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Redefining Liver Fibrosis Risk Assessment in Indians with Type 2 Diabetes: New FIB-4 Score Cutoff for Optimizing Sequential Assessment with Transient Elastography

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Abstract

Introduction: Liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly related to hepatic and extrahepatic outcomes. Clinically Significant Liver Fibrosis (CSLF) screening using FIB-4 score is mandated in all T2D patients. The existing FIB-4 cutoff of 1.3 is derived from Western studies and could differ for Indians. Hence, we aimed to determine the FIB-4 cutoff to rule out Transient Elastography (TE) proven CSLF among Indians with T2D. **Methods:** 551 individuals with T2D underwent laboratory tests for FIB-4 calculation and transient elastography (TE) to detect CSLF defined as Liver Stiffness Measurement (LSM) ≥ 8kPa. The Receiver Operative Characteristic (ROC) curve was used to determine the optimum cutoff value of FIB4 to rule out CSLF. **Results:** 129 (23.4%) of 551 T2D patients in our cohort had CSLF. We found that a FIB-4 of 1.5 rules out CSLF with a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Diagnostic Accuracy (DA) of 82.9%, 79.9%, 55.7%, 93.8%, and 80.6%, respectively, compared with a FIB4 of 1.3 which has values of 91.5%, 67.3%, 46.1%, 96.2%, and 72.9%, respectively. **Conclusion:** A FIB-4 cutoff of 1.5 rather than 1.3 is suggested for Indian subjects with T2DM and needs to be validated in further large multicenter prospective studies, preferably with histopathology as the gold standard.

Keywords: Clinically significant liver fibrosis, FIB4 score, MASLD, transient elastography, type 2 diabetes mellitus

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma in individuals with Type 2 diabetes mellitus (T2D).[1] Fibrosis is a critical prognostic factor in MASLD, linked to adverse liver-related outcomes, cardiovascular complications, and mortality.[2] Current guidelines recommend screening for Clinically Significant Liver Fibrosis (CSLF) using the Fibrosis Index Based on Four Factors (FIB-4) score as an accessible and cost-effective initial assessment.[1,3,4] The Fibrosis-4 (FIB-4) score is calculated based on age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count—variables that are readily available and commonly measured.[5] Transient elastography (TE) serves as the standard of care for confirming hepatic fibrosis severity when FIB-4 scores suggest the need for further evaluation.[6,7] Currently, a FIB-4 score threshold of 1.3, derived from Western population studies, is used to exclude CSLF in individuals with T2D.[1,3,4] This study aims to determine the optimal FIB-4 cutoff value for excluding TE-confirmed CSLF in Indian patients with T2D.

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Materials and Methods

Study population

This cross-sectional descriptive study evaluated 551 consecutive patients with type 2 diabetes mellitus (T2DM) attending the Department of Endocrinology from March to December 2023.

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Participants were aged between 35 and 65 years to align with FIB-4 score efficacy, as it performs less accurately in individuals outside this age range.[8] Exclusion criteria included male patients consuming over 30 g of alcohol per day and female patients consuming more than 20 g per day, as well as patients with secondary causes of hepatic steatosis (e.g., chronic corticosteroid use), positive hepatitis B surface antigen or antihepatitis C virus antibody, and histories of other chronic liver diseases or thyroid dysfunction. Patients on pharmacotherapy for MASLD, including Pioglitazone or Saroglitazar, were also excluded. The diagnosis of T2DM among participants was based on the American Diabetes Association (ADA) criteria.[9] These included fasting plasma glucose levels ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL in individuals with classic symptoms of hyperglycemia. Participants with both newly diagnosed and long-standing T2DM were included, as no minimum duration of diabetes was required for inclusion in the study. In addition, participants managing their diabetes through lifestyle interventions alone, without pharmacotherapy, were eligible for inclusion. While detailed pharmacotherapy data were not collected, it was confirmed that none of the participants were on GLP-1 receptor agonists (GLP-1RA), Pioglitazone, or Saroglitazar, although some were on sodium-glucose cotransporter-2 inhibitors (SGLT-2i) [Figure 1].

The study protocol received approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Sample size calculation

The calculation of sample size was based on prevalence and sensitivity; the estimated sample size required for this study was around 101 patients with liver fibrosis, assuming an unlimited sample size and 5% precision.

The formula used to estimate the sample size was –

$$N = \frac{Z^2 \, x \, Sensitivity \, x \, (1 - sensitivity)}{L^2 \, x \, (1 - prevalence)}$$

$$N = \frac{(1.96)^2 \, x \, 0.95 \, x \, (1 - 0.95)}{(0.05)^2 \, x \, (1 - 0.28)} = 101$$

Z = Standard normal variant (1.96)
L = Precision 5% at 95% CI
Sensitivity of FIB4,[10] = 95%
Prevalence of CSLF in T2DM,[11] = 28%

Based on prevalence from previous studies, we needed to screen only 375 T2D patients to achieve our sample size target but we succeeded in screening as many as 600 T2D patients for our study.

Clinical assessment

Comprehensive clinical assessments included anthropometric measurements of body weight and height. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Blood for complete blood count (CBC) and liver function test (LFT) were collected after TE and analyzed on the same day in the institute's central laboratory.

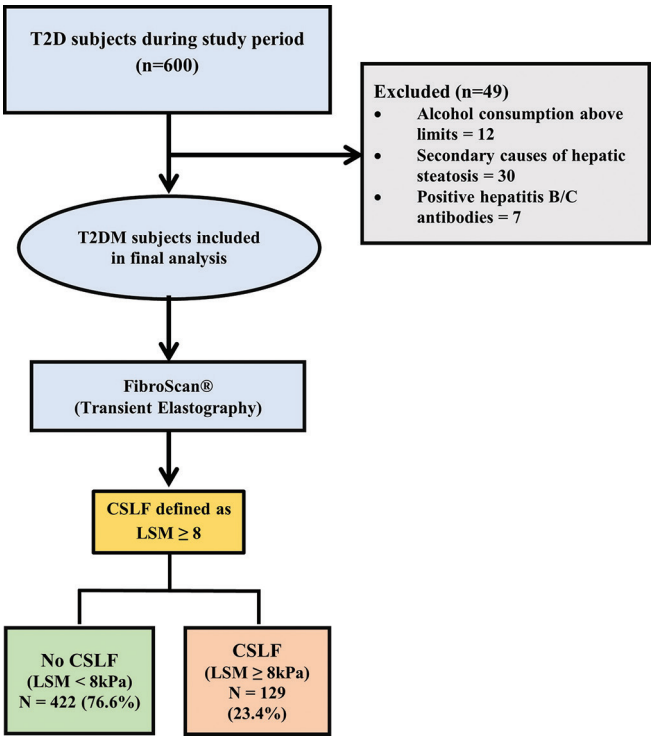

Figure 1: Derivation of the study cohort. LSM, liver stiffness measurement; T2D, type 2 diabetes; CSLF, clinically significant liver fibrosis

Liver stiffness measurements

Liver stiffness was assessed using Transient Elastography (TE), which served as the gold standard in this study for evaluating the diagnostic accuracy of the FIB-4 score. A single operator performed the TE procedure on the right liver lobe, utilizing the FibroScan® Mini+ 430 model by Echosens through the intercostal spaces, with participants positioned flat on their backs and their right arm maximally abducted. Liver stiffness results were reported in kiloPascals (kPa) and liver stiffness measurement (LSM) of ≥8.0 kPa was used as the threshold for Clinically Significant Liver Fibrosis (CSLF), while LSM ≥12.0 kPa indicated advanced fibrosis. These thresholds were chosen based on previous studies, which have demonstrated high positive predictive values (PPVs) for the presence of clinically significant fibrosis.[12]

Calculation of FIB4 score

The FIB4 score was calculated by using the formula:[5]

$$FIB\text{-}4 = \frac{Age\,(years) \times AST\,(U/L)}{Platelets\,(10^9/L) \times ALT^{1/2}\,(U/L)}$$

Statistical analysis

Data were analyzed using the SPSS 20.0 software (IBM, NY, USA). Categorical variables were expressed as frequencies and percentages, while quantitative variables were reported as

means with standard deviations or as medians with interquartile ranges for non-normally distributed data. Continuous data were presented as mean±SD and results of categorical measurements were expressed in terms of frequency and percentage. The Receiver Operative Characteristic (ROC) curve was used to determine the modified cutoff points of the FIB4 index that could best discriminate between the absence and presence of significant fibrosis.

Ethical aspect

The study protocol received approval from the Institutional Ethics Committee (reg no. ECR/609/Instt/WB/2014/RR20) of Nil Ratan Sircar Medical College and Hospital, Kolkata Memo No. NRSMC/IEC/06/2023, approved on 11.01.2023. Written informed consent was obtained from participants for their involvement in the study and the use of data for research and educational purposes. The study adhered to the current version of the World Medical Association Declaration of Helsinki (2013).

Results

A total of 551 T2D patients were included in the analysis after applying the inclusion and exclusion criteria, while 49 participants were excluded for various reasons [detailed in Figure 1]. The cohort's mean age was 49.9 ± 7.7 years, with a predominance of female participants (58.6%). The average BMI was 24.9 ± 3.9 kg/m², with 21.2% of participants categorized as overweight and 47.1% as obese. The average liver stiffness measurement (LSM) was 7.3 ± 6.1 kPa, indicative of varying degrees of hepatic involvement.

Baseline characteristics of participants

129 (23.4%) of 551 T2D patients in our cohort had CSLF. The detailed baseline characteristics of all participants, including demographics, biochemical parameters, and comorbidities, are summarized in Table 1.

ROC curve analysis and FIB-4 cutoff determination

ROC analysis demonstrated an area under the curve (AUROC) of 90.10% [Figure 2] for the FIB-4 score in discriminating CSLF. The proposed FIB-4 cutoff value of 1.5 offered a balance between sensitivity (82.9%) and specificity (79.9%), resulting in a positive predictive value (PPV) of 55.7% and a negative predictive value (NPV) of 93.8%, with a diagnostic accuracy of 80.6%. For reference, the performance of conventional cutoff values and their comparative sensitivity, specificity, PPV, and NPV values are presented in Table 2.

Table 1: Baseline characteristics of all participants, with CSLF and without CSLF

Characteristics	All participants	LSM <8	LSM ≥8
No. of participants	551	422	129
Age (years)	49.9±7.7	49.8±7.7	50.2±7.8
BMI (kg/m²)	24.9±3.9	24.5±3.7	26.6±4.3
Diabetes Duration (years)	7.4±5.3	7.6±5.1	6.9±5.9
Platelet count (×10⁹/L)	215.8±77.0	233.2±74.3	158.9±55.6
AST (U/L)	28.2±16.9	24.2±10.3	41.2±25.8
ALT (U/L)	27.9±19.1	25.6±16.3	35.9±24.6

Data are presented as mean (±SD). BMI, body mass index; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase;

Discussion

The global rise in MASLD prevalence has increased the need for effective, noninvasive screening tools for assessing liver fibrosis, particularly in patients with T2D, a group with elevated liver disease risk. This study aimed to validate and potentially adjust the FIB-4 score cutoff to better suit the Indian population with T2D, where Western-derived thresholds may not be fully applicable.

The new FIB-4 cutoff of 1.5 proposed in this study aligns closely with findings from *Torres et al.,*[10] who reported a 1.49 cutoff for MRE-based fibrosis screening in a Brazilian cohort with MASLD and T2D. This higher cutoff improved specificity in both studies, reducing false positives and limiting unnecessary testing. Notably, studies from Western populations often recommend a lower threshold, around 1.3, for similar screening purposes.[13] This discrepancy may stem from population differences in metabolic profiles, as Asian populations, including the Indian demographic, are known to develop liver-related complications at lower BMI thresholds and with distinct metabolic risk factors compared with Western counterparts.[14,15] These findings support the need for population-specific adjustments in diagnostic criteria.

The proposed FIB-4 cutoff of 1.5 offers a more targeted approach, particularly valuable in settings with limited resources, where access to advanced tests like TE and MRE may be restricted. By enhancing specificity, this cutoff helps reserve such resources for patients at higher risk of CSLF, reducing the clinical and financial burden associated with unnecessary testing. This aligns with existing guidelines suggesting that only T2D patients exceeding the FIB-4 threshold should undergo further testing.[1,3,16]

This study's strength lies in its large, Indian T2D cohort, making it one of the first to propose an adjusted FIB-4 threshold

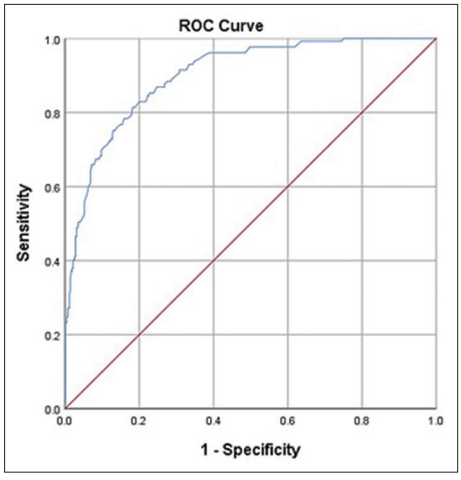

Figure 2: ROC curve of FIB4 score for patients with T2D

Table 2: Analysis and comparison between the sensitivity, specificity, PPV, and NPV of proposed cutoff points and those already used. AUROC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predicted value

Cutoff	AUROC	Sensitivity	Specificity	PPV	NPV
Conventional					
<1.3	90.10%	91.5%	67.3%	46.1%	96.2%
Modified					
<1.2	90.10%	96.1%	59.0%	41.8%	98.0%
<1.4	90.10%	86.8%	73.9%	50.5%	94.8%
<1.5[#]	90.10%	82.9%	79.9%	55.7%	93.8%
<1.6	90.10%	76.7%	85.1%	61.1%	92.3%
<1.7	90.10%	71.3%	88.6%	65.7%	90.9%

[#]proposed cutoff value with optimum sensitivity, specificity, NPV, and PPV

specific to this population. Our study has several limitations that warrant consideration. Being cross-sectional, the study was designed to evaluate associations rather than establish causal relationships between FIB-4 cutoff values and the risk of clinically significant liver fibrosis (CSLF). In addition, as the data were collected from a single tertiary care center, the generalizability of our findings to the broader Indian population may be limited, especially given regional variations in metabolic profiles and healthcare access. Although transient elastography (TE) is a validated non-invasive method for assessing liver fibrosis, it is not equivalent to liver biopsy (the gold standard for diagnosing CSLF) and the absence of histopathological confirmation limits the definitive validation of our findings.[17,18] While our sample size was sufficient for addressing the primary objective, the study was not powered for subgroup analyses, such as stratification by BMI categories, limiting insights into the role of obesity in CSLF risk. Information regarding the use of anti-hyperglycemic drugs among study participants was limited. While none of the participants were on GLP-1 receptor agonists (GLP-1RA), Pioglitazone, or Saroglitazar; some participants were on sodium-glucose cotransporter-2 inhibitors (SGLT-2i), the exact number was not recorded. The potential effects of SGLT-2i on transient elastography findings could not be fully accounted for. Despite these limitations, our study offers valuable preliminary insights into a population-specific FIB-4 cutoff for assessing CSLF in Indian patients with type 2 diabetes, and future multicenter studies involving diverse populations and incorporating histopathology as the gold standard addressing these limitations could further validate and refine our findings.

Conclusion

A FIB-4 cutoff of 1.5 rather than 1.3 is suggested for Indian subjects with T2DM and needs to be validated in further large multicenter prospective studies, preferably with histopathology as the gold standard.

Acknowledgement

We want to thank all study participants for agreeing to take part in the study. We would also like to thank the scientific committee and institutional ethical committee for approval of the study. No funding or financial sponsorship was taken from external sources. Resources and facilities available in our institute were used for the current study.

Authors' contribution

Rajat Deb and Soumik Goswami were involved in the conception and design of the study, along with the drafting of initial manuscript. Rajat Deb, Vibhu Ranjan Khare, Joydip Datta, and Mousumi Das acquisition of data and its analysis. Nilanjan Sengupta, Arjun Baidya, and Debes Ray contributed to the revision of article and final approval of the version to be published.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data supporting this study is not publicly available due to ethical considerations and ongoing analysis. However, data can be accessed upon request by contacting the corresponding author via email.

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