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EDITORIAL

Noninvasive diagnosis of hepatic fibrosis in chronic hepatitis C

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Abstract

Assessment of hepatic fibrosis is important for determining prognosis, guiding management decisions, and monitoring disease. Histological evaluation of liver biopsy specimens is currently considered the reference test for staging hepatic fibrosis. Since liver biopsy carries a small but significant risk, noninvasive tests to assess hepatic fibrosis are desirable. This editorial gives an overview on noninvasive methods currently available to determine hepatic fibrosis and their diagnostic accuracy for predicting significant fibrosis and cirrhosis in chronic hepatitis C. Based on available data, the performance of simple tests derived from routine laboratory parameters appears to be similar to that of more complex and expensive fibrosis panels. Transient elastography seems more accurate than blood tests for diagnosing cirrhosis.

Key words: Noninvasive fibrosis tests; Significant fibrosis; Cirrhosis; Biomarkers; Transient elastography

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INTRODUCTION

Hepatic fibrosis is the basis for the development of portal hypertension, complications of chronic liver disease including esophageal varices and/or ascites, and liver failure. Assessment of the degree of hepatic fibrosis (i.e. staging) is important for several reasons: (1) to determine the prognosis of chronic liver disease, (2) to select patients for specific (antifibrotic) treatment, and (3) to monitor the success of treatment.

Assessment of hepatic fibrosis is especially relevant in the context of chronic hepatitis C. In developed countries, chronic hepatitis C is one of the leading causes of cirrhosis, hepatocellular carcinoma, and liver transplantation. The stage of fibrosis carries important prognostic information as it is closely related to the risk for development of cirrhosis[1]. Antiviral treatment of chronic hepatitis C aims at viral eradication and/or prevention of fibrosis progression. However, current standard treatment with peginterferon/ribavirin has limited efficacy and is associated with severe side effects. Especially in difficult-to-treat patients with hepatitis C virus (HCV) genotype 1 infection and average cure rates of only 50%, the indication for antiviral treatment is selective and based on several factors such as age, concomitant diseases, and fibrosis stage. Hence, in HCV genotype 1 patients antiviral treatment has been primarily recommended for patients with at least significant fibrosis[2].

Currently, histological scoring is the reference test for staging of hepatic fibrosis. However, since liver biopsy is associated with complications, noninvasive methods for assessment of hepatic fibrosis are desired by both clinicians and patients. Different approaches to estimate liver fibrosis noninvasively have been pursued, including indirect fibrosis tests based on routine liver function parameters, direct fibrosis tests based on extracellular matrix proteins, and physical methods that estimate fibrosis by measuring hepatic stiffness.

These noninvasive fibrosis tests are being intensely investigated in liver disease of various etiologies and several comprehensive reviews have been published recently[3-6]. However, the clinical impact of the numerous proposed methods remains unclear at present. This Editorial is intended to give an overview on currently available blood tests and physical methods for assessment of hepatic fibrosis and focuses on comparison of their diagnostic accuracies for predicting clinically relevant stages (significant fibrosis, cirrhosis) of chronic HCV infection.

IS LIVER BIOPSY AN ADEQUATE REFERENCE TEST?

Histological evaluation of percutaneous liver biopsy

specimens is currently used as a gold standard for assessment of hepatic fibrosis in chronic HCV infection. Fibrosis is usually staged semi-quantitatively by the pathologist using one of several published scoring systems. However, liver biopsy carries a significant risk and histological staging has several shortcomings as outlined below that limit its diagnostic accuracy.

Risk of percutaneous liver biopsy

Among the complications of percutaneous liver biopsy are pain (10%-30%), bleeding (which may be severe and necessitate blood transfusion or emergency surgery), biliary peritonitis, and pneumothorax. In large series, mortality has been reported to range from 0.1%-0.01%[7,8]. Percutaneous liver biopsy is contraindicated in the presence of coagulopathy, thrombocytopenia, and ascites. These contraindications may be in part obviated by transjugular liver biopsy; however, this method is not widely available.

Sampling error

An average needle biopsy specimen represents only 1/50 000 of a human liver. Sampling error thus may play an important role in diseases that exhibit a patchy rather than homogenous distribution within the liver. In a study investigating simultaneous biopsies from the left and right liver lobes during laparoscopy, fibrosis scores obtained in both biopsy sites differed by at least one stage in 33% of the patients[9]. Furthermore, Bedossa *et al*[10] demonstrated that the length of the biopsy core is positively related to the precision of fibrosis scoring. Likewise, Colloredo *et al*[11] reported that in liver biopsy specimens of inadequate size stage is likely to be underscored in chronic viral hepatitis. Based on these studies, liver biopsy cylinders with a length of $\geqslant$ 20 mm (at a width of 1.4 mm) and/or at least 11 complete portal tracts have been identified as minimal requirements for optimal histological evaluation of fibrosis in chronic hepatitis C. However, with respect to the evaluation of noninvasive fibrosis tests, most studies did not accurately report whether these requirements for adequate liver biopsy specimens were met[12].

Interobserver variation

As scoring is subjective, observer error also plays an important role. Interobserver variation is largely dependent on the experience of the pathologist. In a study evaluating interobserver variation between 10 different experienced pathologists, substantial agreement was found for staging fibrosis (kappa 0.78) while variation was considerably higher for grading inflammatory activity[13,14].

Lack of a universal scoring system of fibrosis

The interpretation of studies assessing hepatic fibrosis is further hampered by the lack of standardization of hepatic fibrosis scores. Several scoring systems have been developed that classify the degree of hepatic fibrosis either on a 5-step scale (F0-F4) including the Knodell fibrosis score[15], the Scheuer fibrosis score[16], and the METAVIR fibrosis score[13], or on a 7-step scale (F0-F6) such as the Ishak fibrosis score[17]. Significant fibrosis has been defined as F2-F4 or F3-F6 and cirrhosis as F4 or F5-F6, respectively. To date, liver pathologists have not reached a universal consensus on the standardization of scoring systems. However, histopathological scoring of fibrosis by different systems appears to be quite robust as comparison of the Ishak and METAVIR fibrosis scores yielded excellent agreement (weighted kappa 0.998)[14].

INDIRECT FIBROSIS TESTS

Several indirect fibrosis tests (indices composed of routine laboratory parameters that reflect changes in liver function) have been suggested as surrogate marker of hepatic fibrosis. Most of them are readily available at no additional cost, albeit they may require the use of a pocket calculator or access to the internet.

Aspartate aminotransferase/Alanine aminotransferase ratio

Almost three decades ago, the ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT ratio, AAR) has been proposed as a surrogate marker of hepatic fibrosis, with values > 1 being suggestive of cirrhosis[18]. This finding is related to an increased release of mitochondrial AST, decreased AST clearance and/or impaired synthesis of ALT in advanced liver disease. However, discrepant results have been published on the diagnostic accuracy of the AAR. Giannini *et al*[19] reported high diagnostic accuracy of the AAR for prediction of cirrhosis and significant fibrosis[20]. In contrast, Lackner *et al*[21] found the diagnostic accuracy of AAR to be clearly inferior to that of other indirect fibrosis tests based on routine laboratory parameters.

Platelet count

Hepatic fibrosis may lead to thrombocytopenia as a consequence of impaired synthesis of thrombopoietin and/or sequestering of platelets in an enlarged spleen. Surprisingly, few data exist on the diagnostic value of platelet count per se although the platelet count has been included in several composite fibrosis scores. Ono *et al*[22] reported the use of platelet count could discriminate F4 from F1-F3 in 75%-80% of patients with chronic hepatitis C. In our own study, a platelet count of $< 150 \times 10^9$/L had a positive predictive value (PPV) > 90% for significant fibrosis, whereas at a cut-off of $\geqslant 150 \times 10^9$/L it had a negative predictive value (NPV) > 90% for cirrhosis[21].

Platelet count has been combined with age in the age-platelet index[23] or with AAR and prothrombin time in the cirrhosis discriminant score (CDS)[24] but the diagnostic accuracy of these composite scores was not superior to platelet count per se[21]. In addition, platelet count is a component of AST to platelet ratio index (APRI), model 3, Forns index, Fibrometer, and FibroIndex.

AST to platelet ratio index (APRI)

The APRI was described by Wai *et al*[25] from Anna Lok's group at Ann Arbor University. It is calculated as

APRI = [(AST/Upper limit of normal)/platelet count (10^9/L)] × 100

This test is derived from readily available laboratory

parameters and usually requires a pocket calculator. Its diagnostic accuracy for both significant fibrosis and cirrhosis has been confirmed by several external studies[21,26-30]. Using the cut-offs proposed by Wai *et al*, approximately 50% of the patients can be correctly classified without a liver biopsy.

Model 3

Lok *et al*[31] proposed another prognostic model for prediction/exclusion of cirrhosis in patients with chronic hepatitis C which is based on platelet count, AST, and prothrombin time expressed as international normalized ratio (INR). This index may be derived from the regression formula:

log odds = -5.56 - 0.0089 × platelet (× 10^9/L) + 1.26 × AST/ALT ratio + 5.27 × INR

or by a calculator available at the web site of the HALT-C trial (www.haltctrial.org). Using model 3 at a cut-off of < 0.20, cirrhosis could be excluded with an NPV of 99%.

Forns index

Forns *et al*[32] developed an index derived from age, gamma-glutamyl transferase (GGT), cholesterol, and platelet count in a study of 476 untreated HCV patients, which is calculated as follows:

7.811 - 3.131 × ln (platelet count) + 0.781 × ln (GGT) + 3.467 × ln (age) - 0.014 × (cholesterol [mg/dL])

In their study, the area under the receiver operating characteristic curve (AUROC) for prediction of significant fibrosis (F2-F4 according to the Scheuer classification) was 0.86 in the test set and 0.81 in the validation set. The diagnostic accuracy of this index has been confirmed in patients with HIV-HCV coinfection[33].

Fibrotest/Fibrosure

French investigators analyzed an extensive array of biochemical tests in 339 patients with chronic hepatitis C and identified a panel of 5 markers which could best predict the stage of fibrosis: α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, and total bilirubin[34]. This test has been marketed as Fibrotest™ (Biopredictive, Paris, France) in Europe and as Fibrosure™ (LabCorp, Burlington, NC) in the United States. In contrast to the above mentioned indirect fibrosis tests, calculation of the Fibrotest by a patented algorithm is subject to payment of a fee to the manufacturer. The Fibrotest has been validated internally and externally in several studies in patients with chronic hepatitis C[35-38]. Interestingly, a recent study suggested that Fibrotest was a better predictor than histologic staging for complications of chronic hepatitis C[39]. Fibrotest was also found to predict fibrosis in alcoholic[40] and non-alcoholic[41] fatty liver disease. The diagnostic accuracy of this test is limited by hemolysis (leading to a reduction in haptoglobin), Gilbert's syndrome (increasing the bilirubin level), and recent or ongoing infection (leading to elevations of α2-macroglobulin and haptoglobin).

FibroIndex

Recently, Japanese investigators proposed another index composed of platelet count, AST, and gamma globulin:

1.738 - 0.064 (platelets [× 10^4/mm^3]) + 0.005 (AST [IU/L]) + 0.463 (gamma globulin [g/dL])

The AUROC for prediction of significant fibrosis was 0.83 (0.82 in the validation set) which was slightly superior to APRI or the Forns index assessed in the same study[29].

DIRECT FIBROSIS TESTS

Serum levels of extracellular matrix (ECM) proteins reflect the balance between hepatic fibrogenesis and fibrolysis and have been proposed as direct markers (biomarkers) of hepatic fibrosis. In addition, several fibrosis panels (i.e. combinations of such biomarkers) have been developed and some of them are now available for commercial use. While these biomarkers or panels thereof are directly related to the deposition of fibrotic material, their diagnostic performance in hepatic fibrosis may be limited by extrahepatic confounding factors such as systemic inflammation or renal failure.

Hyaluronic acid

Hyaluronic acid (HA) is a polysaccharide present in ECM and elevated in serum in patients with hepatic fibrosis. Commercial test kits are available from Corgenix (Westminster, Colorado). The diagnostic accuracy of HA was found to be superior to that of procollagen type Ⅲ N-terminal peptide (PⅢNP)[42] and its diagnostic accuracy was confirmed in a large study of 486 HCV patients[43]. HA was also found to be an accurate marker of severe hepatic fibrosis in nonalcoholic fatty liver disease[44].

Extracellular matrix proteins

Procollagen peptides: PⅢNP is a product of cleavage of procollagen and has been proposed as a serum marker of hepatic fibrosis more than two decades ago[45]. However, in several studies in patients with chronic HCV infection, this biomarker showed only moderate diagnostic accuracy[42,46,47].

Matrix metalloproteinases and inhibitors: Excess ECM proteins are degraded by matrix metalloproteinases (MMPs) which are in turn inhibited by tissue inhibitors of metalloproteinases (TIMPs). Since both MMPs and TIMPs are related to matrix protein turnover, their serum levels have been used as fibrosis markers. However, studies on the correlation of MMP-1, MMP-2, MMP-9, TIMP-1, and TIMP-2 with hepatic fibrosis have produced conflicting results[48-50]. TIMP-1 is a component of several composite fibrosis panels (see below).

YKL-40: YKL-40 is a glycoprotein believed to play a role in ECM degradation. In a study of 109 patients with chronic HCV infection, this biomarker showed similar diagnostic accuracy to HA for significant fibrosis, while its ability to diagnose cirrhosis was inferior to that of HA[51].

COMPOSITE FIBROSIS PANELS

Combinations of one or more biomarkers with indirect fibrosis tests have been suggested as noninvasive fibrosis tests.

Fibrospect Ⅱ

The Fibrospect Ⅱ assay (Prometheus Laboratories Inc., San Diego, CA) uses HA, TIMP-1 and α2-macroglobulin. This test was found to accurately predict significant fibrosis in a study of 294 HCV patients and validated in an external cohort of 402 HCV patients[52]. This test was further validated in a study comparing the diagnostic accuracies of APRI, Forns index, Fibrotest, and Fibrometer[26].

Enhanced liver fibrosis (ELF)

In a European multicenter study of 1021 patients with chronic liver disease of different etiologies, an algorithm consisting of age, HA, PⅢNP, and TIMP-1 was developed[53]. Using the Scheuer fibrosis score as a reference test, its overall diagnostic accuracy was similar to that of other noninvasive fibrosis tests (AUROC 0.78 for significant fibrosis, 0.89 for cirrhosis). Performance of the algorithm was slightly lower in a subgroup of patients with chronic hepatitis C (n = 325, AUROC 0.77 for prediction of F3-F4). This test is being marketed as Enhanced Liver Fibrosis (ELF™) test by Siemens Medical Solutions Diagnostics (Tarrytown, NY).

Hepascore

This model was developed by Australian investigators and is derived from bilirubin, GGT, HA, α2-macroglobulin, age and sex. High diagnostic performance was reported for both significant fibrosis and cirrhosis[54], but external validation yielded somewhat lower diagnostic accuracies[30].

Fibrometer

The Fibrometer test incorporates α2-macroglobulin, HA, AST, platelet count, prothrombin index, urea, and age. Cales *et al*[26] reported superior diagnostic accuracy of Fibrometer to Forns index, Fibrotest, and APRI. However, this finding was not confirmed in an external validation study[30]. Several Fibrometers are now commercially available at BioLiveScale (Angers, France) for assessment of fibrosis in chronic viral hepatitis (Fibrometer V), alcoholic liver disease (Fibrometer A), and metabolic steatopathy (Fibrometer S).

PHYSICAL METHODS/IMAGING

Radiological techniques such as ultrasound, CT scan or MRI can accurately detect cirrhosis at advanced stages with hepatic nodularity or signs of portal hypertension such as splenomegaly, presence of portosystemic collaterals or ascites. However, these techniques fail to detect earlier stages of hepatic fibrosis or cirrhosis. Recently, special techniques for assessment of liver stiffness (elastography) have been developed.

Transient elastography

Transient elastography by Fibroscan™ (Echosens, Paris, France) is a promising technique that estimates the degree of hepatic fibrosis by measuring liver stiffness[55]. The Fibroscan transmits a vibration of low frequency into the liver from a probe that includes an ultrasonic transducer. The vibration waves induce an elastic shear wave whose velocity is proportional to the stiffness of the tissue. Shear wave velocity is measured by pulse-echo ultrasound and results are expressed in kPa. In cirrhotic patients, liver stiffness measurements (LSM) show a wide range from approximately 12 to 75 kPa. The Fibroscan samples a volume of approximately 4 cm^3 which is considered more representative of the entire liver than a needle biopsy specimen. Measurements can be quickly performed in 5 min and are highly reproducible. However, steatosis may confound its value to estimate fibrosis. Furthermore, measurement is heavily limited or impossible in obesity, ascites or in patients with narrow intercostal spaces.

The Fibroscan has been studied in various liver diseases including chronic hepatitis C[56] and primary biliary cirrhosis[57] demonstrating good diagnostic accuracy. A small study in patients with chronic HCV infection and persistently normal transaminases even reported values of 100% for sensitivity, specificity, PPV and NPV, respectively[58]. In a study of 711 patients with chronic liver disease of various etiologies, LSM was closely related to fibrosis stage (r = 0.73) and high diagnostic accuracy was found for the diagnosis of cirrhosis (AUROC 0.96)[59]. Ganne-Carrie *et al*[60] further elaborated LSM for diagnosing cirrhosis and confirmed high diagnostic accuracy (AUROC 0.95) at a cut-off value of 14.6 kPa with some false-negative results due to inactive or macronodular cirrhosis. Another large study evaluated the success rate and performance of LSM in 935 patients with chronic HCV infection and reported successful measurements in 97% of the patients, while fatty thoracic belt was the major limiting factor[61]. Interestingly, recent data indicate a close correlation between LSM and portal pressure as estimated by the hepatic venous pressure gradient (HVPG) in patients with HCV-related cirrhosis[62] as well as recurring hepatitis C following liver transplantation[63]. Vizzutti *et al*[62] reported a good correlation between LSM and HVPG (r = 0.82) at lower portal pressures (< 12 mmHg) and suggested that, at a cut-off of 13.6 kPa, LSM could reliably predict or exclude clinically significant portal hypertension (CSPH, i.e. a portal pressure of ⩾ 10 mmHg) which is the prerequisite for the formation of esophageal varices. Thus, LSM may be the method of choice to characterize the severity of cirrhosis in patients without CSPH while at the same time it could be used to identify patients with CSPH that may benefit from portal pressure measurement by hepatic vein catheterization. This approach should be prospectively tested in future studies.

Real-time elastography

Another attractive approach is the development of real-time ultrasound systems equipped with special elastography modules that allow estimation of liver fibrosis with conventional ultrasound probes during a routine sonography examination. First results obtained with the Hitachi EUB-8500 system were recently presented[64]. In 79 patients with chronic viral hepatitis, the AUROC for diagnosis of significant fibrosis was 0.75 (elasticity score) or 0.93 (combined elasticity-laboratory score).

Magnetic resonance imaging

Aguirre *et al*[65] from the University of California at San

Diego proposed noninvasive diagnosis of liver fibrosis using double contrast material-enhanced MR imaging. In a retrospective study in 101 patients, this method could detect advanced fibrosis (METAVIR fibrosis score ⩾ 3) with a sensitivity and specificity of > 90%.

COMBINED METHODS

The highest diagnostic accuracies have to date been reported with the combined use of different methods with synergistic performance.

Fibroscan/Fibrotest

Castera *et al*[66] investigated APRI, Fibrotest, Fibroscan and combinations thereof in 183 patients with chronic hepatitis C. For significant fibrosis (but not cirrhosis), the combination of Fibroscan and Fibrotest had superior diagnostic accuracy (AUROC 0.88) to that of respective individual tests.

Sequential algorithms

The sequential use of several markers may overcome some of the limitations of individual markers. Sebastiani *et al*[67] developed three different sequential algorithms (including APRI, Fibrotest and/or Forns index) for the diagnosis of significant fibrosis with elevated ALT, significant fibrosis with persistently normal ALT, and cirrhosis, respectively, which allowed to classify 100% of the patients for each entity.

COMPARISON OF DIFFERENT NONINVASIVE FIBROSIS TESTS

Table 1 gives an overview of the diagnostic accuracies of various noninvasive tests for assessment of clinically relevant stages of hepatic fibrosis. All tests showed a better performance for diagnosing cirrhosis (AUROC 0.90-0.95) than for significant fibrosis (AUROC clustering around 0.80). With respect to significant fibrosis, the diagnostic accuracy of complex biomarker panels or newer physical methods was not superior to that of simple tests based on routine laboratory parameters. However, transient elastography appears more accurate than blood tests for diagnosing cirrhosis and may be especially useful for detection of clinically significant portal hypertension.

It should be noted that many of the reported tests have not yet undergone adequate external validation. Besides, direct comparison of different studies is hampered by variation in the reference test (sampling error, observer variation, use of different scoring systems) and different distribution of fibrosis stages within the study populations. In a recent study, Poynard *et al*[68] reported an important influence of biopsy size and fragmentation on the diagnostic accuracy of the Fibrotest. Such variation of the 'gold standard' may lead to underestimation of the diagnostic performance of noninvasive tests.

Few trials have directly compared different tests in the same populations of patients with chronic hepatitis C. Lackner *et al*[21] evaluated several noninvasive fibrosis tests based on routine laboratory parameters and found superior diagnostic accuracy of APRI to AST/ALT ratio. Bourliere *et al*[27] reported similar performance of Fibrotest, APRI, and Forns index while Cales *et al*[26] found superior diagnostic accuracy of Fibrometer to APRI, Forns index, and Fibrotest. In contrast, in 356 patients with chronic hepatitis C, Halfon *et al*[30] reported similar diagnostic accuracies of Fibrotest, Fibrometer, APRI, and Hepascore for significant fibrosis (AUROC 0.79, 0.78, 0.76, 0.76, respectively). Based on these comparative studies,

Table 1 Overview of studies on noninvasive fibrosis tests in chronic hepatitis C

	n	Significant fibrosis (AUROC)	Cirrhosis (AUROC)	Author
Indirect fibrosis tests				
AST/ALT ratio	194	0.57	0.73	Lackner[21]
	409	0.75	-	Giannini[20]
Platelet count	194	0.71	0.89	Lackner[21]
	409	0.73	-	Giannini[20]
APRI	270	0.80 (0.88[1])	0.89 (0.94[1])	Wai[25]
	194	0.8	0.9	Lackner[21]
	503	0.79	-	Cales[26]
	235	0.71	0.81	Bourliere[27]
	206	0.82	0.84	Parise[28]
	360	0.79 (0.82[1])	-	Koda[29]
	356	0.76	0.92	Halfon[30]
Model 3	1141	-	0.78 (0.81[1])	Lok[31]
Forns index	476	0.86 (0.81[1])	-	Forns[32]
	503	0.82	-	Cales[26]
	235	0.76	-	Bourliere[27]
	360	0.79 (0.84[1])	-	Koda[29]
Fibrotest/Fibrosure	339	0.84 (0.87[1])	0.92	Imbert-Bismut[34]
	352	0.73	-	Poynard[36]
	323	0.84	-	Myers[35]
	125	0.74	-	Rossi[37]
	503	0.81	-	Cales[26]
	519	0.79	-	Halfon[38]
	235	0.81	0.82	Bourliere[27]
	356	0.79	0.86	Halfon[30]
FibroIndex	360	0.83 (0.86[1])	-	Koda[29]
Direct fibrosis tests				
Hyaluronic acid	326	0.86	0.92	Guechot[42]
	206	0.88	0.91	Parise[28]
PIIINP	326	0.69	0.73	Guechot[42]
TIMP-1	78	0.71	0.90	Boeker[49]
YKL-40	109	0.81	0.80	Saitou[51]
Composite fibrosis panels				
Fibrospect Ⅱ	696	0.83 (0.82[1])	-	Patel[52]
	503	0.87	-	Cales[26]
ELF	1021[2]	0.78	0.89	Rosenberg[53]
	503	0.83	-	Cales[26]
Hepascore	221	0.85 (0.82[1])	0.94 (0.89[1])	Adams[54]
	356	0.76	0.89	Halfon[30]
Fibrometer	503	0.88	-	Cales[26]
	356	0.78	0.94	Halfon[30]
Elastography				
Transient elastography	327	0.79	0.97	Ziol[56]
(Fibroscan)	711[2]	0.80	0.96	Foucher[59]
	40[3]	1.00	-	Colletta[58]
	775[2]	-	0.95	Ganne-Carrie[60]
	935	0.79	0.91	Kettaneh[61]
Real-time elastography	79	0.75	0.69	Friedrich-Rust[64]
Combined tests				
Fibroscan + Fibrotest	183	0.88	0.95	Castera[66]

[1]Internal validation set; [2]Chronic liver disease of various etiologies; [3]Chronic HCV with persistently normal ALT.

the diagnostic accuracy of simple noninvasive fibrosis tests such as APRI appears to be similar to that of more complex and expensive fibrosis panels.

CONCLUSION

The main advantages of noninvasive fibrosis tests are the absence of risks and the potential to reflect the status of the entire liver. However, while optimal results are obtained at both ends of the spectrum of liver fibrosis, their most important limitation is the lack of discrimination at intermediate stages of fibrosis. Parkes *et al*[5] evaluated the diagnostic accuracy of several direct and indirect noninvasive fibrosis tests at cut-off levels giving high predictive values (PPV $\geqslant$ 90%, NPV $\geqslant$ 95%) and concluded that serum markers can reliably predict fibrosis only in a minority (about 35%) of patients with chronic hepatitis C. Besides, liver biopsy is still needed to rule out concomitant pathologies known to influence response to antiviral treatment, such as steatosis, steatohepatitis and/or iron overload. Future practice guidelines should address the role of noninvasive tests in assessing the stage of fibrosis in chronic hepatitis C[69].

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