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Review Article

Cirrhosis: Diagnostic Performance Characteristics of Non-invasive Tests

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Abstract

Non-invasive tests for staging liver fibrosis have become a routine part of patient evaluation. Many can be obtained with relative ease and low cost, and they can provide objective information upon which to base future deliberations. The diagnosis of cirrhosis carries with it a variety of significant consequences, including a shortened life expectancy and the need for close monitoring. Under-diagnosis is undesirable as well, since the opportunity to intervene in early stages may be missed. When using such a test, it is important to know how reliable a result is in a particular clinical context and how the information should be used in an overall diagnostic strategy. An abundance of literature now exists that documents the diagnostic performance of individual non-invasive tests in a variety of patient groups. We present a review of these findings and discuss the use of these tests in clinical decision making.

INTRODUCTION

The reference standard for diagnosing early cirrhosis in the absence of portal hypertension is liver biopsy, an expensive, inconvenient, and invasive test that, due to issues with sampling and observer error, serves as an imperfect gold standard [1-3]. It is often that patients present in advanced stages of cirrhosis, when it may be a simple thing to recognize both clinically due to the presence of ascites, jaundice, or hepatic encephalopathy and radiographically in the setting of a small, nodular liver and splenomegaly. But the majority of patients with early cirrhosis, during which phase we can exert the most leverage by medical intervention, are undiagnosed [4]. A significant number of such patients have no detectable physical or biochemical sign of cirrhosis, and the best hope for early diagnosis is accuratetesting of patients at high risk [5]. Other patients are misdiagnosed, when a non-invasive test produces a false positive result or when features of cirrhosis are an incidental finding on routine imaging. When encountering a patient who comes to you with a previously documented fibrosis stage, particularly when assessed to have cirrhosis, it is important to know what test forms the basis for the staging, what its diagnostic performance is, and thereby know the degree of certainty.

A diagnosis of cirrhosis is consequential, grimly altering the outlook for the patient in whom life expectancy is shortened, medications must be tailored, and surgical intervention minimized. In such patients a percutaneous liver biopsy may be avoided due to concern for complications, and biopsy via the trans-jugular route, while useful for obtaining concomitant portal pressure measurements, yields an often limited biopsy specimen. If a patient is diagnosed with cirrhosis, they should be monitored for the development of complications such as hepatic encephalopathy, ascites, gastroesophageal bleeding, and hepatocellular carcinoma and might be evaluated for liver transplantation. The consequences being what they are, the approach to the diagnosis must be appropriately circumspect, but delayed diagnosis is undesirable as well. The chance is lost to alter conditions which contribute to disease progression such as alcohol abuse, obesity and viral hepatitis, and the necessary monitoring is omitted such that patients all too frequently present due to complications of advanced cirrhosis [6,7]. The consequences of an uncertain diagnosis of cirrhosis must be balanced against the effects of delay.

Increasingly, however, we encounter patients carrying an unsubstantiated diagnosis of cirrhosis. In review of data from our institution (unpublished), among 64 patients with a clinical diagnosis of cirrhosis who underwent biopsy for pre-transplant evaluation over the past 1 year, only about 40 (62.5%) have histologic evidence of cirrhosis. The situation is startling for all involved. We find in retrospect the diagnosis of cirrhosis recorded in the patient chart, and copied forward from visit to visit, based upon the flimsiest of evidence, usually a single non-

invasive test whose demonstrated performance characteristics do not warrant such a definitive and life-altering diagnosis. In light of these concerns it is important to individually consider the performance characteristics of non-invasive tests in current use.

In nearly all cases the diagnosis of cirrhosis comes about in one of three ways. First, it may be detected incidentally on the basis of a non-invasive test [8-10] performed for some unrelated reason. We review the data on specificity of the most common imaging modalities below. Second, the diagnosis may derive from a non-invasive test specifically obtained for the evaluation of liver fibrosisin a patient with chronic liver disease or other risk factors for cirrhosis, as a form of high-risk screening [11-14]. It is in this group of patients that a liver biopsy might normally be considered, and we have reviewed the performance characteristics of these tests and considered the ways that they can be used in screening algorithms. Third, the diagnosis of cirrhosis is presumptively made on the basis of clinical evidence of portal hypertension such as the presence of ascites or gastroesophageal varices. This group has a very high likelihood of cirrhosis, but non-cirrhotic portal hypertension is found in up to 23% of all patients with portal hypertension [15-19].

The variety of things called cirrhosis

In considering the question of diagnostic performance it must be stressed that cirrhosis is a progressive process. There is an early ('latent') phase, lacking clinical and biochemical manifestations, followed by clinically apparent cirrhosis that is either compensated or decompensated. In the early phases the diagnosis is essentially a morphologic one, where dynamic changes attributable to altered blood flow and metabolism are not in evidence, defined in essence by histologic findings. These patients are typically classified as having Child Class A cirrhosis with normal liver function tests and no signs or symptoms of portal hypertension. In this phase, treatable and reversible causes of cirrhosis can be sought out and the patient can be appropriately managed to prevent or delay progression of liver disease. The challenge is to diagnose cirrhosis by non-invasive means while the disease is in this phase, and many studies cited below do not clearly delineate or distinguish among the phases of cirrhosis [5, 20-23].

Liver fibrosis is conveyed in semi-quantitative manner, most often according to the Metavir system, ranging from stage 0 (no fibrosis) to 4 (cirrhosis) [24]. The Brunt system was designed for grading and staging in NAFLD, and while the criteria differ somewhat with those of Meta vir, there are 5 stages with stage 4 indicating cirrhosis [25]. In studies concerning diagnostic tests for cirrhosis, some express test performance in relation to 'advanced fibrosis', generally taken to mean stages ≥ 2; however, for our purposes we were concerned with test performance in specific relation to stage 4 only. Lastly, the NAFLD Clinical Research Network developed a score that combines inflammatory activity (grade) and extent of fibrosis (stage) into a single NAFLD activity score (NAS) [26].

Furthermore, cirrhosis is the end stage of multiple liver diseases. Some of these are regularly associated with micronodular cirrhosis, others with macronodular cirrhosis. Fibrosis is initiated paracentrally in some, periportally in others, advancing uniformly in some, haphazardly in others. In a few conditions the background hepatic parenchyma is altered by significant steatosis, siderosis, histiocytosis, or inflammation, while in others the background liver is relatively inert [20,21]. Within this spectrum therefore it can be a blurry line that separates the texture or biochemical profile of cirrhotic and non-cirrhotic liver. This factor, the underlying disease state, affects performance characteristics. Investigators of serum-based non-invasive tests have been careful to study individual disease groups overall, while most studies that considered imaging-based tests appeared to span multiple etiologic groups.

Numerical representations of performance characteristics

Diagnostic laboratory test performance is most often expressed in terms of clinical sensitivity, specificity, positive predictive value (PPV), or negative predictive value (NPV). In order to determine sensitivity, specificity, PPV, and NPV one must select a cut-off value, and these characteristics apply to the test only at that cut-off. Receiver-operator characteristics (ROC) curves are another, and in many ways more informative, way to look at test performance. The ROC curve is a plot of sensitivity versus 1-specificity that represents all of the sensitivities and specificities over a continuous range of potential cut-offs.

One can quickly 'eyeball' the ROC curves of two separate tests and compare them qualitatively; the curve that most closely approximates the upper left-hand corner of the plot is the better test. This observation can be conveyed quantitatively by determining the area under the ROC curve (AUROC). The AUC can range from 0.5 (a test no better than the flip of a coin) to 1.0 (a perfect test) [27]. Tests with AUROC of 0.5 to 0.7 are considered poor, 0.7 to 0.8 fair, 0.8 to 0.9 good, and >0.9 excellent.For perspective, the serum prostate specific antigen (PSA) has AUROC of 0.84 for detecting organ-confined prostatic adenocarcinoma [28].

Non-invasive serum-based tests

Serum markers have been combined into a variety of scoring systems to estimate liver fibrosis.These include the Fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), body mass index AST/ALT ratio diabetes (BARD) score, AST to platelet ratio index (APRI), and the AST/ALT ratio (AAR). Several studies have undertaken to assess their value in identifying hepatic cirrhosis, but the results are mixed [29-34]. Among the most widely validated serum-based tests are the FIB-4 index, NFS, Fibrotest, and APRI; these indices show areas under ROC curve ranging from 0.81 to 0.89, the performance of a 'good' but not 'excellent' test, for cirrhosis [35].

TheFIB-4 index, which combines age, ALT, AST, and platelet count, has been studied in a variety of chronic liver diseases, including initial validation in HIV/HCV coinfection and later studies in HBV and NAFLD. According to ROC curve analysis the FIB-4 index may be the best performing of the serum-based tests, outperforming the APRI (see below) in chronic hepatitis C, but at a cut-off of 1.30 its specificity for cirrhosis in only 68.5% with sensitivity of 84.4% [35]. Perhaps its most impressive feature is anegative predictive value of 94.7% for exclusion of

advanced fibrosis in chronic hepatitis C at a cut-off of 1.45. The positive predictive value at the high cut-off, 3.25, is only 82%, however, and there has been unimpressive performance in the post-transplant setting. In a meta-analysis of studies conducted in NAFLD, the AUROC was about 0.84 and, at cut-off of 1.30, the sensitivity 84% and specificity 68.5% [36-40].

The NFS is derived from six variables: age, BMI, diabetes/impaired glucose tolerance, platelet count, albumin concentration, and AST/ALT ratio. The NFS has two threshold values, one at -1.455 and another at +0.676. Patients falling below -1.455 have low probability of advanced liver fibrosis, those above +0.676 have high probability, and those falling in between are considered indeterminate. At the +0.676 cutoff, the reported specificity for advanced fibrosis in NAFLD is 97%, with sensitivity of 67%, and at the -1.455 cutoff, the sensitivity for advanced fibrosis is 90%Moreover, studies in patients with NAFLD find that between 20% and 58% of patients fall between these two values ('indeterminate'). Thus, 10% of patients with cirrhosis would be classified as 'low risk', 33% of patients with cirrhosis would fail to be classified as 'high risk', and over half of patients subjected to the test would be classified as 'indeterminate' [41-43].

Among the most widely studied indices is the AST-to-platelet ratio index (APRI). It performed well in assessing cirrhosis in hepatitis C during initial studies, but in some later studies less so. This index fared somewhat worse in HIV/HCV co-infected patients and in post-transplant settings, particularly in early cirrhosis, with AUROC as low as 0.63. A recent meta-analysis concluded that with overall AUROC of 0.83 forcirrhosis the performance of the APRI was an unacceptable as a replacement for liver biopsy [44-51].

The FibroTest™/ FibroSure (separately branded in Europe and the United States) takes into account age, gender, haptoglobin, α-2-macroglobulin, apolipoproteinA1, GGT, and bilirubin. In chronic hepatitis C the AUROC for cirrhosis is 0.87 to 0.9, but it is significantly lower in HCV/HIV coinfection and lower still in the post-transplant setting. Its overall sensitivity for cirrhosis is 85% and specificity 72%. A meta-analysis in hepatitis B determined an overall AUROC of 0.87 with, at cut-off of 0.74 a sensitivity of 61% and specificity of 91% [38,46,52-55].

Non-invasive imaging-based tests

We consider the imaging-based tests to exist in two main categories: methods designed for the assessment of liver fibrosis and which have been specifically validated for this purpose, and methods used for body imaging/morphologic assessment in which the impression of 'cirrhosis' is often incidentally mentioned. We find that in our clinical experience the clinical diagnosis of cirrhosis is often based upon the latter, the most commonly used methods being ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI).

With conventional US there are a variety of findings that may indicate cirrhosis, including the sharpness and contour of the liver edge, liver size, parenchymal heterogeneity or coarseness, portal vein velocity, and spleen size. With Doppler US further assessments can be made, including portal vein velocity, congestion index, effective portal liver perfusion, and, with pulsedwave Doppler, waveforms from the hilar vessels. These are changes that precede the development of clinically significant portal hypertension, and while the sensitivity and specificity of conventional grey-scale US for cirrhosis is poor, those of Doppler US are better, with sensitivity 75.9% and specificity 81.8%. Diagnostic performance is adversely affected, however, by both steatosis and inflammation, both of which are extremely common in the population of interest. [8,51,56-67]

Newer US-based modalities have been evaluated for the assessment of liver fibrosis. Contrast-enhanced ultrasound (CEUS) involves observing the behavior of gas-filled bubbles, which have been administered intravenously, as they transit through the hepatic circulation. Several variables have been studied on this basis, including the hepatic vein transit time (HVTT) between hepatic artery/portal vein and hepatic veins which is shortened in cirrhosis. The HVTT has initially shown impressive correlation with progression of fibrosis to cirrhosis but has not yet been extensively studied or become widely available. An important limitation is the confounding factor of liver malignancies that could cause intrahepatic shunting, thus also decreasing HVTT [68-71].

Transient elastography (TE) is an ultrasound-based technique, the most prevalent proprietary product of which is Fibroscan® (Echosens, Paris, France). The basic principle is that liver stiffness can be measured and serve as a correlate for hepatic fibrosis. Mechanical vibration is used to convey a sheer-stress upon the tissue, resulting in the propagation of a low-frequency wave to a depth of 4 cm [72]. The speed at which the wave travels through the tissue is measured ultrasonographically and expressed in centimeters per second or in kilopascals (kPa). The technique has limitations, including a high failure rate of 15% to 20%, due primarily to obesity or ascites and the inability to concurrently visualize and thereby target tissue. When it can be performed successfully its overall diagnostic performance is good, with large validation studies in hepatitis B, hepatitis C, transplant, NAFLD, and autoimmune hepatitis producing sensitivity between 72% and 82%and specificity of 84% to 92% [72-90]. Diagnostic performance is limited by a tendency to misjudge fibrosis in the presence of inflammatory activity, steatosis, and extrahepatic cholestasis. [73-85]. In HCV patients, AUROC ranging from of 0.85 to 0.92 has been reported and in post-transplant patients AUROC as high as 0.99, but it fared relatively poorly in HIV/HCV co-infected patients [76-85]. A few large studies have validated its use in and NAFLD [86,87]; however, its failure in the face of obesity, a common condition associated with NAFLD, is a limiting factor.Newer modalities include Acoustic Radiation Force Impulse(ARFI) imaging and Dynamic Shear Wave Elastography (SWE). Acoustic radiation force impulse imaging (ARFI) utilizes acoustic compression pulses focused to the liver, and relies on the absorbed acoustic energy being released as shear waves. The results are similar to TE with AUROCs of 0.93 for cirrhosis, and with three times more reliable measurements than TE. 2D Shear Wave Elastography (Supersonic Imagine, Aix-en-Provence, France) utilizes focused acoustic energy to generate shear waves capturing the waves in real time. Its advantage compared to TE and ARFI is its capacity to visualize the liver, localize the site of liver stiffness measurement to facilitate future monitoring, and sample multiple areas of interest to reduce sampling variability. Initial results show promising AUROCs of 91% for cirrhosis, with

the added advantage of its use in patients with obesity, NAFLD and ascites [91-93].

Advanced cirrhosis is usually apparent on CT and MRI, particularly when findings attributable to portal hypertension are present, but early cirrhosis is more challenging. A modified caudate-to-right-lobe ratio isone of the indices that has been proposed for this purpose, and in a study of mixed-etiology chronic liver disease had sensitivity of 72% and specificity of 74%. Additional morphologic features of overt cirrhosis include liver surface nodularity (sensitivity 91.8%, specificity 84.3%), right hepatic posterior notch (sensitivity 72%, specificity 98%), expanded gallbladder fossa (sensitivity 68%, specificity 98%), narrow right hepatic vein < 5 mm (sensitivity 59%, specificity 99%), and enlargement of the hilar periportal space > 10 mm (sensitivity 93%, specificity 92%) [94-96].

Magnetic resonance elastography (MRE) is currently considered the most accurate noninvasive imaging technique for detecting and staging liver fibrosis. Its advantages compared to TE include its ability to create regional distribution maps of hepatic fibrosis, and its reproducibility and excellent inter-observer agreement due to its ability to sample a large volume of liver. A recent meta-analysis that considered 5 fairly heterogenous clinical trials reported overall sensitivity of 99%, specificity of 94%, and AUROC of 0.99. Further study is required in specific patient groups to see if this kind of performance is sustained, and at the moment the technique is expensive and not widely available. It does have some limitations in patients with moderate-to-severe hepatic iron deposition, massive ascites, and high body mass index contributing to a 3.5% technical failure rate in a recent study. Further study is required in specific patient groups to see if this kind of performance is sustained, and at the moment the technique is expensive and not widely available [97,89].

Non-invasive diagnostic strategies and dual concordant testing

The challenge is to identify patients in the early, latent, or compensated phase of cirrhosis, who are estimated to represent 0.27% of the adult population in the United States and of whom up to 69% are undiagnosed [4]. Patients in the compensated stage have a median survival of 12 years; whereas in decompensation the median survival is only 2 years [99-103]. From this there derives a powerful impetus to identify and address cirrhosis early, when there is an opportunity to intervene.

Strategies that have been proposed for early detection tend to unfold in three stages: identification of high-risk patients, assessment of non-invasive parameters in them, and liver biopsy in a select few [104-106]. In the proper context, if the performance characteristics of a non-invasive test is known, this kind of approach is reasonable and evidence-based, a variety of individual non-invasive tests have demonstrated performance capable of obviating liver biopsy in only a minority of patients [107-109].

Multiple authors have proposed, and some studies have examined, the combined predictive power of two unrelated (one imaging-based and one serum-based) non-invasive tests done in parallel. [12,35,52,108,110-112]. In patients with chronic hepatitis C, FibroScan and FibroTest, when results were combined performed better than either test alone in avoiding liver biopsy, and this combination was capable of rendering it needless in a majority of patients tested. The AUROC for cirrhosis using the combined test was 0.95. In 94% of cases where the tests were concordant there was agreement with biopsy findings, while this was the case in only 80% to 90% with either test alone. However, the tests were concordant in only 70% of patients [113]. Multiple combination strategies were evaluated in a cohort with NAFLD, finding the best-performing one to be transient elastography plus NFS; their sensitivity was 93% and specificity 100% (only 2 patients concordantly positive), but over 40% of patients were indeterminate. This combination was therefore capable of reducing the number of liver biopsies by about 50–60% [114].

This approach, pending further investigation in specific high-risk groups, may help to realize the maximum potential of non-invasive tests. Such a high degree of negative and positive predictive value, if reproduced in additional studies, would render a single clinic visit sufficient for confident diagnosis or exclusion of cirrhosis, leaving an unfortunately large ‘indeterminate’ group to be evaluated by other means.

CONCLUSIONS

Liver biopsy remains the gold standard for the diagnosis of cirrhosis but has several important limitations: invasiveness, cost, risk, sampling error, and inter- observer variability in interpretation. Non-invasive tests are therefore desirable, and many now exist. A few of them have been studied in a manner sufficient to establish their performance characteristics in a number of specific etiologic settings. Based upon the published findings, it seems that the best among them can only provide a limited level of diagnostic certaintythe adequacy of which may best be judged on a case-by-case basis. That is, considering the pre-test probability, the test’s performance characteristics, and the degree of certainty required in a given clinical situation, one may choose to accept or confirm the result. We may find with further study that dual concordant testing is sufficient for our needs presuming that these tests correlate clinically with the patient’s presentation. In the meantime it is necessary to interpret these tests cautiously and to qualify statements made in the medical record in reference to them.

REFERENCES

1. Gonzalez HC, Jafri SM, Gordon SC. Role of liver biopsy in the era of direct-acting antivirals. Curr Gastroenterol Rep. 2013; 15: 307.
2. Berzigotti A. Advances and challenges in cirrhosis and portal hypertension. BMC Med. 2017; 15: 200.
3. Berzigotti A, Seijo S, Reverter E, Bosch J. Assessing portal hypertension in liver diseases. Expert Rev Gastroenterol Hepatol. 2013; 7: 141-155.
4. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A , et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. J Clin Gastroenterol. 2015; 49: 690-696.
5. Harman DJ, Ryder SD, James MW, Jelpke M, Ottey DS, Wilkes EA, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: A cross-sectional diagnostic study utilising transient elastography. BMJ Open. 2015; 5: e007516.

6. Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. Alcohol Res Health. 2003; 27: 209-219.

7. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. Liver Int. 2012; 32: 79-84.

8. Gaiani S, Gramantieri L, Venturoli N, Piscaglia F, Siringo S, D'Errico A, et al. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. J Hepatol. 1997; 27: 979-985.

9. Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, et al. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. A multicenter collaborative study. Intervirology. 2008; 51: 17-26.

10. Huber A, Ebner L, Heverhagen JT, Christe A. State-of-the-art imaging of liver fibrosis and cirrhosis: A comprehensive review of current applications and future perspectives. Eur J Radiol Open. 2015; 2: 90-100.

11. Bonder A, Tapper EB, Afdhal NH. Contemporary assessment of hepatic fibrosis. Clin Liver Dis. 2015; 19: 123-134.

12. Tapper EB, Afdhal NH. Vibration-controlled transient elastography: a practical approach to the noninvasive assessment of liver fibrosis. Curr Opin Gastroenterol. 2015; 31:192-198.

13. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterol. 2012; 142: 1293-1302

14. Tapper EB, Sengupta N, Hunink MG, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic fatty liver disease with NAFLD fibrosis score and vibration controlled transient elastography. Am J Gastroenterol. 2015; 110: 1298-1304.

15. Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, et al. Noncirrhotic portal fibrosis (idiopathic portal hypertension): Experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002; 17: 6-16.

16. Sarin SK, Kumar A, Chawla YK, Baijal SS, Dhiman RK, Jafri W, et al. Noncirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendations for diagnosis and treatment. Hepatol Int. 2007; 1: 398-413.

17. Schouten JNL, Garcia-Pagan JC, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatology. 2011; 54: 1071-1081.

18. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - Diagnosis and management. Journal of Hepatology. 2014; 60: 421-441.

19. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008; 371: 838-851.

20. D'Amico G,Garcia-TsaoG, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006; 44: 217-231.

21. Asrani SK, Kamath PS. Natural history of cirrhosis. Curr Gastroenterol Rep. 2013; 15: 308.

22. Ginés P, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, et al. Compensated cirrhosis: Natural history and prognostic factors. Hepatology. 1987; 7: 122-128.

23. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology. 2010; 51: 1445-1449.

24. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996; 24: 289-293.

25. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol. 2010; 16: 5286-5296.

26. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41: 1313-1321.

27. Poynard T, Halfon P, Castera L, Munteanu M, Imbert-Bismut F, Ratziu V, et al. Standardization of ROC Curve Areas for Diagnostic Evaluation of Liver Fibrosis Markers Based on Prevalences of Fibrosis Stages. Clinical Chemistry. 2007; 53: 1615-1622.

28. Hoffman, RM, Gilliland FD, Adams-Cameron M, Hunt WC, Key CR. Prostate-specific antigen testing accuracy in community practice. BMC Fam Pract. 2002; 3: 1-8.

29. Fierbinteanu BC, Sporea I, Panaitescu E, Tribus L. Value of acoustic radiation force impulse imaging elastography for non-invasive evaluation of patients with nonalcoholic fatty liver disease. Ultrasound Med Biol. 2013; 39: 1942-1950.

30. Kruger FC, Daniels CR, Kidd M, Swart G, Brundyn K, van Rensburg C , et al. APRI: a simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J. 2011; 101: 477-4780.

31. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009; 7: 1104-1112.

32. Jin W, Lin Z, Xin Y, Jiang X, Dong Q, Xuan S. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis B-related fibrosis: a leading meta-analysis. BMC Gastroenterol. 2012; 12: 14.

33. Francque SM, Verrijken A, Mertens I, Hubens G, Van Marck E, Pelckmans P, et al. Noninvasive assessment of nonalcoholic fatty liver disease in obese or overweight patients. Clin Gastroenterol Hepatol. 2012; 10: 1162-1168.

34. Sun W, Cui H, Li N, Wei Y, Lai S, Yang Y, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD Score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. Hepatol Res. 2016; 46: 862-870.

35. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. World J Gastroenterol. 2014; 20: 4300-4315.

36. Sun W, Cui H, Li N, Wei Y, Lai S, Yang Y, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD Score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. Hepatol Res. 2016; 46: 862-870.

37. Shah AG, Smith PG, Sterling RK. Comparison of FIB-4 and APRI in HIV-HCV coinfected patients with normal and elevated ALT. Dig Dis Sci. 2011; 56: 3038-3044.

38. Beckebaum S, Iacob S, Klein CG, Dechêne A, Varghese J, Baba HA, et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation. 2010; 89: 983-993.

39. Kamphues C, Lotz K, Röcken C, Berg T, Eurich D, Pratschke J, et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant. 2010; 24: 652-659.

40. Lu M, Lamerato L, Rupp LB. Optimal noninvasive markers for fibrosis stage in chronic hepatitis C. Hepatology. 2012; 56.

41. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic

accuracy of non-invasive tests for liver disease severity. Ann Med. 2011; 43: 617-649.

42. Wieckowska A, Zein NN, Yerian LM, Lopez AR, McCullough AJ, Feldstein AE. *In vivo* assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease. Hepatology. 2006; 44: 27-33.

43. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007; 45: 846-854.

44. Kamphues C, Lotz K, Röcken C, Berg T, Eurich D, Pratschke J , et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant. 2010; 24: 652-659.

45. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C related fibrosis: An updated meta-analysis. Hepatology. 2011; 53: 726-736.

46. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet. 2001; 357: 1069-1075.

47. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38: 518-526.

48. Parkes J, Guha IN, Roderick P, Rosenberg W. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. J Hepatol. 2006; 44: 462-474.

49. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. World J Gastroenterol. 2014; 20: 4300-4315.

50. Leroy V, Hilleret MN, Sturm N, Trocme C, Renversez JC, Faure P, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. J Hepatol. 2007; 46: 775-82.

51. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. World J Gastroenterol. 2014; 20: 4300-4315.

52. Salkic NN, Jovanovic P, Hauser G, Brcic M. FibroTest/Fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: a meta-analysis. Am J Gastroenterol. 2014; 109: 796-809.

53. Calès P, Halfon P, Batisse D, Carrat F, Perré P, Penaranda G, et al. Comparison of liver fibrosis blood tests developed for HCV with new specific tests in HIV/HCV co-infection. J Hepatol. 2010; 53: 238-44.

54. Rossi E, Adams L, Prins A, Bulsara M, de Boer B, Garas G, et al. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. ClinChem. 2003; 49: 450-454.

55. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol. 2007; 102: 2589-2600.

56. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: Accuracy of US for Detection - analysis of 300 cases. Radiology. 2003; 227: 89-94.

57. Aubé C, Oberti F, Korali N, Namour MA, Loisel D, Tanguy JY, et al. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. J Hepatol. 1999; 30: 472-478.

58. Lei Shen, Ji-Qiang Li, Min-De Zeng, Lun-Gen Lu, Si-Tao Fan, and Han Bao. Correlation between ultrasonographic and pathologic diagnosis of liver fibrosis due to chronic virus hepatitis. World J Gastroenterol. 2006; 12: 1292-1295.

59. Khan KN, Yamasaki M, Yamasaki K, Inoue O, Yatsuhashi H, Koga M, et al. Proposed abdominal sonographic staging to predict severity of liver diseases: analysis with peritoneoscopy and histology. Dig Dis Sci. 2000; 45: 554-564.

60. Nicolau C, Bianchi L, Vilana R. Gray-scale ultrasound in hepatic cirrhosis and chronic hepatitis: diagnosis, screening, and intervention. Semin Ultrasound CT MR. 2002; 23: 3-18.

61. Chen CH, Lin ST, Yang CC, Yeh YH, Kuo CL, Nien CK. The accuracy of sonography in predicting steatosis and fibrosis in chronic hepatitis C. Dig Dis Sci. 2008; 53: 1699-1706.

62. Kutcher R, Smith GS, Sen F, Gelman SF, Mitsudo S, Thung SN, et al. Comparison of sonograms and liver histologic findings in patients with chronic hepatitis C virus infection. J Ultrasound Med. 1998; 17: 321-325.

63. Arda K, Ofelli M, Calikoglu U, Olçer T, Cumhur T. Hepatic vein Doppler waveform changes in early stage (Child-Pugh A) chronic parenchymal liver disease. J Clin Ultrasound. 1997; 25: 15-19.

64. Kim MY, Baik SK, Park DH, Lim DW, Kim JW, Kim HS, et al. Damping index of Doppler hepatic vein waveform to assess the severity of portal hypertension and response to propranolol in liver cirrhosis: a prospective nonrandomized study. Liver Int. 2007; 27: 1103-1110.

65. Bernatik T, Strobel D, Hahn EG, Becker D. Doppler measurements: a surrogate marker of liver fibrosis? Eur J Gastroenterol Hepatol. 2002; 14: 383-387.

66. Lim AK, Patel N, Eckersley RJ, Kuo YT, Goldin RD, Thomas HC, et al. Can Doppler sonography grade the severity of hepatitis C-related liver disease? AJR Am J Roentgenol. 2005; 184: 1848-1853.

67. Colli A, Cocciolo M, Mumoli N, Cattalini N, Fraquelli M, Conte D. Hepatic artery resistance in alcoholic liver disease. Hepatology. 1998; 28: 1182-1186.

68. Albrecht T, Blomley MJ, Cosgrove DO, Taylor-Robinson SD, Jayaram V, Eckersley R, et al. Non-invasive diagnosis of hepatic cirrhosis by transit-time analysis of an ultrasound contrast agent. Lancet. 1999; 353: 1579-1583.

69. Blomley MJ, Lim AK, Harvey CJ, Patel N, Eckersley RJ, Basilico R, et al. Liver microbubble transit time compared with histology and Child-Pugh score in diffuse liver disease: a cross sectional study. Gut. 2003; 52: 1188-1193.

70. Lim AK, Taylor-Robinson SD, Patel N, Eckersley RJ, Goldin RD, Hamilton G, et al. Hepatic vein transit times using a microbubble agent can predict disease severity non-invasively in patients with hepatitis C. Gut. 2005; 54: 128-133.

71. Kim MY, Suk KT, Baik SK, Kim HA, Kim YJ, Cha SH, et al. Hepatic vein arrival time as assessed by contrast enhanced ultrasonography is useful for the assessment of portal hypertension in compensated cirrhosis. Hepatology. 2012; 56: 1053-1062.

72. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: A multicenter prospective study (the FIBROSTIC study). J Hepatol. 2010; 53: 1013-1021.

73. Foucher J, Castéra L, Bernard PH, Adhoute X, Laharie D, Bertet J, et al. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan in a prospective study of 2114 examinations. Eur J Gastroenterol Hepatol. 2006; 18: 411-412.

74. Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Büchler MW, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology. 2008; 48: 1718-1723.

75. Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, et al.

A meta-analysis of transient elastography for the detection of hepatic fibrosis. J Clin Gastroenterol. 2010; 44: 214-219.

76. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut. 2006; 55: 403-408.

77. Nakamura Y, Aikata H, Fukuhara T, Honda F, Morio K, Morio R, et al. Liver fibrosis assessment by FibroScan compared with pathologic findings of liver resection specimen in hepatitis C infection. Hepatol Res. 2017; 47: 767-772.

78. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a metaanalysis. Gastroenterology. 2008; 134: 960-974.

79. Adebajo CO, Talwalkar JA, Poterucha JJ, Kim WR, Charlton MR. Ultrasound-based transient elastography for the detection of hepatic fibrosis in patients with recurrent hepatitis C virus after liver transplantation: a systematic review and meta-analysis. Liver Transpl. 2012; 18: 323-331.

80. Kirk GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D , et al. Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Clin Infect Dis. 2009; 48: 963-972.

81. Fraquelli M, Rigamonti C, Casazza G, Donato MF, Ronchi G, Conte D, et al. Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C. J Hepatol. 2011; 54: 621-628.

82. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005; 41: 48-54.

83. Arena U, Vizzutti F, Abraldes JG, Corti G, Stasi C, Moscarella S, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut. 2008; 57: 1288-1293.

84. Sirli R, Sporea I, Bota S, Popescu A, Cornianu M. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. Hepat Mon. 2010; 10: 88-94.

85. Kim SU, Jang HW, Cheong JY, Kim JK, Lee MH, Kim DJ, et al. The usefulness of liver stiffness measurement using FibroScan in chronic hepatitis C in South Korea: a multicenter, prospective study. J Gastroenterol Hepatol. 2011; 26: 171-178.

86. Yoneda M, Yoneda M, Mawatari H, Fujita K, Endo H, Iida H, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis. 2008; 40: 371-378.

87. Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int. 2013; 33: 1138-1147.

88. Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Lédinghen V, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int. 2009; 29: 242-247.

89. Kim DY, Kim SU, Ahn SH, Park JY, Lee JM, Park YN , et al. Usefulness of FibroScan for detection of early compensated liver cirrhosis in chronic hepatitis B. Dig Dis Sci. 2009; 54: 1758-1763.

90. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat. 2009; 16: 36-44.

91. Sigrist RMS, Liau J, Kaffas AE, Chammas MC2, Willmann JK1. Ultrasound Elastography: Review of Techniques and Clinical Applications. Theranostics. 2017; 7: 1303-1329.

92. Frulio N, Trillaud H, Perez P, Asselineau J, Vandenhende M, Hessamfar M, et al. Acoustic Radiation Force Impulse (ARFI) and Transient Elastography (TE) for evaluation of liver fibrosis in HIV-HCV co-infected patients. BMC Infect Dis. 2014; 14: 405.

93. Friedrich-Rust M, Nierhoff J, Lupsor M, Sporea I, Fierbinteanu-Braticevici C, Strobel D, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat. 2012; 19: 212-219.

94. Yu JS, Shim JH, Chung JJ, Kim JH, Kim KW. Double contrast-enhanced MRI of viral hepatitis-induced cirrhosis: correlation of gross morphological signs with hepatic fibrosis. Br J Radiol. 2010; 83: 212-217.

95. Aguirre DA, Behling CA, Alpert E, Hassanein TI, Sirlin CB. Liver fibrosis: noninvasive diagnosis with double contrast material-enhanced MR imaging. Radiology. 2006; 239: 425-437.

96. Awaya H, Mitchell DG, Kamishima T, Holland G, Ito K, Matsumoto T. Cirrhosis: modified caudate-right lobe ratio. Radiology. 2002; 224: 769-774.

97. Wang QB, Zhu H, Liu HL, Zhang B. Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: A meta-analysis. Hepatology. 2012; 56: 239-247.

98. Wagner M, Corcuera-Solano I, Lo G, Esses S, Liao J, Besa C, et al. Technical failure of MR elastography examinations of the liver: experience from a large single-center study. Radiology 2017; 284: 401-412.

99. Walker M, El-Serag HB, Sada Y, Mittal S, Ying J, Duan Z, et al. Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. Aliment Pharmacol Ther. 2016; 43: 621-630.

100. Muir AJ1. Understanding the Complexities of Cirrhosis. Clin Ther. 2015; 37: 1822-1836.

101. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006; 44: 217-231.

102. Asrani SK, Kamath PS. Natural history of cirrhosis. Curr Gastroenterol Rep. 2013; 15: 308.

103. Ginés P, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, et al. Compensated cirrhosis: Natural history and prognostic factors. Hepatology 1987; 7: 122-128.

104. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, et al. Evidence-based clinical practice guidelines for liver cirrhosis. J Gastroenterol. 2016; 51: 629-650.

105. Flamm SL. Diagnosis of Cirrhosis and Evaluation of Hepatic Encephalopathy: Common Errors and Their Significance for the PCP. J Fam Prac. 2017; 534-539.

106. Lim JK, Flamm SL, Singh S, Flack-Ytter YT. American Gastroenterological Association Institute Guideline on the Role of Elastography in the Evaluation of Liver Fibrosis. Gastroenterology. 2017; 152: 1536-1543.

107. Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology. 2005; 41: 1376-82.

108. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration controlled transient elastography): Where does it stand in the US practice. Clin Gastroenterol Hepatol. 2015; 13: 27-36.

109. Bonder A, Tapper EB, Afdhal NH2. Contemporary assessment of hepatic fibrosis. Clin Liver Dis. 2015; 19: 123-134.

110. Crespo G, Fernández-Varo G, Mariño Z, Casals G, Miquel R, Martínez SM, et al. ARFI, FibroScan, ELF, and their combinations in the assessment of liver fibrosis: a prospective study. J Hepatol. 2012; 57: 281-287.

111. Poynard T, Vergniol J, Ngo Y, Foucher J, Munteanu M, Merrouche W, et al: Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest™) and transient elastography (FibroScan®). J Hepatol. 2014; 60: 706-714.

112. Poynard T, Vergniol J, Ngo Y, Foucher J, Thibault V, Munteanu M, et al: Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest) and elastography (FibroScan). J Hepatol. 2014; 61: 994-1003.

113. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005; 128: 343-350.

114. Petta S, Vanni E, Bugianesi E, Di Marco V, Cammà C, Cabibi D, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. Liver Int. 2015; 35: 1566-1575.

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