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Original article

CORRELATION OF FIB-4 AND APRI SCORE WITH FIBRO SCAN SCORE TO PREDICT FIBROSIS IN OBESE TYPE-2 DIABETIC PATIENTS.

Amit Kumar Das[1] Anuj Sharma[2], Mohammad Zahid Labrez[3]*
Assistant Professor, Department of Medicine, SKMCH, Muzaffarpur, Bihar, India[1*]
2nd Year Pg, Department of Medicine, SKMCH, Muzaffarpur, Bihar, India[2]
Senior Resident, Department of Medicine, SKMCH, Muzaffarpur, Bihar, India[3]

ABSTRACT.

Background:
Non-invasive assessment methods to assess liver fibrosis are important tools where FibroScan or liver biopsy is not accessible. This study aims to assess the efficacy and performance of the fibrosis index based on four factors (FIB-4) and aspartate transaminase-to-platelet ratio index (APRI) to evaluate liver fibrosis against FibroScan for the stages of liver fibrosis in obese type-2 diabetic patients.

Methods:
This was a cross-sectional study conducted in a tertiary care center in Bihar, India, and the patients were enrolled within two years. During the study period, 80 patients with a confirmed diagnosis of type-2 diabetes mellitus were selected. Laboratory blood testing and FibroScan were performed in all patients with T2DM. APRI and FIB-4 were calculated using a standard formula involving laboratory parameters.

Result:
The performance of FIB-4 scores is nearly similar to APRI, with the area under the curve (AUC) 0.753, (95% CI) (0.711-0.795) ($p<0.0001$) for ≥ F2 fibrosis (significant fibrosis) and even better 0.851 (0.815-0.887) ($p<0.0001$) for the F4 fibrosis (cirrhosis) group. Both the tests are proven good to diagnose fibrosis but FIB-4 has more area under the receiver operating characteristic (AUROC) than APRI in each set, thus FIB-4 is considered better than APRI.

Conclusion:
APRI and FIB-4 scores showed good performance in detecting patients without liver fibrosis as compared with FibroScan. Based on this study, FibroScan can be avoided in patients examined for the diagnosis of mild fibrosis and cirrhosis in the source-constrained area.

Recommendation:
Based on the study findings, it is recommended that in resource-constrained areas, FibroScan may be avoided for diagnosing mild fibrosis and cirrhosis in patients with type-2 diabetes. APRI and FIB-4 scores have demonstrated good performance in detecting patients without liver fibrosis.

Keywords: Liver fibrosis assessment, Non-invasive methods, FibroScan, FIB-4, APRI, Type-2 diabetes patient
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Corresponding Author: Amit Kumar Das
Email: amitdrakd76@gmail.com
Department of Medicine, SKMCH, Muzaffarpur, Bihar, India.

INTRODUCTION

Fibrosis, characterized by the aberrant accumulation of extracellular matrix (ECM) proteins, is frequently observed in diabetic tissues and may contribute to impaired organ function. In certain instances, it is plausible that fibrosis associated with diabetes could be considered an epiphenomenon, indicative of the reparative process following the initial injury. However, a substantial amount of evidence substantiates the concept that the observed metabolic dysregulation in individuals with diabetes can directly trigger a fibrogenic program, resulting in tissue damage and impaired organ function. The pro-fibrotic effects of diabetes may potentially entail the direct activation of resident fibroblasts through the influence of hyperglycemia or insulin resistance. Alternatively, it may involve the initiation of a fibrogenic program within vascular cells, organ-specific parenchymal cells, or immune cells, thereby contributing to the development of fibrosis.
The presence of progressive hepatic fibrosis leading to the subsequent progression of cirrhosis is a hallmark feature

observed in nearly all cases of chronic liver diseases. In individuals diagnosed with chronic hepatitis B (CHB), the precise assessment of the hepatic fibrosis stage holds paramount significance as it serves as a pivotal prognostic factor for disease advancement and signifies the imperative requirement for commencing antiviral therapeutic intervention. Liver biopsy has long been regarded as the definitive method for assessing the extent of fibrosis [6]. Nevertheless, it is imperative to acknowledge that liver biopsy is accompanied by a multitude of inherent constraints. These include its invasive nature, which induces discomfort and pain [7], as well as the infrequent yet plausible occurrence of life-threatening complications [8]. Furthermore, it is crucial to recognize that liver biopsy is susceptible to potential inaccuracies in sampling [9-10]. Consequently, a considerable number of patients afflicted with CHB exhibit hesitancy towards undergoing a liver biopsy, potentially resulting in suboptimal administration of anti-viral treatment at the appropriate juncture. Hence, these mentioned limitations have prompted the exploration of non-invasive modalities.

The FibroScan technique has been recently introduced as a novel, non-invasive modality for the detection and assessment of liver fibrosis. FibroScan utilizes the fundamental concept of transient elastography (TE), wherein the velocity of wave propagation through a uniform tissue is directly proportional to its elasticity, a parameter closely associated with the extent of fibrosis present in the hepatic organ [7]. FibroScan, a highly dependable non-invasive modality, serves as a paramount tool for the evaluation of liver fibrosis. However, due to its exorbitant expense and limited accessibility in smaller urban areas, the utilization of this instrument remains predominantly restricted to tertiary healthcare establishments [11].

Numerous studies have documented the capacity of FibroScan to effectively prognosticate liver fibrosis in individuals afflicted with chronic hepatitis C (CHC) [12-13]. In recent years, a limited number of research studies have conducted FibroScan examinations to assess fibrosis in patients with CHB as well [14-15]. Nevertheless, it is imperative to acknowledge that the mentioned studies predominantly encompassed European nations and the United States. Consequently, it is crucial to exercise caution when attempting to extrapolate the findings to Indian patients diagnosed with T2DM.

Several techniques have been suggested for the non-invasive assessment of fibrosis in patients with CHB, including the utilization of serum markers like FIB-4, TE (FibroScan), and APRI [11,16]. The APRI and FIB-4 scores represent two additional non-invasive techniques that exhibit a notable capacity for accurately diagnosing advanced cirrhosis and fibrosis in patients with chronic hepatitis B when compared to the conventional method of liver biopsy [17].

This study aimed to evaluate the effectiveness of FIB-4 and APRI to differentiate the stages of liver fibrosis against Fribroscan-based staging of liver stiffness in obese type-2 diabetic patients.

MATERIALS AND METHODS.

Study design.

The current work was performed as a cross-sectional study in the Shri Krishna Medical College and Hospital (SKMCH), Muzaffarpur.

Participants.

During the study period, 80 patients with a confirmed diagnosis of Type-2 diabetes mellitus were enrolled.

Variables.

All patients were asked about their exposure to risk factors (i.e. drug addiction, blood transfusion, major or minor surgeries, disease severity, and complications such as ascites, hepatic encephalopathy), presence of ascites, jaundice, hematemesis, melena, pedal edema, easy bruisability, bleeding gums, or recent use of any alternative medicine or alcohol.

Data sources.

Patient history, physical examination, hematological and biochemical investigations like hemogram, liver function tests, serum protein and albumin tests, ultrasonography (USG), and TE were done in all the patients.

Exclusion criteria.

Patients with the presence of other causes of liver disease, HCC, prior interferon therapy, human immunodeficiency virus (HIV), co-infected with HBV, and liver transplantation were excluded from the study.

Laboratory methods.

Hematological and biochemical parameters were determined using commercially available assays. All patients' samples were tested for HBsAg by using a commercial enzyme-linked immunoassay (ELISA) kit (Abbott Laboratories, Chicago, IL). All HBV-positive patients were further investigated for quantitative HBV DNA by reverse transcription-polymerase chain reaction (RT-PCR) (Applied Biosystems, CA). Further, the included patients were investigated for HBeAg and HBeAb.

Statistical Analysis.

IBM's SPSS version 24.0 software was utilized to conduct statistical analysis and to draft the data. For descriptive analysis, median and interquartile range (IQR) were obtained, non-parametric continuous variables, and percentages and numbers were obtained for categorical variables. The diagnostic performance of APRI and FIB-4 scores was measured by the area under the receiver operating characteristic (ROC) curve. The balance between sensitivity (Se), and specificity (Sp) for a particular value of the test to rule out, or rule in the patients of interest was obtained from the coordinates of the curve. Positive predictive values (PPV) and negative

predictive values (NPV) were also obtained for the cut-off value of the test. Statistical significance was defined as $p<0.01$.

RESULTS.

Out of the total 80 patients enrolled in this study, 56 (70%) of patients were males and 24 (30%) were females; however, this difference is statistically insignificant ($p=0.82$). The mean age of the study population was 35.37 ± 15.38 years. The baseline biochemical characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics

Characteristics	*Frequency*
Males	56 (70%)
Females	24 (30%)
Age (Mean ± SD)	35.37 ± 15.38
BMI (kg/m^2)	20.15 ± 3.77
Haemoglobin (gm/dl)	13.59 ± 2.23
Bilirubin (mg/dL)	1.20 ± 0.88
Albumin (gm/dl)	3.89 ± 0.81

The study population was divided into four groups according to fibrosis stage, and we found that 38.75% of the study population had normal liver FibroScan values (F0-F1), 20% of the patients exhibited cirrhosis (F4) (Table 2), while the remaining 41.25% of the population had intermediate fibrosis (F2 and F3). The median score of FibroScan, APRI, and FIB-4 was 7.20, 0.67, and 1.36, respectively.

Table 2: Stages of liver fibrosis

Stages	*Frequency*	*Percentage*

F0-F1 (<7 kPa)	31	38.75%
F2 (7-8.99 kPa)	11	13.75%
F3 (9-12.49 kPa)	22	27.5%
F4 (≥12.5 kPa)	16	20%

Diagnostic performance of APRI and FIB-4 for fibrosis

High AUROC values for APRI and FIB-4 indicated the very good performance of these tests in recognizing significant fibrosis and cirrhosis. AUROC of APRI and FIB-4 to discover significant fibrosis (≥F2) were 0.756 (95% confidence interval [CI] 0.714-0.797) and 0.753 (95% CI 0.711-0.795), respectively. For the diagnosis of cirrhosis AUROC of APRI and FIB-4 were 0.818 (95% CI 0.776-0.861) and 0.815 (95% CI 0.815-0.887), respectively. The performance of APRI and FIB-4 on ROC are plotted in Table 3.

Table 3: FIB-4 and APRI for fibrosis according to Fibro scan

Variable	≥F2 (Mild Fibrosis) (95% CI)	F4 (Cirrhosis) (95% CI)	p-value
FIB-4	0.753 (0.711-0.795)	0.851 (0.815-0.887)	<0.0001
APRI	0.756 (0.714-0.797)	0.818 (0.776-0.861)	<0.0001

The FIB-4 score is nearly similar to APRI, with AUC mean (95% CI) 0.753 (0.711-0.795) (p<0.0001) for significant fibrosis and even better, i.e. 0.851 (0.815-0.887) (p<0.0001) for the cirrhosis group (Table 3). Both the tests proved good for diagnosing fibrosis, but FIB-4 had more AUC than APRI in each set, thus FIB-4 showed better performance than APRI.

Sensitivity and specificity at upper and lower cut-offs for significant fibrosis and cirrhosis for both APRI and FIB-4 were calculated for the study population and compared with values proposed by the WHO HBV guidelines for the same. We also calculated PPV and NPV at the same cut-offs of APRI and FIB-4 for the significant fibrosis and cirrhosis groups. Since there is no defined value of upper and lower cut off for FIB-4 to detect cirrhosis, we tried to set the lower cut off at 1.75 and upper cut-off at 4.00 to detect cirrhosis from the coordinate of AUC with sensitivity and specificity for lower cut-off are 80.0% and 73.8%, respectively, while sensitivity and specificity for the upper cut-off are 53.1% and 90.8%, respectively.

DISCUSSION.

The treatment and outlook of the disease are contingent upon the progression and staging of liver fibrosis. The precise assessment of liver fibrosis holds significant importance in clinical decision-making and subsequent patient monitoring. Only a liver histological examination can accurately confirm the existence of concomitant liver fibrosis, necro inflammatory activity, and steatosis. In the present study, APRI identified significant fibrosis (p<0.0001) with a related AUC mean (95% CI) of 0.756 (0.714-0.797) (Table 3), and cirrhosis (p<0.0001) with a higher AUC mean 0.818 (0.776-0.861) (Table 2). Liver biopsy is widely recognized as the definitive diagnostic method for assessing the various stages of liver fibrosis. However, it is important to acknowledge that this

procedure is invasive, and the limited size of the sample obtained, along with the potential risks associated with sampling, as well as the inherent variability in the interpretation of histopathological findings, may impose certain limitations on the routine utilization of liver biopsy [15]. Due to the non-invasive nature of transient elastography, several recommendations also state that it is an excellent way to assess liver fibrosis [4]. Previously, some small-scale studies suggested that APRI and FIB-4 scores are higher in CHB patients with significant fibrosis (METAVIR staging) [23-24], which was also observed in this study. The advantage of this study includes a comparison with serum fibrosis models and using FibroScan as a reference.

During the study, it was found the area under the receiver operating characteristic curve of APRI for significant fibrosis was 0.756. The results are similar to a meta-analysis of 17 studies (n=3,573) that assessed APRI and found the area under the summary receiver operating characteristic (SROC) curve to be 0.77. In the same study, a summary receiver of the operating characteristic curve of meta-analysis of 11 studies (N = 2,083) that assessed APRI for cirrhosis and found the area under the SROC curve to be 0.75 while our study finds AUROC for the same was 0.818, which is far better [22]. The study also found the AUROC curve of FIB-4 for significant fibrosis and cirrhosis was 0.753 and 0.851, respectively, almost similar to findings of a meta-analysis of 10 studies (n = 1,996) that assessed FIB-4 and found the area under SROC curve to be 0.75 for significant fibrosis and SROC curve of meta-analysis of six studies (N = 1,304) that assessed FIB-4 for the cirrhosis, and found the area under the SROC curve to be 0.87 [22]. Our findings for APRI and FIB-4 in this study are also similar to Liu et al. and Mada PK et al. [25-26].

The study population was compared between cirrhotic and non-cirrhotic at a lower cut-off of 1.0 and an upper cut-off of 2.0 for APRI as described by the WHO guideline against the METAVIR scoring system, and it was found that sensitivity for lower cut-off (80.8 vs 77%), i.e. higher than WHO results, specificity for lower cut-off (76.9 vs 78%) is almost similar, while sensitivity and specificity for upper cut-off (51.5 vs 48% and 90.5 vs 94), i.e. almost near to the WHO guideline. There is no exact cut-off to detect cirrhosis for FIB-4 proposed by WHO guidelines [21]. The lower cut-off was calculated, i.e. 1.75, and the upper cut-off, i.e. 4, to detect cirrhosis by FIB-4 from coordinates of the ROC curve with 80% sensitivity, 91.7% NPV for lower cut-off, and 90.8% specificity, 60.5% PPV for upper cut-off.

APRI and FIB-4 were used primarily in resource-limited areas to predict liver fibrosis and cirrhosis [30]. In the clinical setting, the cut-offs with high specificity (i.e., fewer false-positive results) could be used to diagnose patients with significant fibrosis and cirrhosis, and the cut-offs with high sensitivity (i.e., fewer false-negative results) could be used to rule out the presence of significant fibrosis and cirrhosis. Based on evidence from the systematic review, the WHO guidelines recommended that FibroScan and APRI were the most useful tests for the assessment of cirrhosis in resource-limited settings [21]. The results suggest that APRI and FIB-4 are significantly able to overcome the limitations of Fibro scan in resource-limited areas.

Based on the current study results, it was recommended that FIB-4 should be considered as the preferred non invasive fibrosis test, and FibroScan should be considered when FIB-4 is unavailable. Liver biopsy remains within the assemblage of hepatologists when there are discordances between clinical symptoms and the degree of fibrosis assessed by non-invasive approaches.

CONCLUSION.

Since liver cirrhosis is the driving factor in CHB infection to determine the treatment regimen, duration, and follow-up strategy, the fibrosis test should be able to differentiate the maximum number of cirrhotic and mild fibrosis from normal or early stages of fibrosis. APRI and FIB-4 scores also showed good performance in detecting patients without liver fibrosis compared with fibro Scans. In conclusion, FIB-4 should be considered as the preferred non-invasive fibrosis test, and fibro Scan should be considered when FIB-4 is unavailable. Based on this study, a liver biopsy could be avoided in patients examined for the diagnosis of significant fibrosis and cirrhosis.

LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

RECOMMENDATIONS.

Based on the current study results, it was recommended that FIB-4 should be considered as the preferred non-invasive fibrosis test, and Fibro Scan should be considered when FIB-4 is unavailable. Liver biopsy remains within the assemblage of hepatologists when there are discordances between clinical symptoms and the degree of fibrosis assessed by non-invasive approaches.

LIST OF ABBREVIATION.

FIB-4: Fibrosis Index Based on Four Factors

APRI: Aspartate Transaminase-To-Platelet Ratio Index

T2DM: Type 2 Diabetes Mellitus

CHB: Chronic Hepatitis B

TE: Transient Elastography

CHC: Chronic Hepatitis C

USG: Ultrasonography

HIV: Human Immunodeficiency Virus

HBV: Hepatitis B Virus

DNA: Deoxyribonucleic Acid

RT-PCR: Reverse Transcription-Polymerase Chain Reaction

HBeAg: Hepatitis B e Antigen

HBeAb: Hepatitis B e Antibody

ELISA: Enzyme-Linked Immunoassay

ROC: Receiver Operating Characteristic

Se: Sensitivity

Sp: Specificity

PPV: Positive Predictive Values

NPV: Negative Predictive Values

SD: Standard Deviation

AUROC: Area Under the ROC Curve

AUC: Area Under the ROC Curve

WHO: World Health Organization

SROC: Summary Receiver Operating Characteristic

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Contact: +256775434261(WhatsApp)
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Location: Wisdom Centre Annex, P.O. BOX. 701432 Entebbe, Uganda, East Africa.