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The usefulness of transient elastography by Fibroscan for the evaluation of liver fibrosis

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Abstract:	Abstract Introduction Liver stiffness measurement (LSM) is used for the assessment of liver fibrosis. However there is limited data in Indians patients. Aims and Objective To find the correlation of LSM, aspartate transaminase to platelet ratio index (APRI) with fibrosis as assessed by liver biopsy (LB) and predictors of discordance between LB and LSM. Methods One hundred and eighty-five consecutive patients who underwent liver biopsy and TE were enrolled. Fibrosis was graded by two independent pathologists using the METAVIR classification. Area under receiver operating curves (AUROC) were used to evaluate the accuracy of transient elastography and APRI in diagnosing significant fibrosis (F >2) and cirrhosis (F4). Results Predominant etiologies were hepatitis B (46 %) and hepatitis C (26 %). LSM was unsuccessful in 10 patients (5 %) because of small inter-costal space (n=3) and obesity (n=7). Fibrosis is significantly correlated with LSM (r=0.901, p=0.001) and APRI (r=0.736, p=0.001). There was significant difference in median LSM value in patients with no fibrosis (F0) in comparison to patients having mild fibrosis (F1+F2) (4.5 kPa vs. 7.5 kPa, p=0.001) and advanced fibrosis (F3+F4) (4.5 kPa vs. 19.4 kPa, p=0.001). Similarly there was significant difference in mean APRI value in patients with no F0 in comparison to patients having mild fibrosis (F1+F2) (0.55±0.31 vs. 1.09±0.81, p=0.001) and advanced fibrosis (F3+F4) (2.3±1.3, p=0.001). AUROC for diagnosis of significant fibrosis was 0.98 (95 % CI 0.963-0.999) for TE and 0.865 (95 % CI 0.810-0.920) for APRI. Optimal TE value was 10.0 kPa for diagnosis of significant fibrosis and

	14.7 kPa for cirrhosis with specificity and sensitivity of 89 %, 98 % and 96 %, 97 % respectively. On multivariate analysis, total bilirubin and HAI were identified as an independent predictor of TE inaccuracy. Conclusion LSM is a reliable predictor of hepatic fibrosis in Indians patients. LSM is superior to APRI for non-invasive diagnosis of hepatic fibrosis and cirrhosis and high bilirubin(10.5mg/dL) and Ishak HAI grading (>11) were independent predictors of discordance between LB and LSM.
Response to Reviewers:	Reviewers' comments: Table 1: In this Table, some of the rows are mean with SD, some appear to be median and range, while yet others appear to be numbers. Please put asterisks or other distinguishing marks against different types of values and explain in the footnote what each type is. As per suggestion we have now mentioned the distinguishing marks against different types of values and explain in the footnote what each type is. Table 2: Do the same for mean (SD) and for numbers in this Table. Against each statistically significant difference in columns 2 and 3, indicate using different superscripts the comparison and P value. Place the superscripts and explanations also in the footnote. Eg. @ = P<0.001 for mild fibrosis vs. no fibrosis, # = P<0.001 for severe fibrosis vs. no fibrosis, etc. As per suggestion we have now mentioned at footnote that p value is significant in all comparision except one which also has been mentioned in foot note. Mentioning p value for each column is not needed as p value is significant for all comparisons which has been mentioned in foot note as per reviewer suggestion State the Reference in the Methods for METAVIR fibrosis score. As per suggestion we have now mentioned the reference in the menthod section for METAVIR fibrosis score References: Delete month of issue and issue number. Retain the Year and Volume number only. As per suggestion we have deleted the issue and issue number. —

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ORIGINAL ARTICLE

The usefulness of transient elastography by Fibroscan for the evaluation of liver fibrosis

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Abstract

Introduction Liver stiffness measurement (LSM) is used for the assessment of liver fibrosis. However there is limited data in Indians patients.

Aims and Objective To find the correlation of LSM, aspartate transaminase to platelet ratio index (APRI) with fibrosis as assessed by liver biopsy (LB) and predictors of discordance between LB and LSM.

Methods One hundred and eighty-five consecutive patients who underwent liver biopsy and TE were enrolled. Fibrosis was graded by two independent pathologists using the METAVIR classification. Area under receiver operating curves (AUROC) were used to evaluate the accuracy of transient elastography and APRI in diagnosing significant fibrosis (F >2) and cirrhosis (F4).

Results Predominant etiologies were hepatitis B (46 %) and hepatitis C (26 %). LSM was unsuccessful in 10 patients (5 %) because of small inter-costal space (n=3) and obesity (n=7). Fibrosis is significantly correlated with LSM (r=0.901, p=0.001) and APRI (r=0.736, p=0.001). There was significant difference in median LSM value in patients with no fibrosis (F0) in

comparison to patients having mild fibrosis (F1+F2) (4.5 kPa vs. 7.5 kPa, *p*=0.001) and advanced fibrosis (F3+F4) (4.5 kPa vs. 19.4 kPa, *p*=0.001). Similarly there was significant difference in mean APRI value in patients with no F0 in comparison to patients having mild fibrosis (F1+F2) (0.55±0.31 vs. 1.09±0.81, *p*=0.001) and advanced fibrosis (F3+F4) (2.3±1.3, *p*=0.001). AUROC for diagnosis of significant fibrosis was 0.98 (95 % CI 0.963–0.999) for TE and 0.865 (95 % CI 0.810-0.920) for APRI. Optimal TE value was 10.0 kPa for diagnosis of significant fibrosis and 14.7 kPa for cirrhosis with specificity and sensitivity of 89 %, 98 % and 96 %, 97 % respectively. On multivariate analysis, total bilirubin and HAI were identified as an independent predictor of TE inaccuracy.

Conclusion LSM is a reliable predictor of hepatic fibrosis in Indians patients. LSM is superior to APRI for non-invasive diagnosis of hepatic fibrosis and cirrhosis and high bilirubin(10.5mg/dL) and Ishak HAI grading (>11) were independent predictors of discordance between LB and LSM.

Keywords [Au: kindly provide keywords – not from title or abstract]

Introduction

Prognosis and management of patients with chronic liver diseases depend on the severity of liver fibrosis. Liver biopsy is considered as gold standard for the assessment of liver fibrosis till date, even though it is invasive and evaluates very small part of liver and is subject to intra and inter-observer variability [1, 2]. Similarly monitoring of patients on treatment requires another liver biopsy for assessment of response and any change in fibrosis stage. To overcome these limitations several methods have been proposed to noninvasively stage liver fibrosis including a

variety of imaging modalities and a range of biochemical tests. These include the aspartate transaminase to alanine transaminase (AST/ALT) ratio (AAR), AST to platelet ratio index (APRI) age-platelet count index (API) and many others [3–5]. Among these, APRI has been widely studied because of its simplicity and universal applicability. APRI has been shown to predict significant fibrosis and cirrhosis in 51 % and 81 % of patients with chronic hepatitis C (CHC), respectively [6].

Recently, liver stiffness measurement (LSM) using FibroScan was introduced as a noninvasive device to accurately assess liver fibrosis [7]. LSM can help physicians decide treatment strategies, predict prognosis, and monitor disease progression or regression in patients with chronic liver disease as it is noninvasive and can be done even in outdoor clinics. Several studies have shown significant positive correlation between transient elastography (TE) and the stage of liver fibrosis [8, 9]. Despite the clinical usefulness of LSM, several confounding factors that can diminish the accuracy of LSM have been identified, such as necroinflammatory activity, reflected by a high alanine aminotransferase (ALT) level, cholestasis, or heart failure[10, 11]. Although elevated ALT has been considered to be the single most important confounder on LSM, the effects of necroinflammatory activity, which is closely related to ALT level have not been well determined in majority of studies [11, 12]. The aim of this study was to find the correlation of LSM with fibrosis as assessed by liver biopsy (LB) and predictors of discordance between LB and LSM in patients with chronic liver disease.

Methods

Patients

Between January 2010 and October 2013, consecutive patients with chronic liver disease who underwent both LB and LSM were enrolled. All patients underwent LSM and LB on the same day.

No patient had evidence of decompensated liver cirrhosis, such as a history of variceal bleeding, ascites and hepatic encephalopathy at the time of LB and LSM. Exclusions criteria were as follows: (1) previous antiviral treatment before LB, (2) evidence of liver cancer or another malignancy, (3) coinfection wtih hepatitis C virus, hepatitis D virus, or human immunodeficiency virus, (4) active alcohol consumption in excess of 20 g/day in the previous 2 weeks, (5) LB specimens shorter than 15 mm in length, (6) right-sided heart failure, (7) LSM failure, or (8) unrelaible LSM (10 invalid measurements or success rate <60 %). APRI was calculated according to the formula: [(AST／ULN)／(Platelet count×10^9/L)] × 100 (6). The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and the authors followed the policy concerning informed Consent.

Liver stiffness measurement

TE was done with FibroScan (Echosens, Paris France) using M -probe in compliance with the technical recommendations. A reliable result was defined as at least 10 valid shots, a success rate of at least 60 %, and interquartile range <30 % of the median LSM value. Results were considered unreliable if these criteria were not met and hence were excluded from the study. Failure of the procedure was defined as no valid shot after at least 10 attempts [4].

Liver biopsy and histological evaluation

Percutaneous liver biopsy was done under local anesthesia by the Trucut liver biopsy needle (16G) and the tissue thus obtained was subjected to histological examination and fibrosis was assessed by Metavir scoring system for staging of fibrosis in patients with chronic viral hepatitis. The fibrosis score was assigned a number from 0-4: F0=no fibrosis, F1=mild portal fibrosis, F2=fibrosis with few septa; F3=bridging fibrosis is spreading and connecting to other areas that contain fibrosis, F4=cirrhosis or advanced scarring of the liver **[5].** The inflammation was assessed by modified Ishak Histological Activity Index (HAI) [5]. The liver biopsy specimens were read by two independent, experienced histopathologists who were blinded to the LSM result. Cases, in which there was a disparity in fibrosis grade between the two pathologists, were resolved by consensus agreement.

Statistical analysis

All statistical analyses were performed using SPSS software (version 16; SPSS Inc., Chicago, IL, USA). Bivariate Spearman rank correlation coefficient was used to analyze the correlation between LSM and histological fibrosis grade. Qualitative and quantitative differences between subgroups were compared using Mann–Whitney U- and student's t-test respectively. The degree of interobserver variability in pathological grading was assessed using the kappa statistic. The diagnostic performance of TE and APRI were assessed by receiving operator characteristic (ROC) curves. The area under the ROC curves (AUROC) was used to assess the accuracy of the diagnostic test and to identify optimal cutoff points for the diagnosis of significant fibrosis (defined as METAVIR score F>2) and cirrhosis (METAVIR score F4). Optimal cutoff values were chosen based on a maximum sum of sensitivity and specificity. A two-sided *p*-value of <0.05 was deemed significant.

Results

Patient characteristics

Consecutive patients who were planned for liver biopsy and fibroscan were enrolled. Only those patients who had reliable fibroscan and adequate liver biopsy specimen were taken for analysis. A total of 185 patients were enrolled in the study. Of 185 patients 10 patients had unreliable fibroscan results but none had inadequate liver biopsy results so a total of 175 patients were included in analysis. Demographic characteristics, biochemical parameters and disease etiologies are summarized in Table 1. There were 117 males (67 %) with a mean age of 41±13.1 years. Mean BMI was 25.7±3.4 kg⁄m2. The etiology of liver disease was chronic hepatitis B (CHB) in 79 patients (46 %), chronic hepatitis C (CHC) in 46 (26 %), NAFLD in 30 (17 %) and miscellaneous in 20 (11 %). There was 96 % agreement between the two pathologists in the METAVIR grading (kappa co-efficient 0.85). There was no disagreement in no fibrosis and advanced fibrosis (F3 and F4) so the disagreement was in F1 and F2 fibrosis (*n*=7). In cases where they disagreed, the discrepancy involved only one METAVIR grade. For those cases, they subsequently reviewed the specimens using Orcein, reticulin and Masson's trichrome stains to reach a consensus.

Relationship between the fibrosis stage, liver stiffness measurement and aspartate transaminase to platelet ratio index

Median value of LSM among patients with no (*n*=67), mild (F1+F2, *n*=53) and advanced (F3+F4, *n*=55) fibrosis group were 4.5 (2.7-6.1kPa), 7.5 (3.3-22.8 kPa) and 19.4 (8.8-75.0 kPa)

respectively (Fig. 1). Fibrosis is significantly correlated with LSM (r=0.901, *p*=0.001) and APRI (r=0.736, *p*=0.001).

There was significant difference in median LSM value in patients with no fibrosis (F0) in comparison to patients having mild fibrosis (F1+F2) (4.5 kPa vs. 7.5 kPa, *p*=0.001) and advanced fibrosis (F3+F4) (4.5 kPa v/s 19.4 kPa, *p*=0.001). The difference between median LSM value of mild and advanced fibrosis was also statistically significant (*p*=0.001). Patients with fibrosis ≥F2 (median 17.6 (7.3-75.0kPa) had significantly higher LSM than that of <F2 (5.3, 2.7-16.6) (*p*=0.001). Similar were the results when we subcategorize them according to etiology as shown in Table 2.

Similarly median value of APRI with no fibrosis was 0.47 (0.16-1.7), F1 (0.54, 0.22-3.5), F2 (1.1, 0.46-3.2), F3 (1.1, 0.47-4.7) and F4 (1.9,0.46-16.4) respectively (Fig. 2). There was significant difference in mean APRI value in patients with no fibrosis (F0) in comparison to patients having mild fibrosis (F1+F2) (0.55±0.31 vs. 1.09±0.81, *p*=0.001) and advanced fibrosis (F3+F4) (2.3±1.3, *p*=0.001). The difference between mean APRI value of mild and advanced fibrosis was also statistically significant (1.09±0.81 vs. 2.3±1.3, *p*=0.001). Patients with significant fibrosis ≥F2 (2.1±1.22) had significantly higher APRI than that of <F2 (0.63±0.47) (*p*=0.001).

Area under receiver operating curves analysis for transient elastography and aspartate transaminase to platelet ratio index

The AUROC for significant fibrosis (METAVIR F>2) was 0.98 (95 % CI 0.963–0.999) and the optimal cutoff value for the identification of significant fibrosis was ≥10.0 kPa. The sensitivity and specificity at this cutoff was 98 % and 89 % respectively. The corresponding AUROC for cirrhosis (METAVIR F4) was 0.965 (95 % CI 0.941–0.988) with an optimal cutoff value identified as 14.7 kPa. The sensitivity, specificity was 97 % and 96 % respectively.

Similarly the AUROC for significant fibrosis (>F2) for APRI was 0.865 (0.810-0.920) and the optical cutoff value for the identification of significant fibrosis was 0.87 with a sensitivity of 85.5 % and specificity of 77 %. Cutoff value of 1.37 had sensitivity and specificity of 75 % and 78 % respectively for F4 with AUROC of 0.853 (0.797-0.908).

Predictors of discordance between liver biopsy and FibroScan

In total, 120 patients did not have significant fibrosis on histology (≤F2). Fifteen of these patients had inaccurately elevated Fibroscan readings ranging from 10.2 to 16.4 kPa (ten with METAVIR F1 and five with METAVIR F2). Univariate analysis was performed to identify factors related to the false elevation of Fibroscan values in this subset of patients with no significant fibrosis. This was of clinical importance, as this would be the subgroup of patients who may have been unnecessarily prognosticated about their liver disease. Mean bilirubin (10.9±1.4 vs. 1.8±2.2 mg/dL, p=0.001), ALT (147±66.5 vs. 96±89.5 U/L p=0.03), AST (139±71 vs. 88±93 U/L, p=0.02) and Ishak HAI (10.7±1.4 vs, 3.0±2.9, p=0.001) were significantly different between those incorrectly diagnosed and those accurately diagnosed by Fibroscan. BMI (26.0±3.4 vs. 25.6±3.4, p=0.66) and age (39.0±16.0 vs. 37.7±11.8 yr, p=0.71) was not found to be significantly associated with Fibroscan inaccuracy. However, when subjected to multivariate analysis, total

bilirubin (>10.5mg/dL) and modified Ishak HAI grade (>11) were identified as an independent predictor of TE inaccuracy.

Discussion

We prospectively assessed the performance of TE by Fibroscan, a novel noninvasive method of liver fibrosis assessment in 175 Indian patients, in comparison with LB and serum markers of fibrosis (APRI). TE is significantly correlated with liver fibrosis. Optimal cutoff for the noninvasive diagnosis of clinically significant fibrosis (>F2) was 10.0kPa with a sensitivity of 98 %, and specificity of 89 % respectively. Similarly a value of 14.7kPa and above predicted cirrhosis with high sensitivity (97 %) and specificity (96 %). High bilirubin (>10.5mg/dL) and higher Ishak HAI grade (>11) were independent predictors of falsely high TE value in patients with non significant fibrosis so results should be predicted cautiously in these patients.

TE measures liver stiffness in a volume that approximates a cylinder 1-cm wide and 4-cm long, between 25 and 65 mm below the skin's surface. This volume is at least 100 times bigger than a biopsy sample and therefore is far more representative of the hepatic parenchyma. However we could not do TE in 10 patients due to narrow intercostals space (*n*=3) and obesity (*n*=7). We did not encounter any complications during liver biopsy in our patients but the disagreement was seen in F1 and F2 fibrosis in seven patients. The results of our study are in accordance with previous published studies from West [4–6, 9]. In a recent systematic review assessing TE for prediction of F ≥2 fibrosis, a combined AUROC of 0.83 (95 % CI 0.02 1.00) with summary sensitivity of 63.8 % (95 % CI 49.6–75.9 %) and specificity of 86.5 % (95 % CI 79.8–91.2) at a cutoff threshold of 7.1–8.8 kPa was reported [9]. Hence, our results demonstrate that TE maintains its accuracy in Indian patients with hepatic fibrosis from different etiologies.

We compared the diagnostic accuracy of TE against APRI for the non-invasive identification of significant hepatic fibrosis. APRI can be easily calculated from simple blood tests that are routinely performed for patients during their admission for liver biopsy. APRI has previously been shown to be a reliable predictor of hepatic fibrosis in patients with CHC, with an AUROC of 0.80 (95 % CI 0.74–0.87) [6]. However, the poor performance of APRI in other studies doubts on its reliability in management of patients in day to day clinical hepatology practice [13]. In our study, TE was successful in all except 10 patients, however APRI could be calculated in all as for liver biopsy. In this study we found TE is superior to APRI in the diagnosis of hepatic fibrosis, with a higher AUROC and superior sensitivity, specificity. Hence, our results are in agreement with other study [4].

Assessment of fibrosis by LSM is also get affected by several factors. These included hyperbilirubinemia, transaminitis, and prolonged prothrombin time [10, 14, 15]. These factors were found to cause a significant overestimation of LSM values, leading to false positive identification of fibrosis. However, in our study on multivariate analysis, hyperbilirubinemia and HAI grade were only factors identified. ALT was found on univariate analysis to affect LSM but not on multivariate analysis. In addition to fibrosis stage (F0–2 vs. F3–4) and elevated ALT (>1.5–2× ULN) were proposed as significant extrinsic predictors of discordance. However, controversy remains regarding fibrosis stage. Lucidarme et al. [16] concluded that advanced fibrosis (F3–4) was correlated with discordance, while Kim et al. [17] and Myers et al. [18] proposed minimal fibrosis (F0–2) as a significant predictor of discordance between LB and LSM. In our study ALT affects LSM in univariate analysis in patients with minimal fibrosis but not in multivariate analysis. The other possible explanation could be that with time ALT levels decrease, however necroinflammatory activity still continued in liver and bilirubin level

remained high that might affect LSM more than that of ALT. Hence, we advise caution in interpreting the validity of LSM measurements when performed in patients with hyperbilirubinemia (bilirubin >10.5 mg⁄dL), as this may lead to overestimation of fibrosis grade. In such patients, serial measurements are recommended to reassess the LSM value after resolution of the acute phase of jaundice.

Strength of our study is inclusion of large number of patients with simultaneous LSM and LB of varied etiology and different stages of fibrosis done on the same day. We could not do LSM in all patients and ten patients were excluded from the analysis based on invalid TE. This study which enrolled large number of patients had shown that TE is now an important non invasive tests which could replace liver biopsy in majority of patients for the assessment of liver fibrosis. In conclusion, TE (Fibroscan) provides an accurate and reliable noninvasive diagnosis of significant hepatic fibrosis in Indian patients.

Conflict of interest PS, SD, RB, PT, NB, VS, AK, AM, and AA all declare that they have no conflict of interest.

Ethics statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and the authors followed the policy concerning Informed Consent as shown on Springer.com.

Table 1 Baseline characteristics of patients (*n*=175)

Parameters	
Age (yrs)*	41±13
M:F[≠]	117:58
Body mass index (kg/m^2) *	25.7±3.4
Hemoglobulin (g /dL)*	12.7±2.3

Total leukocyte count ($X10^3$/mL) *	6.9±2.6
Platelet count ($10^3/mm^3$)®	116 (0.60-490)
Total bilirubin (mg/dL)®	0.9 (0.2-12.0)
Albumin (g/dL)*	3.1±0.79
AST (IU/L) ®	54 (14-444)
ALT (IU/L) ®	45 (14-406)
Etiology of liver disease≠ HBV:HCV:NAFLD:others	79:46:30:20
Metavir fibrosis≠ F0:F1:F2:F3:F4	67:35:18:16:39
Modified Ishak HAI grading®	2 (0-14)
Fibroscan (Hz) ®	6.1 (2.7-75.0)

* indicates mean with standard deviation, ®indicates median with range, ≠ indicates absolute numbers

AST aspartate aminotransferase, *ALT* Alanine transaminase, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NAFLD* nonalcoholic fatty liver disease,

Table 2 Subgroup analysis of fibrosis stage with liver stiffness measurement and aspartate transaminase to platelet ratio index

Etiology	No fibrosis (mean±S.D)	Mild fibrosis (mean±S.D)	Advanced fibrosis (mean±S.D)
HBV (*n*=79) Fibroscan (kPa) APRI Number*	 4.5±0.9 0.54±0.27 37*	 8.1±3.7 1.04±0.89 24*	 21.6±16.0 2.2±1.8 18*
HCV (*n*=46) Fibroscan (kPa) APRI Number*	 4.01±0.8 0.44±0.15 13*	 7.3±2.5 1.20±0.60 17*	 23.8±16.6 2.8±1.04 16*
NASH (*n*=30) Fibroscan (kPa) APRI number*	 4.4±0.9 0.66±0.45 13*	 8.1±4.3 1.2±1.05 7*	 24.2±14.5 2.4±1.02 10*
Cryptogenic (*n*=20) Fibroscan (kPa) APRI number	 4.6±0.18 0.64±0.47 4	 10.0±2.9 0.92±0.55# 5	 33.9±13.4 1.5±0.48 11

*indicates absolute number

p<0.001 for all comparison (no fibrosis vs. mild fibrosis, mild fibrosis vs. advanced fibrosis and no fibrosis vs. advanced fibrosis) with respect to Fibroscan value and APRI

P#=not significant (APRI value between no and mild fibrosis in cryptogenic cirrhosis)

HBV hepatitis B virus, *APRI* aspartate aminotransferase to platelet ratio index, *HCV* hepatitis C virus, *NASH* nonalcoholic steatohepatitis

Fig. 1 Box plot diagram showing Fibroscan value and stage of fibrosis

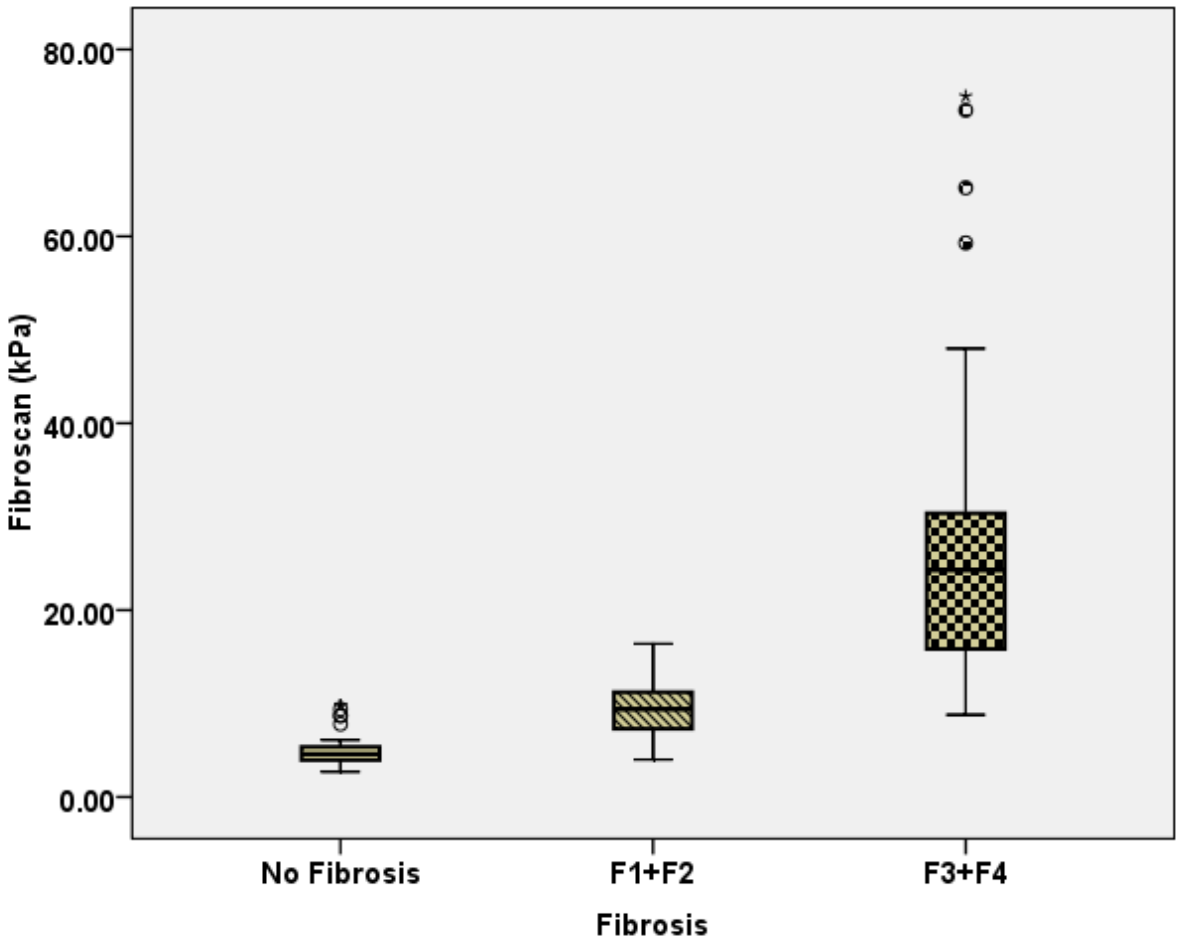


Fig. 2 Box plot diagram showing aspartate aminotransferase to platelet ratio index value and stage of fibrosis

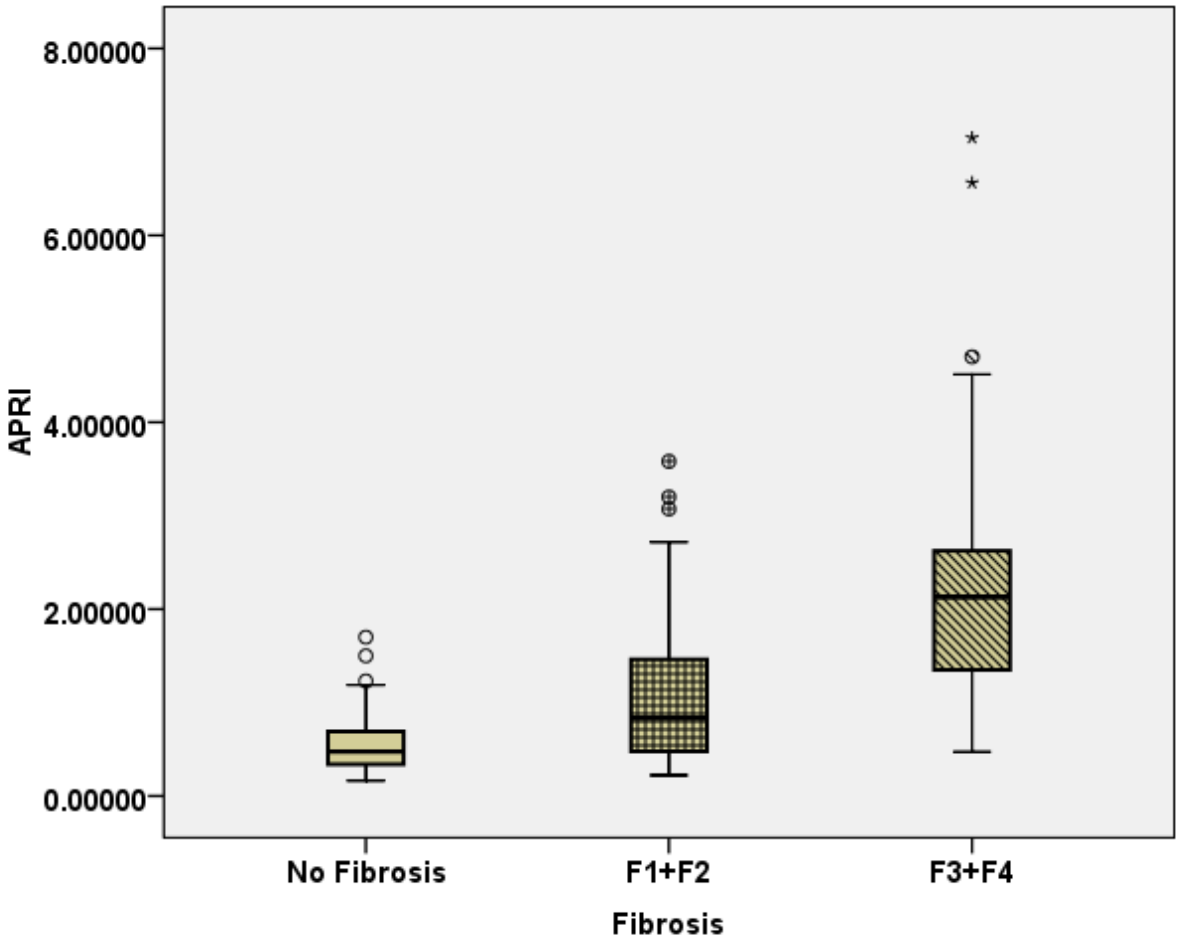


Fig. 3 Receiver operative curve for cirrhosis comparing fibroscan and aspartate aminotransferase to platelet ratio index

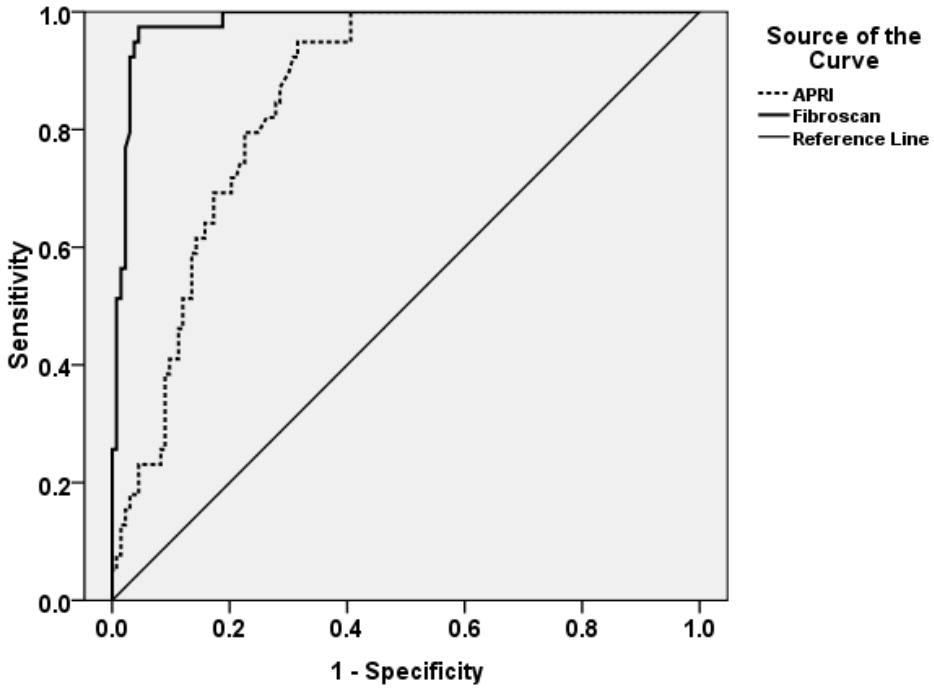
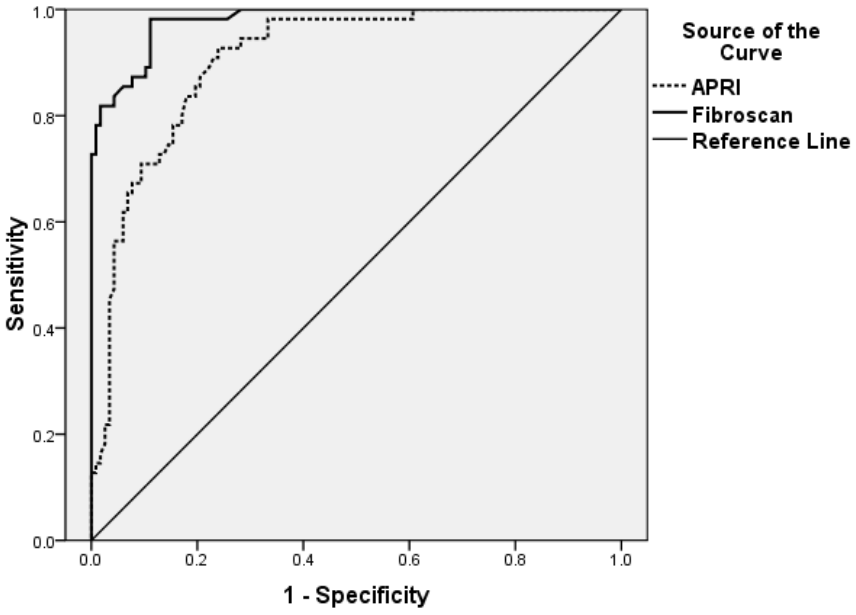


Fig. 4 Receiver operative curve for significant fibrosis (>F2) comparing fibroscan and aspartate aminotransferase to platelet ratio index



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Authors' Response to Reviewers' Comments

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Reviewers' comments:

Table 1: In this Table, some of the rows are mean with SD, some appear to be median and range, while yet others appear to be numbers. Please put asterisks or other distinguishing marks against different types of values and explain in the footnote what each type is.

As per suggestion we have now mentioned the distinguishing marks against different types of values and explain in the footnote what each type is.

Table 2: Do the same for mean (SD) and for numbers in this Table. Against each statistically significant difference in columns 2 and 3, indicate using different superscripts the comparison and P value. Place the superscripts and explanations also in the footnote. Eg. @ = P<0.001 for mild fibrosis vs. no fibrosis, # = P<0.001 for severe fibrosis vs. no fibrosis, etc.

As per suggestion we have now mentioned at footnote that p value is significant in all comparision except one which also has been mentioned in foot note. Mentioning p value for each column is not needed as p value is significant for all comparisons which has been mentioned in foot note as per reviewer suggestion

State the Reference in the Methods for METAVIR fibrosis score.

As per suggestion we have now mentioned the reference in the menthod section for METAVIR fibrosis score

References: Delete month of issue and issue number. Retain the Year and Volume number only.

As per suggestion we have deleted the issue and issue number.

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