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Current and Emerging Surrogate Markers of Hepatic Fibrosis in Primary Biliary Cirrhosis

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Primary biliary cirrhosis (PBC) is a chronic, nonsuppurative cholangitic liver disease, with progressive loss of interlobular and septal bile ducts. PBC can progress to cirrhosis, which may lead to death or liver failure. Aside from liver transplantation for patients with end-stage liver disease, the only approved pharmacologic therapy for PBC is ursodeoxycholic acid (UDCA)(1). However, placebo-controlled trials have revealed that a proportion of UDCA-treated patients experience persistent signs of active disease and an unfavorable outcome (2). As a result, there has been great interest to identify ways for accurately monitoring the risk for disease progression over time.

Liver histology is considered essential for determining the stage of disease in PBC. Scoring systems (3) used in clinical practice and controlled trial settings provide information on the relationship between inflammation and fibrosis stage in addition to the identification of ductopenic variants of PBC. Several limitations, however, continue to hamper the ability for using liver histology to monitor disease progression. These include a lack of necessity to obtain liver histology to make a diagnosis in straightforward cases (4) and misclassification errors from tissue sampling and histopathology interpretation (5). While common to all liver diseases, these concerns appear even more prominent in PBC (6) although studies replicating these initial observations have not been reported. Furthermore, there is still controversy regarding the prognostic value of lymphocyte piecemeal necrosis (LPN) and its role in disease progression and incomplete treatment response to UDCA. Histology (3) and model-based investigations (7) describe a significant association between LPN and the increased risk for advanced fibrosis despite UDCA therapy. However, the value of monitoring LPN by liver biopsy would also seem to be affected by sampling error and its gradual extinction over time with advancing fibrosis. The non-invasive detection of LPN has also been difficult to achieve (8).

The study of noninvasive markers to detect hepatic fibrosis in PBC has been ongoing for over two decades. Early studies focused on individual serum markers including hyaluronic acid and procollagen III aminoterminal propeptide (9،10). Unfortunately, many of these studies did not provide estimates of diagnostic accuracy to assess clinical performance. A recent experience described serum hyaluronic acid levels >90 μg/L with high positive predictive values (> 80%) for the diagnosis of extensive fibrosis in selected cases with PBC (10). Nevertheless, these assays have not been widely used in clinical practice to date.

More recently, composite indices have been proposed to improve the detection of hepatic fibrosis. Simple approaches including the AST/ALT, APRI, and Forns indices (11،12) do not have sufficient accuracy to detect advanced fibrosis and remain understudied in PBC.

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Work from our institution confirms a low sensitivity and specificity with APRI for detecting advanced fibrosis in PBC (unpublished data). The investigation of biological markers of fibrosis including the European Liver Fibrosis panel (ELF) (13), which suggests moderate to high diagnostic accuracy for advanced fibrosis in PBC, requires additional prospective study for validation. In one analysis (10), a serum index achieved by combining total bilirubin and hyaluronic acid levels was examined in patients with PBC. Using a diagnostic threshold score of 1.5, the maximum sensitivity and specificity values were 64% and 74%, respectively, for detecting advanced fibrosis. However, there were a significant number of false positive and false negative diagnoses above and below this cut-off value.

In this issue of the Journal, Farkkila and colleagues (14) present results on the performance of various serological markers for monitoring disease progression in PBC. The authors examined 77 patients with pre-cirrhotic disease who were previously randomized to either UDCA or UDCA and budesonide (15), and compared serum tests with histological features of disease identified at baseline and 3 years following treatment. In terms of fibrosis stage, the APRI and PBC score (which includes AST, hyaluronic acid, procollagen III aminoterminal propeptide, and bile acid levels) were found to discriminate well among subgroups with either F0–F1 or F2–F3 fibrosis. The AST/ALT ratio and Forns index (including age, GGT, platelet count, and cholesterol) results were not as useful in this regard. In terms of diagnostic performance, the PBC score appeared best for detecting stages F2–F3 fibrosis with an area under the curve (AUC) value of 0.785 compared to the other indices. With a diagnostic threshold value of 66, the sensitivity and specificity of the PBC score was 81% and 65%, respectively, for detecting stages F2–F3 fibrosis.

Several issues merit discussion about the investigative approach used in this study. The majority of liver biopsy specimens (96%) were greater than 10 mm in length, with 6 or more portal tracts available for evaluation. However, only 32% of biopsies contained ≥ 11 portal tracts, a feature previously associated with quality specimens needed to minimize sampling error particularly in PBC (6). The timing of liver biopsy and serum biochemical measurements was not clearly described, so fluctuations in laboratory values could have influenced the diagnostic performance of fibrosis indices as well. Notably, the incremental benefit in histological improvement reported with combined UDCA + budesonide therapy could not be detected accurately by any of the noninvasive techniques examined. While the PBC score retained the highest diagnostic performance of all serum-based methods tested, its modest sensitivity and low negative predictive value (reported at 62%) will result in higher than desired misclassification rates when assessing patients with advanced or minimal hepatic fibrosis. Further examination of the PBC score in other populations will be required to ultimately determine its utility in clinical practice.

Farkkila et al. conclude that most of the biochemical parameters used for short-term monitoring of disease progression in PBC are not accurate. With this in mind, is it reasonable to think that other methods could be applied to predict baseline or subsequent fibrosis stage among individual patients with PBC? Novel imaging techniques, which capitalize on the ability to measure biomechanical properties of liver injury such as tissue elasticity (16⁻18), have demonstrated promise for the accurate prediction of hepatic fibrosis in PBC. In the spirit of quantifying the biological effects of chronic liver injury, there may also be a future role for measuring parameters reflecting other pathological aspects including angiogenesis given the inflammatory-based nature of PBC (19). For the substantial number of patients failing to achieve a complete response to UDCA therapy, the ability to identify effective alternate therapies will depend heavily on recognizing valid surrogate markers to detect small but important changes in disease status. Thus, continued efforts in this area of investigation for our patients with PBC is mandatory.

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Abbreviations

PBC	primary biliary cirrhosis
UDCA	ursodeoxycholic acid
LPN	lymphocyte piecemeal necrosis
APRI	AST to platelet ratio index
ELF	European Liver Fibrosis

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