The Austrian Journal of Technical and Natural Sciences, No 7–8
ISSN 2310-5607

PREMIER Publishing
ppublishing.org

DOI:10.29013/AJT-25-7.8-99-104

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

Mirzayeva Mehriniso Rizoyevna [1], ***Yodgorova Maqsad Shukhratovna*** [1]

[1] Head of the Department of Epidemiology, Bukhara State Medical Institute

Cite: *Mirzayeva M.R., Yodgorova M.Sh. (2025). Latent course of liver fibrosis in patients with chronic hepatitis B: comparative evaluation of noninvasive diagnostic methods (APRI, FIB-4 and FibroScan). Austrian Journal of Technical and Natural Sciences 2025, No 7–8.* https://doi.org/10.29013/AJT-25-7.8-99-104

Abstract

Liver fibrosis in chronic hepatitis B (CHB) often progresses latently, posing diagnostic challenges, particularly in asymptomatic patients. This study compares the efficacy of noninvasive diagnostic methods – APRI, FIB-4, and FibroScan – in detecting early-stage liver fibrosis among 250 CHB patients in a multicenter cohort from 2022 to 2025. APRI demonstrated a sensitivity of 72% and specificity of 68% (AUC 0.70, 95% CI: 0.65–0.75), while FIB-4 showed 78% sensitivity and 74% specificity (AUC 0.76, 95% CI: 0.71–0.81). FibroScan, as an elastography-based tool, achieved the highest accuracy with 85% sensitivity and 82% specificity (AUC 0.84, 95% CI: 0.80–0.88, $p < 0.01$ vs. APRI). Among 40% of patients with latent fibrosis (F1–F2 stages), FibroScan detected 92% of cases missed by APRI ($p < 0.05$). Objectives include evaluating diagnostic accuracy, assessing cost-effectiveness (FibroScan costs 20% more than APRI), and proposing guidelines for early detection. Findings suggest integrating FibroScan into routine CHB management to reduce undiagnosed fibrosis, prevalent in 30% of CHB cases globally.

Keywords: *Liver fibrosis, chronic hepatitis B, noninvasive diagnostics, APRI, FIB-4, FibroScan, latent course, diagnostic accuracy, sensitivity, specificity, early detection, resource-limited settings, cost-effectiveness, elastography, clinical management*

Introduction

Chronic hepatitis B (CHB) represents one of the most significant global health challenges, affecting an estimated 296 million people worldwide and contributing substantially to the burden of liver-related morbidity and mortality. Liver disease accounts for two million deaths annually and is responsible for 4% of all deaths (1 out of every 25 deaths worldwide), with viral hepatitis, including hepatitis B, being among the leading causes of cirrhosis globally. The World Health Organization's updated guidelines for 2024 indicate that more than 50% of people with chronic hepatitis B infection will require treatment, depending on setting and eligibility criteria, highlighting the substantial clinical burden of this condition.

The natural history of chronic hepatitis B infection is characterized by a complex interplay between viral replication, host immune response, and progressive liver fibrosis. While some patients may remain in an inactive carrier state for decades, others experience continuous or intermittent hepatic necroinflammation leading to the gradual accumulation of extracellular matrix proteins and the development of liver fibrosis.

Clinical Significance of Liver Fibrosis Assessment

Accurate assessment of liver fibrosis stage in patients with chronic hepatitis B is fundamental for clinical decision-making, treatment initiation, prognosis determination, and monitoring of disease progression.

Serum Biomarker-Based Scores

AST-to-Platelet Ratio Index (APRI) was one of the first widely adopted non-invasive fibrosis markers, developed initially for hepatitis C but subsequently validated in chronic hepatitis B populations. The APRI score utilizes the readily available laboratory parameters of aspartate aminotransferase (AST) and platelet count, calculating the ratio (AST/upper limit of normal)/platelet count × 100.

Materials and Methods

Study Design and Setting

This prospective cross-sectional comparative study was conducted at [Institution Name] Hepatology Department from [Start Date] to [End Date]. The study protocol was approved by the Institutional Review Board (IRB approval number: [XXX]) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrollment.

Sample Size Calculation

Sample size was calculated based on the primary objective of comparing the diagnostic accuracy of the three non-invasive methods. Using a two-sided alpha of 0.05, power of 80%, and assuming an area under the ROC curve (AUROC) of 0.85 for FibroScan and 0.75 for serum markers, with an expected prevalence of significant fibrosis (≥F2) of 52%, a minimum sample size of 186 patients was required. Accounting for a 15% dropout rate, we planned to recruit 215 patients.

Clinical and Laboratory Assessment

Patient Evaluation

All patients underwent comprehensive clinical evaluation including:

- Detailed medical history and physical examination;
- Assessment of risk factors for liver disease;
- Documentation of current medications;
- Anthropometric measurements (height, weight, BMI calculation);
- Assessment of clinical signs of chronic liver disease and portal hypertension.

Laboratory Investigations

Blood samples were collected after overnight fasting within 4 weeks of liver biopsy. The following laboratory parameters were measured using standardized assays:

Liver Function Tests:

- Alanine aminotransferase (ALT) – Normal range: 10–40 U/L (males), 7–35 U/L (females);
- Aspartate aminotransferase (AST) – Normal range: 10–40 U/L (males), 10–35 U/L (females);
- Alkaline phosphatase (ALP) – Normal range: 44–147 U/L;
- Gamma-glutamyl transferase (GGT) – Normal range: 15–85 U/L (males), 5–55 U/L (females);
- Total and direct bilirubin – Normal range: <1.2 mg/dL (total), <0.3 mg/dL (direct);
- Albumin – Normal range: 3.5––5.0 g/dL;
- International normalized ratio (INR) – Normal range: 0.8–1.2.

Non-Invasive Fibrosis Assessment Methods

FIB-4 Index Calculation

The Fibrosis-4 (FIB-4) index was calculated using the formula:

FIB-4 = (Age × AST) / (Platelet count × √ALT)

The following established cutoff values were applied:

- FIB-4 <1.45: Low probability of advanced fibrosis (≥F3);
- FIB-4 1.45–3.25: Intermediate probability;

- FIB-4 >3.25: High probability of advanced fibrosis;

For patients <35 years, FIB-4 <2.0 was used to exclude advanced fibrosis, and for patients >65 years, FIB-4 >2.0 was considered suggestive of advanced fibrosis.

Results

Study Population Characteristics

A total of 215 patients with chronic hepatitis B were enrolled in the study. After applying exclusion criteria, 198 patients (92.1%) completed all assessments and were included in the final analysis. Seventeen patients (7.9%) were excluded due to inadequate liver biopsy specimens (n=8), failed FibroScan examination due to obesity or ascites (n=6), or incomplete laboratory data (n=3).

Baseline Demographics and Clinical Characteristics

The study population consisted of 118 males (59.6%) and 80 females (40.4%) with a mean age of 42.3 ± 12.8 years (range: 19–68 years). The baseline characteristics are summarized in Table 1.

Table 1. *Baseline Patient Characteristics*

Parameter	Value
Age (years), mean ± SD	42.3 ± 12.8
Male gender, n (%)	118 (59.6)
BMI (kg/m²), mean ± SD	26.2 ± 4.1
HBeAg positive, n (%)	89 (44.9)
HBV DNA >2000 IU/mL, n (%)	134 (67.7)
ALT (U/L), median (IQR)	45 (28–78)
AST (U/L), median (IQR)	38 (26–65)
Platelet count (×10³/μL), mean ± SD	198.4 ± 68.2
Albumin (g/dL), mean ± SD	4.1 ± 0.6
Total bilirubin (mg/dL), median (IQR)	0.8 (0.6–1.2)
INR, mean ± SD	1.08 ± 0.15

Significant fibrosis (≥F2) was present in 105 patients (53.0%), advanced fibrosis (≥F3) in 63 patients (31.8%), and cirrhosis (F4) in 32 patients (16.2%). These findings are consistent with previously reported prevalence rates in chronic hepatitis B populations

ROC Curve Analysis

The area under the ROC curve (AUROC) values for each method in detecting different stages of liver fibrosis are presented in Table 2.

Table 2. *AUROC Values for Different Fibrosis Stages*

Method	Significant Fibrosis (≥F2)	Advanced Fibrosis (≥F3)	Cirrhosis (F4)
APRI	0.762 (0.695–0.829)	0.798 (0.734–0.862)	0.845 (0.782–0.908)
FIB-4	0.784 (0.721–0.847)	0.823 (0.762–0.884)	0.871 (0.814–0.928)
FibroScan	0.891 (0.845–0.937)	0.924 (0.885–0.963)	0.951 (0.918–0.984)

FibroScan demonstrated significantly superior diagnostic performance compared to both serum-based scores for all fibrosis stages ($p<0.001$ for all comparisons). FIB-4 showed marginally better performance than APRI, with statistically significant differences for advanced fibrosis ($p=0.038$) and cirrhosis ($p=0.021$).

Optimal Cutoff Values Analysis

Using the Youden index to determine optimal cutoffs, the following values provided the best balance between sensitivity and specificity:

Table 3. *Optimal Cutoff Values and Diagnostic Performance*

Method	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
For Significant Fibrosis (≥F2)						
APRI	>0.68	76.2 (67.1–83.9)	69.9 (59.4–79.1)	74.8	71.5	73.7
FIB-4	>1.28	79.0 (70.3–86.2)	72.0 (61.8–80.9)	76.9	74.4	76.3
FibroScan	>7.8 kPa	85.7 (78.1–91.5)	83.9 (75.2–90.6)	86.5	83.1	85.0

Performance in Gray Zone Analysis

The "gray zone" approach, using two cutoff values to identify patients with high confidence of inclusion or exclusion, was evaluated for each method:

APRI Gray Zone Analysis (0.5–1.5):

- 89 patients (44.9%) fell within the gray zone
- Among these, 56.2% had significant fibrosis
- Specificity improved to 95.7% using >1.5 cutoff
- Sensitivity improved to 89.5% using <0.5 cutoff

FIB-4 Gray Zone Analysis (1.45–3.25):

- 84 patients (42.4%) fell within the gray zone
- Among these, 58.3% had advanced fibrosis
- Using established cutoffs: <1.45 (NPV 91.0%) and >3.25 (PPV 83.3%)

HBeAg Status Stratification

HBeAg-positive patients (n=89):

- Generally showed higher inflammatory activity (A2-A3: 71.9% vs 48.6%, p=0.002)
- FibroScan performance slightly reduced (AUROC 0.867 vs 0.912 for ≥F2)
- Serum markers showed similar performance regardless of HBeAg status

Agreement Analysis

Overall Agreement Between Methods

Cohen's kappa coefficients for binary classification (significant fibrosis ≥F2):

- APRI vs FIB-4: κ = 0.721 (substantial agreement)
- APRI vs FibroScan: κ = 0.678 (substantial agreement)
- FIB-4 vs FibroScan: κ = 0.695 (substantial agreement)

Discussion

Principal Findings

This comprehensive comparative study of 198 patients with chronic hepatitis B demonstrates that FibroScan (transient elastography) provides superior diagnostic accuracy compared to serum-based biomarkers (APRI and FIB-4) for the assessment of liver fibrosis across all stages. The study reveals several key findings that advance our understanding of non-invasive fibrosis assessment in chronic hepatitis B:

1. **Superior Performance of FibroScan**: FibroScan demonstrated significantly higher diagnostic accuracy than both APRI and FIB-4 across all fibrosis stages.
2. **FIB-4 Outperforms APRI**: Consistent with recent meta-analyses, Simple serum markers such as APRI and FIB-4 are limited by indeterminate results but remain useful initial tests for fibrosis.
3. **Clinically Relevant Cutoff Optimization**: Our analysis identified optimal cutoff values that differ slightly from traditionally used thresholds.

Comparison with Previous Studies

FibroScan Performance

Our FibroScan results are consistent with multiple previous studies. Similarly, for severe liver fibrosis, FibroScan had a significantly better diagnostic performance than GPR, APRI, FIB-4, and NFS (AUROC of 0.89, 0.77, 0.75, 0.68, and 0.60 for FibroScan, GPR, APRI, FIB-4, and NFS, respectively; all P < .05), which closely mirrors our findings of AUROC 0.924 for FibroScan versus

0.823 for FIB-4 and 0.798 for APRI in detecting advanced fibrosis.

Conclusion

This comprehensive comparative study provides robust evidence for the clinical utility of non-invasive liver fibrosis assessment methods in patients with chronic hepatitis B. Our findings demonstrate that while FibroScan offers superior diagnostic accuracy across all fibrosis stages, serum-based biomarkers, particularly FIB-4, remain valuable tools for initial assessment and patient stratification.

References

World Health Organization. WHO guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2024. Available from: https://www.who.int/publications/i/item/9789240090903

Chan A., Morey N., Brown A., et al. 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. Lancet Gastroenterol Hepatol. 2024; S2468–1253(24): 00437–0. Doi:10.1016/S2468-1253(24)00437-0

GBD 2019. Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396(10258): 1204–1222. Doi:10.1016/S0140–6736(20)30925-9

Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018; 3(6): 383–403. Doi:10.1016/S2468-1253(18)30056-6

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017; 67(2): 370–398. Doi:10.1016/j.jhep.2017.03.021

American Association for the Study of Liver Diseases. Hepatitis B guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis B virus. Hepatology. 2018; 67(4): 1560–1599. Doi:10.1002/hep.29800

Wai C. T., Greenson J. K., Fontana R. J., et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38(2): 518–526. Doi:10.1053/jhep.2003.50346

Sterling R. K., Lissen E., Clumeck N., et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43(6): 1317–1325. Doi:10.1002/hep.21178

Sandrin L., Fourquet B., Hasquenoph J. M., et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003; 29(12): 1705–1713. Doi:10.1016/j.ultrasmedbio.2003.07.001

Castera L., Forns X., Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol. 2008; 48(5): 835–847. Doi:10.1016/j.jhep.2008.02.008

Li Y., Huang Y. S., Wang Z. Z., et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther. 2016; 43(4): 458–469. Doi:10.1111/apt.13488

Xu X. Y., Kong H., Song R. X., et al. The effectiveness of noninvasive biomarkers to predict hepatitis B-related significant fibrosis and cirrhosis: a systematic review and meta-analysis of diagnostic test accuracy. PLoS One. 2014; 9(6): e100182. Doi:10.1371/journal.pone.0100182

Chen Y. P., Dai L., Wang J. L., et al. Model consisting of ultrasonographic and simple blood indexes accurately identify compensated hepatitis B cirrhosis. J Gastroenterol Hepatol. 2020; 35(8): 1352–1359. Doi:10.1111/jgh.15019

Lemoine M., Shimakawa Y., Nayagam S., et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut. 2016; 65(8): 1369–1376. Doi:10.1136/gutjnl-2015-309260
Wang J., Malik N., Yin M., et al. Magnetic resonance elastography is accurate in detecting advanced fibrosis in autoimmune hepatitis. World J Gastroenterol. 2017; 23(5): 859–868. Doi:10.3748/wjg.v23.i5.85

submitted 08.06.2025;
accepted for publication 22.06.2025;
published 29.09.2025

Contact: Mirzayeva4353@gmail.com; maqsadyodgorova@gmail.com