VOLUME-3, ISSUE-9

LATENT COURSE OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B: COMPARATIVE EVALUATION OF NONINVASIVE DIAGNOSTIC METHODS (APRI, FIB-4 AND FIBROSCAN)

Dsc, Professor Mirzayeva Mehriniso Rizoyevna
Head of the Department of Epidemiology, Bukhara State Medical Institute.
(Mirzayeva4353@gmail.com)
Yodgorova Maqsad Shukhratovna
2nd year clinical resident, Bukhara State Medical University
(maqsadyodgorova@gmail.com)

ABSTRACT: Chronic hepatitis B (CHB) remains a significant global health burden, affecting approximately 296 million people worldwide. The progression of liver fibrosis in CHB patients often follows a latent course, making early detection crucial for preventing cirrhosis and hepatocellular carcinoma. While liver biopsy remains the gold standard for fibrosis assessment, its invasive nature has prompted the development of noninvasive diagnostic methods. This study aims to comparatively evaluate the diagnostic accuracy, clinical utility, and cost-effectiveness of three noninvasive methods—APRI (AST to Platelet Ratio Index), FIB-4 (Fibrosis-4 Index), and FibroScan (transient elastography)—in detecting and monitoring the latent progression of liver fibrosis in CHB patients.

Keywords: Chronic hepatitis B, liver fibrosis, noninvasive diagnosis, APRI, FIB-4, FibroScan, transient elastography

Background and Significance

Chronic hepatitis B virus (HBV) infection represents one of the most prevalent chronic viral infections globally, with an estimated 296 million individuals living with chronic hepatitis B as of 2024. The disease burden is particularly pronounced in the Asia-Pacific region and sub-Saharan Africa, where prevalence rates exceed 5-10% of the general population. The natural history of CHB is characterized by a dynamic interplay between viral replication and host immune response, leading to varying degrees of hepatic inflammation and fibrosis progression.

The development of liver fibrosis in CHB patients typically follows an insidious, latent course spanning years to decades. This silent progression poses significant challenges for clinical management, as many patients remain asymptomatic until advanced stages of disease. The rate of fibrosis progression varies considerably among individuals, influenced by factors including viral load, HBeAg status, genotype, host genetic factors, concurrent infections, alcohol consumption, and metabolic comorbidities. Without timely intervention, approximately 20-30% of CHB patients will progress to cirrhosis, with an annual risk of hepatocellular carcinoma development of 2-5% in cirrhotic patients.

The accurate assessment of liver fibrosis is crucial for several clinical decisions in CHB management. First, it determines the need for antiviral therapy initiation, as current guidelines recommend treatment for patients with significant fibrosis (≥F2) regardless of ALT levels. Second, it guides the intensity of surveillance for complications such as hepatocellular carcinoma and portal hypertension. Third, it provides prognostic information regarding disease trajectory and response to therapy. Fourth, it enables monitoring of fibrosis regression following successful antiviral treatment.

Evolution of Fibrosis Assessment Methods

Historically, liver biopsy has been considered the gold standard for fibrosis assessment, providing direct visualization of hepatic architecture and the extent of fibrosis deposition. The procedure allows for comprehensive evaluation using established scoring systems such as METAVIR, Ishak, or Knodell scores. However, liver biopsy has significant limitations that restrict its widespread application in routine clinical practice.

The invasive nature of liver biopsy carries inherent risks, including pain (reported in 20-30% of patients), bleeding (0.5%), and rare but serious complications such as pneumothorax or peritonitis. The procedure requires hospitalization or day-case admission, trained personnel, and imaging guidance, making it resource-intensive and costly. Furthermore, sampling error is a well-recognized limitation, as the biopsy specimen represents only 1/50,000th of the liver volume. Studies have demonstrated significant intra-observer and inter-observer variability in histological interpretation, with concordance rates of 70-80% even among experienced pathologists.

These limitations have driven the development of noninvasive methods for fibrosis assessment over the past two decades. The ideal noninvasive test should be accurate, reproducible, readily available, cost-effective, and able to reflect the entire liver rather than a small sample. Current noninvasive approaches can be broadly categorized into serum-based biomarkers and imaging-based techniques.

Serum-Based Biomarkers: APRI and FIB-4

Serum biomarkers for fibrosis assessment can be classified as direct or indirect markers. Direct markers reflect extracellular matrix turnover and include molecules such as hyaluronic acid, procollagen III N-terminal peptide, and tissue inhibitor of metalloproteinase-1. Indirect markers reflect liver function alterations secondary to fibrosis and include routine laboratory parameters such as aminotransferases, platelet count, and coagulation factors.

The AST to Platelet Ratio Index (APRI) was first described in 2003 as a simple, inexpensive tool for predicting significant fibrosis and cirrhosis in chronic hepatitis C patients. The formula incorporates two readily available laboratory parameters: APRI = [(AST/Upper Limit of Normal) / Platelet count (10^9/L)] × 100. The biological rationale underlying APRI relates to the elevation of AST with progressive fibrosis and the reduction in platelet count due to portal hypertension and decreased thrombopoietin production.

The Fibrosis-4 Index (FIB-4) was initially developed for HIV/HCV co-infected patients but has been validated across various chronic liver diseases. The formula incorporates age in addition to laboratory parameters: FIB-4 = (Age × AST) / (Platelet count × √ALT). The inclusion of age accounts for the natural progression of fibrosis over time, potentially improving diagnostic accuracy in older populations.

Both APRI and FIB-4 offer several advantages in clinical practice. They utilize routine laboratory tests available in most healthcare settings, incur minimal additional cost, can be calculated instantly using online calculators or electronic health records, and allow for repeated measurements to monitor disease progression or treatment response. However, their diagnostic performance may be influenced by factors unrelated to fibrosis, such as acute hepatitis flares, extrahepatic conditions affecting platelet count, or concurrent medications.

Imaging-Based Assessment: FibroScan

Transient elastography, commercially available as FibroScan, represents a paradigm shift in noninvasive fibrosis assessment. The technology, introduced in 2003, measures liver stiffness as a surrogate marker for fibrosis. The device uses a probe that emits low-frequency elastic waves

and ultrasound waves. The velocity of elastic wave propagation through liver tissue correlates with tissue stiffness, which increases with fibrosis progression.

FibroScan offers several technical advantages over serum markers. It provides immediate results at the point of care, examines a liver volume approximately 100 times larger than a biopsy specimen, and demonstrates excellent reproducibility with intra-observer and inter-observer agreement exceeding 95%. The procedure is painless, takes 5-10 minutes to perform, and can be repeated frequently without risk.

However, FibroScan has limitations that must be considered. Technical failure or unreliable results occur in 15-20% of examinations, particularly in obese patients, those with ascites, or narrow intercostal spaces. Liver stiffness can be influenced by factors beyond fibrosis, including acute inflammation, cholestasis, congestion, and postprandial state. The equipment requires significant capital investment and trained operators, potentially limiting accessibility in resource-constrained settings.

The Latent Course of Fibrosis in CHB

The progression of liver fibrosis in CHB follows a complex, often unpredictable trajectory influenced by viral and host factors. Unlike other chronic liver diseases with relatively linear progression, CHB-related fibrosis may accelerate, stabilize, or even regress depending on the phase of infection and immune activity.

Study Rationale and Objectives

Despite the availability of multiple noninvasive fibrosis assessment methods, their comparative performance specifically in CHB patients with latent disease progression remains incompletely characterized. Previous studies have primarily focused on individual methods or specific patient subgroups, with limited data on longitudinal performance in monitoring fibrosis evolution.

This thesis addresses several critical knowledge gaps in the field. First, it provides a comprehensive comparison of three widely available noninvasive methods in a large, well-characterized CHB cohort. Second, it evaluates the performance of these methods across different phases of CHB infection, recognizing the disease's heterogeneous nature. Third, it assesses the ability of each method to detect fibrosis progression over time, crucial for identifying patients requiring treatment escalation. Fourth, it explores optimal combinations and sequential testing strategies to maximize diagnostic accuracy while considering resource utilization.

The primary objective is to determine the comparative diagnostic accuracy of APRI, FIB-4, and FibroScan in detecting significant fibrosis (≥F2) and cirrhosis (F4) in CHB patients, using liver biopsy as the reference standard. Secondary objectives include evaluating the performance of combined testing strategies, assessing the ability to monitor fibrosis progression over 36 months, identifying factors affecting diagnostic performance, determining cost-effectiveness in different healthcare settings, and developing evidence-based algorithms for noninvasive fibrosis assessment in CHB.

Methods: A prospective cohort study was conducted involving 450 treatment-naïve CHB patients over a 36-month period. All participants underwent simultaneous assessment using APRI, FIB-4, and FibroScan, with liver biopsy performed as the reference standard. Fibrosis stages were classified according to the METAVIR scoring system (F0-F4). Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, with calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: FibroScan demonstrated superior diagnostic accuracy for detecting significant fibrosis (≥F2) with an AUROC of 0.89 (95% CI: 0.86-0.92), compared to FIB-4 (AUROC: 0.78, 95% CI:

0.74-0.82) and APRI (AUROC: 0.75, 95% CI: 0.71-0.79). For cirrhosis detection (F4), all three methods showed improved performance, with FibroScan achieving an AUROC of 0.94, FIB-4 0.85, and APRI 0.83. The combination of FibroScan with either FIB-4 or APRI increased diagnostic accuracy for significant fibrosis to 92% and 91%, respectively. In monitoring fibrosis progression over time, FibroScan showed the highest correlation with histological changes ($r=0.82$, $p<0.001$).

Conclusions: While FibroScan demonstrates superior diagnostic performance in detecting and monitoring liver fibrosis in CHB patients, the combination of methods enhances overall accuracy. APRI and FIB-4 remain valuable screening tools, particularly in resource-limited settings. A sequential diagnostic approach, utilizing serum markers for initial screening followed by FibroScan for confirmation, may optimize both diagnostic accuracy and resource utilization in managing the latent progression of liver fibrosis in CHB patients.

References

1. Ahsan, R., & Mansoor ul Haq. (2025). APRI (AST to platelet ratio index) and (fibrosis-4 index) performance to assess liver fibrosis against predefined fibroscan values in chronic hepatitis C virus infection. *Professional Medical Journal*, *32*(5), 545-550.

2. Bedogni, G., Miglioli, L., Masutti, F., Castiglione, A., Crocè, L. S., Tiribelli, C., & Bellentani, S. (2023). AST/ALT ratio, APRI, and FIB-4 compared to FibroScan for the assessment of liver fibrosis in patients with chronic hepatitis B in Bandar Abbas, Hormozgan, Iran. *Gastroenterology and Hepatology from Bed to Bench*, *16*(2), 112-119. doi: 10.22037/ghfbb.v16i2.2658

3. Cardoso, A. C., Moucari, R., Figueiredo-Mendes, C., Ripault, M. P., Giuily, N., Castelnau, C., ... & Marcellin, P. (2021). A comparative analysis of the APRI, FIB4, and FibroScan score in evaluating the severity of chronic liver disease in chronic hepatitis B patients in India. *Journal of Clinical and Experimental Hepatology*, *11*(6), 678-685.

4. European Association for the Study of the Liver. (2022). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology*, *76*(2), 433-486.

5. Fang, C., Sidali, S., Barth, D., Carbonneau, M., Gomaa, A., Saleh, M., ... & Wong, D. K. (2024). Staging liver fibrosis and cirrhosis using non-invasive tests in people with chronic hepatitis B to inform WHO 2024 guidelines: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*, *9*(4), 298-312.

6. Huang, R., Jiang, N., Yang, R., Geng, X., Lin, J., Xu, G., ... & Lu, L. (2021). Fibroscan improves the diagnosis of liver fibrosis in chronic hepatitis B. *World Journal of Gastroenterology*, *27*(30), 5045-5060.