Research Article

Non-Invasive Diagnosis of Liver Fibrosis and Cirrhosis: Role of Apri, Fib-4 and its Correlation with Liver Stiffness Measurements (LSM) by Fibroscan

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Abstract

Background: Liver fibrosis and liver cirrhosis represent a major health care burden. Liver fibrosis is the excessive accumulation of extracellular matrix proteins like collagen that occurs in most types of chronic liver diseases. This study was done to assess role of non-invasive diagnosis of liver fibrosis. APRI and FIB-4 are two simple, easy to calculate indices which are used in the diagnosis of liver fibrosis. **Methods:** This study included 143 patients who presented to Medicine and Gastroenterology OP and were advised fibro scan for the evaluation of liver fibrosis. Age of the patient, platelet counts, AST, ALT, viral markers (HbsAg, Anti-HCV), history of alcohol consumption, Ultrasound abdomen and pelvis, Liver stiffness measurements (LSM) values by fibro scan (elastography) are collected. APRI and FIB-4 was calculated and compared with that of fibro scan (Elastography). **Results:** Statistical analysis was performed using IBM SPSS version 20.0 software. To test the statistical significance of the difference in the findings of APRI and FIB with elastography, McNemar's Chi-square test was used. The results showed there is statistically no significant difference between FIB-4 values and elastography findings (p value = 1.00) with sensitivity of 82.5% and specificity 89.5%. Whereas, APRI did not co-relate with fibroscan. But when the patients were classified based on aetiology of liver fibrosis, both APRI and FIB-4 performed well in patients with NAFLD, Chronic Hepatitis B and C. FIB-4 performed well in patients with Alcoholic Liver Disease also. **Conclusion:** APRI and FIB-4 are valuable non- invasive markers in assessment of fibrosis of liver. Overall, when compared to elastography values, FIB-4 was better than APRI in predicting early fibrosis of liver. In primary centres where elastography is not available, APRI and FIB-4 act as an important aid for assessing fibrosis of liver

Keywords: Liver fibrosis; Elastography; APRI; FIB-4

Introduction

Liver fibrosis and liver cirrhosis represent a major health care burden. [1] Liver fibrosis is the excessive accumulation of extracellular matrix proteins like collagen that occurs in most types of chronic liver diseases. Characteristic feature of chronic liver disease is progressive liver fibrosis. Its implication is evolution toward cirrhosis, liver failure, and hepatocellular carcinoma with advancement in time. [2] The major causes of liver fibrosis are viral hepatitis *i.e.*, Chronic Hepatitis C (Chc) And Hepatitis B (CHB), autoimmune liver disease, alcohol and non-alcoholic steatohepatitis. [3]

Fibrosis is defined as a response of wound healing in which the damaged regions are encapsulated by an extracellular matrix or scar. It develops in almost all the patients with chronic liver injury at variable rates depending upon the cause of liver disease and host factors. [4]

Liver fibrosis and cirrhosis always has an increased risk of morbidity and mortality. Liver biopsy is considered as the gold standard for the diagnosis of cirrhosis and staging of fibrosis of liver. Though it is used universally, liver biopsy is an invasive method with multiple pitfalls and complications. In order to overcome the limitations of liver biopsy, a number of non-invasive techniques have been investigated for the assessment of fibrosis and cirrhosis. [5]

These non-invasive markers of cirrhosis can be broadly classified into radiological or serum-based markers. Radiologic techniques are based on ultrasound, magnetic resonance imaging and elastography. They have been used to assess liver fibrosis. Serum-based biomarkers of cirrhosis can be further classified into indirect and direct markers. Direct biomarkers, reflect extracellular matrix turnover, and include molecules that

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are involved in hepatic fibrogenesis. Indirect biomarkers reflect liver function, which may deteriorate with the onset of cirrhosis. Altogether radiologic and serum markers of fibrosis correlate well with biopsy scores, especially for excluding cirrhosis or excluding fibrosis. This feature is certainly clinically useful as it avoids liver biopsy in many cases. [6]

This study was performed to assess the role of APRI and FIB-4 in the diagnosis of liver fibrosis and to correlate with elastography values.

Methods

Selection and description of participants

The study recruited patients who presented to General Medicine and Gastroenterology OPD and were advised Fibroscan (elastography) for the evaluation of liver fibrosis.

All the established Chronic liver disease patients, acute viral hepatitis/ ischemic hepatitis, other causes for thrombocytopenia like ITP, MDS and infections were excluded from the study.

Based on the sensitivity of APRI (60%) and FIB-4 (80%) with fibroscan for predicting fibrosis of liver observed in a small pilot study conducted with 20 samples, with 20% allowable error and 95% Confidence, sample size comes to 23 and 15 positive cases respectively. The minimum sample size for my study was 69. I could recruit 143 patients in my study.

A signed informed consent was taken from every patient who enters the study after he/she has been explained the exact nature of the same. The ethics committee of Amrita Institute of Medical Sciences approved this study.

Technical information

The primary objective of this study is to assess fibrosis of liver by non- invasive methods such as serological markers Aspartate-aminotransferase to Platelet Ratio Index (APRI), FIB-4 and fibroscan (elastography) and to estimate the agreement of results between these two methods. Whereas the secondary objective is to assess the role of non-invasive methods of diagnosis of liver fibrosis and cirrhosis in different aetiologies of cirrhosis.

Age of the patient, platelet counts, AST, ALT, viral markers (HbsAg, Anti-HCV), history of alcohol consumption, Ultrasound abdomen and pelvis, LSM values by fibroscan (elastography) are collected.

Liver Stiffness Measurement (LSM) value of ≤ 7 kPa is taken as no significant fibrosis and FIB-4 and APRI will be calculated based on below formulae:

FIB4=(Age*AST)/(Platelets*√ALT)-FIB-4 value of <1.3 is taken as no significant fibrosis

APRI=(AST/upper limit of normal) x 100 /platelet count -APRI value of ≤ 0.7 is taken as no significant fibrosis.

Statistics

Data was collected in Microsoft excel. Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables are expressed frequency and percentage. Continuous variables are presented by mean and standard deviation. To test the statistical significance of the difference in the findings of APRI and FIB findings with elastography findings, McNemar's Chi-square test was used. Diagnostic measures such as sensitivity, specificity, predictive value positive and negative and accuracy was computed.

Results

One hundred and forty-three subjects were enrolled in the study, sex ratio is 2:1. Gender wise and age wise distribution is tabulated hereunder [Table 1].

Out of 143 patients 49 (34.2%) were diabetic, 31 (21.6%) are hypertensive, 27 (18.8%) have dyslipidaemia and 14 (9.7%) are hypothyroid.

Among 143 patients who underwent elastography, 57 patients (39.9%) had significant fibrosis whereas 86 patients (60.1%) did not have significant fibrosis. The cut-off for significant fibrosis is taken as greater than 7.

Among 57 patients who have significant fibrosis by elastography, 34 (59.6%) had significant fibrosis by APRI. Among 86 patients who had no significant fibrosis by elastography, 82 (95.3%) did not have significant fibrosis by APRI [Table 2].

The results showed there is statistically significant difference between APRI values and elastography findings (p value <0.001) with sensitivity of 59.6% and specificity 95.3%.

Table 1: Details of the study population.

	Category	Frequency	Percentage
Gender distribution	Male	95	66.4
	Female	48	33.5
Age distribution	20-29 Years	08	5.5
	30-39 Years	20	13.9
	40-49 Years	32	22.3
	50-59 Years	49	34.2
	60-69 Years	26	18.1
	>70 Years	08	5.5
Comorbidities distribution	Diabetes mellitus	49	34.2
	Hypertension	31	21.6
	Dyslipidaemia	27	18.8
	Hypothyroidism	14	9.7

Table 2: Comparison of APRI with elastography.

Significant fibrosis by APRI	Significant fibrosis by elastography		p Value
	Yes (>7) n = 57(%)	No (≤7) n = 86(%)	
Yes (≥0.7)	34 (59.6)	04 (4.7)	<0.001
No (<0.7)	23 (40.4)	82 (95.3)	

Table 3: Comparisison of FIB-4 with elastography.

Significant fibrosis by FIB-4	Significant fibrosis by elastography		p Value
	Yes (>7) n = 57(%)	No (≤7) n=86(%)	
Yes (≥1.3)	47 (82.5)	09 (11.5)	
No (<1.3)	10 (17.5)	77(89.5)	1.000

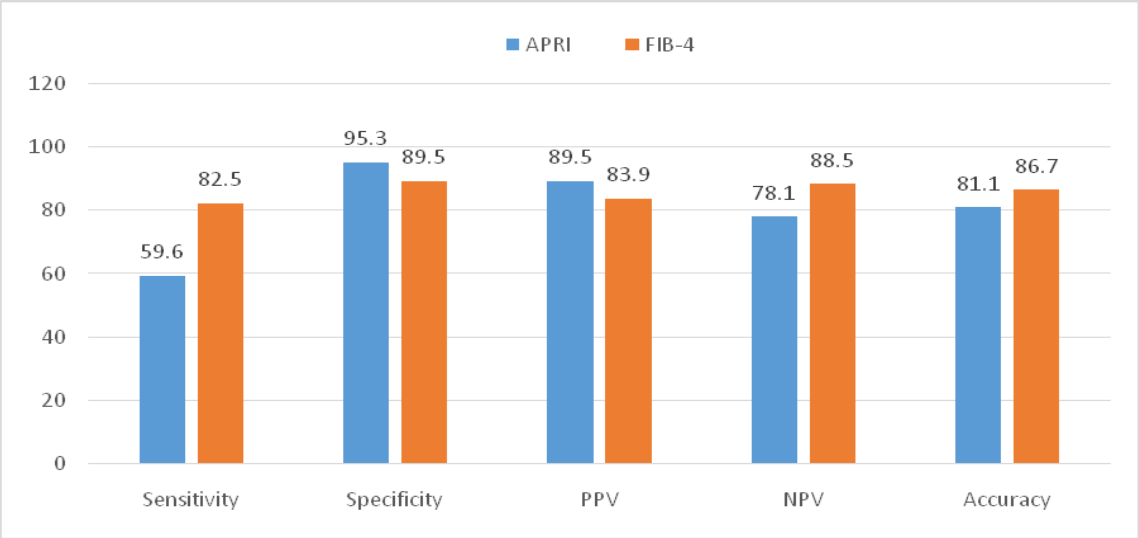

Figure 1: Comparision of diagnostic measures.

Among 57 patients who have significant fibrosis by elastography, 47 (82.5%) had significant fibrosis by FIB-4. Among 86 patients who had no significant fibrosis by elastography, 77 (89.5%) did not have significant fibrosis by FIB-4 [Table 3].

The results showed there is statistically no significant difference between FIB-4 values and elastography findings (p=1.00) with sensitivity of 82.5% and specificity 89.5%. Comparison of diagnostic measures in depicted in Figure 1

All the patients who underwent elastography were classified based on their aetiology. Of them 43 (30%) patients are with Alcoholic Liver Disease (ALD), 37 (25%) patients are with Non-Alcoholic Fatty Liver Disease (NAFLD), 15 (10%) patients are with Chronic Hepatitis B (CHB) and 9 (6.2%) patients are with Chronic Hepatitis C (CHC).

APRI had p values of 0.002, 0.219, 1.000, 0.250 in patients with ALD, NAFLD, CHB and CHC respectively whereas as FIB-4 had p values of 0.625, 0.625, 0.125, 0.500. The results showed there was no significant difference between APRI and elastography values in NAFLD, CHB and CHC patients whereas FIB-4 performed well in all sub-groups.

Discussion

In total of 143 patients included in the study, 57 (40%) had significant fibrosis on elastography and rest 86 (60%) did not have significant fibrosis. Aim was to elucidate the effectiveness of non-invasive markers-APRI and FIB-4 in diagnosing significant fibrosis.

Overall, the performance of APRI was not comparable to that of elastography whereas, FIB-4 was better in predicting the significant fibrosis. Even the sensitivity was much better for FIB-4 when compared to that of APRI, though the latter had better specificity. p value for APRI and FIB-4 was <0.001 and 1.000 respectively.

As demonstrated in study conducted by Lieber et.al, APRI was not accurate in the diagnosis of significant fibrosis in the sub-group of alcoholic liver disease. [7] When calculated on the whole, the figures were not significant for APRI as the major chunk of the patients included in the study belonged to ALD and NAFLD groups. The same was proved when analysis was done separately after dividing the study population based on the aetiology. In patients with ALD, there was significant difference between elastography findings and APRI values. Whereas in NAFLD group, performance of APRI was comparable to that of elastography values as previously demonstrated by Angulo P in retrospective study involving 320 NAFLD patients. [8]

In patients with CHB, APRI was able to identify significant fibrosis as witnessed in the previous studies done by Shin WG and Ayed et al. [9,10] Moreover, the accuracy was better than that of FIB-4.

APRI was initially and rather extensively studied in Chronic Hepatitis C (CHC) and HIV/HCV co-infection, it had best values in this subgroup when compared to all. This study showed similar performance in the CHB and CHC subgroup, though the representation was minimal.

Overall, APRI values were not comparable to that of elastography values but in NAFLD and chronic viral hepatitis, the performance was better. Even though the sensitivity was less, specificity is better than that of FIB-4.

The second serological score that was studied was FIB-4. The overall performance of FIB-4 was comparable to that of elastography values, with p value of 1.00. Rather it had better sensitivity and accuracy when compared to APRI.

Based on aetiology, in ALD patients as previously demonstrated in a study done by Lech chrostek [11] FIB-4 had higher sensitivity and accuracy. FIB-4 has an added advantage in ALD patients as APRI was not effective in the diagnosis of significant fibrosis.

Shah et al proved that FIB4 index is superior to 7 other non-invasive markers of fibrosis in patients with NAFLD, similar results were achieved in our study. Though both APRI and FIB-4 are comparable to that of elastography, FIB-4 had a better accuracy and sensitivity when compared to APRI.

FIB-4 score was comparable to that of elastography values in chronic viral hepatitis. In patients with CHB, FIB-4 had better

sensitivity though APRI had better specificity and accuracy. FIB-4 was extensively studied in HCV mono-infected patients. As demonstrated in previous studies done by Vallet-pichard et al, [12] Amorim TG [13] FIB-4 was able to diagnose significant fibrosis with better sensitivity and accuracy.

Limitations

Low representation of chronic viral hepatitis (CHB, CHC) patients, the comparison of serological markers was made with elastography values but not with liver biopsy which is considered as a gold standard method.

Conclusion

APRI and FIB-4 are valuable non- invasive markers in assessment of fibrosis of liver. Overall, when compared to elastography values, FIB-4 was better than APRI in predicting early fibrosis of liver.

In different aetiologies of fibrosis of liver, APRI was better in CHB patients whereas FIB-4 performed well in case of ALD, NAFLD, CHC patients.

APRI values are not reliable for assessment of liver fibrosis in ALD patients

In primary centres where elastography is not available, APRI and FIB-4 act as an important aid for assessing fibrosis of liver

Competing Interests

The authors report no competing (commercial/academic) interests.

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