Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C☆

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Background & Aims: Non-invasive assessment of liver fibrosis is a challenging area. Several methods have been proposed in patients with chronic hepatitis C (CHC) but their performance may be improved when they are combined as suggested by recently proposed algorithms using either transient elastography (TE) and Fibrotest (FT) (Castera) or AST-to-Platelet Ratio Index (APRI) and FT (SAFE biopsy). The aim of this prospective study was to compare the performance of these two algorithms for diagnosing significant fibrosis and cirrhosis in 302 CHC patients.
Methods: All patients underwent TE, FT and APRI the same day as liver biopsy, taken as reference standard.
Results: Significant fibrosis (Metavir $F \geqslant 2$) was present in 76% of patients and cirrhosis (F4) in 25%. TE failure was observed in eight cases (2.6%). For significant fibrosis, Castera algorithm saved 23% more liver biopsies (71.9% vs. 48.3%, respectively; $p < 0.0001$) than SAFE biopsy but its accuracy was significantly lower (87.7% vs. 97.0%, respectively; $p < 0.0001$). Regarding cirrhosis, accuracy of Castera algorithm was significantly higher than that of SAFE biopsy (95.7% vs. 88.7%, respectively; $p < 0.0001$). The number of saved liver biopsies did not differ between the two algorithms (78.8% vs. 74.8%; p = NS).
Conclusions: Both algorithms are effective for non-invasive staging of liver fibrosis in chronic hepatitis C. Although the number of liver biopsies avoided does not differ between algorithms for diagnosing cirrhosis, it is significantly higher with Castera algorithm than SAFE biopsy for significant fibrosis.

Keywords: Hepatitis C; Fibrosis; Non-invasive; FibroScan; Fibrotest; APRI.
Received 29 May 2009; received in revised form 6 August 2009; accepted 1 September 2009; available online 24 November 2009

☆ Part of this work has been presented as oral presentation at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston (USA), November 2–6, 2007.

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Abbreviations: CHC, chronic hepatitis C; TE, transient elastography; FT, Fibrotest; APRI, AST-to-platelet ratio; SAFE, sequential algorithms for fibrosis evaluation; HCV, hepatitis C virus; HBV, hepatitis B virus; kPa, kilopascal; IQR, interquartile range; AUROC, area under the ROC curve; DANA, difference between advanced and non-advanced fibrosis.

Introduction

In patients with chronic hepatitis C (CHC), the precise stage of hepatic fibrosis is the most important predictor of disease progression and indicates the need for initiating antiviral therapy [1,2]. For many years, liver biopsy has been considered the gold standard for the staging of fibrosis and it is still recommended in the majority of patients with CHC for treatment indication [3]. However, liver biopsy has several limitations: it is an invasive and painful procedure [4,5], with rare but potentially life-threatening complications [6], and prone to sampling errors [7–10]. Thus many patients with CHC are reluctant to undergo liver biopsies and may not start antiviral therapy for this reason.

These limitations have stimulated the search for new non-invasive approaches [11–14]. A variety of methods including serum markers ranging from simple routine laboratory tests such as the AST-to-platelet ratio index (APRI) [15] to more complex scores such as the Fibrotest (FT) [16], and more recently measurement of liver stiffness by transient elastography (TE) [17,18], have been proposed for the non-invasive assessment of fibrosis in patients with CHC. These three methods are currently the most widely used [19] and better validated [20–22]. In addition, TE and FT have been recently approved, after an independent systematic review, by the French Health Authorities, for first line assessment of fibrosis in patients with CHC [23]. When comparing TE with APRI and FT, we have shown that their diagnostic performance were equivalent [17]. However, combined use of TE and FT reached the best diagnostic performance in the identification of both significant fibrosis ($F \geqslant 2$) and cirrhosis (F4). Accordingly, we proposed a clinical management algorithm using the combination of TE and FT as first line assessment of fibrosis in patients with CHC. Based on this algorithm, liver biopsy could be avoided in more than 75% of the patients examined for the diagnosis of significant fibrosis. Similarly, a sequential algorithm combining APRI and FT, named Sequential algorithms for Fibrosis Evaluation (SAFE) biopsy, was also proposed [24,25]. Using this algorithm, liver biopsy could be avoided in 50% of cases for the diagnosis of significant fibrosis and in 70% of cases for identification of cirrhosis.

The aim of this prospective study was to compare in the same population the diagnostic performance for significant fibrosis and cirrhosis of these two algorithms.

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Patients and methods

Patients

The study cohort included 314 consecutive patients with chronic hepatitis C who underwent percutaneous liver biopsy between June 2003 and February 2007. Chronic hepatitis C was defined by detectable serum anti-HCV antibodies and HCV RNA with chronically elevated serum alanine aminotransferase (ALT) levels. Elevated ALT were defined as values above the upper limit of normal (ULN) range (50 IU/L) on at least two consecutive measurements over a period of 6 months. Exclusion criteria were: coinfection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), other causes of liver disease, decompensated liver disease, and liver transplantation.

The study protocol conformed to the ethical guidelines of the 1975 Helsinski declaration and was approved by our institutional review board. Patients were enrolled after giving their written informed consent.

Liver stiffness measurement

Liver stiffness measurements were performed the day of liver biopsy using TE (FibroScan, Echosens, Paris, France). Details of the technical background and examination procedure have been previously described [26]. Ten successful measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value of successful measurements was considered representative of the liver stiffness in a given patient, according to the manufacturer's recommendations (interquartile range (IQR) less than 30% of the median value and success rate >60%) [27]. When analyzing discordance between TE and liver biopsy, it was considered attributable to TE when these criteria were not fulfilled.

Serum fibrosis scores

The parameters (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl-transpeptidase, total bilirubin, α2-macroglobulin, apolipoprotein A1, haptoglobin and platelet count) allowing to calculate FT and APRI were determined in the same laboratory on blood sampled the day of liver biopsy. The FT score was purchased from Biopredicitve website (www.biopredictive.com). Formula and cut-offs for APRI were taken from the original publication [15]. When analysing discordance between FT and liver biopsy, it was considered attributable to FT when the quality criteria recommended by the manufacturer (Gilbert's disease, hemolysis, acute inflammation) were not fulfilled [28].

Liver histology and staging of liver fibrosis

Liver biopsy was performed by senior operators using the Menghini technique with a 1.6-mm-diameter needle (Hepafix®, Braun, Melsungen, Germany). Biopsy specimens were fixed in formalin and embedded in paraffin. All biopsy specimens were analyzed by the same trained pathologist blinded to the results of non-invasive markers. Specimens with a length of less than 10 mm and/or less than 6 portal tracts were excluded. Liver fibrosis was staged on a 0–4 scale according to the Metavir scoring system [29] as follows: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis.

Algorithms

SAFE biopsy

Two distinct algorithms [25] for detection of significant fibrosis and of cirrhosis based on sequential use of APRI, FT and liver biopsy were applied to the patients and the results were compared with the histological diagnosis of liver biopsy taken as gold standard. The two algorithms use APRI as initial screening test, followed by FT as second step and limiting the use of liver biopsy in patients in which the non-invasive markers have inadequate accuracy. Figs. 1 and 3 describe the two algorithms (significant fibrosis and cirrhosis) including cut-off values for APRI and FT and related decisional tree.

Castera algorithm

The proposed algorithm uses the combination of TE and FT as first line assessment of fibrosis: when TE and FT agree, no liver biopsy is performed whereas when TE and FT disagree a liver biopsy is needed (Figs. 2 and 4). Cut-offs used were those proposed in the original publication [17]. Also, in patients in whom no liver stiffness measurements could be obtained a liver biopsy was considered necessary.

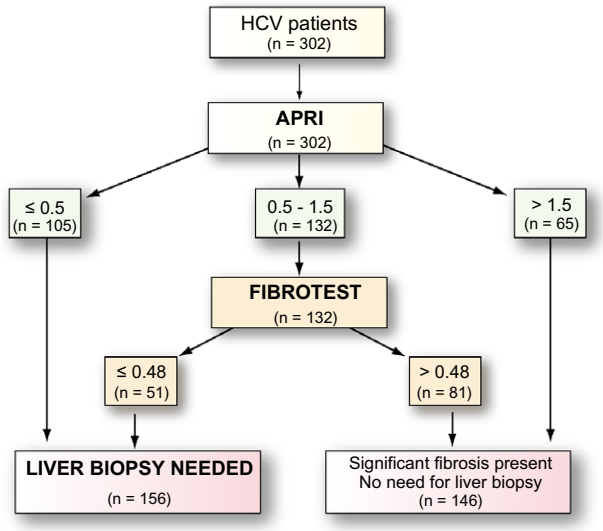

Fig. 1. SAFE biopsy for significant fibrosis (> F2 by Metavir). The figure reports the cut-off used for APRI and Fibrotest in the decisional tree and also the distribution of patients in the different directions when the algorithm was applied to the 302 HCV patients of this study. [This figure appears in colour on the web.]

Statistical analysis

Patients characteristics are given as mean ± SD or as median and interquartile range as appropriate. The chi-square test was applied for comparison of frequency data. Tests were two-tailed and p-values <0.05 were considered significant. Receiver operating characteristics (ROC) curves were constructed. Sensitivity, specificity, positive and negative predictive, accuracy, positive and negative likelihood ratio (LR) were calculated using cut-offs previously described [17,24]. The diagnostic value of the algorithms combining non-invasive methods was expressed using the Area under the ROC curve (AUROC) and its corresponding 95% confidence intervals (CI). AUROCs were calculated using the trapezoidal rule. AUROCs were adjusted according to the prevalence of fibrosis stages using the DANA (Difference between advanced and non-advanced fibrosis = [(prevalence F2 × 2 + prevalence F3 × 3 + prevalence F4 × 4)/(prevalence F2 + prevalence F3 + prevalence F4)] − [prevalence F1/(prevalence F0 + prevalence F1)] as recently proposed [30]. The adjusted AUROCs were calculated as follows: AdjAUROC = obAUROC + (0.1056) × (2.5 − DANA).

Comparisons of AUROCs were done using the method described by Hanley and McNeil for correlated data [31]. Bonferroni adjustment was used for multiple pairwise comparisons. Analyses were performed using Stata V8.0 (StataCorp 2003. Stata Statistical Software: release 8.0. College Station TX).

Results

Patients

Twelve patients that had a biopsy length of less than 10 mm and/or less than 6 portal tracts were excluded, thus 302 patients were studied. Their characteristics at the time of liver biopsy are shown in Table 1. There were 176 men and 126 women, mean age being 52 ± 12 yrs. The mean liver biopsy length was 20 ± 8 mm and the mean number of portal tracts was 15 ± 8. Biopsy length was greater than 15 mm in 70% of patients and greater than 25 mm in 25%. Significant fibrosis (F2–3–4) was