Published in final edited form as:

J Clin Gastroenterol. 2014 April ; 48(4): 370–376. doi:10.1097/MCG.0b013e3182a87e78.

Evaluation of the APRI (AST, platelet ratio index) and ELF™ (Enhanced Liver Fibrosis) tests to detect significant fibrosis due to chronic hepatitis C

John R Petersen, Ph.D.¹, Heather L. Stevenson, M.D., Ph.D.¹, S. Kasturi Krishna, M.D.², Ashutosh Naniwadekar, M.D.³, Julie Parkes, M.D.⁴, Richard Cross, Ph.D.⁵, William M. Rosenberg, M.D.⁶, Shu-Yuan Xiao, M.D.⁷, and Ned Snyder, M.D.⁸

¹Department of Pathology, University of Texas Medical Branch, Galveston, TX

²Hernando Gastroenterology Associates, 12190 Cortez Blvd, Brooksville, FL

³Riverside Health System, 805 Progress Court, Newport News, VA

⁴Public Health and Medical Statistics, University of Southampton, Southampton, United Kingdom

⁵iQur Limited, London, United Kingdom

⁶The Institute for Liver and Digestive Health, Division of Medicine, University College London, London, United Kingdom

⁷Department of Pathology, University of Chicago, Chicago, IL

⁸Internal Medicine, Division of Gastroenterology, Kelsey-Seybold Clinic, Houston, TX

Abstract

Background—The assessment of liver fibrosis in chronic hepatitis C patients is important for prognosis and making decisions regarding antiviral treatment. Although liver biopsy is considered the reference standard for assessing hepatic fibrosis in patients with chronic hepatitis C, it is invasive and associated with sampling and inter-observer variability. Serum fibrosis markers have been utilized as surrogates for a liver biopsy

Methods—We completed a prospective study of 191 patients in which blood draws and liver biopsies were performed on the same visit. Using liver biopsies the sensitivity, specificity, and negative and positive predictive values for both APRI and ELF™ were determined. The patients were divided into training and validation patient sets to develop and validate a clinically useful algorithm for differentiating mild and significant fibrosis.

Results—The AUROC for the APRI and ELF™ tests for the training set was 0.865 and 0.880, respectively. The clinical sensitivity in separating mild (F0–F1) from significant fibrosis (F2–F4) was 80% and 86.0% with a clinical specificity of 86.7% and 77.8%, respectively. For the validation sets the AUROC for the APRI and ELF™ tests was, 0.855 and 0.780, respectively. The clinical sensitivity of the APRI and ELF™ tests in separating mild (F0–F1) from significant (F2–F4) fibrosis for the validation set was 90.0% and 70.0% with a clinical specificity of 73.3% and

Address for Correspondence: John R Petersen, Ph.D., Department of Pathology, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0551, jrpeters@utmb.edu, ph: 409-772-1350, Fax: 409-772-9231.

W.M.R. has financial relationships with the following companies: Siemens, Roche Pharma, Gilead, MSD, iQur Limited.

The content of this paper includes discussions of a product (ELF) developed through an academic collaboration between Bayer Healthcare and the European Liver Fibrosis Group and licensed to Siemens in which there was a financial interest (W.M.R.) or a paid employee (R.C.).

The authors of this manuscript did not receive any funding for undertaking this study.

86.7%, respectively. There were no differences between the APRI and ELF™ tests in distinguishing mild from significant fibrosis for either the training or validation sets ($p=0.61$ and 0.20 , respectively). Using the APRI as the primary test followed by ELF™ for patients in the intermediate zone, would have decreased the number of liver biopsies needed by 40% for the validation set. Overall, use of our algorithm would have decreased the number of patients that needed a liver biopsy from 95 to 24, a 74.7% reduction.

Conclusion—This study has shown that the APRI and ELF™ tests are equally accurate in distinguishing mild from significant liver fibrosis and combining them into a validated algorithm improves their performance in distinguishing mild from significant fibrosis.

Keywords

APRI; ELF™; liver fibrosis; hepatitis C virus

Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of liver injury resulting in hepatic fibrosis that can potentially lead to cirrhosis, hepatocellular carcinoma and end stage liver disease. According to recent estimates, the global burden of HCV infection is substantial, with about 130 – 170 million people affected worldwide.¹ Accurate assessment of hepatic fibrosis is of utmost importance for clinical decision making related to prognosis and antiviral therapy in chronic hepatitis C patients.² Liver biopsy has traditionally been the gold standard test for estimating and staging liver fibrosis. However, the inherent limitations of this invasive procedure, sampling bias, and inter-observer variability have highlighted the need to develop non-invasive methods for assessing hepatic fibrosis.^{3, 4} Because of these issues, the development of an accurate non-invasive method to evaluate liver fibrosis has been of great interest to gastroenterologists and was stated as a high priority in the final statement from the 2002 Consensus Conference on Hepatitis C (NIH 2002).⁵ In addition, an accurate index for hepatic fibrosis could potentially decrease the number of pretreatment staging liver biopsies for chronic hepatitis C and also potentially provide a method to more accurately follow untreated and unresponsive patients.

Over the past few years research on hepatic fibrosis markers has focused upon serologic tests which serve as either direct or indirect surrogates for hepatic extracellular matrix metabolism or its synthetic function.⁴ We and others have studied the AST/platelet ratio index (APRI) and have shown it to be an accurate and simple index to estimate fibrosis in patients with chronic HCV.^{6–9} The utility of the APRI is that it is calculated by using routine laboratory values [$APRI = (AST/\text{upper limit of normal}) \times 100/\text{platelet count}$]. In previous studies testing the performance of the APRI, we have found it to perform as well as several other available hepatic fibrosis marker panels including FIBROSpect II.⁷ Recently we had the opportunity to evaluate and compare the APRI with the Enhanced Liver Fibrosis or ELF™ test [hyaluronic acid, tissue inhibitor of metalloproteinase 1 (TIMP-1), and procollagen III amino terminal peptide (PIIINP)]; Siemens Healthcare Diagnostics Inc., Deerfield, IL] a hepatic fibrosis panel that has been extensively studied as a marker of liver fibrosis in patients chronically infected with HCV and other diseases causing liver fibrosis.^{10, 11} It was originally developed to separate mild/moderate fibrosis (F0–F2) from advanced fibrosis (F3–F4).

In the current study, we examined the accuracy of the APRI and ELF™ methods in estimating liver fibrosis in a prospective study of patients undergoing pretreatment liver biopsies, and specifically examined whether the combination of the two tests would increase the number of patients that could be accurately characterized.

Methods

Patient Samples

We collected serum from 191 HCV RNA positive patients undergoing pretreatment staging percutaneous liver biopsies from March 2003 through March 2007. Patients were excluded if they were consuming significant amounts of alcohol (>15 g/d), had received anti-viral therapy in the last year, were co-infected with HIV or HBV, had an organ transplant, or hepatocellular carcinoma. The history of alcohol intake was obtained by the attending gastroenterologist or hepatologist upon entrance of the patient into the study. Patients with recent anti-viral therapy were not included since interferon decreases platelets, and the effect of therapy itself on components of the extra cellular hepatic matrix was unknown. Informed consent was obtained from all patients in the study, and the patients were part of a prospective study of hepatic fibrosis markers approved by the University of Texas Medical Branch Institutional Review Board (IRB), and the Texas Department of Criminal Justice (TDCJ). Blood was drawn on the day of biopsy and the serum was stored at -80°C .

Clinical and laboratory assessment

The platelets were measured using the Sysmex SE 9500 (Sysmex, Mundelein, IL) and AST was measured using either the Vitros 950 or 5.1 FS (Ortho Clinical diagnostics, Raitan, NJ). The ELFTM test was subsequently performed by iQur Limited (London, UK) without any information other than the patient had chronic HCV. All liver biopsies had a length of at least 1.0 cm (average biopsy length: $2.3 \pm 1.1\text{cm}$). All biopsies were read by a single pathologist who was blinded except for the information that the patient had chronic hepatitis C. Liver biopsies were staged by using a modification⁸ of the Batts-Ludwig criteria¹² as mild (F0–F1) or significant (F2–F4) fibrosis. The fibrosis score is based on a five point scale: stage 0 = no fibrosis; 1 = either mild pericellular fibrosis in the lobules or mild portal fibrosis; 2 = periportal fibrosis or portal fibrosis plus lobular pericellular fibrosis; 3 = septal or bridging fibrosis without evident parenchymal remodeling; 4 = cirrhosis (with architectural remodeling and nodular formation). There were two reasons for separating mild for significant. First, the APRI was developed for this purpose. Second, at the time it was felt that treatment was indicated for those with significant fibrosis⁵. In general, hepatic fibrosis markers have performed better by separating mild from significant fibrosis or mild/moderate from advanced than predicting individual stages. The rationales of including lobular pericellular fibrosis in our staging system are: (1) that this type of fibrosis is frequently observed among patients with chronic HCV infection, and (2) that zone 3 (or centrilobular) hepatic stellate cell activation is common in liver biopsies from patients monoinfected with hepatitis C.¹³

Statistical Analysis

All results are expressed as mean $\pm$ SD unless otherwise indicated. Statistical analysis was performed in conjunction with University College London by investigators using the SPSS v14.0 software (SPSS Inc, Chicago, IL, USA) and MedCalc 12.1.4 (MedCalc Software, Belgium). ROC curves along with area under the ROC curve (AUROC) were constructed using MedCalc. A $p < 0.05$ was considered the criterion for statistical significance. ROC curves were also used to determine the most useful cut-offs for the ELFTM.

Results

Identification of Test and Validation sets of Patients

The patients included in the study were split into two groups; an initial or training patient set to identify the best stepwise algorithm and a validation patient set to assess the predictive

power of the algorithm. To eliminate the potential of long term storage or patient demographic drift over the time period of the study every other patient was included in the training set (i.e. patient number 1, 3, 5...) and validation set (i.e. patient number 2, 4, 6...). The cut-offs used for the APRI were optimized from our previous study for the separation of mild fibrosis and significant fibrosis⁸. The cut-offs for the ELFTM test, established using ROC curves, were those levels having high sensitivity (100% for the low level cut-off) or specificity (95.6% for the high level cut-off).

Patient characteristics

One patient was eliminated due to lack of an ELFTM test result, leaving 190 patients that were included in the study. The baseline patient characteristics for the training (N = 95) and validation (N = 95) patient sets are described in Table 1. No statistical differences were noted for the two patient sets. For the training and validation patient sets the median age at the time of initial biopsies for both patient sets was 45.8 ± 8.5 years with the majority (74.7%) of patients were male; 62.1% were Caucasian, 19.5% were African American, 16.8% were Hispanic and 1.6% were Asian. Over half (53.2%) of the patients had significant fibrosis (F2–F4) and the average biopsy length for all patients was 2.3 ± 1.1 cm.

APRI and ELFTM tests are able to differentiate mild and significant fibrosis

The results of the APRI and the ELFTM tests for the training and validation patient sets are summarized in Tables 2 and 3. Using cut-offs for the APRI of 0.42 and 1.2, as optimized in this and our previous study for the separation of mild fibrosis and significant fibrosis⁸, we determined that the APRI was an excellent predictor in our patient population. A cutoff of 0.42 correctly predicted mild fibrosis in 17 of 28 patients for a negative predictive value (NPV) of 89.5% for the training set and correctly predicted mild fibrosis in 20 of 45 patients for a NPV of 95.0% for the validation set. Likewise, a cutoff of 1.2 correctly predicted 26 of 50 patients as having significant fibrosis for a positive predictive value (PPV) of 89.7% for the training set and correctly predicted significant fibrosis in 32 of 51 patients for a PPV of 89.7% for the validation set. This left an intermediate or gray zone of 39 patients (41.1%) for the training set and an intermediate or gray zone of 40 patients (42.1%) for the validation set. The ROC curves for the APRI for the training and validation sets are shown in Figures 1 and 2. The area under the curve (AUC) for the training and validation set was 0.856 (95% CI 0.769–0.919) and 0.885 (95% CI 0.769–0.919), respectively.

The most useful cutoffs for the ELFTM test as determined by ROC curves were 8.19 (100% sensitivity) and 9.88 (95.6% specificity) for the separation of mild fibrosis and significant fibrosis. These cut-offs correctly predicted mild fibrosis in 19 of the 45 patients for a NPV of 100% for the training set and correctly predicted mild fibrosis in 10 of 44 patients for a NPV of 76.9% for the validation set. Likewise, a cutoff of 9.88 correctly predicted 27 of 51 patients as having significant fibrosis for a PPV of 96.4% for the training set and correctly predicted significant fibrosis in 29 of 51 patients for a PPV of 87.9% for the validation set. This left an intermediate or gray zone of 48 patients (50.5%) for the training set and an intermediate or gray zone of 49 patients (51.6%) for the validation set. The ROC curves for the ELFTM for the training and validation sets are shown in Figures 1 and 2. The area under the curve (AUC) for the training and validation set was 0.880 (95% CI 0.797–0.937) and 0.780 (95% CI 0.684–0.859), respectively. Although the APRI appears slightly better than the ELFTM in distinguishing mild (F0, F1) from significant (F2–F4) fibrosis, statistically they are similar ($p = 0.20$).

Combining the APRI and ELFTM tests increases the diagnostic accuracy

While similar in their ability to detect both mild and significant fibrosis, the two tests measure different aspects of the fibrotic process. To this end, they were combined to

determine if additional patients with either mild or significant fibrosis could be identified. For the training patient set we used an APRI of 0.42 and 1.20 as the primary screen for mild and significant fibrosis followed by screening those patients that fall between the two cutoffs (intermediate or grey zone) by using an ELF™ 8.19, our algorithm was able to correctly identify an additional 11 patients as having mild fibrosis with only no additional false negatives. This increased the number of patients correctly identified as having mild fibrosis from 17 (17.9%) to 28 (29.5%). Of importance, none of the false negatives were identified by biopsy as having stage F4 fibrosis. In addition, by using an ELF™ 10.05 another 7 patients were correctly identified as having significant fibrosis with only 1 additional false positive, 1 with stage F0. This increased the number of patients correctly identified as having significant fibrosis from 26 (27.4%) to 33 (34.7%). This also reduced the number of patients in the intermediate zone from 47 (49.5%) to 28 (29.5%). This is similar to our previous results when we combined the APRI with the FIBROSpect II.⁷ As visualized in Figure 1, APRI and ELF™ values for patients with mild or significant fibrosis have less overlap, and are, therefore, more easily separated from one another. To validate the algorithm (see Figure 3) we used the second set of patients and an APRI of 0.42 and 1.20 as the primary screen for mild and significant fibrosis followed by screening those patients that fall between the two cutoffs (intermediate or grey zone) initially by using an ELF™ 8.19. Our algorithm was thus able to correctly identify an additional 6 patients as having mild fibrosis with only 2 additional false negatives. This increased the number of patients correctly identified as having mild fibrosis from 19 (20.0%) to 25 (26.3%). Again none of the false negatives were identified by biopsy as having stage F4 fibrosis. In addition, by using an ELF™ 9.88 another 5 patients were correctly identified as having significant fibrosis with 3 additional false positives, 1 with stage F0. This increased the number of patients correctly identified as having significant fibrosis from 32 (33.7%) to 37 (38.9%). Although the combination of the APRI and ELF™ tests is able to significantly improve the accuracy of fibrosis staging using non-invasive biochemical markers, 24 (25.3%) of patients still fell into the intermediate zone and would have needed a liver biopsy. However, we did decrease the number of patients that would have needed a liver biopsy from the original number of 95 to only 24, a 74.7% reduction.

Discussion

Non-invasive assessment of liver fibrosis is a focus of continuing interest to find a marker that is cost-effective, easy to perform with standard laboratory tests, accurately reflective of the stage of hepatic fibrosis, and valid over a wide patient population.¹⁴ The APRI is a simple test that can reliably differentiate mild from significant fibrosis in chronic HCV patients.^{6,8,15} While most studies utilizing the APRI have used the original proposed cutoffs of 0.5 and 1.5, we were able to improve the sensitivity and specificity when compared to other studies¹⁶ by decreasing the lower APRI cutoff to 0.42 (sensitivity 97%, specificity 40%) and decreasing the upper APRI cutoff to 1.2 (sensitivity 57%, specificity 92.2%).⁸ We used these cutoffs in this study since we have consistently found them to improve the negative and positive predictive values, and also increase the percentage of patients that can be classified. The original study by Wai et al. did not publish other cutoff values⁶, and we are not aware of other studies that have compared cutoffs. Therefore, we maintain that 0.42 and 1.2 may be the ideal values. As with any hepatic fibrosis marker, the sensitivity and specificity can be affected by changing the cut-off values.^{19,20,21} A review by Stauber and Lackner comparing non-invasive tests for chronic hepatitis C showed that the significant fibrosis AUROC score for the APRI (0.88) is as good, if not better, when compared to other tests.² ELF™ is a non-invasive test that has been developed and validated to detect the presence of advanced fibrosis in patients with chronic liver disease of multiple etiologies including non-alcoholic fatty liver disease and primary biliary cirrhosis.^{11,17} In the original study, it appeared to perform better in alcoholic liver disease and non-alcoholic fatty liver

disease than in chronic HCV.¹¹ In our study it was utilized to separate mild from significant fibrosis rather than mild/moderate from advanced fibrosis. In our validation study, the AUROC for the ELFTM (0.78) was similar to the AUROC for patients with HCV in the original study by Rosenberg *et al.* (0.773).¹¹ We did not detect a difference in performance of the APRI or ELFTM tests between Caucasians, African Americans, or Hispanics within in our study population (data not shown). Similar to the original study, ours was prospective in design, with blood draws performed on the same day as the liver biopsy, and all of our patients were stable and undergoing staging, pretreatment liver biopsies. A recent study using a simplified version of the ELFTM to separate mild/moderate (F0–F2) from advanced fibrosis (F3–F4) showed an AUROC of 0.85 (95% CI 0.81–0.89)¹⁸ similar to the AUROC of 0.88 for our training patient set. One of the limitations of our research study and others is the use of liver biopsy as the Gold Standard, which in itself is not a perfect test because of sampling error.^{22–25} This may explain why few studies have reported hepatic fibrosis markers with AUROC values above 0.90. A recent study on non-invasive fibrosis markers by Sebastiani *et al.* determined that the performance of the APRI and Fibrotest-Fibrosure was higher than other biomarkers, although the ELFTM test was not investigated.²⁶ The APRI test showed the best performance in HCV monoinfected patients with an adjusted AUROC value of 0.77 and 0.83 for stages F2 and F4, respectively. Other studies have developed combination algorithms to help determine stages of liver fibrosis in HCV, and it has been determined that the SAFE biopsy and Fibropaca algorithms, both which combine the APRI along with other biomarkers, have the best overall performance in HCV patients. However, even the Fibropaca algorithm, determined to have the best performance, was only able to decrease the need for liver biopsies by 51.7 %, over 20% less than the results of our study.²⁷ To our knowledge, the current study is the first to use our cut-off values in combination with the APRI and ELFTM tests in an algorithm.

The APRI and ELFTM may measure different aspects of the fibrotic process allowing them to evaluate different aspects of liver injury in HCV infection (i.e., impaired synthesis and cell leakage/possible apoptosis for the APRI and fibrogenesis for the ELFTM test). This study shows that both the APRI and the ELFTM test are equally good in distinguishing mild from significant liver fibrosis. The APRI is based on changes in hepatic function and by using cutoff values for the APRI of 0.42 or 1.2 for our population, previously shown by our group as being optimal, the APRI has >90% accuracy with an intermediate zone of 45.8%. In contrast, the ELFTM focuses more on hepatic extracellular matrix components and also had >90% accuracy for the same set of patients using cutoff values 8.19 or 9.88. However, in the training set (Table 2) of patients, the ELFTM test has a slighter larger intermediate zone (50.6%) than the APRI (49.5%). A similar trend was also for the training set of patients. Since the two indexes measure different aspects of liver fibrosis, we hypothesized that the combination of the two marker sets may enhance the sensitivity and specificity, or narrow the intermediate zone. Several previous studies have suggested that the use of two or more hepatic fibrosis markers including the APRI in an algorithm can enhance results and further decrease the need for liver biopsy in chronic hepatitis C and B.^{7,19–21}

While the algorithm combining the APRI and ELFTM tests for the validation set of patients did not enhance sensitivity and specificity compared to the APRI, the combination did, however, increase the number of patients that can be accurately screened as having either mild or significant fibrosis. By using our algorithm we were able to reduce the intermediate zone for the APRI from 42.1% to 25.3% for differentiating mild (F0, F1) from significant fibrosis (F2–F4). Regardless of these promising results, it would be beneficial to validate these tests in a different population of chronic HCV patients outside of our university hospital setting. In this setting, patients with APRI results falling within the intermediate zone, the ELFTM test could potentially decrease the number of liver biopsies and thus health care costs.

Conclusions

This study shows that the APRI and ELFTM tests are essentially equivalent in the prediction of mild and significant fibrosis in chronic hepatitis C and complimentary in clinical utility. We propose that the cheap and easily calculated APRI be an initial screening test. For those patients who fall between cut offs in the intermediate zone, the ELFTM can be used to increase the number of patients properly classified. The utilization of these two tests could potentially decrease the need for liver biopsy in almost three fourths of patients with chronic hepatitis C.

Acknowledgments

iQur Limited provided the ELFTM test studies on the patients.

The samples were collected while patients were in the General Clinical Research Center at the University of Texas Medical Branch at Galveston, funded by grant M01 RR 00073 from the National Center for Research Services, NIH, USPHS.

Abbreviations

AST	aspartate aminotransferase
ALT	alanine aminotransferase
APRI	AST, platelet ratio index
ELFTM	enhanced liver fibrosis
HCV	hepatitis C virus

Reference List

1. Lavanchy D. The global burden of hepatitis C. *Liver Int.* 2009; 29 (Suppl 1):74–81. [PubMed: 19207969]
2. Stauber RE, Lackner C. Noninvasive diagnosis of hepatic fibrosis in chronic hepatitis C. *World J Gastroenterol.* 2007; 28;13:4287–4294.
3. Huwart L, Sempoux C, Salameh N, et al. Liver fibrosis: noninvasive assessment with MR elastography versus aspartate aminotransferase-to-platelet ratio index. *Radiology.* 2007; 245:458–466. [PubMed: 17940304]
4. Manning DS, Afdhal NH. Diagnosis and quantitation of fibrosis. *Gastroenterology.* 2008; 134:1670–1681. [PubMed: 18471546]
5. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10–12, 2002). *Gastroenterology.* 2002; 123:2082–2099. [PubMed: 12454863]
6. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003; 38:518–526. [PubMed: 12883497]
7. Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clin Chim Acta.* 2007; 381:119–123. [PubMed: 17442291]
8. Snyder N, Gajula L, Xiao SY, et al. APRI: an easy and validated predictor of hepatic fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2006; 40:535–542. [PubMed: 16825937]
9. Trang T, Petersen JR, Snyder N. Non-invasive markers of hepatic fibrosis in patients co-infected with HCV and HIV: comparison of the APRI and FIB-4 index. *Clin Chim Acta.* 2008; 397:51–54. [PubMed: 18692034]

10. Guha IN, Parkes J, Roderick P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology*. 2008; 47:455–460. [PubMed: 18038452]
11. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology*. 2004; 127:1704–1713. [PubMed: 15578508]
12. Batts KP, Ludwig J. Chronic hepatitis: An update on terminology and reporting. *Am J Surg Pathol*. 1995; 19:1409–1417. [PubMed: 7503362]
13. Lau DTY, Luxon BA, Xiao s-Y, Beard B, Lemon S. Intrahepatic gene expression profile and alpha smooth muscle patterns in hepatitis C virus induced fibrosis. *Hepatology*. 2005; 42:273–281. [PubMed: 15986378]
14. Fabris C, Smirne C, Toniutto P, et al. Usefulness of six non-proprietary indirect markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chem Lab Med*. 2008; 46:253–259. [PubMed: 18324909]
15. Paggi S, Colli A, Fraquelli M, et al. A non-invasive algorithm accurately predicts advanced fibrosis in hepatitis C: a comparison using histology with internal-external validation. *J Hepatol*. 2008; 49:564–571. [PubMed: 18706734]
16. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: a systematic review. *Hepatology*. 2007; 46:912–921. [PubMed: 17705266]
17. Mayo MJ, Parkes J, ms-Huet B, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. *Hepatology*. 2008; 48:1549–1557. [PubMed: 18846542]
18. Parkes J, Guha N, Roderick P, et al. Enhanced liver fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *J Viral Hepatitis*. 2010; 59:1245–1251.
19. Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol*. 2006; 44:686–693. [PubMed: 16490278]
20. Sebastiani G, Vario A, Guido M, et al. Sequential algorithms combining non invasive markers and biopsy for the assessment of fibrosis in chronic hepatitis B. *World J Gastroenterol*. 2007; 13:525–531. [PubMed: 17278217]
21. Bouliere M, Penoranda G, Ouzan D, et al. Optimized stepwise algorithms of non invasive liver fibrosis scores including the Hepascore in chronic hepatitis C patients. *Aliment Pharmacol Ther*. 2008; 15:28:458–467.
22. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002; 97:2614–2618. [PubMed: 12385448]
23. Bedossa P, Carrat F. Liver biopsy: the best, not the gold standard. *J Hepatol*. 2009; 50:1–3. [PubMed: 19017551]
24. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology*. 2003; 38:1449–1457. [PubMed: 14647056]
25. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol*. 2003; 39(2):239–244. [PubMed: 12873821]
26. Sebastiani G, Castera L, Halfon P, Pol S, Mangia A, Di Marco V, Pirisi M, Voiculescu M. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. *Aliment Pharmacol Ther*. 2011; 34(10):1202–1216. [PubMed: 21981787]
27. Sebastiani G, Halfon P, Castera L, Mangia A, Di Marco V, Pirisi M, Voiculescu M, Bourliere M, Alberti A. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther*. 2012; 35(1):92–104. [PubMed: 22035045]

Figure 1.

ROC curves for the APRI and ELFTM Test for the training patient set (N = 95). The AUROC for the APRI, ELFTM Test, and Algorithm were 0.856, 0.880 and 0.886, respectively (p = 0.607 for APRI vs. ELFTM Test, p = 0.048 for APRI vs. Algorithm, and p = 0.881 for ELFTM Test vs. Algorithm). triangles = ELF, circles = APRI, squares = algorithm

Figure 2.

ROC curves for the APRI and ELFTM Test for the validation patient set (N = 95). The AUROC for the APRI, ELFTM Test, and Algorithm were 0.855, 0.780 and 0.862, respectively ($p = 0.20$ for APRI vs. ELFTM Test, $p = 0.686$ for APRI vs. Algorithm, and $p = 0.111$ for ELFTM Test vs. Algorithm). triangles = ELF, circles = APRI, squares = algorithm

Figure 3.

Algorithm using an APRI ≤ 0.42 or ≥ 1.20 as the first screen and an ELFTM ≤ 8.19 or ≥ 10.05 as the secondary screen for the validation patient set.

Table 1

Patient Demographics for Training and Validation Patient Groups

	Training Group	Validation Group	p-value
N total	95	95	
Age (SD)	45.3 (8.9)	46.4 (8.1)	0.41
Sex			
Male	72 (75.8%)	70 (73.7%)	
Female	23 (24.2%)	25 (26.3%)	
			0.87
Race/Ethnicity			
Asian	2 (2.1%)	1 (1.1%)	
African American	15 (15.8%)	22 (23.2%)	
Caucasian	60 (63.2%)	58 (61.1%)	
Hispanic	18 (18.9%)	14 (14.7%)	
			0.41
Stage of Fibrosis			
F0 (%)	13 (13.7%)	8 (8.4%)	
F1 (%)	32 (33.7%)	36 (37.9%)	
F2 (%)	23 (24.2%)	23 (24.2%)	
F3 (%)	12 (12.6%)	11 (11.6%)	
F4 (%)	15 (15.8%)	17 (17.9%)	
			0.81
F0-F1 (mild fibrosis)	45 (47.4%)	44 (46.3%)	
APRI (SD)	45 (47.4%)	0.63 (0.48)	0.89
ELF™ test (SD)	8.43 (1.42)	8.94 (1.03)	0.07
F2+F3+F4 (significant fibrosis)	50 (52.6%)	51 (53.7%)	
APRI (SD)	1.92 (2.12)	1.79 (1.62)	0.65
ELF™ test (SD)	10.28 (1.30)	10.05 (1.17)	0.38
Average Biopsy length (cm)	2.2 (0.8)	2.4 (1.4)	0.27
ALT (SD)	123.1 (99.9)	118.8 (81.6)	0.75
AST (SD)	81.1 (71.9)	76.4 (52.0)	0.60
Platelets (10⁹/L)(SD)	205.0 (64.4)	200.9 (72.6)	0.68

Sensitivity, Specificity, Negative Predictive Value, and Positive Predictive Value for the APRI and ELF™ Tests for the training set of patients.

Table 2

	TP	FP	FN	TN	Sensitivity	Specificity	NPV	PPV
APRI								
0.42	48	28	2	17	96.0%	37.8%	89.5%	63.2%
1.20	26	3	24	42	52.04%	93.3%	63.6%	89.7%
Intermediate zone (0.43 – 1.19) = 47 patients (49.5%)								
ELF™ test (Cut-offs identified using ROC curves)								
8.19	50	26	0	19	100%	42.2%	100%	65.8%
9.88	27	1	24	43	52.9%	97.7%	64.2%	96.4%
Intermediate zone (8.20 – 10.04) = 47 patients (50.5%)								
Algorithm								
APRI 0.42 and <1.20 and ELF™ Test 8.19	48	17	2	28	96.0%	62.2%	93.3%	73.8%
APRI 0.42 and <1.20 and ELF™ Test 9.88	33	4	17	41	66.0%	91.1%	70.7%	89.2%
Intermediate zone = 28 patients (29.5%)								

TP, true positive; FP, false positive; FN, false negative; TN, true negative; NPV, negative predictive value; PPV, positive predictive value

Table 3

Sensitivity, Specificity, Negative Predictive Value, and Positive Predictive Value for the APRI and ELF™ Tests for the validation set of patients.

	TP	FP	FN	TN	Sensitivity	Specificity	NPV	PPV
APRI								
0.42	50	25	1	19	98.0%	43.2%	95.0%	66.7%
1.20	32	3	19	41	62.8%	93.2%	68.3%	91.4%
Intermediate zone (0.43 – 1.19) = 40 patients (42.1%)								
ELF™ test								
8.19	48	34	3	10	94.1%	22.7%	76.9%	58.5%
9.88	29	4	22	40	56.9%	90.9%	64.5%	87.9%
Intermediate zone (8.20 – 10.04) = 49 patients (51.6%)								
Algorithm								
APRI 0.42 and <1.20 and ELF™ Test 8.19	48	19	3	25	94.1%	56.8%	89.3%	71.6%
APRI 0.42 and <1.20 and ELF™ Test 9.88	37	6	14	38	72.6%	86.4%	73.1%	86.1%
Intermediate zone = 24 patients (25.3%)								

TP, true positive; FP, false positive; FN, false negative; TN, true negative; NPV, negative predictive value; PPV, positive predictive value