type of evidence may allow for earlier multidisciplinary intervention, more efficient resource allocation, and better long-term outcomes in settings where resources are limited.

METHODOLOGY

It was a descriptive cross-sectional study carried out in the Departments of Gastroenterology and Cardiology of tertiary care hospitals from Karachi and Hyderabad, Pakistan, after approval by the Institutional Ethical Review Committee for six months from 1st February 2025 to 31st July 2025. This study aimed to evaluate the relationship between non-invasive liver fibrosis scores (the Fibrosis-4 (FIB-4) index and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and estimated cardiovascular risk among adults with metabolic dysfunction-associated steatotic liver disease (MASLD).

The sample size needed was computed using the WHO Sample Size Calculator under the assumptions of a 95% confidence level, a 5% margin of error, and an anticipated prevalence of MASLD based on published literature (36.5%) (8). Data in hand were limited in number, as the minimum sample size calculated for this study was 348. Patients were recruited in a consecutive manner by a non-probability consecutive sampling technique until the targeted sample size was reached to cover incomplete records, unavailability of laboratory investigations, and loss-to-follow-up.

Inclusion Criteria

Adult patients aged 18 years and above of either sex diagnosed with MASLD were eligible for inclusion. MASLD was diagnosed according to contemporary international consensus criteria based on evidence of hepatic steatosis on abdominal ultrasonography or transient elastography (FibroScan), together with the presence of at least one cardiometabolic risk factor, including overweight/obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, or other evidence of metabolic dysfunction. Only patients who provided written informed consent were enrolled.

Exclusion Criteria

Patients were excluded if they were younger than 18 years, had significant alcohol consumption exceeding accepted diagnostic thresholds, chronic viral hepatitis B or C, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, drug-induced liver injury, hepatocellular carcinoma, previous liver transplantation, pregnancy, active malignancy, end-stage renal disease requiring dialysis, congestive heart failure, acute infectious illness, or incomplete clinical or laboratory records required for calculation of FIB-4, APRI, or cardiovascular risk scores.

Data Collection

Data were collected readily using a structured predesigned proforma by the principal investigator and trained research assistants, after obtaining written informed consent. Demographic data included age, sex, marital status, education level, employment status, residence area (urban vs rural), smoking history, and family history of cardiovascular disease. Anthropometric measurements, including height, weight, body mass index (BMI), waist circumference and blood pressure, were measured according to the standard procedures.

Clinical data comprised duration of MASLD, diabetes mellitus, hypertension, dyslipidemia, obesity, metabolic syndrome and concomitant drugs as well as other important comorbidities. Clinical records, abdominal ultrasonography and/or FibroScan findings, laboratory investigations and specialist gastroenterology assessment confirmed the diagnosis of MASLD.

In-hospital venous blood samples were analysed in the hospital laboratory as per standard operating procedures after an overnight fast. Laboratory investigations included CBC, FBS, HbA1c, liver function tests (serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase GGT, total bilirubin), serum creatinine and fasting lipid profile where available, along with platelet count and INR.

Assessment of non-invasive liver fibrosis by laboratory-based indices: Fibrosis-4 (FIB-4) Index and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) calculated from routine laboratory values. Patients were grouped by fibrosis stage per established cut-off values into low-, intermediate-, and high-risk groups.

Cardiovascular risk was estimated using the ACC/AHA Atherosclerotic Cardiovascular Disease (ASCVD) 10-year Risk Estimator (9) for age, sex, systolic blood pressure, diabetes status, smoking status, and total cholesterol with high-density lipoprotein cholesterol; antihypertensive treatment was also included as

appropriate in those taking one or more medications simultaneously, while lipid-lowering therapy was added as indicated. Patients were classified as low (<5%), borderline (5.0–7.4%), intermediate (7.5–19.9%) and high risk (≥20%) for cardiovascular events.

Operational Definitions

Metabolic dysfunction-associated steatotic liver disease (MASLD) was defined according to current international consensus criteria as hepatic steatosis detected by imaging together with at least one cardiometabolic risk factor and in the absence of alternative causes of hepatic steatosis.

FIB-4 Index was calculated using the standard validated formula incorporating age, AST, ALT, and platelet count. Scores <1.3 were considered low risk, 1.3–2.67 intermediate risk, and >2.67 high risk for advanced liver fibrosis.

APRI was calculated using serum AST concentration and platelet count. Higher APRI values indicated a greater probability of advanced liver fibrosis according to established guideline-recommended cut-off values.

Estimated cardiovascular risk was defined as the predicted 10-year probability of developing a first major atherosclerotic cardiovascular event using the ACC/AHA ASCVD Risk Estimator.

Outcome Variables

The primary outcome of the study was the association between non-invasive liver fibrosis scores (FIB-4 and APRI) and estimated 10-year cardiovascular risk among adults with MASLD.

Secondary outcomes included the association of liver fibrosis scores with individual cardiometabolic risk factors, obesity, diabetes mellitus, hypertension, dyslipidemia, anthropometric measurements, liver biochemical parameters, and the severity of cardiovascular risk categories.

Data Analysis

Data were entered, cleaned, and analyzed using version 26.0 of the Statistical Package for the Social Sciences (SPSS; IBM Corp.; Armonk, NY, USA). Normality of continuous variables such as age, BMI, waist circumference, blood pressure, laboratory parameters, FIB-4 score, APRI score, and estimated cardiovascular risk was evaluated using the Shapiro-Wilk test and expressed as mean ± standard deviation (SD) or median with interquartile range according to data distribution. Numerical and categorical variables, including sex and smoking status (former smoker vs active smokers), diabetes mellitus, hypertension, dyslipidemia, obesity category (BMI≥30 kg/m2), fibrosis categories, and cardiovascular risk classes were described as frequencies/percentages.

Chi-square test or Fisher's exact test (where appropriate) were carried out to compare categorical variables. Because the distribution of some variables was not normal, we used the independent-samples t-test or one-way analysis of variance (ANOVA) for normally distributed data and the Mann–Whitney U test or Kruskal–Wallis test for nonnormally distributed variables to compare continuous variables. The correlations between FIB-4 score, APRI score, and estimated cardiovascular risk were assessed by Pearson's or Spearman's correlation coefficient as appropriate.

A multivariable logistic regression analysis was conducted to determine independent predictors of intermediate-to-high CV risk after adjustment for potential confounding factors (age, sex, BMI [body mass index], DM [diabetes mellitus], HTN [hypertension], smoking status, dyslipidemia). Results are presented as crude and adjusted odds ratios with 95% confidence intervals. Statistical significance is assigned a two-tailed p-value ≤0.05.

RESULTS

A descriptive cross-sectional study included 348 adults with metabolic dysfunction-associated steatotic liver disease (MASLD). The mean age was 51.6 ± 11.8 years, with most participants aged 41–60 years (162, 46.6%). There were 206 (59.2%) males and 142 (40.8%) females. Based on the FIB-4 index, 154 (44.3%) participants were classified as low risk, 118 (33.9%) as intermediate risk, and 76 (21.8%) as high risk for advanced liver fibrosis, while 94 (27.0%) had advanced fibrosis according to the APRI score. Estimated 10-year cardiovascular risk was categorized as low in 129 (37.1%), borderline in 72 (20.7%), intermediate in 91 (26.1%), and high in 56 (16.1%) participants. Diabetes mellitus, hypertension, and obesity were present in 39.7%, 43.4%, and 42.0% of participants, respectively. Baseline demographic and clinical characteristics are presented in Table 1.

Table 1. Baseline demographic and clinical characteristics of study participants (n = 348)

Variable	Frequency (%)
Age Group (Years)	
18–40	78 (22.4)
41–60	162 (46.6)
>60	108 (31.0)
Gender	
Male	206 (59.2)
Female	142 (40.8)
FIB-4 Category	
Low risk	154 (44.3)
Intermediate risk	118 (33.9)
High risk	76 (21.8)
Advanced Fibrosis by APRI	94 (27.0)
Diabetes Mellitus	138 (39.7)
Hypertension	151 (43.4)
Obesity (BMI ≥30 kg/m²)	146 (42.0)
Dyslipidemia	167 (48.0)

Participants with high FIB-4 scores demonstrated significantly greater estimated cardiovascular risk than those with low or intermediate FIB-4 scores. Intermediate-to-high cardiovascular risk was observed in 59 (77.6%) participants with high FIB-4 compared with 82 (30.2%) among those with low or intermediate FIB-4 scores ($p < 0.001$). Similarly, advanced fibrosis identified by APRI was significantly associated with higher cardiovascular risk, diabetes mellitus, hypertension, and obesity. Detailed associations are presented in Table 2.

Table 2. Association between liver fibrosis scores and estimated cardiovascular risk

Variable	High FIB-4 n (%)	Low/Intermediate FIB-4 n (%)	p-value
Intermediate/High Cardiovascular Risk	59 (77.6)	82 (30.2)	<0.001
Advanced Fibrosis by APRI	47 (61.8)	47 (17.3)	<0.001
Diabetes Mellitus	43 (56.6)	95 (35.0)	0.001
Hypertension	48 (63.2)	103 (37.9)	<0.001
Obesity	41 (53.9)	105 (38.6)	0.021
Dyslipidemia	46 (60.5)	121 (44.5)	0.016

Figure 1 demonstrates the distribution of the estimated 10-year cardiovascular risk among adults with MASLD. The largest proportion of participants had low cardiovascular risk (37.1%), followed by intermediate risk (26.1%), borderline risk (20.7%), and high cardiovascular risk (16.1%). Overall, 42.2% of participants were classified as having intermediate-to-high cardiovascular risk, indicating a substantial burden of future cardiovascular events in this population.

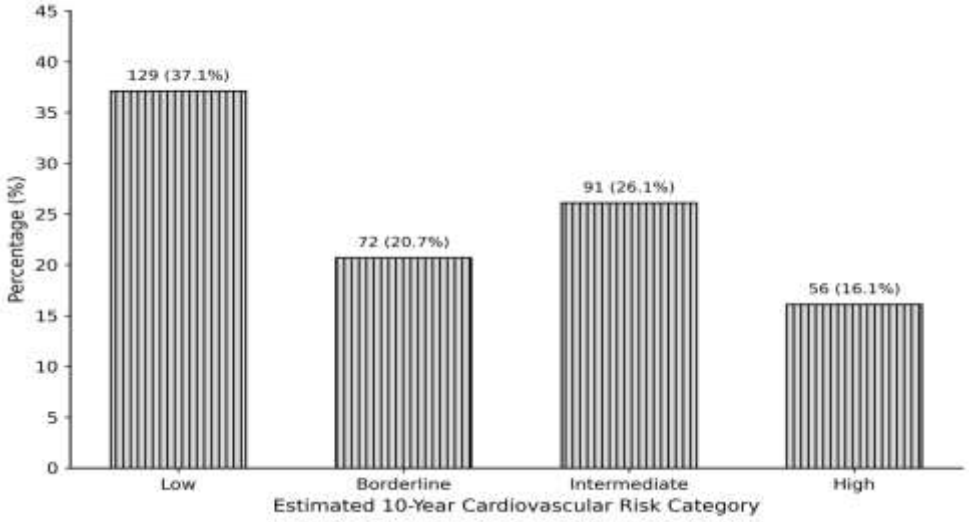

Figure 1. Distribution of estimated cardiovascular risk according to FIB-4 categories

Multivariable logistic regression analysis demonstrated that high FIB-4 remained an independent predictor of intermediate-to-high estimated cardiovascular risk after adjustment for age, sex, diabetes mellitus, hypertension, obesity, and dyslipidemia. Participants with high FIB-4 had 3.6-fold greater odds of intermediate-to-high cardiovascular risk (AOR: 3.6; 95% CI: 2.0–6.4; p < 0.001). Advanced fibrosis by APRI, diabetes mellitus, and hypertension were also independently associated with increased cardiovascular risk, whereas obesity showed a borderline significant association.

Table 3. Multivariable logistic regression analysis for predictors of intermediate-to-high cardiovascular risk

Variable	Reference Category	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
High FIB-4 score	Low/Intermediate FIB-4	3.62	2.04–6.43	<0.001
Advanced fibrosis (APRI)	Non-advanced fibrosis	2.81	1.61–4.91	<0.001
Age ≥60 years	<60 years	2.08	1.19–3.64	0.010
Male sex	Female	1.29	0.78–2.13	0.316
Diabetes mellitus	No	2.34	1.42–3.87	0.001
Hypertension	No	1.92	1.16–3.18	0.011
Obesity (BMI ≥30 kg/m²)	BMI <30 kg/m²	1.48	0.88–2.48	0.136
Dyslipidemia	No	1.74	1.05–2.89	0.032

Dependent variable: Intermediate-to-high estimated 10-year cardiovascular risk (ASCVD risk ≥7.5%).
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FIB-4, Fibrosis-4 Index; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index.

DISCUSSION

The current study assessed the relationship between non-invasive liver fibrosis scores (FIB-4 and APRI) and estimated 10-year cardiovascular risk among adults diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD). In total, out of 348 participants: high FIB-4 score with a value ≥1.45 in 76 (21.8%), and advanced fibrosis according to APRI score, with a value >2.0 in up to 94 (27%). Moreover, 147 (42.2%) participants were defined as intermediate–high estimated cardiovascular risk. The prevalence of intermediate-to-high cardiovascular risk was significantly higher in patients with a high FIB-4 score (77.6% vs. 30.2%, p<0.001), even after adjustment for potential confounders (aOR=3.62, 95% CI: 2.04–6.43). These results strengthen the idea that liver fibrosis associates directly with cardiovascular disease among patients with MASLD (10, 11).

The presence of advanced liver fibrosis seen in our study confirms comparable findings seen with international cohorts. Similarly, studies from Malaysia (12) and South Korea (13) have shown around 20–30% prevalence of advanced fibrosis in adults with MASLD based on non-invasive fibrosis scores. Similarly, FIB-4 was independently associated with both increased-risk cardiovascular prediction and subclinical atherosclerosis by Chinese investigators (14). Some of the similarities among these populations are likely due to common mechanisms such as chronic low-grade inflammation, insulin resistance, endothelial dysfunction, and accelerated atherosclerosis that accompanies progressive hepatic fibrosis (also known as nonalcoholic fatty liver disease).

Based on our findings, 59 of 76 (77.6%) participants with a high FIB-4 score had intermediate-to-high cardiovascular risk versus only 82 of 272 (30.2%) with low or intermediate FIB-4 scores. Somewhat similarly, APRI advanced fibrosis (56.6% vs 35.0%), hypertension (63.2% vs 37.9%), dyslipidemia (60.5% vs 44.5%), and obesity (53.9% vs 38.629). Similar results were observed in USA (15) and Japanese (16) studies with progressive increases in cardiovascular risk scores and adverse cardiometabolic profiles with increasing fibrosis severity. These findings support the notion that fibrosis severity reflects systemic metabolic dysfunction rather than discrete liver injury.

There is still limited evidence available from Pakistan; however, a number of previous local studies have shown a high prevalence of metabolic risk factors in subjects with MASLD (17). Similar frequencies of diabetes mellitus (39.7%), hypertension (43.4%), obesity (42.0%), and dyslipidemia 48.0% identified in the present study are comparable to those reported in hospital-based Pakistani cohorts (18). The high burden of these abnormal metabolic traits may account for the large number of participants placed at cardiovascular risk. The differences between Pakistani and Western populations may be due to lifestyle, diet, genetic susceptibility, accessibility to health care/utilization, and delayed diagnosis of metabolic disorders.
High FIB-4 score (aOR=3.62), advanced fibrosis via APRI (aOR=2.81), diabetes mellitus (aOR=2.34), hypertension (aOR=1.92), and age ≥60 years

(aOR=2.08) were identified as independent predictors of intermediate-to-high cardiovascular risk by multivariable logistic regression analysis. More than half of patients with NAFLD demonstrated a high cardiovascular risk but encounter poor control in clinical practice, implicating the importance of early diagnosis without any complications such as diabetes development to improve prognosis in this patient population. On the other hand, obesity was not independently related to cardiovascular risk after adjustment for metabolic variables. Comparative studies with obesity as the major risk factor for cardiovascular events have also confirmed our findings that hormonal and metabolic responses (e.g., insulin resistance, diabetes, hypertension), but not body weight alone, mediate adverse cardiovascular effects of obesity (19, 20).

These results have significant clinical implications. Given that FIB-4 and APRI are cheap, widely available, and based on conventional laboratory tests, it may be feasible to use them in the identification of MASLD patients at high risk of cardiovascular complications, especially in resource-limited health care contexts such as Pakistan. Combining the assessment of liver fibrosis with cardiovascular risk could allow us to tier our intervention in a much more targeted fashion, managing metabolic risk factors earlier and potentially reducing cardiovascular morbidity down the line.

CONCLUSION

Higher non-invasive liver fibrosis scores were significantly associated with increased estimated 10-year cardiovascular risk among adults with MASLD. FIB-4 and APRI independently predicted elevated cardiovascular risk beyond conventional metabolic risk factors, suggesting that these simple, low-cost indices may be useful for combined hepatic and cardiovascular risk stratification. Routine incorporation of these scores into the evaluation of patients with MASLD may improve early identification of high-risk individuals and support timely preventive interventions.

Conflict of Interest: The authors declare no conflict of interest.

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