Utility of Noninvasive Markers of Fibrosis in Cholestatic Liver Diseases

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KEYWORDS

• Primary biliary cirrhosis • Primary sclerosing cholangitis • Surrogate markers
• Elastography • Liver biopsy • Prognosis

KEY POINTS

- In classical histologic systems, fibrosis is only partly addressed through stages 3 and 4 (ie, bridging fibrosis and cirrhosis), making them poorly appropriate for an accurate staging of fibrosis.
- In cholestatic liver diseases, noninvasive markers of hepatic fibrosis have been studied much more in primary biliary cirrhosis (PBC) than in primary sclerosing cholangitis (PSC).
- In PBC the best compromise between reported performance, data robustness, validation status, and prognostic relevance is vibration-controlled transient elastography.
- Liver stiffness as measured by vibration-controlled transient elastography is the only credible noninvasive marker of liver fibrosis in PSC.
- Liver stiffness measurement and enhanced liver fibrosis score are both able to provide independent long-term prognostic information in PBC and PSC.

Since their first description in the 1980s, major advances were made in the development of noninvasive markers of liver fibrosis. Whether generated from biochemical analyses or imaging techniques, surrogate indices of liver fibrosis have progressively replaced liver biopsy in the management of the most prevalent chronic liver diseases, including viral hepatitis infections and alcoholic and nonalcoholic fatty liver diseases. As yet, however, chronic cholestatic liver diseases, namely primary biliary cirrhosis and primary sclerosing cholangitis, do remain a branch of hepatology in which the

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Clin Liver Dis 20 (2016) 143–158
http://dx.doi.org/10.1016/j.cld.2015.08.013 **liver.theclinics.com**
1089-3261/16/$ – see front matter

use of such markers does not command consensus. Yet, a large body of evidence now supports the reliability and efficiency of noninvasive fibrosis markers in both primary biliary cirrhosis and primary sclerosing cholangitis, even though histologic examination of the liver has probably not said its last word.

WHY EVALUATE FIBROSIS IN CHRONIC CHOLESTATIC LIVER DISEASES?

Chronic cholestatic diseases can be defined as liver conditions for which progression and prognosis are impacted to a large extent by the effects of bile acid accumulation in the liver, regardless of the mechanisms involved.[1] In adults, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) account for more than 90% of all patients. Despite different phenotypes and courses, progression of both diseases is characterized histologically by progressive loss of bile ducts, periportal ductular reaction, extensive fibrosis, and eventually cirrhosis. Therefore, as observed in most chronic liver diseases, the extent of fibrotic scares within the hepatic parenchyma marks the progression and severity of chronic cholestatic liver diseases. The progression of fibrosis is closely linked to the parallel processes of bile duct loss and periportal biliary or lymphocytic interface hepatitis, thus likely resulting from a dual cholestatic and necro-inflammatory mechanism.[2] Progressive hyperbilirubinemia, which characterizes severe cholestatic liver diseases, has been recognized as a major predictor of clinical outcomes in both PBC and PSC.[3,4] However, most patients with PBC and PSC are now diagnosed at an early asymptomatic stage, underlying the need for more sensitive prognostic indices. Studies in the 1980s clearly pointed out the importance of fibrosis stage as an independent prognostic factor of these disease conditions.[5,6] However, with the development of popular prognostic models built on noninvasive measurements,[7,8] the use of liver biopsy fell into disgrace. Yet, several recent studies have revived the interest in liver histology to assess prognosis, highlighting the independent and additive prognostic value of histologic stage and, more specifically, of advanced fibrosis and cirrhosis.[9–11] **Fig. 1** shows the significant impact of fibrosis stage (expressed here as stages III or IV of the Ludwig's histologic system) on the survival of patients with either PBC or PSC. Fibrosis stage is,

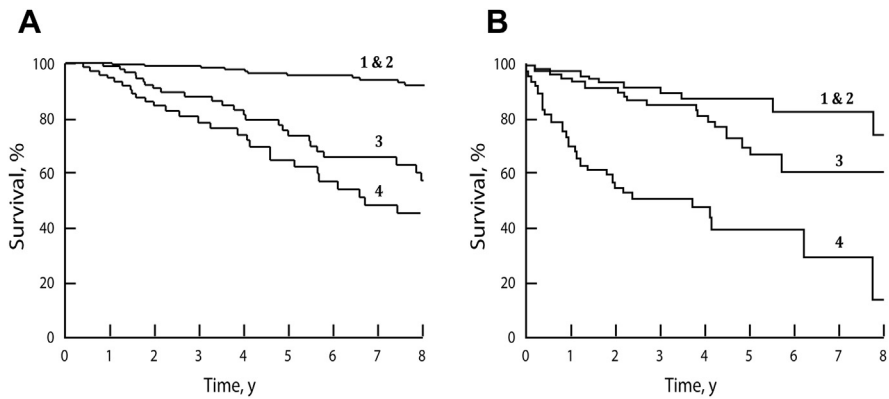

Fig. 1. Impact on survival of histologic stage in PBC and PSC. Kaplan-Meier estimated survival by Ludwig's histologic stage on initial liver biopsy. (*A*) Personal data derived from 292 patients with PBC receiving ursodeoxycholic acid therapy. (*B*) Data from 174 patients with PSC. (*Data from* Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48:871–7; and Wiesner RH, Grambsch PM, Dickson ER, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989;10:430–6.)