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ORIGINAL ARTICLE

Prevalence of Hepatic Fibrosis and Performance of Non-invasive Liver Fibrosis Scores in an Eastern Indian Diabetic Population with NAFLD

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Abstract

Objectives. Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease, especially in patients with type 2 diabetes mellitus (T2DM). Significant prevalence of liver fibrosis has been observed in Indian diabetic patients with fatty liver. Early detection of liver fibrosis in persons with diabetes prevents serious problems. This study compares non-invasive liver fibrosis scores and vibration-controlled transient elastography (VCTE) utilising FIBROSCAN™ to assess fibrosis prevalence in patients with T2DM and NAFLD.

Methodology. This cross-sectional, observational study enrolled 351 patients with T2DM and NAFLD from September to October 2023 from eight West Bengal diabetes facilities. Liver stiffness measurement (LSM) via VCTE was used to detect fibrosis. Non-invasive tests (NITs), including fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), fibrotic NASH-index (FNI), and AST to platelet ratio index (APRI) were also calculated. To evaluate NIT diagnostic performance, AUROC curve calculations were used.

Results. Among patients with T2DM, 26.5% had fibrosis and 3.13% of individuals had advanced fibrosis (≥F3), whereas 11.97% had significant fibrosis (≥F2). Fibrotic NASH-index could detect fibrosis best with area under the curve (AUROC) >0.70, whereas FIB-4 and NFS were better (AUROC >0.8) to identify advanced fibrosis, and APRI struggle to diagnose severe fibrosis.

Conclusion. In patients with T2DM with NAFLD, VCTE detects fibrosis. FNI is best tool for detection of fibrosis, whereas FNI and NFS are better for distinguishing advanced fibrosis in such patients. To increase fibrosis identification in this population, multiple diagnostic approaches are needed.

Key words: non-alcoholic fatty liver disease (NAFLD), vibration-controlled transient elastography (VCTE), fibrosis-4 index (FIB-4), NAFLD-fibrosis score (NFS), AST to platelet ratio index (APRI)

Clinical trial registration number (CTRI): CTRI/2023/08/056193 dated 7th August 2023

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), an important cause of chronic liver disease (CLD), is defined as excessive hepatic fat accumulation (≥5%) with no secondary factors such as excessive alcohol use, hepatotoxic drugs, or other chronic liver disorders. Histological features of NAFLD may vary from fatty liver to steatohepatitis, which can progress to fibrosis, cirrhosis, or even hepatocellular carcinoma.[1] Worldwide prevalence of NAFLD is reported to be 25.24%, with a recent meta-analysis reporting 29.62% prevalence in Asia and 28-32% in India.[2,3] A significant regional variation (44.1% to 72.4%) in NAFLD prevalence exists between different parts of India.[4-6]

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When this condition is significantly associated with metabolic disorders such as type 2 diabetes mellitus (T2DM), obesity, and dyslipidaemia, it is known as metabolic dysfunction-associated steatohepatitis liver disease (MASLD).[7] Non-alcoholic fatty liver disease in patients with T2DM is associated with increased mortality and cardiovascular risk.[8] There is a high prevalence of NAFLD among Indian patients with T2DM ranging from 45% to 72%.[9,10] In patients with T2DM, rapid progression of NAFLD to advanced fibrosis, cirrhosis, or increased hepatic and extrahepatic morbidity and mortality justify liver fibrosis screening in all patients with T2DM, as per most guidelines, including American Diabetes Association (ADA).[11,12] The global prevalence of NASH and advanced fibrosis is reported to be 37.3% and 17%, respectively, in patients with T2DM and NAFLD.[13]

The assessment and staging of liver fibrosis remain the basis for clinical decision-making, prognosis, and therapeutic monitoring in patients with chronic liver disease. Although liver biopsy is the gold standard for identifying and staging liver fibrosis, its use is limited due to its invasive nature and intra- and interobserver variability.[4,14] Prior research has assessed non-invasive methods, such as vibration-controlled transient elastography (VCTE) for evaluating liver fibrosis and steatosis in individuals with nonalcoholic fatty liver disease (NAFLD). The usefulness of VCTE in fibrosis assessment has been shown by research,[15] and comparisons of several non-invasive procedures have revealed variations in diagnostic accuracy.[16] Moreover, VCTE has been used in diabetic population research to screen for both liver fibrosis and steatosis.[17]

Alternative, non-invasive approaches to measure and stage liver fibrosis include imaging modalities (elastography-based or magnetic resonance imaging techniques) measuring liver stiffness or clinical predictive scores using serum biomarkers. The most reliable non-invasive screening method that can simultaneously measure liver steatosis and accurately assess the degree of fibrosis is vibration-controlled transient elastography (VCTE) with FIBROSCAN™ (Echosense, Paris, France) utilizing controlled attenuation parameter (CAP) measurement.[18,19] It is the first elastography method approved by the Food and Drug Administration (FDA).[20] Due to its higher sensitivity (80%–85% or more), VCTE is considered a more accurate approach for diagnosing even mild steatosis.[19,21]

Non-invasive predictive scores are most feasible in clinics, especially when assessing a large number of patients. The most commonly used predictive scores or non-invasive tests (NITs) to evaluate fibrosis are fibrosis-4 index (FIB-4), NAFLD-fibrosis score (NFS), aspartate aminotransferase (AST) to platelet ratio index (APRI), body mass index (BMI), AST/ALT (alanine aminotransferase) ratio, diabetes score (BARD), fibrotic NASH-index (FNI), etc.[22,23] Such NITs are easily accessible and reliable tools to differentiate patients with NAFLD in different stages of fibrosis. Also, NITs enable quick assessment of large numbers of patients, resulting to increased utility in clinical practice and clinical trials.[24,25]

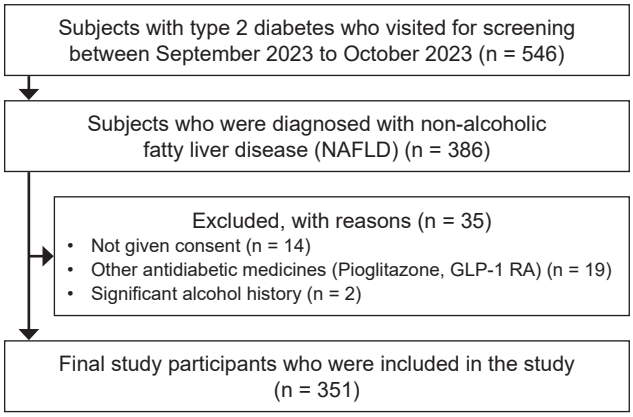

Figure 1. Flowchart of participants.

Fibrosis has been found to be independently associated with micro and macrovascular complications in patients with T2DM.[18] Thus, such NITs help comprehensively evaluate patients with diabetes for hepatic and cardiovascular complications.

There is however a dearth of information about the diabetic population in Eastern India. By assessing the non-invasive fibrosis scores' performance in this particular cohort, this study seeks to close this gap. The present study evaluated the prevalence of fibrosis in MASLD diagnosed through transient elastography compared to various non-invasive liver fibrosis scores in the East Indian population with T2DM.

METHODOLOGY

Study design

A cross-sectional, observational, multicentric study was conducted on Indian patients with T2DM at eight diabetes centers in West Bengal, India. Patients who reported between September 2023 and October 2023 were screened, and those with NAFLD were included in the study (Figure 1).

Study objectives

The primary objective of the study was to evaluate the prevalence of fibrosis in T2DM through VCTE. The performance of different non-invasive liver fibrosis scores to diagnose the presence of fibrosis, significant fibrosis (SF), and advanced fibrosis (AF) in patients with diabetes was also assessed.

Study population

The study screened 546 patients with T2DM (HbA1c ≥6.5%) aged over 18 years, and enrolled 351 participants. Those who consented to fibrosis evaluation via VCTE

were included. A total of 195 patients were excluded due to chronic viral hepatitis, significant alcohol consumption, other liver diseases, prior use of medications such as pioglitazone and GLP-1 RA, or current use of saroglitazar, vitamin E, pentoxifylline, ursodeoxycholic acid (UDCA), or obeticholic acid (OCA).

Participants were recruited using a consecutive sampling method. Eligible patients visiting eight diabetes centers in West Bengal, India, between September and October 2023 were screened based on predefined inclusion and exclusion criteria. Those meeting the criteria were enrolled sequentially until the required sample size was achieved, ensuring a representative sample while minimizing selection bias.

Ethics committee approval

The study was approved by a central ethics committee (OrciVita Independent Ethics Committee – OIEC/07/01/2023 dated – 6th July 2023) and was conducted in line with the principles of the Helsinki Declaration. Clinical Trials Registry-India (CTRI) registration of the study was also carried out (CTRI registration no: CTRI/2023/08/056193 dated 7th August 2023). Written informed consent was obtained from all the participants before enrolment in the study.

Clinical assessment

Clinical and laboratory data were collected prospectively from all the included patients during VCTE. Past medical history included present medication use and alcohol use. Demographic measurements comprised of age, gender, BMI calculated as weight (in kilograms)/m^2, systolic and diastolic blood pressure, and duration of T2DM. On the day of the VCTE examination, a venous blood sample for laboratory parameters was obtained early in the morning following an overnight fast. Random blood sugar, HbA1c, ALT, AST, albumin and platelet count levels were analyzed. The laboratory parameters of patients at all eight study sites were submitted to one single laboratory to reduce variability in outcomes.

Liver stiffness measurement (LSM) using transient elastography

The LSM measurements were performed by trained technicians using FIBROSCAN™ (430 mini+, Echosense, Paris, France) as per the manufacturer's recommendations using either M or XL probes. The distance between the skin and liver capsule, known as a probe to liver capsule distance, was determined to establish the ideal probe size. The M probe was employed if it was <25 mm, while the XL probe was used if it was >25 mm. Measurement was done once all requirements were satisfied (proper layering on TM mode, an aligned line of imagination on A mode, and enough probe pressure). The patient was positioned supine with the right arm raised to its full height, and the LSM of the right lobe of the liver was taken from the intercostal space. The median value was used to derive the LSM value, which was expressed in kilopascals (kPa). The VCTE examination was considered reliable for those with a median interquartile range value of less than 30% among 10 valid measurements and a success rate of at least 60%. Success rate was determined as the ratio of valid measurements to total measurements conducted.[26,27]

The presence of liver fibrosis was graded based on LSM values provided by the manufacturer, i.e., absence of fibrosis (F0-≤7.0 kPa), mild (F1-≥7.1–10 kPa), moderate fibrosis (F2-≥10.1-13.0 kPa), severe fibrosis (F3-≥13.1-16.0 kPa) and cirrhosis (F4-≥16.1 kPa). The ≥F2 and ≥F3 scores were considered SF and AF, respectively. The CAP values obtained from the device were used when the VCTE examination was valid for that signal and expressed in decibels per meter (dB/m). The CAP scores of ≥238 dB/m were considered to have hepatic steatosis. Grading of hepatic steatosis was done based on the CAP value and was categorized as as mild (S1 - 238-260 dB/m), moderate (S2 - 261-292 dB/m), and severe (S3 - ≥293 dB/m). Values were provided by the FIBROSCAN™ manufacturer.

Non-invasive tests

Various non-invasive scores such as FIB-4, NFS, FNI, and APRI were calculated using the collected data. Fibrosis-4 index, NFS and APRI were calculated using the formula described by Alqahtani and others,[22] and FNI was calculated as per the formula described in the literature.[23] The rule-out and rule-in cut-off values of FIB-4, NFS, FNI, and APRI were 1.3 and 2.67, -1.455 and 0.676, 0.10 and 0.33, and 0.5 and 2.0, respectively.[25]

Sample size

The sample size was initially determined based on prevalence estimation to ensure sufficient representation of patients with T2DM and NAFLD. With power at 85%, significance level of 0.05, and a reported T2DM prevalence of 11% in India, of which 70% have NAFLD, the required sample size was 546. This calculation was designed to provide robust prevalence estimates while accounting for potential exclusions and subgroup analyses.

To ensure adequate power for diagnostic accuracy assessment, a separate calculation was conducted using expected sensitivity (90%), specificity (90%), prevalence of 11%, precision of ±10%, 95% confidence level, and a 10% dropout rate. This resulted in a required minimum sample size of 350. After applying eligibility criteria and exclusions, 351 participants were included in the final analysis, ensuring sufficient power for both prevalence estimation and diagnostic accuracy evaluation. The study was conducted using the prevalence-based sample size determination, but the final sample size also met the requirements for diagnostic accuracy validation.

Statistical analysis

Categorical variables were expressed as percentages (%), while continuous variables were expressed as mean ± standard deviation (SD). The chi-square test was used to compare the categorical variables, while the independent t-test was used to compare continuous variables. Statistical significance was set at a value of $p<0.05$. Receiver operating characteristic (ROC) curves with area under the ROC (AUROC) were calculated to determine the diagnostic utility of FIB-4, NFS, FNI, and APRI scores for non-invasive assessment of fibrosis or AF in diabetic patients with NAFLD. To generate the ROC curve, PROC logistic procedure in SAS software was used while the DeLong test[28] was utilized to compare each AUROC with the LSM value. The AUROC curve ranges from 0 to 1.0, with 0 indicating a perfectly inaccurate marker, while 1.0 represents a perfectly accurate marker. A value of 0.5 indicates that the tests cannot discriminate between patients with or without fibrosis.[29] In general, tests with an AUROC greater than 0.80 are thought to be clinically helpful.[30]

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for FIB-4, NFS, FNI, and APRI scores with exact binomial 95% confidence interval (CI.) All four NITs were also evaluated to select the optimal predicted probability cut-off using the Youden index (J value). The optimal probability cut-off is where J is the maximum. The SAS software (version 9.4; SAS Institute Inc., USA) was used to perform all the data analyses.

RESULTS

We prospectively included 351 (56% males) patients with T2DM and NAFLD in our study. The mean age and BMI were 51 ± 9 years and 25.8 ± 4.2 kg/m^2, respectively. The total study population was categorised into two groups: absence (F0) and presence (≥F1) of fibrosis. Ninety-three (26.50%) subjects had liver fibrosis as per LSM by VCTE, while 258 (73.50%) subjects did not have fibrosis. The mean glycosylated haemoglobin in both groups was 7.6 ± 1.8%, significantly different (p = 0.0014) among the groups. The demographic and laboratory parameters of the patients with T2DM and NAFLD with and without fibrosis are described in Table 1.

Prevalence of fibrosis based on LSM and CAP values

The prevalence of fibrosis among patients with T2DM was found to be 26.5% (F1 to F4), with a mean LSM of 10.2 ± 2.6 kPa (F1 to F4). Significant fibrosis (SF) (≥F2, LSM >10.0 kPa) was reported in 42 patients (11.97%), and 11 patients (3.13%) reported AF (≥F3, LSM >13.0 kPa). The prevalence of steatosis among patients with T2DM was 70.7% (S1 to S3), with a mean CAP of 293.4 ± 34 dB/m (S1 to S3). Significant steatosis (S2-S3) was found in 204 (58%) patients with a CAP score above 261 dB/m.

Performance of FIB-4, NFS, FNI, and APRI tests

The distributions of various parameters (FIB-4, NFS, FNI, and APRI) by the presence or absence of fibrosis are presented in Table 2. The mean score of FIB-4, NFA, FNI, and APRI was 1.8 ± 0.9, -0.4 ± 1.1, 0.6 ± 0.2, and 0.5 ± 0.4, respectively, in absence of fibrosis (F0) while 1.8 ± 1, -0.5 ± 1.3, 0.7 ± 0.2, and 0.6 ± 0.4, respectively in presence of fibrosis (≥F1).

The accuracy of these tests for detecting fibrosis, SF, or AF was measured using AUROC (Figure 2).

Table 1. Demographic and laboratory parameters of patients with type 2 diabetes with or without fibrosis based on LSM values

Demographics		Absence of Fibrosis (F0) (n = 258)	Presence of Fibrosis (≥F1) (n = 93)	Total (F0 to F4) (n = 351)	*p*-value
Age (mean ± SD), years		52 ± 8	50 ± 9	51 ± 9	0.0465[a]
Gender, n(%)	Male	156 (60%)	42 (45%)	198 (56%)	0.0107[a]
	Female	102 (40%)	51 (55%)	153 (44%)	
BMI (mean ± SD), kg/m²		25.2 ± 3.8	27.3 ± 4.9	25.8 ± 4.2	<0.0001[a]
T2DM (mean ± SD), duration in months		98 ± 85	85 ± 66	95 ± 81	0.1823
HbA1c (mean ± SD), %		7.4 ± 1.8	8.1 ± 1.8	7.6 ± 1.8	0.0014[a]
AST (mean ± SD), U/L		32.2 ± 20	42.2 ± 24.5	34.8 ± 21.7	0.0001[a]
ALT (mean ± SD), U/L		33.6 ± 18.8	50.7 ± 40.3	38.2 ± 27.3	<0.0001[a]
Albumin (mean ± SD), g/dL		4.4 ± 0.3	4.3 ± 0.3	4.4 ± 0.3	0.0062[a]
Platelet Count (mean ± SD), x 10³ / µL		179.1 ± 67.8	195 ± 66	183.3 ± 67.6	0.0517
CAP (mean ± SD), dB/m		257.5 ± 49.2	291.9 ± 53.4	266.6 ± 52.5	<0.0001[a]
LSM (mean ± SD), kPa		5 ± 1.1	10.2 ± 2.6	6.4 ± 2.8	<0.0001[a]

The values are expressed as mean ± standard deviation (SD), count (n) and proportion (%)

[a] *p*-value less than 0.05 is considered statistically significant measured by Chi-square test

AST: Aspartate aminotransferase; ALT: Alanine transaminase; BMI: Body mass index; CAP: Controlled attenuation parameter; DBP: Diastolic blood pressure; HbA1c: Glycosylated haemoglobin; HDL-C: High-density lipoprotein cholesterol; h/o: History of; LDL-C: Low-density lipoprotein cholesterol; LSM: Liver stiffness measurement; NAFLD: Non-alcoholic fatty liver disease; RBS: Random blood sugar; SBP: Systolic blood pressure; T2DM: Type 2 diabetes mellitus

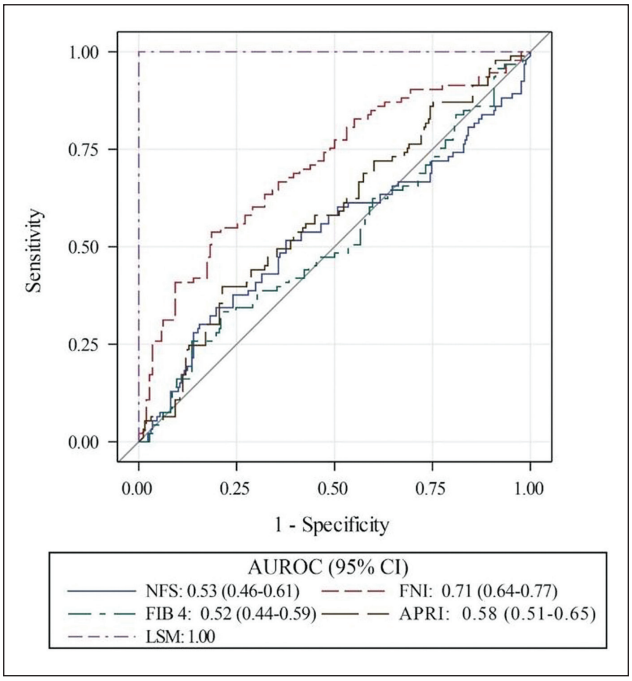

Figure 2A. Area under the receiver operator curves (AUROC) of non-invasive tests for presence of fibrosis.

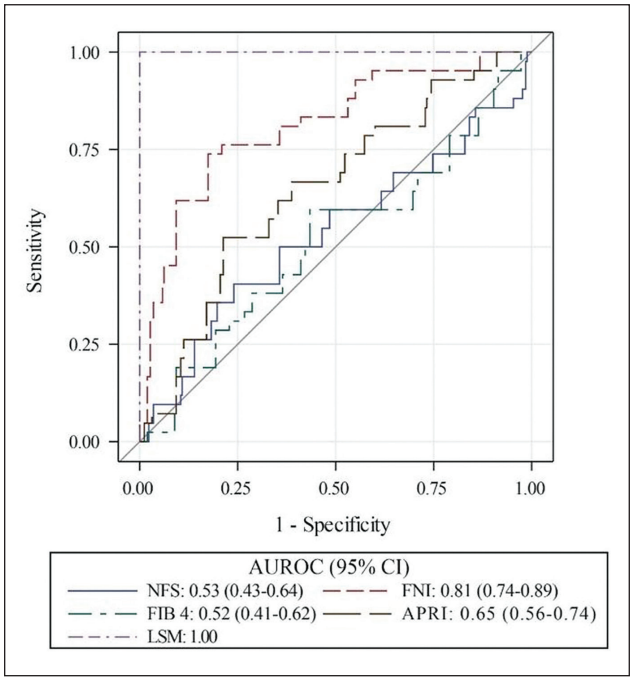

Figure 2B. Significant fibrosis (SF).

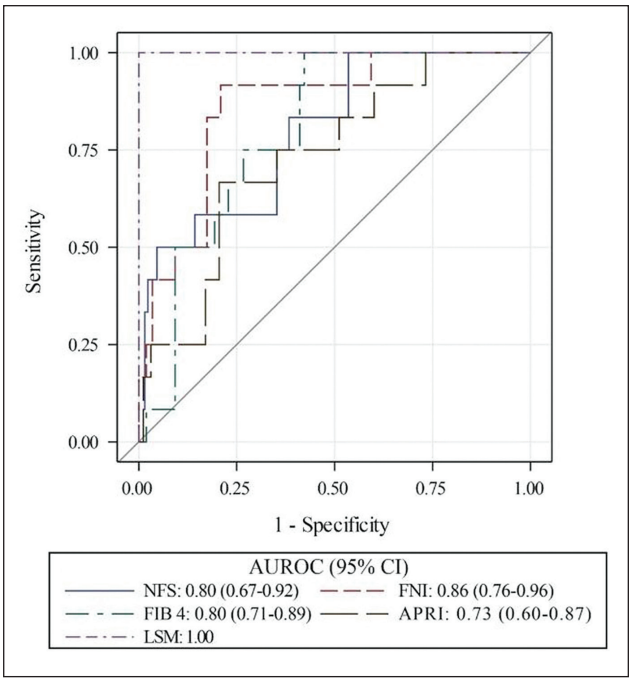

Figure 2C. Advanced fibrosis (AF).

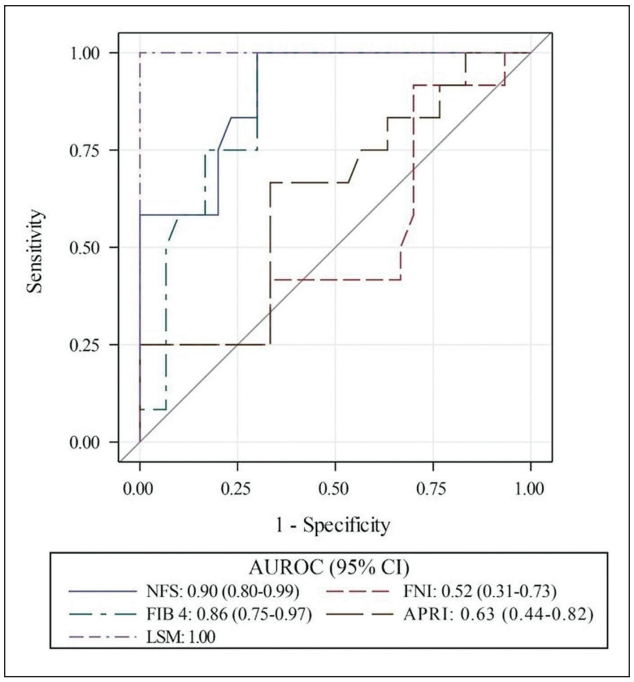

Figure 2D. Differentiating SF from AF in patients with type 2 diabetes.

DISCUSSION

As the landscape of liver diseases evolves, there is a growing recognition of the significant impact of metabolic dysfunction on liver health. While the term NAFLD remains widely used, there is a growing recognition of the critical role metabolic dysfunction plays in the development and progression of fatty liver disease. Metabolic dysfunction-associated steatotic liver disease, affecting a substantial portion of the global population, highlights the complex nature of liver diseases, particularly in patients with advanced liver fibrosis.[34] Our study found a 26.5% fibrosis prevalence in patients with T2DM and NAFLD by VCTE via FIBROSCAN™. Significant fibrosis (≥F2, LSM >10.0 kPa) was found in 42 patients (11.97%), and 11 patients (3.13%) reported AF (≥F3, LSM >13.0 kPa). The mean score of FIB-4, NFA, FNI, and APRI was 1.8 ± 0.9, -0.4 ± 1.1, 0.6 ± 0.2, and 0.5 ± 0.4, respectively, in absence of fibrosis (F0)

while 1.8 ± 1, -0.5 ± 1.3, 0.7 ± 0.2, and 0.6 ± 0.4, respectively in presence of fibrosis (≥F1). Although most patients with T2DM and NAFLD assessed to have fibrosis had high FIB-4, NFS, FNI, and APRI scores, a significant percentage had normal values.

Using the published cut-offs,[25-30] the performance of FIB-4, NFS, and APRI for the diagnosis of fibrosis and SF were relatively poor with AUROC <0.64, while that of FNI was acceptable (AUROC >0.70) (Table 3). On the other hand, the performance of FNI and APRI were poor (AUROC <0.64) for the diagnosis of AF, and that of FIB-4 and NFS were better (AUROC >0.8) (Table 3). Prasad et al., reported that while the FIB-4 score demonstrated moderate diagnostic accuracy (AUROC: 0.634 for any fibrosis, 0.640 for advanced fibrosis), the NAFLD Fibrosis Score (NFS) showed lower discriminatory power, requiring further validation in Indian patients.[31]

Previous study in eastern India found similar (26%) hepatic fibrosis prevalence in patients with T2DM.[9] Previous studies have indicated a higher risk of developing fibrosis in the presence of T2DM.[8,31] Our study also found significantly higher age, HbA1c, BMI, AST, and ALT in patients with T2DM and fibrosis. This observation corroborates with previous studies indicating that age, obesity, and

Table 2. Percentage prevalence of different grades of liver fibrosis in patients with type 2 diabetes based on FIB-4, NFS, FNI, and APRI score cut-off values

NIT score cut-off values	F0	F1	F2	F3	F4
FIB-4					
<1.3 (n = 104)	72 (69.2)	19 (18.3)	13 (12.5)	0 (0)	0 (0)
1.3 to 2.67 (n = 204)	156 (76.5)	27 (13.2)	15 (7.4)	4 (2)	2 (1)
>2.67 (n = 43)	30 (69.8)	5 (11.6)	2 (4.7)	5 (11.6)	1 (2.3)
NFS					
<-1.455 (n = 65)	39 (60)	15 (23.1)	11 (16.9)	0 (0)	0 (0)
1.455 to 0.675 (n = 244)	192 (78.7)	27 (11.1)	19 (7.8)	5 (2)	1 (0.4)
≥0.676 (n = 42)	27 (64.3)	9 (21.4)	0 (0)	4 (9.5)	2 (4.8)
FNI					
<0.10 (n = 18)	15 (83.3)	3 (16.7)	0 (0)	0 (0)	0 (0)
0.10 to 0.33 (n = 99)	88 (88.9)	9 (9.1)	2 (2)	0 (0)	0 (0)
>0.33 (n = 234)	155 (66.2)	39 (16.7)	28 (12)	9 (3.8)	3 (1.3)
APRI					
<0.5 (n = 206)	159 (77.2)	31 (15)	13 (6.3)	2 (1)	1 (0.5)
0.5 to 2 (n = 138)	95 (68.8)	19 (13.8)	17 (12.3)	5 (3.6)	2 (1.4)
>2 (n = 7)	4 (57.1)	1 (14.3)	0 (0)	2 (28.6)	0 (0)

The values are expressed as n(%)

APRI: aspartate aminotransferase-to-platelet ratio; FIB-4: Fibrosis-4 index; FNI: fibrotic non-alcoholic steatohepatitis index; NAFLD: Non-alcoholic fatty liver disease; NFS: non-alcoholic fatty liver disease fibrosis score

Table 3. Sensitivity, specificity, and positive and negative predictive value of non-invasive tests for detection of presence of fibrosis (F1-F4), significant fibrosis - SF (≥F2), advanced fibrosis - AF (≥F3) and differentiation of SF and AF in patients with type 2 diabetes with non-alcoholic fatty liver disease

	Optimal Cut-offs	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	*p*-value
Fibrosis								
FIB-4	1.17	0.52 (0.44-0.59)	33.33	79.07	36.47	76.69	66.95	0.8365
NFS	-1.16	0.53 (0.46-0.61)	34.41	80.23	38.55	77.24	68.09	0.6387
FNI	0.66	0.71 (0.64-0.77)	53.76	81.40	51.02	83.00	74.07	<0.0001[a]
APRI	0.62	0.58 (0.51-0.65)	39.78	78.68	40.22	78.38	68.38	0.0764
Significant fibrosis (SF)								
FIB-4	1.77	0.52 (0.41-0.62)	59.52	56.59	18.25	89.57	57.00	0.9295
NFS	-1.04	0.53 (0.43-0.64)	40.48	75.97	21.52	88.69	71.00	0.6129
FNI	0.67	0.81 (0.74-0.89)	73.81	82.56	40.79	95.09	81.33	<0.0001[a]
APRI	0.62	0.65 (0.56-0.74)	52.38	78.68	28.57	91.03	75.00	0.0487[a]
Advanced fibrosis (AF)								
FIB-4	1.81	0.80(0.71-0.89)	100.00	57.75	9.92	100.00	59.63	0.0084[a]
NFS	-0.31	0.80 (0.67-0.92)	100.00	46.51	8.00	100.00	48.89	0.0001[a]
FNI	0.62	0.86 (0.76-0.96)	91.67	79.07	16.92	99.51	79.63	<0.0001[a]
APRI	0.63	0.73 (0.60-0.87)	66.67	79.46	13.11	98.09	78.89	0.0129[a]
Significant vs. Advanced fibrosis								
FIB-4	1.81	0.86 (0.75-0.97)	100.00	70.00	57.14	10.00	78.57	0.0020[a]
NFS	-0.31	0.90 (0.80-0.99)	100.00	70.00	57.14	10.00	78.57	0.0039[a]
FNI	0.97	0.52 (0.31-0.73)	25.00	100.00	100.00	76.92	78.57	0.5278
APRI	0.63	0.63 (0.44-0.82)	66.67	66.67	44.44	83.33	66.67	0.0747

[a] *p*-value less than 0.05 is considered statistically significant measured by Chi Square test.

APRI: aspartate aminotransferase-to-platelet ratio; AUROC: area under the receiver operating curves; CI: confidence interval; FIB-4: Fibrosis-4 index; FNI: fibrotic non-alcoholic steatohepatitis index; NFS: non-alcoholic fatty liver disease fibrosis score; NPV: negative predictive value; PPV: positive predictive value

higher levels of AST and ALT are independent predictors for the development of fibrosis.[32,33]

Screening for fibrosis is challenging due to the high prevalence of NAFLD in the general population and more so in subjects with T2DM.[34] Magnetic resonance imaging, particularly MR elastography (MRE), offers superior accuracy for staging liver fibrosis and is considered the gold standard non-invasive imaging modality. However, VCTE is more accessible and cost-effective, making it a practical choice for widespread screening.[34] Vibration-controlled transient elastography by FIBROSCAN™ is an FDA-approved, effective, non-invasive tool for detecting steatosis and fibrosis. A meta-analysis reported the sensitivity and specificity of transient elastography (FIBROSCAN™) to be 83.7% and 78.2% for fibrosis stage F1, 87.5% and 78.4% for fibrosis stage F2, 93.7% and 91.1% for fibrosis stage F3 and 96.2% and 92.2% for fibrosis stage F4.[35] Thus, VCTE has good clinical usefulness in diagnosing fibrosis stages, ruling out advanced fibrosis, and may be an alternative to invasive liver biopsy.[36,37] It has been found to be effective in screening for steatosis and fibrosis in patients with T2DM and has also been validated for diagnosing fibrosis in Indian patients.[38]

However, this test is only appropriate for specialised medical settings because it entails training and expensive equipment, and inconsistent outcomes between observers may be seen. Thus, using NITs to stage liver steatosis and fibrosis is a significant advantage for patients with NAFLD, particularly for periodic assessments required for disease progression monitoring.[39]

The present study investigated four different NITs or predictive scoring systems: FIB-4, NFS, FNI, and APRI. All these tests are based on measurements that are conducted in routine clinical practice. Many studies have been performed to validate the diagnostic accuracy of these tests for liver fibrosis. A recent meta-analysis concluded that simple NITs like FIB-4, NFS, and LSM-VCTE could be employed to predict clinical outcomes in patients with NAFLD without needing biopsies.[40] A meta-analysis of 64 studies reported pooled sensitivities and specificities of FIB-4, NFS, and APRI for detecting AF as 64.8% and 72.9%, 66.8% and 87.5%, and 59.7% and 78.9%, respectively. The summary AUROC at published cut-offs for FIB-4 and APRI were found to be 0.73 and 0.76, respectively, while that of NFS was unavailable due to few studies evaluated.[25] Most of these studies reported diagnostic accuracy in the general population, not the diabetic population. The sensitivity and specificity of FNI for detecting NASH were found to be 92% and 71%, with an AUROC of 0.93 in patients with NAFLD in general, while the same in the diabetic population was found to be 97% and 36%, respectively, with an AUROC of 0.89.[41] Our study reports optimised AUROC for detecting the presence of fibrosis, SF, and AF as well as for differentiating SF and AF at previously published cut-offs (FIB-4:<1.3, NFS: <-1.455, FNI:<0.10, APRI: <0.5).

We found that the sensitivity and specificity of FIB-4 and NFS were low for detecting fibrosis and SF compared to LSM. These results support previous studies wherein both these tests have reported <70% sensitivity and specificity for detecting fibrosis and SF compared to LSM.[25,42] The optimised AUROC for detecting the presence of fibrosis were 0.52, 0.53, 0.71, and 0.58 for FIB-4, NFS, FNI, and APRI, respectively. The optimised AUROC for SF and AF were 0.52 and 0.80, 0.53 and 0.80, 0.81 and 0.86, and 0.65 and 0.73 for FIB-4, NFS, FNI and APRI, respectively.

However, FIB-4 and NFS effectively detect AF in T2DM patients at the cut-off of <1.3 and -1.455, respectively. Our results are consistent with earlier studies on the usefulness of FIB-4 and NFS in detecting AF.[27,40] The accuracy of APRI for detecting fibrosis was not better than LSM; however, it was found to be more accurate than FIB-4 and NFS for detecting SF and AF, with a specificity of 75-80%. An earlier meta-analysis also reported the specificity of APRI at a cut-off of 0.43 for the detection of SF and AF to be more than 70%.[27]

One important finding in our study is that FNI showed significantly better performance in detecting fibrosis, SF, and AF than LSM compared to FIB-4, NFS, or APRI. The specificity of FNI at a cut-off of <0.1 for detecting fibrosis, SF, and AF approximates 80%, while the sensitivity increases progressively for detection of fibrosis, SF, and AF from 50% to 90%. Previous studies also found FNI outperforming FIB-4 in detecting fibrosis.[23,41]

The main finding of the present study was that all of these scores had a relatively high NPV (>85%) for detecting liver SF and AF in patients with T2DM, which was consistent with earlier research.[43] Thus, these NITs can be used reliably to rule out or exclude significant or advanced liver fibrosis in patients with T2DM. Testing the patients with one or more such NITs followed by LSM can increase the detection of fibrosis and decrease false positives. However, there is a chance that too many people may be referred to liver specialists by adopting this strategy; thus, these NITs should be used to rule out rather than diagnose fibrosis in patients with T2DM. This approach can help select patients requiring further investigations and referral to specialised liver clinics, to decrease the likelihood of developing cirrhosis in the future. Findings in the present study are in conjunction with the existing guidelines that recommend the usage of NITs for ruling out fibrosis[44-47] However, since the PPV and accuracy of the individual tests are low, they need to be utilized in conjunction with other complex tests to estimate the degree of fibrosis accurately.

Our study did encounter some limitations, such as the small sample size. A larger study population of patients with T2DM and NAFLD could have increased the reliability of these NITs. Furthermore, we compared the performance of these tests with VCTE and not with the gold standard recommended for detecting liver fibrosis, i.e., liver biopsy. Thus, further studies comparing the performance of

these NITs with liver biopsy could shed more light on the application of these tests for screening in large populations.

CONCLUSION

Our study found a 26.4% prevalence of fibrosis in patients with T2DM and NAFLD by FIBROSCAN™. Though most patients with T2DM and NAFLD afflicted with fibrosis had high FIB-4, NFS, FNI, and APRI scores, a significant percentage had normal values. Fibrosis-4 index, NFS and APRI had poor sensitivity for detecting the presence of fibrosis and SF, while FNI was acceptable. Fibrosis-4 index and NFS were better for detecting AF, while FNI and APRI performed poorly. A lower cut-off to detect fibrosis may be considered, especially for SF and AF by NITs.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DS: Conceptualization, Formal analysis, Investigation, Data Curation, Writing – original; draft preparation, Supervision, Funding acquisition; **SC:** Methodology, Software, Validation, Resources, Visualization, Project administration; **SG:** Conceptualization; **AD:** Resources, Writing – review and editing, Supervision; **ASC:** Investigation, Writing – review and editing, Visualization; **SM:** Investigation, Writing – original draft preparation; **SB:** Software, Writing – review and editing, Projection; **SRC:** Methodology, Software, Validation, Resources, Visualization, Project administration; **MS:** Software, Writing – review and editing, Project administration.

Data Availability Statement
Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure
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