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Original Research Article

Role of acoustic radiation force impulse elastography, aminotransferase to platelet ratio index and fibrotest for the assessment of significant fibrosis and cirrhosis in chronic liver disease

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ABSTRACT

Background: Accurate grading of hepatic fibrosis is important for the application of appropriate intervening strategy. Liver biopsy is the golden standard of fibrotic grading, however wide clinical application is hindered by its inherent drawbacks. Biomechanical-based ultrasonic elastography has received mass attention. However, several clinical studies found that the sole application of ultrasonic elastography may bring evident errors in diagnosing hepatic fibrosis. It is suggested that a combination of ultrasonic elastography and serum liver functions tests holds the potential to overcome those disadvantages. Aims and objectives was to study the diagnostic accuracy of ultrasonography elastography, APRI, fibrotest for significant fibrosis and cirrhosis in patients with chronic liver disease and established the correlation between ARFI elastography, APRI, Fibrotest in grading of liver fibrosis
Methods: Sixty three patients with chronic liver disease were studied. Liver stiffness was evaluated with ARFI elastography. Histologic staging of liver fibrosis served as the reference standard except a very few cirrhotic patients who were graded as cirrhotic on the basis of clinical examination. The required APRI, Fibrotest parameters and relevant clinical history was recorded. Fibrosis stage was assessed according to the METAVIR classification.
Results: ARFI, APRI, and Fibrotest demonstrated a significant correlation with the histological stage. According to ARFI and APRI for evaluating fibrotic stages more than F2, ARFI showed an enhanced diagnostic accuracy than APRI. The combined measurement of ARFI and APRI exhibited better accuracy than ARFI alone when evaluating ≥ F2 fibrotic stage that showed significant concordance i.e. 79.3% cases, out of which 69.8% of total cases were correctly diagnosed on comparison with the gold standard. Fibrotest and ARFI elastography show significant concordance in grading of fibrosis i.e. 82.5%. Cases out of which 68.3% of total cases were correctly diagnosed on comparison with the gold standard.
Conclusions: APRI, ARFI, and fibrotest are novel tools among non-invasive modalities to rule out significant fibrosis and cirrhosis in patients with chronic liver disease. ARFI with APRI and ARFI with fibrotest showed enhanced diagnostic accuracy than ARFI or APRI or fibrotest alone for significant liver fibrosis.

Keywords: Acoustic radiation force impulse, Aspartate aminotransferase to platelet ratio index, Fibrotest, Non-invasive diagnosis

INTRODUCTION

An accurate staging of liver fibrosis is critical for prognosticating Chronic liver injury (CLI). Liver biopsy

is the gold standard for staging hepatic fibrosis, however use is limited due to inherent limitations, such as pain, bleeding, inaccurate staging from sampling error, and variability of biopsy interpretation.[1-3] Acoustic radiation force impulse (ARFI) is a new quantitative assessment method of estimating tissue stiffness through measurement of shear wave velocity (SWV, measured in m/s). Its quantitative representation is named as virtual touch tissue quantification, which gives an objective numerical evaluation of the tissue stiffness.[4-6] ARFI imaging offers a quantitative assessment of the hepatic parenchyma elasticity to noninvasively grade and stage hepatic fibrosis. In addition, ARFI is often performed with serum liver functions tests to generate better prediction and evaluation of liver fibrosis.[7] Among these, aspartate aminotransferase platelet ratio (APRI) is a serum hepatic function test which has been proposed as a non-invasive tool for the assessment of liver fibrosis.[8]

FibroTest is a serum surrogate fibrosis marker that correlates with the severity and prognosis of liver fibrosis.[9] One of the advantages of APRI and fibrotest over the other noninvasive tests is that they are based on readily available blood tests and simple to use.[10,11] Their accuracy for hepatic fibrosis grading are still not comparable with liver biopsy. Therefore, a combined use of these non-invasive methods may be another promising and practical diagnostic application in hepatic firbrosis grading in chronic liver disease patients. In the current study, we aimed to compare the accuracy among ARFI, APRI, Fibrotest and their combinations for non-invasive diagnosis grading and prognosis of patients having chronic liver disease.

METHODS

This observational prospective study was approved by the ethical committee of Leelavati Hospital Mumbai. All patients were fully informed about the research protocol including the data handling and the privacy of personal data. A written informed consent was obtained from all the patients. A total of 63 subjects were consecutively enrolled from November 2015 to November 2017.

Inclusion criteria

All the diagnosed cases of hepatitis B, C and D, non-alcoholic fatty liver disease, alcoholic fatty liver disease and autoimmune hepatitis. The duration from period of diagnosis is greater than six months to label it chronic liver disease. The patients with blood workup done within three weeks of the elastography and biopsy within three months are accepted.

Exclusion criteria

Patients with pre-diagnosed diffuse malignancy of liver, patients with right ventricular failure and patients with obstructive cholestasis

The APRI and Fibrotest values of the patient were assessed. The associated clinical symptom, previous surgical history and histopathological reports were recorded. After taking verbal and written consent, patients were asked to come for elastography with strict fasting of 4-6 hours. At the time of examination, patient were examined in slight left lateral decubitus position with hips extended, arms abducted and abdomen exposed. First, the routine B mode ultrasonography and Doppler examination of liver was performed. A Philips iU-22 ultrasound machine with curvilinear transducer probe, with a frequency of 2-5 MHz was used for the same. B mode ultrasonography findings were recorded - Echotexture, Surface nodularity, liver span, Flow along the portal vein with its peak systolic velocity. Presence/absence of collateral circulation.

Following this, elastography software was run based on ARFI principle using the same probe by implementing following steps. The patient is placed in slight left lateral decubitus position with right arm elevated above head. Then patient is asked to make a shallow breath hold. Then region of interest is placed in right lobe of liver, particularly in segment VII and VIII, upto 6 cm beneath the Glissons capsule perpendicular to it. The large vessels and biliary ducts are avoided and value is acquired.

The elastography values were graded in three groups to grade fibrosis: Not significant fibrosis [METAVIR stages of F1 Value are < 5.7kPa (<1.37m/s)], Significant fibrosis [corresponds to METAVIR grades of >=F2 – F3 Values are >=5.7 kPa – 15 kPa (>=1.37 m/s - 2.2 m/s)] and Cirrhosis [corresponds to METAVIR stages of F4 or some stages of F3 Values are >15kPa (>2.2m/s)]

A provisional grading for liver fibrosis was given on elastography, APRI and Fibrotest with comparison of data was made against standard of reference which serves as gold standard. The standard of reference is histopathological examination in most of the cases. However, few patients fulfilling clinical and imaging criteria of liver cirrhosis did not undergo liver biopsy on the ground of lack of clinical relevance and were automatically graded as cirrhotic.[12]

The clinical and imaging criteria for cirrhosis are;Patients with portal hypertension (portal pressure greater than normal value of 1-5 mm Hg), hypersplenism, ascites, presence of either hepatopulmonary/hepatorenal syndrome, hepatic encephalopathy, marked increase in prothrombin time and ultrasonography features of cirrhosis which includes shrunken and nodular liver, reduced peak systolic velocity in portal vein (Normal value 16-20 mm Hg), presence of collateral circulation were noted as cirrhosis. Rest of all the patients including those who showed disagreement between grading of APRI, Fibrotest and Elastography and were in grey areas in either of the modality were biopsied and graded accordingly.

Hence, the phrase histopathological/Clinical examination and Standard of reference can be used interchangeable in results and discussion. Qualitative data was represented in form of frequency and percentage.

Among Qualitative data, Nominal data included sex of the cases, symptoms, Previous surgical history, status on APRI grading (Cirrhosis, Significant fibrosis, Not significant), status based on Fibrotest grading (Cirrhosis, Significant fibrosis, Not significant), status based on Elastography value (Cirrhosis, Significant fibrosis, Not significant), status of Matching between various grades, etc. McNemar-Bowker Test was used to assess internal symmetry between qualitative variables with more than 2 rows and Columns and McNemarTest was used for 2 X 2 tables. Measure of Agreement between status on various tests (APRI grading, Fibrotest grading, Elastography value and status on Histopathology/Clinical examination) was assessed by Symmetric Measures table using the Cohen's kappa (κ). The κ-value was interpreted as recommended by Altman DG Practical statistics for medical research. Diagnostic efficacy of various tests (APRI grading, Fibrotest grading, Elastography value) as compared to Histopathology/Clinical correlation as well as among themselves, was assessed by calculating Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood ratio, Negative Likelihood ratio and Youden's index. Appropriate statistical software, including but not restricted to MS Excel, PSPP version 1.0.1 were used for statistical analysis. Graphical representation was done in MS Excel 2010.

RESULTS

Out of 63 patients majority had age <52 years (46.1%) which ranges from 33 to 80 years with male preponderance (60.3%). Twenty (31.7%) patients had previous history of liver surgery/resection/transplant.

Table 1: The patients' characteristics at the time of ARFI elastography.

Parameter	Mean value
Age	54.4±14
Male patients	54.8±16
Female patients	52.2±18
BMI(kg/m^2)	26±6
Waist circumference	94±17
AST	69±68
ALT	95±11.6
Total bilirubin	15±13.5
Platelet count	198±6 78

Table 2: Statistical parameters for APRI, fibrotest and elastography.

Variables	Mean	SD	Median	1QR	Mode	Minimum	Maximum
APRI value	1.01	0.49	0.95	1.39	2.20	0.30	2.50
Fibrotest value	0.50	0.20	0.50	0.41	0.73	0.19	0.79
Elastography value	10.57	4.68	9.70	8.10	6.10.	3.80	20.10

Table 3: Mean values of APRI, fibrotest and elastography in different stages of fibrosis with standard deviation.

Parameters	Cirrhosis	Significant fibrosis	Not significant
APRI	1.68±0.34	0.79±0.07	0.46±0.09
Fibrotest	0.74±0.02	0.51±0.12	0.25±0.04
Elastography	17.30±1.50	9.95±2.15	4.86±0.58

Data is expressed as mean ± standard deviation

The cause of chronic liver disease was viral hepatitis in 31 patients (hepatitis C, n=13; hepatitis B, n=12; hepatitis E, n=3; mixed viral hepatitis, n=3), alcoholic 14 and NASH disease in 12 patients, and other chronic liver diseases in 6 patients (unexplained chronic cytolysis, autoimmune hepatitis, primary biliary cirrhosis, and overlap syndrome, drug-induced liver injury, hemochromatosis and primary sclerosis cholangitis) (Table 1). In this study, among 63 cases of chronic liver disease, 63.5% patients had B-mode ultrasonography findings consistent with changes of chronic liver disease while 36.5% patients had no such findings, thus pertaining that B mode ultrasonography is not capable of diagnosing chronic liver disease in early stage, as well as grade the severity of fibrosis. Table 2 shows out of 63 patients included in the study, 23.8% (15 out of 63) patients were cirrhotic, 58.7% (37 out of 63) patients were having significant fibrosis while 17.5% (11 out of 63) patients had no significant fibrosis.

Association among the cases between APRI and elastography

Out of 20 patients with APRI value greater than 1.0, 14 patients (70%) had an elastography value of greater than 15kPa, 3 patients (15%) had an elastography value of 5.7-

15 kPa and 3 patients (15%) had an elastography value of less than 5.7kPa. Out of 34 patients with APRI value between 0.7- 1.0m 28 patients had an elastography value between 5.7 - 15kPa, 2 patients had elastography value greater than 15kPa while 4 patients (11.8%) had an elastography value less than 5.7kPa. Out of 9 patients with APRI value less than 0.7, 8 patients (88.9%) had an elastography value less than 5.7kPa while 1 patient had an elastography value between 5.7- 15kPa. Above mentioned tests show significant association between APRI and elastography. The combination of APRI and elastography shows significant agreement with each other (k value - 0.662).

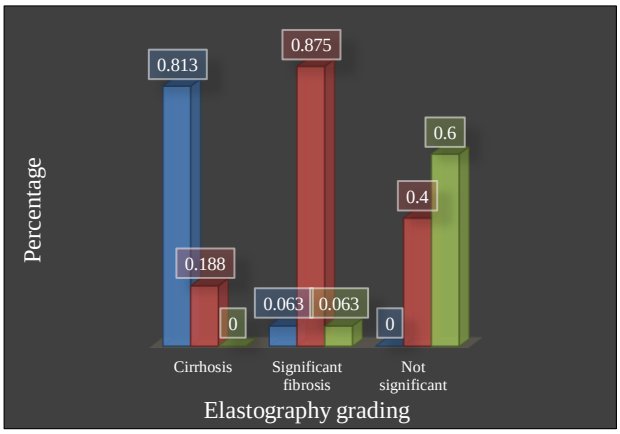

Figure 1: Association among the cases between cirrhosis, significant fibrosis and not-significant fibrosis on elastography with cirrhotic, significant and non-significant on histopathological/clinical examination.

Association among the cases between fibrotest and elastography

Out of 17 patients with fibrotest value of greater than 0.72, 14 patients (82.4%) had corresponding value of elastography value to be greater than 15kPa and 3 patients (17.6%) had elastography value between 5.7-15kPa.Out of 29 patients with fibrotest value between 0.32- 0.72, 2 patients (6.9%) had an corresponding elastography value of greater than 15kPa, 25 patients (86.2%) had an elastography value between 5.7kpa-15kPa while while 2 patients (6.9%) cases had an elastography value of less than 5.7kPa. Out of 17 patients with Fibrotest value less than 0.32, 4 patients (23.5%) had an elastography value between 5.7 - 15kPa while 13 patients (76.5%) had an elastography of value less than 5.7kPa. Above mentioned tests show significant association between fibrotest and elastography. The combination of fibrotest and elastography shows significant agreement with each other (k value - 0.724).

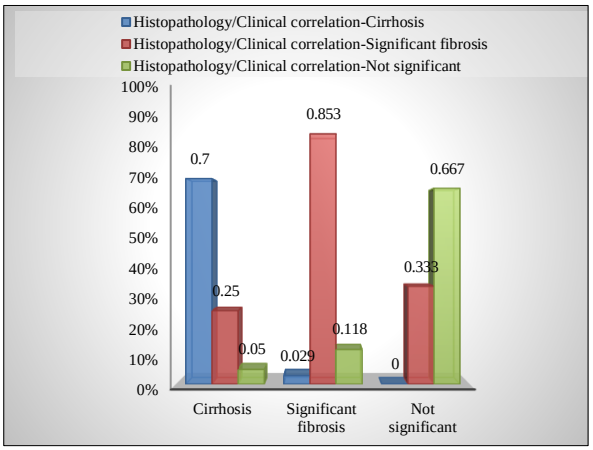

Figure 2: Association among the cases between cirrhosis, significant fibrosis and not-significant fibrosis on APRI with corresponding cirrhotic, significant and non-significant status on histopathological/clinical examination.

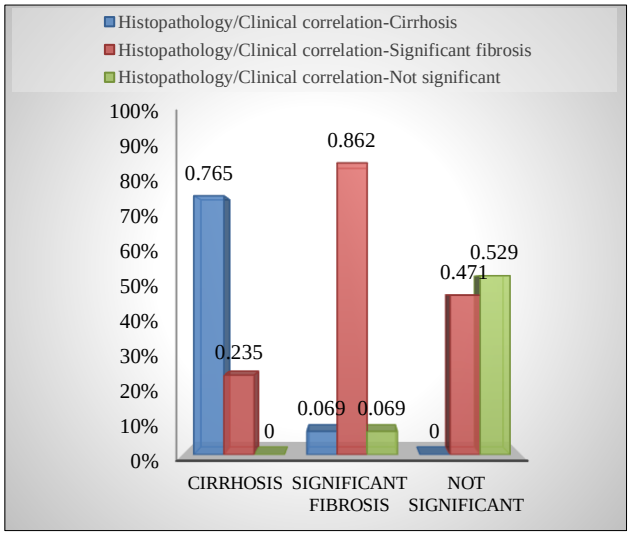

Figure 3: Association among the cases between cirrhosis, significant fibrosis and not-significant fibrosis on fibrotest with cirrhotic, significant and non-significant on histopathology.

Table 4: Matching of grading on APRI and elastography with histopathological/clinical correlation.

APRI grading and elastography value	APRI grading and elastography value with histopathology/clinical correlation		Total
	Matched	Mismatched	
Matched	44 (88)	6 (12)	50 (100)
Mismatched	0 (0)	13 (100)	13 (100)
Total	44 (69.8)	19 (30.2)	63 (100)

Data is expressed as no. of patients (percentage)

Table 5: Matching of grading on fibrotest and elastography with histopathological/clinical correlation.

Elastography value and fibrotest grading	Elastography value and fibrotest grading with histopathology/Clinical correlation		Total
	Matched	Mismatched	
Matched	43 (82.7)	9 (17.3)	52 (100)
Mismatched	0 (0)	11 (100)	11 (100)
Total	43 (68.3)	20 (31)	63 (100)

Data is expressed as no of patients (percentage)

DISCUSSION

To date, the gold standard for the diagnosis of liver fibrosis remains to be liver biopsy. In most circumstances, patients find it difficult to accept liver biopsy due to its complications. From 2009, with the introduction of ARFI, the clinical research on non-invasive assessment of fibrosis rapidly progressed. As an advanced imaging technology, ARFI is capable of providing biomechanical information on the tissue stiffness and elasticity using conventional ultrasound scanning of anatomical location and structure.[13,14] However, its utility, particularly in combination with other non-invasive methods, has not been adequately evaluated. In the current study, Chronic liver disease patients with different stages of liver fibrosis were diagnosed by ARFI, APRI, Fibrotest and their combined assessments. Our results demonstrated that the mean SWV value from ARFI was highly correlated with the staging of liver fibrosis classified by liver biopsy (METAVIR classification) (Table 2). This result indicated that biomechanical properties (e.g., hepatic elasticity and stiffness) had progressed from liver fibrosis to cirrhosis during the development of cirrhosis, which was consistent with the pathological progression of hepatocyte degeneration, necrosis, inflammation reaction, hepatocyte regeneration, formation of connective tissue fiber intervals, and liver lobule structural failure during the course of liver fibrosis.[15]

In the present study, for the assessment of diagnostic accuracy of ultrasonography elastography for significant fibrosis, the sensitivity, specificity, positive predictive value and negative predictive value were 75.68% (C.I. 58.8-88.2%), 84.32% (C.I. 65.1-95.6%), 87.5% (C.I. 71.1-96.4%) and 70.97% (C.I.- 51.9685.78%) respectively. Similarly, in assessment of diagnostic accuracy of ultrasonography elastography for cirrhosis, the sensitivity, specificity, positive predictive value and negative predictive value were 86.67% (C.I.59.54-98.34%), 93.75% (C.I. 82.80-98.69%), 81.25% (C.I. 54.35-95.95%) and 95.74% (C.I.85.46-99.48%) respectively (Table 3). This results were very much similar to the findings of Cassinotto et al performed a study on 321 patients with which included the cases of chronic viral hepatitis (n=136), alcoholic and non-alcoholic steatohepatitis (n=113) and miscellaneous reasons (n=72). He implemented ARFI elastography, fibroscan and fibrotest on above patients and compared the results with liver biopsy. He concluded that sensitivity/specificity of ARFI in diagnosis of significant fibrosis and cirrhosis were 71%/78% and 82%/84% respectively.[16] Similarly, on comparison with above mentioned studies, our sensitivity and specificity to diagnose cirrhosis on ARFI elastography was found to lie in range of 82%-97% and 84%-100% without any significant difference.

Ultrasonography elastography has a great negative predictive value (>90%) to rule out cirrhosis and significant fibrosis and thus avoiding unnecessary biopsies.

In the present study for assessment of diagnostic accuracy of APRI for significant fibrosis, the sensitivity, specificity, positive predictive value and negative predictive value were 78.38% (C.I. 61.79-90.17%), 80.77% (C.I. 60.65-93.45%), 85.29% (C.I. 68.94-95.05%) and 72.41% (C.I.- 52.76-87.27%), respectively. Similarly, in assessment of diagnostic accuracy of APRI for cirrhosis, the sensitivity, specificity, positive predictive value and negative predictive value were 93.33% (C.I.68.05-99.83%), 87.50% (C.I. 74.75-95.27%), 70.00% (C.I. 45.72-88.11%) and 97.67% (C.I. 87.71-99.94%), respectively. Similar observations were made by Dong et al conducted a study on patients with chronic viral hepatitis B. He compared ARFI elastography, APRI and Forns index with liver biopsy. He concluded that sensitivity/ specificity of APRI to diagnose significant fibrosis and cirrhosis was 68.5%/82.7% and 83.3%/67.2%, respectively.[17]

On comparison with above mentioned studies, the sensitivity/specificity of APRI to diagnose significant fibrosis lies within the range of 33.1- 77.0% and 72-96.6%, respectively with no significant difference.

In the current study for assessment of diagnostic accuracy of fibrotest for significant fibrosis, the sensitivity, specificity, positive predictive value and negative predictive value were 67.57% (C.I. 50.2181.99%), 84.62% (C.I. 65.13-95.64%), 86.21% (C.I. 68.34-9.11%) and 64.71% (C.I.- 46.4980.25%) respectively. Similarly, in assessment of diagnostic accuracy of fibrotest for cirrhosis, the sensitivity, specificity, positive predictive value and negative predictive value were 86.67% (C.I.

59.5498.34%), 91.67% (C.I. 80.02-97.68%), 76.47% (C.I. 50.10-93.19%) and 95.65% (C.I. 85.1699.47%) respectively (Table 4 and 5). Which is similar to the results of Kim et al, conducted a study comparing fibrotest and elastography with liver biopsy in 194 patients with chronic hepatitis B. He concluded that sensitivity/specificity to diagnose significant fibrosis and cirrhosis was 79.3%-93.3% and 80.0%/84.0% respectively.[18]

On comparison with previous studies, our sensitivity and specificity of Fibrotest to diagnose significant fibrosis lie in the range of 71.2-80.8% and 81.4-93.3% without any significant difference

Dong et al. demonstrated that ARFI, APRI and Forns index correlated well with the histological liver fibrosis stages in CHB patients. ARFI showed better accuracy than APRI when evaluating F2, F3 and F4 stages. Combined check with ARFI and APRI showed a significant enhancement of diagnostic accuracy than ARFI or APRI alone.[17]

In the present study, out of 63 patients , 50 patients (79.3%) showed concordant fibrosis grading between APRI and elastography out of which 44 patients (69.8%) were correctly classified on comparison with histopathology/clinical examination (Figure 1 and 2). The kappa value came out to be 0.752 which designate significant agreement. Similar observations were made by Dong et al. demonstrated that ARFI, APRI and Forns index correlated well with the histological liver fibrosis stages in CHB patients. ARFI showed better accuracy than APRI when evaluating F2, F3 and F4 stages. Combined check with ARFI and APRI showed a significant enhancement of diagnostic accuracy than ARFI or APRI alone.[17]

According to Kim et al, who conducted a comparative study between Fibrotest and elastography in 194 patients of chronic hepatitis B patients, 111 patients (63.4%) showed exact histopathological grading between fibrotest and elastography. Out of them 88 patients (45.4%) proved to be histologically correct.[18] Our study show better correlation between total and correctly graded cases i.e. 82.5% and 68.3% respectively (Figure 3).

Castera et al conducted a study in 116 patients who were coinfected with HIV/HCV. He implemented APRI, Fibrotest and elastography in all patients and compared the results with liver biopsy. Out of 116 patients, 80 patients (69%) had concordant fibrosis grading in Fibrotest and elastography. Among these 71 patients (61.2%) patients were correctly classified when compared with histopathology/clinical examination.[19] Out study showed better correlation between total and correct correlation between two modalities, i.e. 82.5% and 68.3% respectively.

Currently, serological diagnostic assays for noninvasive assessment of liver fibrosis are available including direct and indirect methods. The main purpose of these methods is to identify the existence of fibrosis. In this study, APRI and Fibrotest were also used to stage liver fibrotic stage. Although the sensitivity and specificity of these methods for the diagnosis of liver fibrosis was lower than ARFI, they partially reflected the pro-inflammatory response and hepatic compensation. The most important finding of this study was that combined measurement of ARFI and APRI exhibited better accuracy than ARFI or APRI alone when evaluating ≥ F2 fibrosis stage.

CONCLUSION

Ultrasonography elastography and serum biomarkers are novel tools among non-invasive modalities to rule out significant fibrosis and cirrhosis in patients with chronic liver disease. Both elastography and fibrotest have a high negative predictive value (NPV>90%) to rule out cirrhosis and significant fibrosis. They can distinguish the patients with minimal/no fibrosis from advanced fibrosis/cirrhosis with great accuracy. Thus, unnecessary biopsies can be avoided in patients with extreme values. Combined check with ARFI with APRI and ARFI with Fibrotest showed a significant enhancement of diagnostic accuracy than ARFI or APRI or fibrotest alone. This study provides an ideal and convenient non-invasive diagnostic method for the detection of hepatic fibrosis in chronic liver disease patients in clinical practice.

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