Gastroenterology 2014;146:970–979

Baseline Values and Changes in Liver Stiffness Measured by Transient Elastography Are Associated With Severity of Fibrosis and Outcomes of Patients With Primary Sclerosing Cholangitis

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this CME activity, successful learners will be able to interpret liver stiffness measurement (LSM) assessed by transient elastography (TE) in patients with primary sclerosing cholangitis (PSC).

See editorial on page 890.

BACKGROUND & AIMS: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease that leads to extensive liver fibrosis and cirrhosis, which are associated with poor outcome. However, there are no validated noninvasive markers of liver fibrosis in patients with PSC. We assessed the diagnostic performance, reproducibility, longitudinal changes, and prognostic value of liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE). **METHODS:** In a prospective study, we analyzed percutaneous liver biopsy specimens from 73 consecutive patients with PSC from January 2005 to December 2010. Patients underwent VCTE no more than 6 months after the biopsy specimens were collected. The biopsy specimens were analyzed by a pathologist blinded to the results of VCTE for the stage of fibrosis, and LSM was associated with the stage of fibrosis and other variables using the Kruskal–Wallis and Spearman correlation tests. The cutoff values of LSM were selected based on the accuracy with which they identified the stage of fibrosis on receiver-operating characteristic analysis. The rates of LSM progression were assessed using a linear mixed model, and the association between LSM values and clinical outcomes were evaluated using Cox regression analysis in 168 patients with PSC treated with ursodeoxycholic acid and followed up from November 2004 to July 2013 (mean follow-up period, 4 years). **RESULTS:** LSM was independently linked to the stage of fibrosis. Cutoff values for fibrosis stages ≥F1, ≥F2, ≥F3, and F4 were 7.4 kPa, 8.6 kPa, 9.6 kPa, and 14.4 kPa, respectively. The adjusted diagnostic accuracy values for severe fibrosis and cirrhosis were 0.83 and 0.88, respectively. The diagnostic performance of LSM was comparable to that of hyaluronic acid measurement but superior to the aspartate aminotransferase/platelet ratio index, FIB-4 score, and Mayo risk score in differentiating patients with significant or severe fibrosis from those without. LSM had a high level of reproducibility between operators for the same measurement site and for the same operator between 2 adjacent sites. LSM increased significantly and exponentially over time. Baseline measurements and rate of LSM progression were strongly and independently linked with patients' outcomes. **CONCLUSIONS:** VCTE is able to differentiate severe from nonsevere liver fibrosis with high levels of confidence in patients with PSC. Baseline measurements of LSM and longitudinal changes are prognostic factors for PSC.

Keywords: FibroScan; Surrogate Marker; Prognosis; Survival.

Primary sclerosing cholangitis (PSC) is a rare condition of the liver characterized by progressive sclerosis and obstruction of the large and small bile ducts by multifocal fibro-obliterative lesions of unknown etiology.[1] The disease manifests itself by chronic cholestasis and intermittent cholangitis and eventually leads to severe liver fibrosis and cirrhosis, which are recognized predictors of poor outcome.[2,3] The risk of primary liver cancer (cholangiocarcinoma and hepatocarcinoma) is increased, but most liver-related morbidity and mortality is generally related to cirrhotic complications and chronic liver failure.[4,5] Unfortunately, the course of PSC is highly variable, and so far no medical treatments have been shown to efficiently prevent bile duct obstruction or liver fibrosis and to decrease mortality and liver transplantation needs. Most established

Abbreviations used in this paper: **ACC, accuracy; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; APRI, aspartate aminotransferase/platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristic curve; CI, confidence interval; HA, hyaluronic acid; HCV, hepatitis C virus; ICC, intraclass correlation coefficient; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; PSC, primary sclerosing cholangitis; SE, sensitivity; SP, specificity; VCTE, vibration-controlled transient elastography; UDCA, ursodeoxycholic acid.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.12.030

prognostic markers in PSC, including late histological stages,[2] hyperbilirubinemia,[2] hypoalbuminemia,[6] variceal bleeding,[6] or radiological evidence of portal hypertension or hepatic dysmorphism,[7] are characteristic of advanced chronic liver diseases and therefore are intrinsically inappropriate to predict outcomes in asymptomatic, early-stage patients. Accordingly, continued efforts in developing new prognostic tools are urgently needed to better assess and predict the progression of the disease, particularly through the perspective of future therapeutic trials.

Liver stiffness measurement (LSM) based on vibration-controlled transient elastography (VCTE) has been emerging for a number of years as a powerful noninvasive marker of chronic liver disease assessment.[8] LSM has been shown to correlate well with histological fibrosis stage and severity of portal hypertension in various chronic liver diseases,[9,10] making it at present a widely used surrogate marker of disease severity, particularly in Europe. In addition, it was recently shown to be a prognostic indicator in close relationship with liver-related complications and mortality, making it a potent predictor of clinical outcome.[11,12] In PSC, however, data regarding the performance and usefulness of VCTE in clinical practice are scarce. A few years ago, we reported a significant correlation between LSM and stage of fibrosis in 28 patients with PSC, but the number of patients was too small to draw any firm conclusions.[13] In the present study, we describe the largest series to date of patients with PSC who underwent both hepatic histological examination and VCTE and assess not only the diagnostic performance and reproducibility of this procedure for the evaluation of fibrosis but also the progression rates of LSM used as a continuous indicator of the liver state and its predictive value on long-term clinical outcome.

Patients and Methods

In this study, PSC was diagnosed based on typical radiological (multiple strictures of the large intrahepatic or extrahepatic bile ducts on endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography) and/or histological (periductular fibrosis and/or obliterative, nonsuppurative cholangitis on liver biopsy) features. Exclusion criteria included a history of liver transplantation, causes of secondary sclerosing cholangitis (including immunoglobulin G4–associated cholangitis), untreated dominant stricture of the common bile duct or primary hepatic ducts, and hepatic complications including ascites, hepatic encephalopathy, gastrointestinal bleeding due to portal hypertension, cholangiocarcinoma, or hepatocellular carcinoma. Small duct PSC and PSC with features of autoimmune hepatitis (AIH) were not excluded. Patients were recruited from the Department of Hepatology of Saint-Antoine Hospital (Paris, France).

Diagnostic Accuracy

The diagnostic cohort consisted of 73 patients with PSC who were consecutively investigated with percutaneous liver biopsy between January 2005 and December 2010. All patients were additionally evaluated for liver stiffness using VCTE no more than 6 months after the biopsy was performed. Twenty-eight patients (38%) participated in our previous study.[13] The biopsy specimens were analyzed by an experienced pathologist blinded to the VCTE results. Specimens <8 mm in length were not considered eligible. Liver fibrosis and necroinflammatory activity were evaluated according to a METAVIR-derived scoring system.[13,14] In brief, fibrosis was staged on a 0 to 4 scale as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal and periportal fibrosis with few septa; F3, portal and periportal fibrosis with numerous septa without cirrhosis; and F4, cirrhosis. Activity was graded as follows: A0, none; A1, mild; A2, moderate; and A3, severe. The count of interlobular bile ducts was assessed by calculating the ratio of portal tracts with at least one interlobular bile duct to the total number of portal tracts. Ductopenia was defined as an interlobular bile duct ratio $<50\%$. VCTE was performed using the M probe of FibroScan (Echosens, Paris, France).[15] Patients were not required to fast, but examinations were performed not shortly after a meal and mostly between 10:00 AM and 12:00 PM. Every procedure was performed by a hepatologist. The operators were blinded to the histological findings. Only procedures with 10 valid measurements, a success rate $\geq 60\%$, and an interquartile range/median ratio $\leq 30\%$ were considered eligible. The relationships linking LSM with stage of fibrosis or any other categorical variables were assessed using the Kruskal–Wallis test. The correlations linking LSM with any continuous parameters were assessed using the Spearman coefficient. The performance of VCTE in differentiating stages of liver fibrosis was assessed in terms of sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), accuracy (ACC), and area under the receiver-operating characteristic curve (AUROC). Calculations were determined both without (per-protocol) and with (intent-to-diagnose) consideration of the feasibility of VCTE. Diagnostic thresholds were defined at the maximum total SE and SP. Because of the limited number of patients and nonharmonious distribution of fibrosis stages, the variability of the estimates was assessed using a bootstrap method and 100 internal random replications of the original data set. The diagnostic performance of VCTE was compared with that of 3 other markers of liver fibrosis, namely serum hyaluronic acid (HA) concentration, aspartate aminotransferase (AST)/platelet ratio index (APRI) score, and FIB-4 score,[16] as well as the Mayo risk score.[6] Paired AUROCs were compared using the DeLong test.

Concordance Analysis

Thirty-one patients with PSC were blindly investigated on the same day by 2 independent operators who performed VCTE at the same intercostal space. The relationships between the difference and the average were assessed using Bland–Altman analysis. Crude correlations were estimated using the Spearman coefficient. Interobserver agreement was evaluated using the 2-way random effects model 2,1 of the intraclass correlation coefficient (ICC), in which both operators and patients are considered random effects.[17] Twenty-one patients with PSC and 24 controls with hepatitis C virus (HCV) infection matched for histological fibrosis stage were further evaluated at both the seventh and eighth intercostal spaces by a single operator. Intraobserver agreement was assessed using the 2-way mixed model 3,1 of ICC, in which the operator is assumed to be a fixed effect.[17] Concordance was categorized as poor, fair, moderate, strong, and excellent when the ICC was