

Non-Invasive Markers for Disease Activity and Stage in Chronic Hepatitis B

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The degree of hepatic necroinflammation (grade) and fibrosis (stage) are strongly associated with the natural history and risk of complications in patients with chronic hepatitis B virus (HBV) infection.^{1,2} Therefore, a liver biopsy is frequently recommended in assessing disease severity and selecting antiviral treatment candidates. However, liver biopsy has limitations, including sampling artifact and inter-individual as well as intra-individual variability in scoring. Furthermore, serial liver biopsies are not a practical means of assessing fibrosis progression due to potential complications, costs, and patient/physician reluctance. As a result, simple and reliable non-invasive markers such as blood tests and/or liver imaging modalities that accurately correlate with disease activity and stage are urgently needed to assist in the management of chronic HBV patients worldwide.

The level and duration of HBV replication have been associated with the natural history of chronic HBV.³ However, HBV replicative markers are not independent correlates of disease severity due to the importance of the host immune response in mediating liver damage (e.g., Immune tolerance with high HBV DNA vs. chronic active HBV with high HBV DNA). Therefore, most clinicians utilize widely available laboratory tests of liver injury (i.e., serum AST and ALT levels) in conjunction with HBV replicative markers when estimating disease activity in chronic HBV.^{2,4,5} However, a single serum AST or ALT level may under-or over-represent disease severity due to the fluctuating nature of disease activity, particularly in HBeAg-negative patients. The serum AST/ALT ratio has been reported to be a marker of advanced fibrosis in chronic HBV, but some patients with cirrhosis may have only mildly elevated or even normal aminotransferase levels. A model incorporating serum albumin and AST levels was a moderate predictor of histological activity in both HBeAg + and HBeAg – patients (AUROC = 0.74).⁶ However, 62% of patients were not classifiable and 22% were incorrectly categorized compared to biopsy.⁶ More complex models incorporating baseline liver biochemistries predicted the presence of bridging fibrosis with an AUROC of 0.77 to 0.83.⁶ Similar results were reported in a cross-sectional study of 235 chronic HBV treatment candidates that incorporated BMI, platelet count, serum albumin, and bilirubin levels.⁶

A panel of blood tests that reflect hepatic fibrogenesis and/or fibrolysis have also been proposed as a non-invasive means of assessing disease severity in chronic HBV.⁵ However, available serum fibrosis marker panels can not reliably distinguish between individual stages of fibrosis but rather provide a binary categorization of disease severity (e.g., F0/F1 vs. F2/F3/F4). An exploratory study of 372 HBeAg + Chinese patients failed to show any significant correlation of serum PIIINP, laminin, and type IV collagen levels with liver fibrosis stage.⁹ A model incorporating GGTP, α 2macroglobulin, and hyaluronic acid combined with subject age had an AUROC of only 0.77.⁹ In another study of 209

French HBV patients, routine blood tests and the Fibrotest (α 2macroglobulin, apolipoprotein A, haptoglobin, GGTP, bilirubin) and Actitest (ALT + fibrotest) were correlated with disease stage and activity.⁵ A serum AST or ALT < 30 IU/ml had a similar AUROC to the Actitest and excluded significant disease activity (A2-A3) with 96% certainty. The Fibrotest AUROC (0.78) was similar to that obtained with serum AST (0.74) or serum ALT alone (0.71) in modeling significant fibrosis (F2-F4).⁵ Similar AUROC for the Fibrotest and Actitest were reported in a multicenter trial of 283 chronic HBV patients treated with lamivudine.⁸ Therefore, currently available serum fibrosis marker panels do not provide substantial incremental information to that obtained with routine laboratory tests in chronic HBV.

Imaging modalities proposed for non-invasive disease staging in HBV include ultrasound, which has limited sensitivity for detecting severe fibrosis.¹⁰ Contrast-enhanced ultrasound is more sensitive and specific in detecting cirrhosis but requires IV access and prolonged scanning time and is also operator dependent.¹¹ Although CT and MRI scanning are more sensitive for radiological features of advanced fibrosis, the costs and limited availability of these techniques are prohibitive.¹² Quantitative liver function tests such as the ¹³C-Caffeine breath test have also been proposed but are expensive, cumbersome, and not widely available.¹³

Measurement of liver elastography has emerged as a promising means of assessing disease severity in HCV patients.¹⁴ By sampling a core of liver tissue that is 3 to 4 cm long and ~ 1 cm in diameter, the potential for sampling artifact is markedly reduced. In a pilot study of 170 French HBV patients, liver stiffness was strongly correlated with a Metavir fibrosis score of ≥ 2 and ≥ 3 with an AUROC of 0.81 and 0.92, respectively.¹⁵ However, potential limitations of liver elastography include the overestimation of fibrosis severity with concomitant hepatic steatosis and the applicability of this technique to overweight or obese individuals. Nonetheless, the simplicity and rapidity of this non-invasive modality mandates further study.

Future studies of non-invasive markers of disease severity in chronic HBV will likely rely upon liver biopsy as the gold standard with all of its intrinsic limitations. Future studies should include routine liver biochemistries and platelet count as comparators or adjuvants to the newer diagnostic tests and will likely need to account for HBeAg status, HBV DNA level, and patient age as well as antiviral treatment. Single or combination blood tests are attractive for future development since they can be automated and standardized. Proteomic or genomic approaches may help identify candidate biomarkers that can be further refined and validated in cross-sectional studies.¹⁶ However, prospective, longitudinal studies will be needed to determine the utility of non-invasive laboratory and radiological markers in predicting disease progression and/or regression over several years. In the immediate future, liver biopsy in conjunction with routine laboratory parameters and HBV replicative markers will likely continue to play an important role in assessing disease activity and severity in chronic HBV and to help identify patients in need of antiviral treatment.

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