



Original Research Article

Clinical and Biochemical Predictors of Advanced Liver Stiffness in Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study

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ABSTRACT

Background: Fibrosis severity is the principal determinant of liver-related outcomes in non-alcoholic fatty liver disease. Simple clinical and biochemical markers may help identify patients who require confirmatory elastographic assessment.

Aim: To identify clinical and biochemical predictors of advanced liver stiffness among adults with non-alcoholic fatty liver disease.

Methods: This secondary analysis used individual-level data from a cross-sectional study of 101 adults with ultrasonographic or elastographic evidence of non-alcoholic fatty liver disease (NAFLD) at an Indian tertiary centre. Advanced liver stiffness was defined a priori as a vibration-controlled transient elastography (VCTE) liver stiffness measurement (LSM) of at least 8.8 kPa, corresponding to the F3–F4 range used in the parent protocol. Group comparisons used Mann–Whitney U and Fisher exact tests with effect sizes. Sparse-event associations were assessed with Firth bias-reduced logistic regression. Discrimination was quantified using receiver operating characteristic curves with bootstrap 95% confidence intervals.

Results: Advanced liver stiffness was present in 14 of 101 participants (13.9%; 95% confidence interval, 8.4%–21.9%). Participants with advanced liver stiffness had lower platelet counts (median, 118 vs 240 $\times 10^9/L$; $U=40.5$; $p<0.001$; rank-biserial $r=-0.933$), higher aspartate aminotransferase-to-platelet ratio index values (0.75 vs 0.30; $U=999.5$; $p<0.001$; $r=0.641$), and higher Fibrosis-4 index values (2.15 vs 0.97; $U=1018.0$; $p<0.001$; $r=0.672$). After adjustment for body mass index and diabetes, each 1-unit increase in Fibrosis-4 was associated with higher odds of advanced liver stiffness (adjusted odds ratio, 3.33; 95% confidence interval, 1.61–6.91; $p=0.001$). A sensitivity model demonstrated an independent association for each 0.5-unit increase in the aspartate aminotransferase-to-platelet ratio index (adjusted odds ratio, 4.30; 95% confidence interval, 1.86–9.94; $p=0.001$). Platelet count, Fibrosis-4, and the aspartate aminotransferase-to-platelet ratio index yielded areas under the curve of 0.967, 0.836, and 0.821, respectively.

Conclusions: Platelet count and platelet-based fibrosis scores were the strongest markers of advanced liver stiffness in this tertiary-care cohort, whereas body mass index, diabetes, and routine aminotransferase thresholds were not independently discriminatory. These findings support sequential risk stratification with inexpensive blood-based markers followed by elastography, but require prospective external validation.

Keywords: advanced liver stiffness; APRI; FIB-4; metabolic dysfunction-associated steatotic liver disease; non-alcoholic fatty liver disease; platelet count; transient elastography.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), now encompassed predominantly within metabolic dysfunction-associated steatotic liver disease (MASLD), is a leading cause of chronic liver disease and is closely linked to obesity, insulin

resistance, type 2 diabetes, dyslipidaemia, and cardiovascular risk [1–4]. The updated nomenclature emphasizes positive cardiometabolic criteria rather than diagnosis by exclusion; nevertheless, the present cohort and its eligibility criteria were established under the NAFLD framework, and that term is retained throughout this report for fidelity to the parent protocol [2,3].

The clinical importance of NAFLD is determined less by the degree of steatosis than by the presence and severity of fibrosis. Long-term cohort studies and meta-analyses have consistently demonstrated that increasing fibrosis stage is associated with progressively greater risks of liver-related complications, transplantation, and mortality [5–7]. Because most patients are asymptomatic and aminotransferase concentrations can remain normal despite advanced disease, fibrosis cannot be reliably identified by symptoms or routine liver enzyme testing alone [1,8].

Liver biopsy remains the reference standard for histological staging but is unsuitable for broad case-finding because it is invasive, resource-intensive, subject to sampling variability, and associated with procedural risk. Contemporary guidance therefore recommends a sequential non-invasive strategy: an inexpensive blood-based score, most commonly the Fibrosis-4 (FIB-4) index, followed by vibration-controlled transient elastography (VCTE) or another imaging-based test when the initial result is indeterminate or elevated [1,2,8–10]. VCTE provides a liver stiffness measurement (LSM) that correlates with fibrosis severity, but its thresholds are not perfectly interchangeable across populations, devices, probes, and clinical contexts [8,10–13]. Accordingly, an elevated LSM should be interpreted as a fibrosis-risk phenotype rather than histological proof of advanced fibrosis.

Several routinely available variables may contribute to risk stratification. Age, obesity, diabetes, and hypertension reflect the metabolic milieu associated with progressive steatotic liver disease. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and platelet count may reflect hepatocellular injury, synthetic function, or evolving portal hypertension. Composite scores such as FIB-4 and the AST-to-platelet ratio index (APRI) integrate these components and are readily calculated from standard laboratory tests [14,15]. Their principal clinical value is often the exclusion of advanced fibrosis at low values; positive predictive performance is more variable and depends strongly on disease prevalence, age, and the population tested [1,8,16].

Indian tertiary-care cohorts frequently include patients with substantial metabolic risk, but the relative discriminatory value of simple clinical characteristics, individual biochemical variables, and composite fibrosis scores against VCTE-defined advanced liver stiffness is incompletely characterized. The parent dissertation enrolled 101 adults with NAFLD and recorded demographic, metabolic, biochemical, ultrasonographic, controlled attenuation parameter, and LSM data. The present secondary analysis was designed to identify clinical and biochemical predictors of advanced liver stiffness, quantify their effect sizes and diagnostic performance, and determine whether platelet-based scores remained associated with the outcome after parsimonious adjustment for body mass index and diabetes.

MATERIALS AND METHODS

Study design and setting

This was a post hoc secondary analysis of an 18-month cross-sectional observational study conducted in the Department of Medical Gastroenterology, Osmania General Hospital, Hyderabad, India. The parent study recruited 101 consecutive adults from inpatient and outpatient gastroenterology services [20].

Participants

Adults aged 18–70 years with ultrasonographic or elastographic evidence of NAFLD were eligible. Exclusion criteria were alcohol intake exceeding 30 g/day in men or 20 g/day in women; secondary causes of hepatic steatosis, including hepatitis C virus infection, hepatotoxic medications, and Cushing syndrome; known cirrhosis; pregnancy; malignancy; and refusal of informed consent. The present analysis included all 101 records in the master dataset after data-quality review.

Clinical and laboratory assessment

Demographic and clinical variables included age, sex, height, weight, body mass index (BMI), diabetes mellitus, hypertension, and other recorded comorbidities. Laboratory variables included fasting plasma glucose, triglycerides, AST, ALT, serum albumin, platelet count, APRI, and FIB-4. BMI was recalculated as weight in kilograms divided by height in metres squared. FIB-4 was calculated as age $\times$ AST divided by platelet count $\times$ the square root of ALT. APRI was calculated from AST relative to its upper limit of normal and platelet count according to the standard formula [14,15]. Values were rederived from source variables when internally inconsistent derived values were identified in the master chart.

Ultrasonography and vibration-controlled transient elastography

Abdominal ultrasonography was used to document hepatic steatosis and grade it as mild, moderate, or severe according to the parent protocol.

VCTE with controlled attenuation parameter was performed using a FibroScan® system (Echosens, Paris, France). LSM was recorded in kilopascals (KPa) and controlled attenuation parameter (CAP) in decibels per metre (dB/m).

Outcome definition

The primary outcome was advanced liver stiffness, defined as LSM ≥ 8.8 kPa. This threshold combined the F3 category (8.8–10.3 kPa) and F4-range category (≥ 10.4 kPa) specified in the parent study. LSM < 7.0 kPa was categorized as F0–F1 range, and 7.0–8.7 kPa as F2 range. Because liver biopsy was not performed and known cirrhosis was an exclusion criterion, the terms “advanced liver stiffness” and “F4-range LSM” are used instead of “biopsy-confirmed advanced fibrosis” or “cirrhosis.” The planned secondary outcome was significant-or-greater liver stiffness, defined as LSM ≥ 7.0 kPa.

Data quality and variable selection

The participant-level master chart was audited before analysis. BMI was recalculated from height and weight, and derived metabolic indices were checked against their component variables. Candidate predictors were selected a priori on clinical grounds and included age, sex, BMI, diabetes, hypertension, fasting glucose, triglycerides, AST, ALT, serum albumin, platelet count, APRI, and FIB-4. Triglyceride–glucose indices were intentionally not evaluated because they were reserved for a separate analysis addressing the parent dissertation’s primary comparison.

Statistical analysis

Continuous variables were inspected for distribution and are reported as median with interquartile range for outcome-group comparisons; overall age and BMI are additionally reported as mean $\pm$ standard deviation for clinical description. Categorical variables are presented as number and percentage. The prevalence of advanced liver stiffness is accompanied by a Wilson 95% confidence interval. Continuous variables were compared using the Mann–Whitney U test, with rank-biserial correlation as the effect size. Categorical variables were compared using two-sided Fisher exact tests; odds ratios with 95% confidence intervals and phi coefficients were reported as effect estimates.

Because only 14 participants met the primary outcome and several predictors were highly correlated, multivariable analysis was deliberately parsimonious. Firth bias-reduced logistic regression was used to reduce small-sample and separation bias [17,18]. The primary model included FIB-4 per 1-unit increase, BMI per 5 kg/m² increase, and diabetes. A prespecified sensitivity model replaced FIB-4 with APRI per 0.5-unit increase. FIB-4 and APRI were not entered together because both incorporate AST and platelet count.

Discrimination was evaluated using receiver operating characteristic curves. Areas under the curve (AUCs) were estimated with 95% confidence intervals from 5,000 bootstrap resamples. Diagnostic performance was calculated for platelet count $< 150 \times 10^9/L$, FIB-4 ≥ 1.3 , and APRI ≥ 0.5 , with Wilson confidence intervals for sensitivity, specificity, positive predictive value, and negative predictive value. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using Python 3.13.5 (Python Software Foundation, Wilmington, Delaware, United States), pandas 2.2.3, SciPy 1.17.0, statsmodels 0.14.6, scikit-learn 1.8.0, and matplotlib 3.10.8. Firth regression was implemented using the adjusted-score method described by Firth and Heinze and Schemper [17,18].

Ethical considerations

The parent study was approved by the Institutional Ethics Committee of Osmania Medical College. Written informed consent was obtained from all participants. The present analysis used de-identified study data and involved no additional patient contact.

RESULTS

The cohort comprised 101 participants with a mean age of 43.03 ± 10.82 years; 58 (57.4%) were female. Mean recalculated BMI was 30.57 ± 6.03 kg/m², 53 participants (52.5%) had obesity, 29 (28.7%) had diabetes, and 22 (21.8%) had hypertension.

Based on participant-level LSM values, 64 participants (63.4%) were in the F0–F1 range, 23 (22.8%) in the F2 range, seven (6.9%) in the F3 range, and seven (6.9%) in the F4-range category. Thus, 37 participants (36.6%) had significant-or-greater liver stiffness (LSM ≥ 7.0 kPa), and 14 (13.9%; 95% confidence interval, 8.4%–21.9%) had advanced liver stiffness (LSM ≥ 8.8 kPa).

Clinical, metabolic, and biochemical characteristics according to advanced liver stiffness are summarized in Table 1. Age, BMI, controlled attenuation parameter, fasting glucose, triglycerides, AST, ALT, sex, diabetes, and hypertension did not differ significantly between groups. By contrast, the advanced-liver-stiffness group had a markedly lower platelet count and higher APRI and FIB-4 values. Serum albumin was numerically lower in the advanced group, with a moderate rank-biserial effect size, but the continuous comparison did not reach conventional statistical significance.

Table 1. Clinical and biochemical characteristics according to advanced liver stiffness

Variable	No advanced liver stiffness (n=87)	Advanced liver stiffness (n=14)	Statistical test	Effect size
Age, years	42.0 (35.5–50.0)	44.5 (42.0–48.8)	U=704.0; p=0.353	rank-biserial r=0.156

Variable	No advanced liver stiffness (n=87)	Advanced liver stiffness (n=14)	Statistical test	Effect size
Body mass index, kg/m ²	30.4 (26.0–34.5)	30.5 (25.0–32.1)	U=559.0; p=0.627	rank-biserial r=-0.082
Controlled attenuation parameter, dB/m	272 (244–298)	252 (224–292)	U=495.0; p=0.265	rank-biserial r=-0.187
Fasting glucose, mg/dL	108 (88–132)	108 (88–134)	U=614.5; p=0.961	rank-biserial r=0.009
Triglycerides, mg/dL	144 (126–188)	141 (102–188)	U=504.5; p=0.307	rank-biserial r=-0.172
Aspartate aminotransferase, U/L	26 (20–40)	36 (24–64)	U=763.5; p=0.130	rank-biserial r=0.254
Alanine aminotransferase, U/L	32 (18–46)	34 (24–40)	U=608.0; p=0.996	rank-biserial r=-0.002
Serum albumin, g/dL	4.30 (4.10–4.63)	4.12 (3.54–4.50)	U=396.0; p=0.083	rank-biserial r=-0.300
Platelet count, ×10 ⁹ /L	240 (174–288)	118 (112–122)	U=40.5; p<0.001	rank-biserial r=-0.933
Aspartate aminotransferase-to-platelet ratio index	0.30 (0.20–0.50)	0.75 (0.53–1.35)	U=999.5; p<0.001	rank-biserial r=0.641
Fibrosis-4 index	0.97 (0.64–1.27)	2.15 (1.44–3.77)	U=1018.0; p<0.001	rank-biserial r=0.672
Male sex	37 (42.5)	6 (42.9)	Fisher exact p=1.000	odds ratio=1.01; phi=0.002
Diabetes mellitus	23 (26.4)	6 (42.9)	Fisher exact p=0.218	odds ratio=2.09; phi=0.125
Hypertension	18 (20.7)	4 (28.6)	Fisher exact p=0.498	odds ratio=1.53; phi=0.066
Any recorded comorbidity	28 (32.2)	7 (50.0)	Fisher exact p=0.232	odds ratio=2.11; phi=0.129

Continuous variables are median (interquartile range) and were compared using the Mann–Whitney U test; rank-biserial r is the effect size. Categorical variables are number (percentage) and were compared using two-sided Fisher exact tests; odds ratios and phi coefficients are effect estimates. Advanced liver stiffness was defined as liver stiffness measurement ≥ 8.8 kPa. Serum albumin was available for 100 participants; all other variables were complete. Controlled attenuation parameter is expressed in decibels per metre.

Categorical associations are presented in Table 2. Platelet count $<150 \times 10^9/\text{L}$ was present in 85.7% of participants with advanced liver stiffness and 16.1% without it (odds ratio, 31.29; 95% confidence interval, 6.30–155.34; Fisher exact $p<0.001$; phi=0.550). FIB-4 ≥ 1.3 and APRI ≥ 0.5 were also strongly associated with the outcome. Serum albumin <4.0 g/dL showed a weaker association, whereas obesity, diabetes, hypertension, and conventional aminotransferase thresholds were not statistically significant.

Table 2. Categorical clinical and biochemical markers associated with advanced liver stiffness

Candidate marker	Advanced liver stiffness	No advanced liver stiffness	Odds ratio (95% confidence interval)	Fisher exact p value	Phi
Age ≥ 50 years	3/14 (21.4)	23/87 (26.4)	0.76 (0.19–2.96)	1.000	0.040
Obesity (body mass index ≥ 30 kg/m ²)	8/14 (57.1)	45/87 (51.7)	1.24 (0.40–3.89)	0.779	0.037
Diabetes mellitus	6/14 (42.9)	23/87 (26.4)	2.09 (0.65–6.66)	0.218	0.125
Hypertension	4/14 (28.6)	18/87 (20.7)	1.53 (0.43–5.46)	0.498	0.066
Aspartate aminotransferase >40 U/L	6/14 (42.9)	22/87 (25.3)	2.22 (0.69–7.09)	0.203	0.136

Candidate marker	Advanced liver stiffness	No advanced liver stiffness	Odds ratio (95% confidence interval)	Fisher exact p value	Phi
Alanine aminotransferase >40 U/L	3/14 (21.4)	33/87 (37.9)	0.45 (0.12–1.72)	0.368	0.119
Serum albumin <4.0 g/dL	6/14 (42.9)	14/87 (16.1)	3.91 (1.17–13.02)	0.030	0.232
Platelet count <150 ×10 ⁹ /L	12/14 (85.7)	14/87 (16.1)	31.29 (6.30–155.34)	<0.001	0.550
Aspartate aminotransferase-to-platelet ratio index ≥0.5	12/14 (85.7)	27/87 (31.0)	13.33 (2.79–63.73)	<0.001	0.388
Fibrosis-4 index ≥1.3	11/14 (78.6)	20/87 (23.0)	12.28 (3.12–48.38)	<0.001	0.416

Values in the outcome columns are number/denominator (percentage). Odds ratios compare presence versus absence of the listed marker. P values are from two-sided Fisher exact tests. Phi describes the strength of association in the 2×2 table. Body mass index was recalculated from recorded height and weight. Aspartate aminotransferase-to-platelet ratio index and Fibrosis-4 are composite non-invasive fibrosis scores.

Firth regression results are shown in Table 3. In the primary model, each 1-unit increase in FIB-4 was associated with 3.33-fold higher adjusted odds of advanced liver stiffness after adjustment for BMI and diabetes. BMI and diabetes were not independently associated with the outcome. In the sensitivity model, each 0.5-unit increase in APRI was associated with 4.30-fold higher adjusted odds, while BMI and diabetes again remained non-significant.

Table 3. Firth bias-reduced logistic regression models for advanced liver stiffness

Model	Predictor	Adjusted odds ratio (95% confidence interval)	Wald statistic	z	p value
Primary model	Fibrosis-4 index, per 1-unit increase	3.33 (1.61–6.91)	3.23		0.001
Primary model	Body mass index, per 5 kg/m ² increase	1.12 (0.63–2.00)	0.39		0.700
Primary model	Diabetes mellitus	1.21 (0.30–4.98)	0.27		0.788
Sensitivity model	Aspartate aminotransferase-to-platelet ratio index, per 0.5-unit increase	4.30 (1.86–9.94)	3.41		0.001
Sensitivity model	Body mass index, per 5 kg/m ² increase	1.04 (0.60–1.83)	0.15		0.882
Sensitivity model	Diabetes mellitus	1.99 (0.51–7.76)	0.99		0.323

The primary model included Fibrosis-4, body mass index, and diabetes mellitus. The sensitivity model replaced Fibrosis-4 with the aspartate aminotransferase-to-platelet ratio index. The two composite scores were not entered together because both include aspartate aminotransferase and platelet count. Advanced liver stiffness was defined as liver stiffness measurement ≥8.8 kPa.

Receiver operating characteristic performance is summarized in Table 4 and Figure 1. Platelet count demonstrated excellent discrimination, with an AUC of 0.967. At a threshold below 150 ×10⁹/L, sensitivity was 85.7%, specificity 83.9%, and negative predictive value 97.3%. FIB-4 and APRI showed good discrimination, with AUCs of 0.836 and 0.821, respectively. Their negative predictive values exceeded 95%, whereas positive predictive values were lower, reflecting the 13.9% prevalence of advanced liver stiffness in this selected cohort.

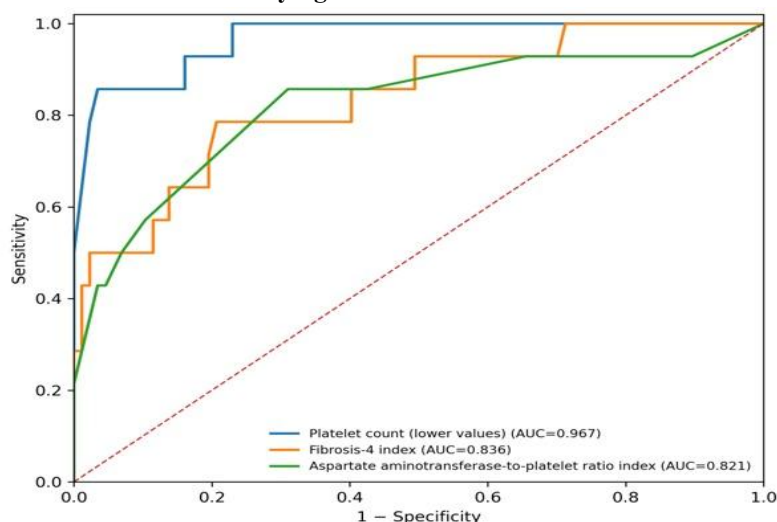
Table 4. Diagnostic performance of simple biochemical markers for advanced liver stiffness

Marker and prespecified threshold	Area under the curve (95% confidence interval)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Platelet count <150 ×10 ⁹ /L	0.967 (0.917–0.998)	85.7% (60.1–96.0)	83.9% (74.8–90.2)	46.2% (28.8–64.5)	97.3% (90.8–99.3)
Fibrosis-4 index ≥1.3	0.836 (0.705–0.943)	78.6% (52.4–92.4)	77.0% (67.1–84.6)	35.5% (21.1–53.1)	95.7% (88.1–98.5)
Aspartate aminotransferase-to-platelet ratio index ≥0.5	0.821 (0.664–0.945)	85.7% (60.1–96.0)	69.0% (58.6–77.7)	30.8% (18.6–46.4)	96.8% (89.0–99.1)

Area under the curve confidence intervals were obtained from 5,000 bootstrap resamples. Sensitivity, specificity, positive predictive value, and negative predictive value are presented with Wilson 95% confidence intervals. Predictive values are

specific to the 13.9% prevalence of advanced liver stiffness in this tertiary-care cohort and should not be extrapolated directly to populations with different prevalence.

Figure 1. ROC curves for platelet count, Fibrosis-4, and the aspartate aminotransferase-to-platelet ratio index in identifying advanced liver stiffness.



For platelet count, the direction was inverted so that lower values indicated greater risk. AUC, area under the curve; FIB-4, Fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index.

DISCUSSION

This secondary analysis identified a distinct biochemical profile among patients with VCTE-defined advanced liver stiffness. Fourteen of 101 participants met the prespecified threshold of LSM ≥ 8.8 kPa. The strongest univariable marker was platelet count, followed by FIB-4 and APRI. FIB-4 remained independently associated with the outcome after adjustment for BMI and diabetes, and APRI showed a similar association in a separate sensitivity model. In contrast, BMI, diabetes, hypertension, fasting glucose, triglycerides, and conventional AST or ALT thresholds were not independently discriminatory.

These findings are clinically relevant because fibrosis severity, rather than steatosis alone, is the histological feature most consistently linked to liver-related outcomes and mortality in NAFLD [5–7]. Current AASLD and EASL-EASD-EASO guidance therefore emphasizes case-finding for advanced fibrosis using a sequential non-invasive strategy [1,2,8,9]. The present results align with that framework: inexpensive blood-based markers had high negative predictive values, while elastography supplied the imaging-based outcome needed for further risk stratification.

The association between thrombocytopenia and higher liver stiffness was large, with a rank-biserial correlation of -0.933 and an odds ratio exceeding 30 for platelet count $<150 \times 10^9/L$. Progressive fibrosis can reduce platelet count through portal-hypertension-related splenic sequestration, reduced thrombopoietin production, and other mechanisms. Nevertheless, platelet count is not liver-specific; nutritional deficiency, marrow disease, immune thrombocytopenia, medications, and infection can produce similar abnormalities. The striking discrimination observed here should therefore be regarded as a cohort-specific signal rather than a stand-alone diagnostic rule. It also partly explains the performance of FIB-4 and APRI, both of which include platelet count in the denominator.

FIB-4 had an AUC of 0.836 and a negative predictive value of 95.7% at a threshold of 1.3. Its independent association persisted in the bias-reduced model. These findings are consistent with the role of FIB-4 as a first-line blood-based test in contemporary clinical pathways [1,2,8,9]. FIB-4 was originally developed in a different liver-disease population, and its accuracy is affected by age and the underlying disease spectrum [14,16]. It is therefore most useful as a rule-out test, not as a definitive measure of fibrosis stage. The lower positive predictive value in this cohort illustrates the predictable consequence of applying a screening threshold when outcome prevalence is modest.

APRI also showed good discrimination and a high negative predictive value, but lower specificity than platelet count or FIB-4 at the selected threshold. APRI was developed for chronic hepatitis C and is less consistently recommended as the preferred first-line score in metabolic liver disease [8,15]. Even so, it may remain useful where age data are unreliable or where automated FIB-4 calculation is unavailable. The independent association observed in the sensitivity model supports its value as an alternative signal, but not as a replacement for VCTE.

Serum albumin <4.0 g/dL was associated with advanced liver stiffness in the categorical analysis, although the continuous comparison did not reach statistical significance. Albumin may decrease with impaired hepatic synthesis, systemic inflammation, renal or gastrointestinal protein loss, or malnutrition. Given the cross-sectional design and the limited number of events, this finding should be interpreted as exploratory. Similarly, AST showed a small-to-moderate effect direction without statistical significance, whereas ALT did not discriminate between groups. Normal or mildly elevated aminotransferases therefore cannot be used to exclude advanced disease, consistent with current practice guidance [1].

The absence of independent associations for BMI and diabetes should not be interpreted as evidence that metabolic risk is unimportant. Both are established determinants of NAFLD development and progression [1,2,4]. Several features may explain the null results: more than half of the cohort already had obesity, nearly one-third had diabetes, the sample contained only 14 advanced-LSM events, and referral to a tertiary gastroenterology service may have narrowed the metabolic contrast between groups. Cross-sectional measurements also cannot capture cumulative glycaemic exposure, duration of obesity, weight trajectories, or treatment effects.

The VCTE outcome itself requires careful interpretation. LSM is influenced not only by fibrosis but also by acute inflammation, cholestasis, hepatic congestion, food intake, probe selection, and technical quality [8,10–13]. The threshold of 8.8 kPa was selected because it defined the F3 range in the parent protocol, but thresholds vary across studies and guidelines. Furthermore, known cirrhosis was excluded and no biopsy reference was available. The manuscript therefore deliberately reports “advanced liver stiffness” rather than claiming histologically proven advanced fibrosis. In clinical practice, an elevated LSM should prompt review of technical reliability, competing causes, and—when appropriate—repeat or complementary testing.

The practical implication is a tiered pathway. In adults with imaging-defined steatosis, routine age, AST, ALT, and platelet data can be used to calculate FIB-4. A low score may reduce the probability of advanced liver stiffness, whereas an elevated or indeterminate score should lead to VCTE or another validated second-line test [1,2,8,9]. The present results support this sequence but do not establish a new threshold or justify withholding elastography solely on the basis of a normal platelet count or low APRI. Prospective validation in a larger, independently recruited cohort is needed.

Strengths and Limitations

Strengths of this study include analysis of individual participant data rather than reliance on aggregate dissertation tables, reconstruction of fibrosis categories directly from measured LSM, prespecified separation of an advanced-LSM outcome from lower stiffness categories, and reporting of test statistics, confidence intervals, and effect sizes. The analysis also used Firth bias-reduced regression to limit small-sample and separation bias and bootstrap confidence intervals for discrimination estimates.

The study also has important limitations. It was conducted at a single tertiary centre using consecutive but clinically selected participants, limiting generalisability. Only 14 participants had advanced liver stiffness, restricting multivariable model complexity and producing wide confidence intervals. Liver biopsy was not performed, so the outcome cannot be equated with histological F3–F4 fibrosis.

The study was cross-sectional and cannot establish temporality or causal prediction. APRI, FIB-4, and platelet count are mathematically and biologically interdependent, so their apparent performance should not be interpreted as independent mechanistic evidence. One record exceeded the stated upper age criterion and requires confirmation against the source case form.

CONCLUSIONS

In adults with NAFLD evaluated at a tertiary centre, platelet count, FIB-4, and APRI were the most informative markers of VCTE-defined advanced liver stiffness. FIB-4 and APRI remained associated with the outcome in separate parsimonious bias-reduced models, whereas BMI and diabetes did not independently discriminate within this selected cohort. The high negative predictive values of these inexpensive tests support their use as first-line risk-stratification tools followed by elastography. Prospective multicentre validation with standardized VCTE quality criteria and histological or longitudinal outcome assessment is required.

DECLARATIONS

Ethics approval and consent to participate: The parent study was approved by the Institutional Ethics Committee of Osmania Medical College. Written informed consent was obtained from all participants.

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

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