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Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease☆

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***Background/Aims*: The aim of this study was to assess the accuracy of liver stiffness measurement (LSM) for the diagnosis of extensive fibrosis and cirrhosis in patients with alcoholic liver disease (ALD).**

***Methods*: One hundred and seventy-four patients with ALD were enrolled in four liver units and underwent concomitant liver biopsy and LSM. Fibrosis was assessed using the Brunt et al. and the Chevallier et al. scoring systems. Steatosis and histological alcoholic hepatitis (HAH) were quoted in classes.**

***Results*: Twenty-seven patients had inadequate biopsy or LSM. Distribution in 147 patients according to the Brunt score (median LSM) was: *F*1: $n = 13$ (5.7 kPa); *F*2: $n = 24$ (8.3 kPa); *F*3: $n = 31$ (17.5 kPa) and *F*4: $n = 79$ (40.9 kPa) ($P < 0.0001$). LSM was correlated with the amount of fibrosis according to the Chevallier score ($r = 0.70$, $P < 0.0001$). LSM was correlated to fibrosis stage (tau beta, 0.53; $P < 0.0001$) and HAH (tau beta, 0.30; $P < 0.0001$). In multivariate analysis, fibrosis was the only parameter correlated with LSM. The areas under the ROC curve were 0.94 and 0.87 for the diagnosis of extensive fibrosis (Brunt et al. score $\geqslant 3$) and cirrhosis, respectively (threshold-values: 12.9 and 22.6 kPa).**

***Conclusions*: LSM accurately assesses extensive fibrosis and cirrhosis in alcoholic patients.**

***Keywords*: Alcoholic liver disease; Transient elastography; Fibrosis; Cirrhosis**

1. Introduction

Excessive chronic alcohol consumption remains a major health issue as it may lead to cirrhosis and life-threatening complications. The diagnosis of cirrhosis or extensive fibrosis in patients with excessive alcohol intake before the onset of end-stage liver disease is of major interest as it could reinforce the management of alcohol abuse and indicate specific screening procedures for esophageal varices or hepatocellular carcinoma. Liver

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Abbreviations: ALD, alcoholic liver disease; HAH, histological alcoholic hepatitis; LB, liver biopsy; LSM, liver stiffness measurement.

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fibrosis assessment in that setting is a challenge for the physician; unless liver biopsy (LB), with its well known limitations, is performed non-invasive algorithms mixing physical examination, laboratory tests, ultra-sound and endoscopy findings are often not powerful enough to identify those among alcoholic patients exposed to severe liver-related complications of cirrhosis [1–3].

Recently, liver stiffness measurement (LSM) has been shown to be a fairly reproducible and reliable non-invasive method for the assessment of liver fibrosis and cirrhosis [4–11]. Initial studies in chronic hepatitis C patients helped to determine optimal thresholds predictive of histological fibrosis scores [4,11,12]. Nevertheless, as FIBROSCAN® has now been available for a few years, it seems that these specific cut-off values were not the most suitable for the assessment of liver fibrosis and the diagnosis of cirrhosis in patients with other chronic liver disease such as ALD [6,8,13]. Furthermore, wider ranges and variations of LSM values are currently observed in these patients, giving rise to the hypothesis that other parameters such as steatosis, or histological alcoholic hepatitis (HAH) may influence these values.

The aim of this study was (1) to evaluate the overall performance of LSM for the assessment of fibrosis in patients with ALD, (2) to assess the best cut-off values for the prediction of extensive fibrosis and cirrhosis in ALD and (3) to study the possible influence on LSM of other histological parameters reflecting liver injury, mainly steatosis and HAH.

2. Patients and methods

2.1. Patients

Between November 2005 and November 2006, all new consecutive patients referred to four hepatology units for liver biopsy for suspected ALD were included after giving their informed written consent if they fulfilled the following criteria: (1) alcohol intake >80 g per day for more than 10 years, (2) absence of ascites, (3) absence of HIV, hepatitis B or C virus infection, (4) acceptance of LSM and LB, (5) Performance of LSM and LB on the same day. For each patient, the following anamnestic and bio-clinical data were recorded at the time of inclusion defined as the day LB and LSM were performed (age, gender, BMI, diabetes mellitus, serum AST, ALT, and GGT activities, bilirubin levels, prothrombin time, platelet count, serum albumin, γ-globulins).

2.2. Liver biopsy

Liver biopsy specimens were fixed in formalin and embedded in paraffin. Four-micrometer-thick sections were stained with hematoxylin–eosin–saffran and picrosirius red. All biopsy specimens were analyzed by two experienced hepatopathologists (I.T., M.Z.) on a multipipe microscope with no knowledge of LSM results and clinical data. A consensus score was reached and used for the study. Liver fibrosis was evaluated according to two scoring systems: (1) the Brunt et al. [14], initially designed for non-alcoholic fatty liver disease (Stage 0: no fibrosis; stage 1: Zone 3 perivenular, perisinusoidal or pericellular fibrosis, focal or extensive; stage 2: as above with focal or extensitve periportal fibrosis; stage 3: bridging fibrosis, focal or extensive; stage 4: cirrhosis) and the semi-quantitative Chevallier et al. [15] designed to reflect morphometric measurements of fibrosis and taking separately into account fibrosis deposits in centrolobular veins (CLV), perisinusoidal space (PS), portal tract (PT) and septa along with number (NS) and width of septa (WS). Steatosis was also graded according to the Brunt et al. system : grade 1: < 33% of hepatocyte affected; grade 2: 33–66%; grade 3: >66%. Alcoholic hepatitis was defined by the association of hepatocyte ballooning, Mallory's hyalin and neutrophil infiltration [16]. All 3 features were needed to establish this diagnosis. Fibrosis was graded as absent, mild when only occasional foci were observed, moderate when several foci were detected and marked when confluent foci of liver-cell necrosis were observed.

2.3. Liver stiffness measurement

LSM was performed with FIBROSCAN® (EchoSens, Paris, France) on the same day as liver biopsy by an experienced, independent operator who was blinded to the clinical and biological data. Details of the technical description and examination procedure have been previously described. The measurement depth was between 25 and 65 mm. Ten successful acquisitions were performed for each patient. The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. The median value was kept as representative of the liver elastic modulus. Only results of LSM obtained with 10 successful acquisitions and a success rate of at least 50% were considered reliable. Results are expressed in kilopascal (kPa).

2.4. Statistical analysis

Qualitative variables were compared using the Fischer exact χ^2 test, while quantitative variables were compared using the non-parametric Wilcoxon test. Group means were compared by one-way analysis of variance (ANOVA) followed by Bonferroni tests.

Spearman correlation coefficient was calculated to measure the relationship between variables. Stiffness measurements were not normally distributed. Therefore, we compared the results of this test with the categories of the consensus fibrosis stage using the Kruskall–Wallis nonparametric analysis of variance. Unless otherwise mentioned, results were given as the median and 25th to 75th percentile values. The correlation coefficient of Kendall estimated the trend between the test results and the ordinate fibrosis stages.

The receiver-operating characteristics (ROC) curves were computed, and areas under the curves as well as 95%CI were calculated with the Mann–Whitney statistic as described by Hanley and McNeil [17,18]. Efficiency of LSM for the prediction of fibrosis stages was evaluated in the whole studied population. Sensitivity, specificity, likelihood ratios, positive and negative predictive values were computed for the stiffness value at the maximum total sensitivity and specificity. Internal validation was performed by the jack-knife method [19]: the fibrosis stage in one patient was predicted by the liver stiffness cut-offs obtained from the whole included population minus this subject. The procedure was repeated for all the patients to establish a cross-validated performance of the test.

All tests were two-sided with a significance level of 5%. Statistical analyses were performed with StatsDirect statistical software v2.31 (StatsDirect Ltd., 2003, Cheshire, England) and NCSS 2004 (Statistical Systems, Kayville, UT).

3. Results

3.1. Characteristics of patients and histological parameters

A total of 174 patients fulfilled the inclusion criteria. Among them, 15 were excluded because of inadequate LSM and 12 because LB was considered unsuitable for histological examination by both patholgists (less than