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Accuracy of Ultrasound and Noninvasive Markers of Fibrosis to Identify Patients with Cirrhosis

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Abstract

Background—Accurate identification of patients with cirrhosis using non-invasive markers of fibrosis is useful for esophageal varices and hepatocellular carcinoma surveillance programs. The aims of our study were to characterize the accuracy of ultrasonography, AST to platelet ratio index (APRI), and FIB-4 as non-invasive markers to identify the presence of cirrhosis.

Methods—We conducted a retrospective cohort study of patients who underwent liver biopsy at a large urban safety-net institution between November 2008 and July 2011. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy using receiver operator characteristic curve analysis for the detection of cirrhosis were calculated for each non-invasive marker.

Results—Liver biopsy was performed in 388 patients, of whom 93 (24.0%) had cirrhosis. C-statistics for APRI and FIB-4 predicting the presence of cirrhosis were 0.68 (95%CI 0.63 – 0.74) and 0.73 (95%CI 0.68 – 0.78), respectively. The c-statistic for a nodular appearance on ultrasound was 0.78 (95%CI 0.72-0.83). The PPV of a shrunken nodular-appearing liver was 64.8%; however, PPV was significantly higher in the subset with a cirrhotic-appearing liver and signs of portal hypertension (PPV 83.6%, $p=0.01$) as well as in the subset with a non-invasive fibrosis marker also suggesting cirrhosis (PPV 77.8%, $p<0.001$).

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Conclusion—Serum and imaging non-invasive markers of fibrosis may have insufficient accuracy when used in isolation; however, a combination of markers may allow sufficient accuracy to systematically identify patients with cirrhosis.

Keywords

Ultrasound; non-invasive markers of fibrosis; cirrhosis; APRI

INTRODUCTION

Chronic liver disease affects more than 5.5 million patients in the United States and results in over 1 million hospitalizations per year¹. Furthermore, the burden of cirrhosis is anticipated to increase further over the next 10 years given the high number of advanced hepatitis C virus (HCV) and non-alcoholic steatohepatitis (NASH) cases^{2, 3}. Patients with chronic liver disease often remain asymptomatic during the years to decades of progressive fibrosis until they develop cirrhosis and its associated complications⁴.

Although fibrosis assessment is becoming less important for HCV treatment consideration given improvements in anti-viral efficacy and safety⁵, it is still necessary to identify those with cirrhosis for monitoring to help prevent life-threatening complications. Patients with cirrhosis can be enrolled in esophageal varices and hepatocellular carcinoma (HCC) surveillance programs, which are associated with improved overall survival^{6, 7}. Liver biopsy has historically been the gold standard method for assessing the degree of fibrosis in patients with liver disease⁸; however, it remains invasive and is associated with a risk of complications⁹. In addition, liver biopsy is not ideal given that inter-observer variability and sampling error can both lead to inaccurate staging¹⁰. Finally, patients are often reluctant to undergo repeated biopsies to monitor for disease progression.

In response to these limitations of liver biopsy, several non-invasive markers of liver fibrosis have been developed¹¹⁻¹³. The aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 are two serum-based markers that are based on objective and readily available laboratory variables, which have been shown to be useful for evaluation of cirrhosis^{12, 13}. Similarly, ultrasonography is an inexpensive, readily available non-invasive radiologic procedure that is often performed in patients with liver disease and can be a simple method to screen for cirrhosis without exposure to radiation. Cirrhosis can manifest as a nodular appearing liver, with or without signs of portal hypertension (e.g. splenomegaly or intra-abdominal varices) on imaging¹⁴.

Many patients with chronic liver disease have liver enzymes, platelet counts, and ultrasounds monitored, as part of clinical care, so non-invasive markers such as APRI and FIB-4 are routinely available. Therefore, a non-invasive marker with high positive and negative predictive values could facilitate systematic identification of cirrhotic patients within a health care system for variceal and HCC surveillance programs. The aims of our study were to 1) characterize the accuracy of non-invasive markers (ultrasonography, APRI, and FIB-4) to identify the presence of cirrhosis, 2) identify correlates of ultrasound accuracy, and 3) identify correlates of accuracy for APRI and FIB-4.

METHODS

Study Population

We conducted a retrospective cohort study of patients who underwent percutaneous or transjugular liver biopsy at Parkland Memorial Health and Hospital System, the safety-net system for Dallas County, between November 2008 and July 2011. Patients were initially identified by CPT codes for liver biopsy (155.0 or 155.2).

Exclusion criteria for the study included clinical evidence of drug hepatotoxicity, other causes of acute aminotransferase elevation, hepatocellular carcinoma, prior liver or bone marrow transplantation, immunosuppressive therapy, and any primary hematologic disorders that could result in thrombocytopenia. Patients with insufficient liver tissue for staging of fibrosis or unavailable laboratory data within twelve months of liver biopsy were also excluded. If more than one set of laboratory results were available, the results closest to time of the biopsy were used. This study was approved by the Institutional Review Board of UT Southwestern Medical Center.

Data Collection

Patient demographics, clinical history, and laboratory results were obtained through review of patient electronic medical records. Age, gender, race/ethnicity, body mass index (BMI), HIV status, and alcohol history were recorded, with active alcohol abuse defined as drinking more than 40 grams/day. Data regarding liver disease included underlying etiology and the presence of ascites, encephalopathy, and/or esophageal varices. We classified patients according to etiology of liver disease, including HCV, hepatitis B virus (HBV), alcohol-related liver disease, NAFLD, and other. NAFLD was often associated with components of the metabolic syndrome but was a diagnosis of exclusion, only made in the absence of other causes of liver disease including viral hepatitis and alcohol abuse. Laboratory results of interest included platelet count, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, albumin, and international normalized ratio (INR) within 12 months of liver biopsy. For patients with multiple laboratory data, we used the values closest to time of liver biopsy. APRI was calculated using AST, expressed as a ratio to the upper limit of normal, divided by platelet count. FIB-4 was calculated as $(\text{age} * \text{AST}) / (\text{platelets} * \text{ALT}^{1/2})$. We evaluated APRI and FIB-4 given they are derived from clinical data that is routinely available in patients with liver disease and do not require specialized testing.

To study the performance of non-invasive markers and radiology in an effectiveness setting, we obtained histologic and radiologic data from review of electronic medical records. Per routine clinical care at Parkland, all liver biopsies are interpreted by a small group of subspecialty-trained hepatopathologists. The pathologists have access to patient clinical data through the electronic medical record including presence of ascites or varices; however, results of non-invasive markers are not stored as a discrete data field. Similarly, all ultrasounds at Parkland are interpreted by a limited set of radiologists. Radiologists interpret ultrasounds with a recommended, but not required, protocol including routine assessment for a nodular surface and other signs of cirrhosis. Histologic data included biopsy length, grade

of inflammation, and fibrosis stage. Fibrosis stage was assessed using the Batts-Ludwig system: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis with rare bridges; F3, bridging/septal fibrosis; and F4, cirrhosis. For imaging data, we collected date of ultrasound closest to liver biopsy, liver morphology (presence of shrunken nodular liver), and any signs of portal hypertension (splenomegaly or intra-abdominal varices). An experienced hepatopathologist (P.G.) and experienced abdominal radiologist (G.K.) were available to review and discuss any biopsies or ultrasounds with unclear data as needed. Both of these investigators were blinded to results of other tests, including non-invasive markers of fibrosis.

Statistical Analysis

We first determined the proportion of patients who could be classified by each non-invasive marker – APRI, FIB-4 and ultrasound. On ultrasonography, cirrhosis was defined as the presence of a nodular liver, with or without any signs of portal hypertension. An APRI value of >1 and FIB-4 value of >3.25 are standard cutoffs for identifying severe fibrosis that have been validated in prior work^{13, 15}. Stage of fibrosis as determined by liver biopsy was regarded as the gold standard in each case. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of cirrhosis were calculated for each non-invasive marker. We also evaluated the potential benefit of using non-invasive serum markers with ultrasonography to determine presence or absence of cirrhosis. The overall diagnostic value was assessed using receiver operating characteristic (ROC) curves. C-statistics in ROC analysis range from 0.5 to 1.0, with values of 0.5 indicating the model is no better than chance and 1.0 indicating the model perfectly discriminates two outcomes. Models are considered reasonable if the c-statistic exceeds 0.70 and strong if greater than 0.80. The ROC c-statistic for each non-invasive marker was compared using the Delong method. Finally, we assessed for correlates of accuracy for each non-invasive marker using ROC analysis and the Delong method. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

RESULTS

Study Population

Between November 2008 and July 2011, 388 patients who underwent percutaneous or transjugular liver biopsy at Parkland Hospital met inclusion criteria for our study. Baseline characteristics of patients are shown in Table 1. The median age of patients was 49.7 years, and 50.3% of patients were male. Our population was racially diverse, with 27.1% non-Hispanic Caucasians, 34.0% Hispanic Caucasians, and 33.0% African Americans. The most common etiologies of cirrhosis were HCV (45.6%), NAFLD (10.8%), and alcohol-induced liver disease (10.3%). Approximately 11% of the patients with known HIV serostatus (n=277) were HIV positive. Our cohort was diverse with respect to fibrosis stage, with 176 (45.4%) having stage 0-1 fibrosis, 69 (17.8%) stage 2 fibrosis, 50 (12.9%) stage 3 fibrosis, and 93 (24.0%) cirrhosis.

Performance of APRI

APRI was able to be calculated using lab variables within 6 months of liver biopsy in all 388 cases. The mean APRI value of the cohort was 3.5, with 159 (41.0%) having a value above 1.0 suggesting the presence of cirrhosis. The sensitivity and specificity of APRI for the presence of cirrhosis were 68.8% and 67.8%, respectively (Table 2). The PPV and NPV for APRI were 40.3% and 87.3%, respectively. In the subset of patients with an APRI > 1.0 and a cirrhotic appearing liver on ultrasound, the PPV for cirrhosis significantly higher at 78.3% ($p<0.001$).

The c-statistic for APRI, using the suggested cut-off of 1.0, predicting the presence of cirrhosis was 0.68 (95%CI 0.63 – 0.74). There was no significant difference in the accuracy of APRI by age, gender, race, HIV status, or length of biopsy. Although the accuracy of APRI was lower among Hispanic patients, this did not reach statistical significance (c-statistics 0.71 (95%CI 0.64-0.78) vs. 0.63 (95%CI 0.54-0.73), $p=0.20$). Similarly, the accuracy of APRI was lower among patients with ongoing inflammation on biopsy compared to those without inflammation, but this did not reach statistical significance (c-statistics 0.80 (95%CI 0.64-0.95) vs. 0.66 (95%CI 0.60-0.72), $p=0.12$). The only predictor of APRI accuracy was etiology of liver disease, with significantly better accuracy among patients with viral liver disease (c-statistics 0.74 (95%CI 0.66-0.82) vs. 0.63 (95%CI 0.55-0.70), $p=0.04$) in patients with other etiologies of liver disease.

Performance of FIB-4

FIB-4 was able to be calculated using lab variables within 6 months of liver biopsy in all 388 cases. The mean FIB-4 value of the cohort was 6.9, with 115 (29.6%) having a value above 3.25 suggesting the presence of cirrhosis. The sensitivity and specificity of FIB-4 for the presence of cirrhosis were 64.5% and 81.4%, respectively (Table 2). The PPV and NPV for FIB-4 were 52.2% and 87.9%, respectively. In the subset of patients with FIB-4 > 3.25 and a cirrhotic appearing liver on ultrasound, the PPV for cirrhosis was significantly higher at 81.8% ($p<0.001$).

The c-statistic for FIB-4, using the suggested cut-off of 3.25, predicting the presence of cirrhosis was 0.73 (95%CI 0.68 – 0.78). There was no significant difference in the accuracy of FIB-4 by age, gender, race, etiology of liver disease, or length of biopsy. Although the accuracy of FIB-4 was lower among Hispanic patients, this did not reach statistical significance (c-statistics 0.76 (95%CI 0.69-0.82) vs. 0.68 (95%CI 0.59-0.77), $p=0.21$).

Performance of Ultrasound

Of the 388 patients, 367 (94.6%) had an ultrasound within 12 months of liver biopsy. The presence of a cirrhotic-appearing liver was assessed in 342 of cases. Ninety-one (26.6%) patients were reported as having a liver with a shrunken nodular appearance, suggesting the potential presence of cirrhosis. Of patients with an ultrasound, 134 also had CT scan alone, 9 had MRI alone, and 32 patients had both CT and MRI scan. The presence of a cirrhotic-appearing liver was confirmed in 29 of cases by CT alone, 5 by MRI alone, and 14 by both CT and MRI. Eleven patients had a shrunken nodular liver on ultrasound that was not

confirmed by CT and/or MRI. There were signs of portal hypertension in 55 (60.4%) of the 91 patients with a nodular-appearing liver on ultrasound.

The sensitivity and specificity of a nodular liver contour on ultrasound for the presence of cirrhosis were 67.8% and 87.5%, respectively (Table 2). The PPV of a nodular appearing liver was only 64.8%; however, this was significantly higher at 83.6% in the subset of patients with both a nodular liver contour and signs of portal hypertension ($p=0.01$). The PPV for the presence of cirrhosis was also significantly higher in the subset of patients with findings confirmed on CT or MRI compared to those with a cirrhotic-appearing liver on ultrasound alone (83.3% vs. 44.2%, $p<0.001$).

We next evaluated the accuracy of ultrasound when combined with non-invasive serum markers of fibrosis (Table 2). The PPV of ultrasound was significantly higher in the subset of patients who also had a non-invasive marker (APRI or FIB-4) suggesting cirrhosis compared to those with a nodular-appearing liver on ultrasound alone (77.8% vs. 35.7%, $p<0.001$). Similarly, the PPV of ultrasound was significantly higher at 81.8% among patients with a cirrhotic-appearing liver on ultrasound and associated thrombocytopenia.

The c-statistics for a nodular appearance and signs of portal hypertension on ultrasound were 0.78 (95%CI 0.72-0.83) and 0.75 (95%CI 0.69 – 0.80), respectively. There was no significant difference in the accuracy of ultrasound by gender, race, obesity, or the presence of ascites. However, the accuracy of a cirrhotic appearance on ultrasound was significantly lower in older patients and those with HIV infection. When dichotomized at the median age of our cohort, the accuracy of ultrasound was significantly lower in patients older than age 50 compared to younger patients (c-statistics 0.85 (95%CI 0.78-0.92) vs. 0.71 (95%CI 0.63-0.79), $p=0.01$). Similarly, accuracy was lower in the 25 HIV-positive patients (c-statistic 0.53, 95%CI 0.27-0.79) than those without HIV infection (c-statistic 0.81, 95%CI 0.75-0.87) ($p=0.04$).

DISCUSSION

In this study, we evaluated the accuracy of imaging and serum markers for identifying patients with cirrhosis. We found that serum noninvasive markers, APRI and FIB-4, both had low positive predictive values for identifying patients with cirrhosis. A cirrhotic-appearing liver on ultrasound alone also had a low positive predictive value for cirrhosis; however, this was significantly higher at approximately 80% when confirmed using CT, MRI, or a noninvasive serum biomarker. Therefore, a combination of non-invasive serum and radiologic non-invasive markers may allow sufficient positive predictive value to systematically identify patients with cirrhosis. However, liver biopsy may still play a role for indeterminate cases in which only one non-invasive marker suggests the presence of cirrhosis.

Although patients with ascites or hepatic encephalopathy can be easily recognized as having cirrhosis, patients can remain “compensated” for years without any overt signs or symptoms of cirrhosis⁴. Despite being asymptomatic and having compensated cirrhosis, these patients carry a risk of developing serious complications including variceal bleeding, ascites, hepatic

encephalopathy, and hepatocellular carcinoma (HCC). Prior studies have demonstrated underuse of HCC and variceal screening in patients with cirrhosis, in part related to difficulty recognizing patients with pre-clinical cirrhosis¹⁶⁻¹⁹.

An accurate non-invasive marker could be used to facilitate systematic identification of patients with cirrhosis for variceal and HCC surveillance programs. Many patients with chronic liver disease are monitored with liver enzymes, platelet counts, and liver ultrasounds as part of clinical care, so non-invasive markers such as APRI and FIB-4 are routinely available. For example, Stravitz and colleagues demonstrated that patients who presented with HCC in the setting of unrecognized cirrhosis had an elevated APRI in nearly 50% of cases and elevated FIB-4 in two-thirds of cases²⁰. Of note, a high positive predictive value is critical to avoid unnecessary surveillance in patients without cirrhosis, which not only exposes patients to risk of harms (e.g. contrast and radiation exposure for cross-sectional imaging and/or risks of biopsy) but also increases healthcare costs with minimal benefit. The low positive predictive value of any single noninvasive marker precludes their use in isolation.

The poor positive predictive value of ultrasound may in part be related to the operator dependent nature of ultrasound, leading to large variations in effectiveness²¹⁻²³. Most prior studies assessed non-invasive markers in efficacy settings, in which expert radiologists interpreted all imaging studies. The low positive predictive value in our study may in part be related to its effectiveness design, in which all imaging studies were interpreted as part of routine clinical care. However, we believe liver nodularity is an imperfect marker for internal architectural distortion, necessitating the use of confirmatory findings such as the presence of portal hypertension or non-invasive markers.

We found the positive predictive value and specificity of non-invasive markers significantly increased when they were used in combination. For example, the positive predictive value of APRI increased from 40% to 78% when combined with findings on ultrasound. The use of both serum and imaging non-invasive markers in combination more closely mirrors clinical practice, where practitioners use all available clinical data.

Although the positive predictive value of non-invasive markers was disappointingly low, the negative predictive value of each marker exceeded 80%. Radiologic and serum non-invasive markers had equally high negative predictive values, and using non-invasive markers in combination did not increase the negative predictive value. Therefore, it may be possible to use non-invasive markers to exclude the presence of cirrhosis in patients with a lower likelihood of having cirrhosis.

We evaluated correlates of accuracy for ultrasound, APRI, and FIB-4 to determine if any non-invasive marker performs better in particular subgroups. For example, we found APRI had worse accuracy among patients with non-viral liver disease, but the same association was not seen for FIB-4. If confirmed in larger studies, this would suggest that FIB-4 may be preferred over APRI in this subset of patients. Prior studies have suggested APRI might also have lower accuracy in HIV-infected patients^{24, 25}; however, this interaction was not seen in our cohort. We also found APRI and FIB-4 had lower accuracy in Hispanic patients,

although the differences did not reach statistical significance – perhaps related to small sample size. Of interest, we found the accuracy of ultrasound was significantly lower in older patients and those with HIV infection, although it is unclear why this would be the case. Surprisingly, we found no effect of BMI or the presence of ascites on the accuracy of ultrasound to identify patients with cirrhosis. Further studies should continue to explore subgroups of patients in whom particular non-invasive markers may perform better and be preferred.

Newer methods, such as Fibrotest and MR elastography, are also able to non-invasively assess level of fibrosis²⁶. Fibrotest has sensitivity and specificity exceeding 80% but requires specialized testing instead of relying on readily available data²⁷. MR elastography is highly accurate, with a sensitivity and specificity of 100% and 96%; however, its widespread adoption has been hindered due to the need for expensive equipment or specific expertise^{28, 29}.

We acknowledge that our study had several limitations. It was performed in a single large safety-net hospital and may not be generalized to other practice settings. For example, ultrasound is known to be operator dependent so its performance may vary between sites. Given its retrospective nature, our study was also limited by possible unmeasured confounders and missing data. Finally, as discussed above, there is the inherent problem of intra-observer variability and sampling error when using the liver biopsy as a gold standard. In fact, divergent results may be a result of inadequate biopsies rather than inaccurate non-invasive markers. The vast majority of liver biopsy samples were at least 15 mm in length, minimizing the risk that biopsy size affected the performance of APRI and/or FIB-4. Overall, we believe the limitations of our study were outweighed by its strengths including our large patient cohort that was diverse with regard to demographics and fibrosis stage.

In summary, non-invasive markers of fibrosis can serve as powerful tools for identifying patients to enroll in systematic screening programs as well as for routine clinical practice. However, serum and imaging non-invasive markers of fibrosis appear to have insufficient positive predictive values when used in isolation. Their accuracy is significantly increased when used in combination; therefore, using a combination of radiologic and serum-based non-invasive markers may be the optimal method for identifying patients with cirrhosis. Liver biopsy may still play a role for indeterminate cases in which only one non-invasive marker suggests the presence of cirrhosis.

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Table 1

Patient Characteristics

Variable *	Patients without cirrhosis (stage 0-3) (n=295)	Patients with cirrhosis (stage 4) (n=93)	p-value
Age	48.4 (40.2 – 56.1)	51.3 (46.5 – 58.8)	0.003
Gender (% male)	144 (48.8%)	51 (54.8%)	0.31
Race			0.54
Caucasian	77 (26.1%)	28 (30.1%)	
Black	92 (31.2%)	36 (38.7%)	
Hispanic	110 (37.3%)	22 (23.7%)	
Body mass index	27.6 (24.4 – 32.3)	29.3 (24.2 – 33.1)	0.28
Etiology of liver disease			0.03
Hepatitis C virus	140 (47.5%)	37 (39.8%)	
Hepatitis B virus	15 (5.1%)	2 (2.2%)	
Alcohol-induced	14 (4.8%)	26 (28.0%)	
NASH	31 (10.5%)	11 (11.8%)	
Presence of ascites	23 (7.8%)	50 (53.8%)	< 0.001
Presence of hepatic encephalopathy	6 (2.0%)	24 (26.1%)	< 0.001
Presence of esophageal varices	12 (4.1%)	51 (54.9%)	< 0.001
HIV status	26 (12.5%)	5 (7.4%)	0.25
Platelet	225 (171 – 276)	117 (77 – 178)	< 0.001
AST	54 (34 – 100)	75 (43 – 118)	0.88
ALT	68 (38 – 128)	44 (30 – 71)	0.07
Alkaline phosphatase	93 (71 – 159)	145 (103 – 178)	0.78
Bilirubin	0.5 (0.3 – 0.9)	1.3 (0.5 – 5.5)	< 0.001
Albumin	4.0 (3.5 – 4.2)	3.1 (2.4 – 3.7)	< 0.001
INR	1.0 (0.9 – 1.1)	1.2 (1.0 – 1.6)	0.67
APRI	0.63 (0.38 – 1.16)	1.37 (0.83 – 3.16)	0.33
FIB-4	1.51 (1.01 – 2.33)	4.37 (2.81 – 9.12)	0.33
Grade of inflammation			< 0.001
Grade 0-1	133 (46.0%)	22 (26.8%)	
Grade 2	92 (31.8%)	21 (25.6%)	

Variable *	Patients without cirrhosis (stage 0-3) (n=295)	Patients with cirrhosis (stage 4) (n=93)	p-value
Grade 3	43 (14.9%)	25 (30.5%)	
Grade 4	21 (7.3%)	14 (17.1%)	

ALT - Alanine aminotransferase; APRI - AST to platelet ratio index; AST - Aspartate aminotransferase; INR - international normalized ratio; NASH – nonalcoholic steatohepatitis

* Data presented as n(%) and median (inter-quartile range) for categorical and continuous variables, respectively

Table 2

Accuracy of Non-invasive markers for detection of cirrhosis

Test	Cut-off	Sensitivity	Specificity	PPV	NPV
APRI	> 1.0	64/93 (68.8%)	200/295 (67.8%)	64/159 (40.3%)	200/229 (87.3%)
FIB-4	> 3.25	60/93 (64.5%)	240/295 (81.4%)	60/115 (52.2%)	240/273 (87.9%)
APRI or FIB-4	As above	68/93 (73.1%)	195/295 (66.1%)	68/168 (40.5%)	195/220 (88.6%)
Ultrasound	Nodular shrunk liver	59/87 (67.8%)	223/255 (87.5%)	59/91 (64.8%)	223/251 (88.8%)
Ultrasound	Nodular shrunk liver and portal hypertension	46/87 (52.9%)	246/255 (96.5%)	46/55 (83.6%)	246/287 (85.7%)
CT or MRI	Nodular shrunk liver	53/69 (76.8%)	115/134 (85.8%)	53/72 (73.6%)	115/131 (87.8%)
Ultrasound plus CT or MRI	Nodular shrunk liver	40/63 (63.5%)	106/114 (93.0%)	40/48 (83.3%)	106/129 (82.2%)
Ultrasound plus non- invasive marker	Nodular shrunk liver and positive APRI or FIB-4	49/87 (56.3%)	241/255 (94.5%)	49/63 (77.8%)	241/279 (86.4%)

APRI - AST to platelet ratio index; NPV – negative predictive value; PPV – positive predictive value