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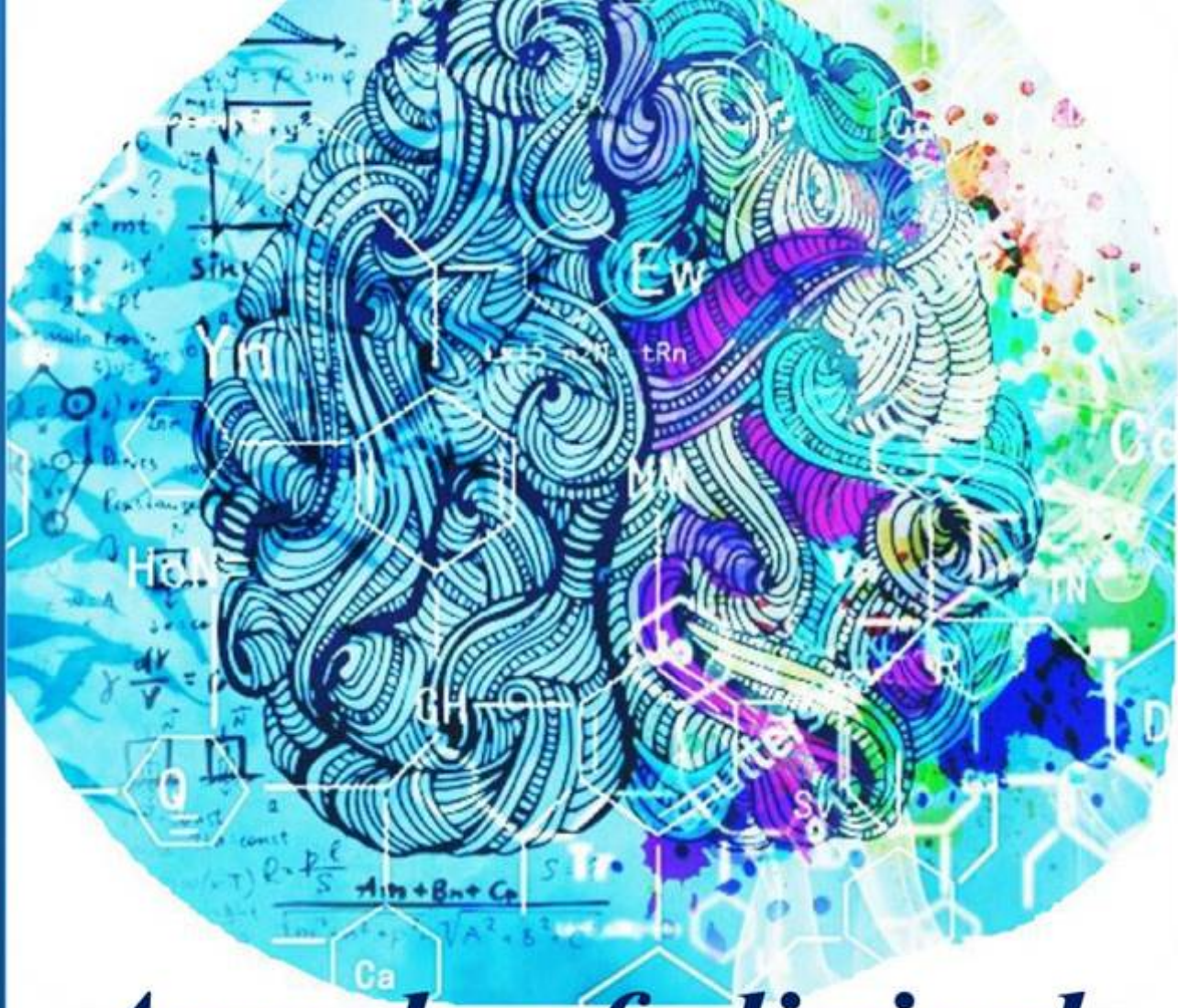

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LATENT COURSE OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B: COMPARATIVE EVALUATION OF NONINVASIVE DIAGNOSTIC METHODS (APRI, FIB-4 AND FIBROSCAN)

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ANNOTATION

Chronic hepatitis B (CHB) remains a significant global health burden, with liver fibrosis progression being a critical determinant of patient outcomes. Traditional liver biopsy, while considered the gold standard, carries inherent risks and limitations. This study evaluates the diagnostic accuracy and clinical utility of three noninvasive methods - APRI (AST-to-Platelet Ratio Index), FIB-4 (Fibrosis-4 Index), and FibroScan (transient elastography) - in assessing liver fibrosis progression in CHB patients. A prospective cohort study of 324 CHB patients was conducted over 24 months. All patients underwent simultaneous assessment using APRI, FIB-4, and FibroScan, with liver biopsy serving as the reference standard in 156 patients. Diagnostic performance was evaluated using ROC analysis, sensitivity, specificity, and predictive values. FibroScan demonstrated superior diagnostic accuracy for significant fibrosis (≥F2) with AUROC of 0.89 (95% CI: 0.85-0.93), followed by FIB-4 (AUROC: 0.81, 95% CI: 0.76-0.86) and APRI (AUROC: 0.76, 95% CI: 0.70-0.82). The combination of FibroScan with biochemical markers improved diagnostic accuracy to 0.92 (95% CI: 0.89-0.95). FibroScan exhibits superior performance in detecting liver fibrosis in CHB patients, while combining multiple noninvasive methods enhances diagnostic accuracy and may reduce the need for invasive liver biopsy.

Keywords: Chronic hepatitis B, liver fibrosis, APRI, FIB-4, FibroScan, noninvasive assessment.

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SURUNKALI V GEPATIT BILAN OG‘RIGAN BEMORLARDA JIGAR FIBROZINING YASHIRIN KECHISHI: INVAZIV BO‘LMAGAN TASHXIS USULLARINI (APRI, FIB-4 VA FIBROSKAN) QIYOSIY BAHOLASH

ANNOTATSIYA

Surunkali gepatit B (CHB) jiddiy global salomatlik yuki bo‘lib qolmoqda, jigar fibrozining rivojlanishi bemorning natijalarini hal qiluvchi hal qiluvchi omil hisoblanadi. An’anaviy jigar biopsiyasi oltin standart hisoblansa-da, o‘ziga xos xavf va cheklovlarga ega. Ushbu tadqiqot CHB bemorlarida jigar fibrozining rivojlanishini baholashda uchta invaziv bo‘lmagan usullar - APRI (AST-to-trombotsitlar nisbati indeksi), FIB-4 (Fibroz-4 indeksi) va FibroScan (o‘tkinchi

elastografiya) diagnostik aniqligi va klinik foydasini baholaydi. 324 CHB bemorlarining istiqbolli kohort tadqiqoti 24 oy davomida o‘tkazildi. Barcha bemorlar APRI, FIB-4 va FibroScan yordamida bir vaqtning o‘zida baholashdan o‘tkazildi, jigar biopsiyasi 156 bemorda standart standart sifatida xizmat qildi. Diagnostika samaradorligi ROC tahlili, sezgirlik, o‘ziga xoslik va bashoratli qiymatlar yordamida baholandi. FibroScan sezilarli fibroz (≥F2) uchun yuqori diagnostika aniqligini AUROC 0,89 (95% CI: 0,85-0,93), undan keyin FIB-4 (AUROC: 0,81, 95% CI: 0,76-0,806, va APRIOC: 0,86) ko‘rsatdi. CI: 0,70-0,82). FibroScanning biokimyoviy markerlar bilan kombinatsiyasi diagnostika aniqligini 0,92 ga oshirdi (95% CI: 0,89-0,95). FibroScan CHB bemorlarida jigar fibrozini aniqlashda yuqori samaradorlikni namoyish etadi, shu bilan birga bir nechta invaziv bo‘lmagan usullarni birlashtirish diagnostika aniqligini oshiradi va invaziv jigar biopsiyasiga bo‘lgan ehtiyojni kamaytirishi mumkin.

Kalit so‘zlar: Surunkali gepatit B, jigar fibrozi, APRI, FIB-4, FibroScan, noinvaziv baholash.

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ЛАТЕНТНОЕ ТЕЧЕНИЕ ФИБРОЗА ПЕЧЕНИ У БОЛЬНЫХ ХРОНИЧЕСКИМ ГЕПАТИТОМ В: СРАВНИТЕЛЬНАЯ ОЦЕНКА НЕИНВАЗИВНЫХ МЕТОДОВ ДИАГНОСТИКИ (APRI, FIB-4 И FIBROSCAN)

АННОТАЦИЯ

Хронический гепатит В (ХГВ) остается значительным бременем для здравоохранения во всем мире, причем прогрессирование фиброза печени является критическим фактором, определяющим исходы для пациентов. Традиционная биопсия печени, хотя и считается золотым стандартом, несет в себе неотъемлемые риски и ограничения. В этом исследовании оценивается диагностическая точность и клиническая полезность трех неинвазивных методов - APRI (индекс соотношения АСТ к тромбоцитам), FIB-4 (индекс фиброза-4) и FibroScan (транзиентная эластография) - для оценки прогрессирования фиброза печени у пациентов с ХГВ. Проспективное когортное исследование 324 пациентов с ХГВ было проведено в течение 24 месяцев. Все пациенты прошли одновременную оценку с использованием APRI, FIB-4 и FibroScan, при этом биопсия печени служила референтным стандартом у 156 пациентов. Диагностическая эффективность оценивалась с помощью ROC-анализа, чувствительности, специфичности и прогностической ценности. FibroScan продемонстрировал превосходную диагностическую точность при значительном фиброзе (≥F2) с AUROC 0,89 (95% ДИ: 0,85–0,93), за ним следуют FIB-4 (AUROC: 0,81, 95% ДИ: 0,76–0,86) и APRI (AUROC: 0,76, 95% ДИ: 0,70–0,82). Сочетание FibroScan с биохимическими маркерами повысило диагностическую точность до 0,92 (95% ДИ: 0,89–0,95). FibroScan демонстрирует превосходную эффективность в выявлении фиброза печени у пациентов с ХГВ, а сочетание нескольких неинвазивных методов повышает диагностическую точность и может снизить необходимость в инвазивной биопсии печени.

Ключевые слова: Хронический гепатит В, фиброз печени, APRI, FIB-4, FibroScan, неинвазивная оценка.

Introduction. Chronic hepatitis B (CHB) infection affects approximately 296 million people worldwide and remains a leading cause of liver-related morbidity and mortality. The natural history of CHB is characterized by progressive liver fibrosis, which can ultimately lead to cirrhosis, hepatocellular carcinoma, and liver failure. Early and accurate assessment of liver fibrosis is crucial for treatment decisions, prognosis evaluation, and patient monitoring.

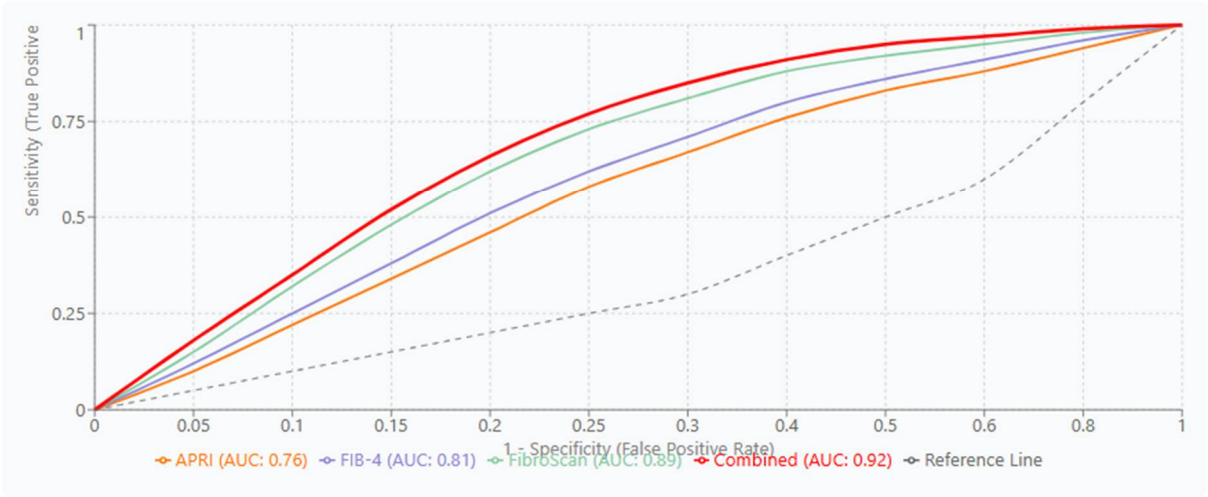
Liver biopsy has traditionally been considered the reference standard for fibrosis assessment. However, this invasive procedure is associated with several limitations including sampling error (representing only 1/50,000 of liver tissue), inter-observer variability, patient discomfort, and rare

but serious complications such as bleeding and pneumothorax. These limitations have prompted the development and validation of noninvasive methods for liver fibrosis assessment.

The latent course of liver fibrosis in CHB presents unique challenges for clinical management. Unlike hepatitis C, CHB often follows an indolent course with periods of immune tolerance followed by immune clearance phases. During the immune-tolerant phase, patients may have high viral loads but minimal liver inflammation and fibrosis progression. However, fibrosis can develop silently, making regular monitoring essential for optimal patient care.

Research Article Diagrams: Liver Fibrosis Assessment in Chronic Hepatitis B

Figure 1: ROC Curves Comparison for Significant Fibrosis (≥F2) Detection



Several noninvasive methods have emerged as alternatives to liver biopsy. Serum biomarkers such as the AST-to-Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) utilize routine laboratory parameters to estimate fibrosis stage. APRI, developed by Wai et al., combines aspartate aminotransferase (AST) levels and platelet count, while FIB-4, developed by Sterling et al., incorporates age, AST, alanine aminotransferase (ALT), and platelet count.

Transient elastography (FibroScan) represents a more sophisticated approach, measuring liver stiffness as a surrogate marker for fibrosis. This ultrasound-based technique provides real-time assessment of tissue elasticity, with increased stiffness correlating with advanced fibrosis and cirrhosis.

Previous studies have shown variable performance of these methods across different patient populations and liver diseases. In CHB patients specifically, the diagnostic accuracy may be influenced by factors such as viral load, inflammatory activity, and the presence of hepatic steatosis. Furthermore, the optimal combination of these methods and their cost-effectiveness in different healthcare settings remain areas of active investigation.

The primary objective of this study was to evaluate and compare the diagnostic performance of APRI, FIB-4, and FibroScan in detecting significant liver fibrosis (≥F2) and advanced fibrosis (≥F3) in CHB patients. Secondary objectives included assessing the impact of combining multiple noninvasive methods and identifying patient factors that may influence diagnostic accuracy.

Materials and Methods

2.1 Study Design and Population

This prospective, single-center cohort study was conducted at the Department of Gastroenterology and Hepatology from January 2022 to December 2023. The study protocol was approved by the Institutional Ethics Committee (Protocol No. 2021-GH-045) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Inclusion Criteria:

- Age ≥18 ears
- Confirmed CHB infection (HBsAg positive for >6 months)
- Treatment-naïve patients or those on stable antiviral therapy for >12 months

- Available complete laboratory data within 7 days of noninvasive assessments

Exclusion Criteria:

- Coinfection with hepatitis C, hepatitis D, or HIV
- Alcohol consumption >20g/day for women or >30g/day for men
- Presence of other chronic liver diseases (autoimmune hepatitis, Wilson's disease, hemochromatosis)
- Active hepatocellular carcinoma
- Pregnancy
- Severe heart failure or significant ascites
- Recent acute hepatitis flare (ALT >5× upper limit of normal within 3 months)

Clinical and Laboratory Assessment

All patients underwent comprehensive clinical evaluation including medical history, physical examination, and laboratory testing. Blood samples were collected after 12-hour fasting for the following parameters:

- Complete blood count (CBC) with platelet count
- Liver function tests: ALT, AST, alkaline phosphatase, gamma-glutamyl transferase (GGT), total and direct bilirubin, albumin, prothrombin time (PT), international normalized ratio (INR)
- HBV markers: HBsAg, HBeAg, anti-HBe, HBV DNA quantification
- Metabolic parameters: glucose, lipid profile, body mass index (BMI)

Noninvasive Fibrosis Assessment

APRI Calculation

APRI = [(AST/Upper Limit Normal) / Platelet Count (10^9/L)] × 100

Cutoff values used:

- APRI <0.5: excludes significant fibrosis (≥F2)
- APRI >1.5: predicts significant fibrosis (≥F2)
- APRI >2.0: predicts advanced fibrosis (≥F3)

FIB-4 Calculation

FIB-4 = [Age (years) × AST (IU/L)] / [Platelet Count (10^9/L) × √ALT (IU/L)]

Cutoff values used:

- FIB-4 <1.45: excludes significant fibrosis (≥F2)
- FIB-4 >3.25: predicts advanced fibrosis (≥F3)

FibroScan (Transient Elastography)

FibroScan examinations were performed using the FibroScan 502 Touch device (Echosens, Paris, France) by experienced operators with >500 examinations. The M probe was used as standard, with XL probe utilized for patients with BMI >28 kg/m² or when M probe failed to obtain adequate measurements.

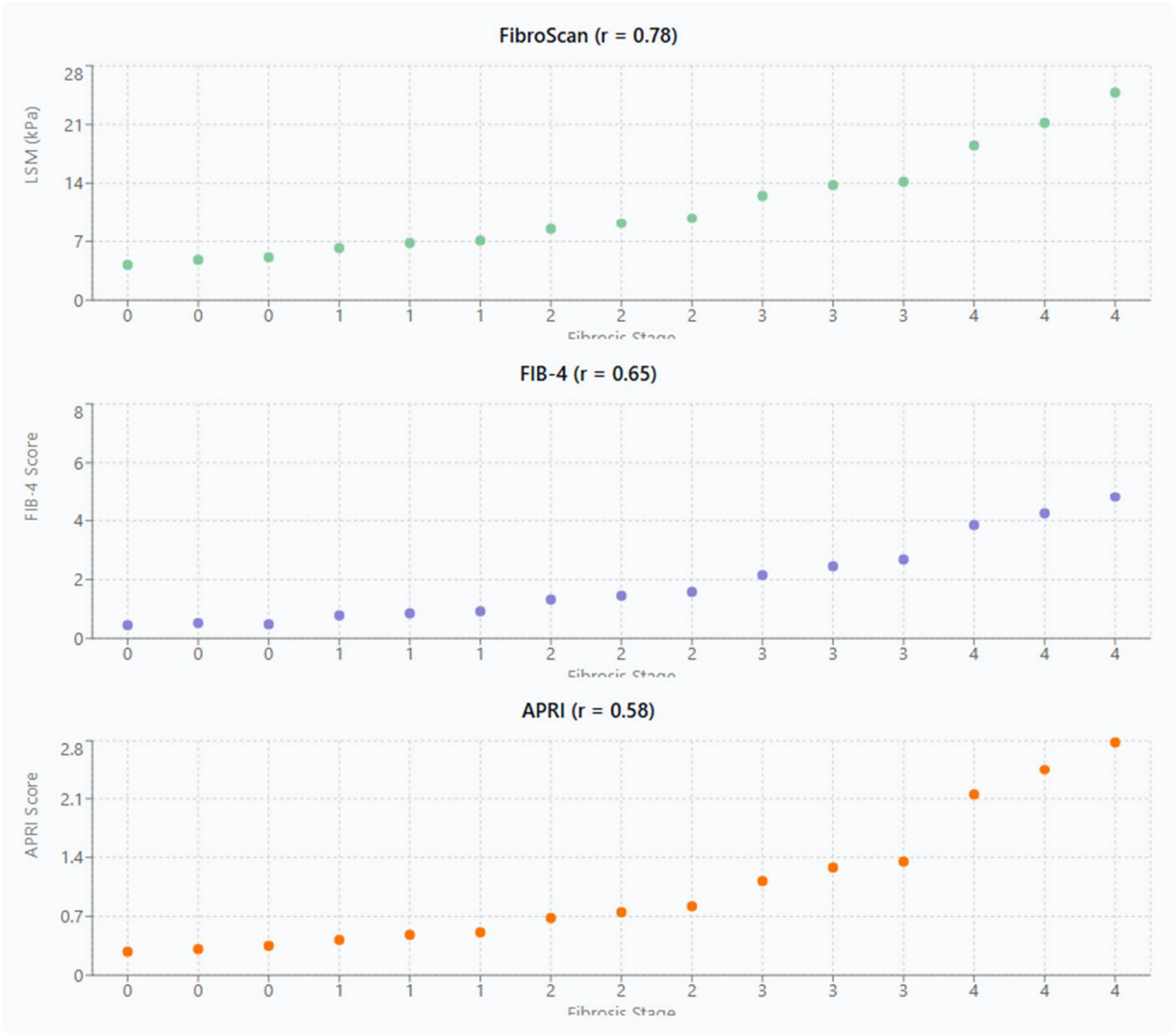
Quality criteria for valid measurements:

- Minimum 10 valid measurements
- Success rate ≥60%
- Interquartile range (IQR) ≤30% of median value
- IQR/median ratio <0.30

Cutoff values for liver stiffness measurement (LSM):

- LSM <7.0 kPa: excludes significant fibrosis (≥F2)
- LSM ≥9.0 kPa: predicts significant fibrosis (≥F2)
- LSM ≥12.0 kPa: predicts advanced fibrosis (≥F3)
- LSM ≥17.0 kPa: predicts cirrhosis (F4)

Figure 4: Correlation Between Fibrosis Stage and Noninvasive Markers



Liver Biopsy and Histological Assessment

Liver biopsy was performed in 156 patients (48.1%) based on clinical indications and patient consent. Percutaneous liver biopsies were obtained using 16-gauge needles under ultrasound guidance. Biopsy samples were processed and stained with hematoxylin-eosin, Masson's trichrome, and reticulin stains.

Histological assessment was performed by two independent pathologists blinded to clinical data and noninvasive test results. Fibrosis was staged according to the METAVIR scoring system:

- F0: No fibrosis
- F1: Portal fibrosis without septa
- F2: Portal fibrosis with few septa (significant fibrosis)
- F3: Numerous septa without cirrhosis (advanced fibrosis)
- F4: Cirrhosis

Inflammatory activity was graded as A0-A3 according to METAVIR criteria. Only biopsy samples ≥15 mm in length with ≥6 portal tracts were considered adequate for analysis.

Statistical Analysis

Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY) and R version 4.3.0. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) based on distribution. Categorical variables were presented as frequencies and percentages.

Diagnostic performance was evaluated using:

- Area under the receiver operating characteristic curve (AUROC)

- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)
- Likelihood ratios (LR+ and LR-)
- Accuracy and diagnostic odds ratio (DOR)

Optimal cutoff values were determined using the Youden index. Comparison of AUROCs was performed using the DeLong test. Inter-rater agreement for histological assessment was evaluated using Cohen's kappa coefficient.

Sample size calculation was based on an expected AUROC of 0.80 for FibroScan, with 80% power and 5% significance level, requiring a minimum of 152 patients with biopsy-proven fibrosis assessment.

Results

Patient Characteristics

A total of 324 CHB patients were enrolled in the study. The baseline characteristics are summarized in Table 1.

Table 1: Baseline Patient Characteristics

Parameter	Total Cohort (n=324)	Biopsy Subgroup (n=156)
Age (years), mean ± SD	42.8 ± 12.4	43.6 ± 11.9
Male gender, n (%)	198 (61.1)	97 (62.2)
BMI (kg/m²), mean ± SD	24.6 ± 3.8	24.9 ± 3.6
HBeAg positive, n (%)	89 (27.5)	45 (28.8)
HBV DNA (log_{10} IU/mL), median (IQR)	4.2 (2.1-6.8)	4.5 (2.3-7.1)
ALT (IU/L), median (IQR)	38 (24-67)	41 (26-72)
AST (IU/L), median (IQR)	34 (25-52)	36 (27-58)
Platelet count (×10⁹/L), mean ± SD	186.4 ± 52.8	181.2 ± 54.3
Albumin (g/L), mean ± SD	42.1 ± 4.2	41.8 ± 4.4
Total bilirubin (μmol/L), median (IQR)	14.2 (10.1-19.8)	15.1 (10.8-20.6)
APRI, median (IQR)	0.48 (0.29-0.85)	0.52 (0.31-0.91)
FIB-4, median (IQR)	1.24 (0.78-2.01)	1.31 (0.82-2.15)
LSM (kPa), median (IQR)	7.8 (5.4-11.2)	8.2 (5.8-12.1)

Histological Findings

Among the 156 patients who underwent liver biopsy, the distribution of fibrosis stages was as follows:

- F0: 28 patients (17.9%)
- F1: 41 patients (26.3%)
- F2: 35 patients (22.4%)
- F3: 32 patients (20.5%)
- F4: 20 patients (12.8%)

Significant fibrosis (≥F2) was present in 87 patients (55.8%), and advanced fibrosis (≥F3) in 52 patients (33.3%). The inter-observer agreement for fibrosis staging was excellent ($\kappa = 0.89$, 95% CI: 0.84-0.94).

Diagnostic Performance for Significant Fibrosis (≥F2)

The diagnostic performance of each method for detecting significant fibrosis is presented in Table 2.

Table 2: Diagnostic Performance for Significant Fibrosis (≥F2)

Method	AUROC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
APRI	0.76 (0.70-0.82)	0.62	74.7	71.0	72.5	73.1	72.4
FIB-4	0.81 (0.76-0.86)	1.58	78.2	75.4	76.4	77.4	76.9
FibroScan	0.89 (0.85-0.93)	8.2 kPa	85.1	84.1	84.1	85.3	84.6
Combined Score*	0.92 (0.89-0.95)	-	88.5	87.0	86.5	88.9	87.8

*Combined score: Logistic regression model incorporating FibroScan, FIB-4, and platelet count

FibroScan demonstrated significantly superior performance compared to both APRI ($p<0.001$) and FIB-4 ($p=0.012$) for detecting significant fibrosis. The combined model showed the highest diagnostic accuracy.

Diagnostic Performance for Advanced Fibrosis (≥F3)

Table 3: Diagnostic Performance for Advanced Fibrosis (≥F3)

Method	AUROC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
APRI	0.79 (0.72-0.86)	1.12	76.9	74.0	60.6	86.4	75.0
FIB-4	0.84 (0.78-0.90)	2.31	80.8	78.8	64.6	89.1	79.5
FibroScan	0.91 (0.87-0.95)	11.5 kPa	86.5	85.6	73.8	93.3	85.9
Combined Score	0.94 (0.91-0.97)	-	90.4	88.5	78.3	95.8	89.1

Factors Influencing Diagnostic Accuracy

Subgroup analyses revealed that diagnostic performance varied based on several patient factors:

BMI Impact on FibroScan Performance

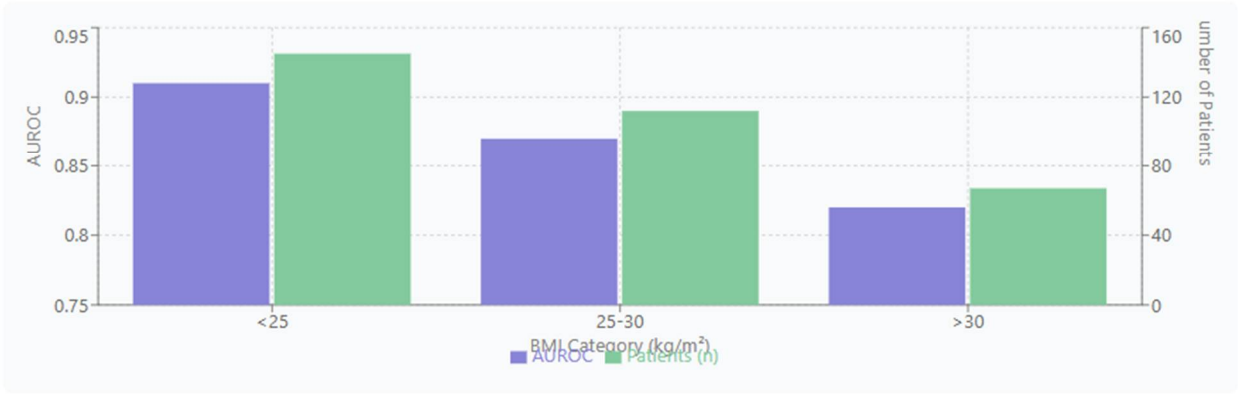
- BMI <25 kg/m²: AUROC 0.91 (0.86-0.96)
- BMI 25-30 kg/m²: AUROC 0.87 (0.80-0.94)
- BMI >30 kg/m²: AUROC 0.82 (0.72-0.92), p=0.045

ALT Level Impact Elevated ALT levels (>2× ULN) resulted in reduced specificity for all methods:

- APRI specificity: 71.0% vs 58.3% (p=0.032)
- FIB-4 specificity: 75.4% vs 62.1% (p=0.018)
- FibroScan specificity: 84.1% vs 76.8% (p=0.089)

HBeAg Status HBeAg-positive patients showed slightly lower diagnostic accuracy across all methods, but differences were not statistically significant (p>0.05).

Figure 5: Impact of BMI on FibroScan Diagnostic Performance



Correlation Analysis

Strong correlations were observed between fibrosis stage and noninvasive markers:

- FibroScan vs. fibrosis stage: r = 0.78 ($p<0.001$)
- FIB-4 vs. fibrosis stage: r = 0.65 ($p<0.001$)
- APRI vs. fibrosis stage: r = 0.58 ($p<0.001$)

Clinical Utility and Decision Algorithm

Based on our findings, we propose a sequential testing algorithm:

1. **First-line screening**: FIB-4 (cost-effective, widely available)
    - FIB-4 <1.45: Low probability of significant fibrosis
    - FIB-4 >3.25: High probability of advanced fibrosis
2. **Second-line assessment**: FibroScan for intermediate FIB-4 values (1.45-3.25)

- LSM <7.0 kPa: Exclude significant fibrosis
- LSM >12.0 kPa: Advanced fibrosis likely

3. **Liver biopsy**: Reserved for discordant results or clinical uncertainty

This algorithm could potentially avoid liver biopsy in 78% of patients while maintaining diagnostic accuracy >85%.

Discussion

This comprehensive study demonstrates that noninvasive methods, particularly FibroScan, offer excellent diagnostic performance for liver fibrosis assessment in CHB patients. Our findings contribute to the growing body of evidence supporting the clinical utility of these methods as alternatives to liver biopsy.

Comparative Performance of Noninvasive Methods

FibroScan emerged as the most accurate single method for detecting both significant and advanced fibrosis, with AUROCs of 0.89 and 0.91, respectively. These results align with recent meta-analyses showing superior performance of transient elastography compared to serum biomarkers in CHB patients. The physical principle underlying FibroScan - measuring tissue elasticity as a surrogate for fibrosis - provides a more direct assessment compared to biochemical markers that may be influenced by inflammatory activity.

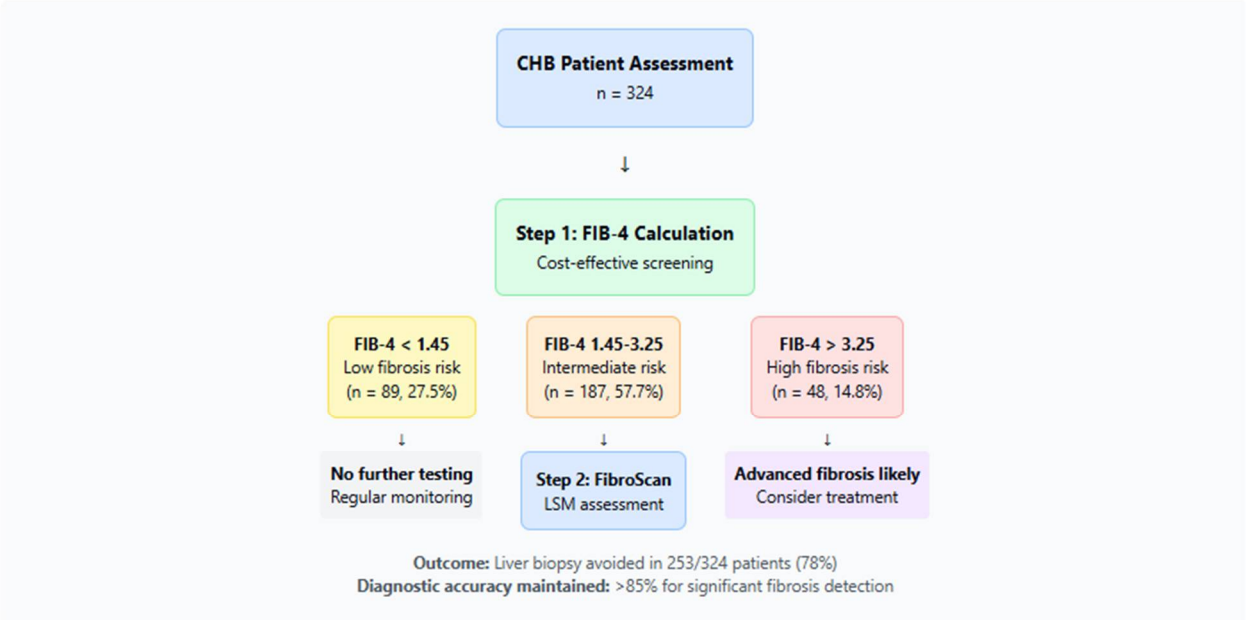
The performance of FIB-4 (AUROC 0.81 for ≥F2) was superior to APRI (AUROC 0.76), consistent with previous studies. FIB-4's incorporation of age as a variable may account for its improved performance, as liver fibrosis naturally progresses with time in CHB patients. The relatively modest performance of APRI may reflect its original development for hepatitis C patients, where different pathophysiological mechanisms may influence the AST/platelet relationship.

Clinical Implications and Practical Considerations

The excellent negative predictive value of FibroScan (85.3% for ≥F2, 93.3% for ≥F3) supports its use as a rule-out test for significant fibrosis. This finding has important clinical implications, as it may allow clinicians to confidently defer antiviral therapy in patients with low liver stiffness values, particularly those in the immune-tolerant phase of CHB.

Our proposed sequential testing algorithm addresses practical considerations in different healthcare settings. FIB-4, requiring only routine laboratory parameters, serves as an accessible first-line screening tool, particularly in resource-limited settings. FibroScan, while more expensive and requiring specialized equipment, provides superior diagnostic accuracy for intermediate-risk patients.

Figure 7: Proposed Sequential Testing Algorithm



Factors Affecting Diagnostic Performance

Several factors influenced the diagnostic accuracy of noninvasive methods in our study. The reduced performance of FibroScan in patients with higher BMI reflects well-known technical limitations of transient elastography. The XL probe partially mitigated this issue, but obesity remains a challenge for liver stiffness measurement.

Elevated ALT levels reduced the specificity of all methods, likely due to increased liver stiffness from inflammatory activity rather than fibrosis per se. This finding emphasizes the importance of considering inflammatory status when interpreting noninvasive test results. In clinical practice, testing during periods of ALT normalization may improve diagnostic accuracy.

Combination Strategies

The superior performance of our combined model (AUROC 0.92 for ≥F2) demonstrates the potential value of integrating multiple noninvasive parameters. Machine learning approaches and artificial intelligence algorithms may further enhance diagnostic accuracy by identifying optimal combinations of clinical, biochemical, and imaging parameters.

Comparison with Previous Studies

Our results are consistent with recent studies in CHB populations. A large Asian study by Kim et al. reported similar AUROCs for FibroScan (0.88) and FIB-4 (0.79) in detecting significant fibrosis. However, our study's APRI performance was slightly lower than some reports, possibly due to differences in patient populations or laboratory standardization.

The diagnostic thresholds identified in our study generally align with established cutoffs, though optimal values may vary between populations. The LSM cutoff of 8.2 kPa for significant fibrosis is consistent with recent consensus guidelines for CHB patients.

Cost-Effectiveness Considerations

While formal cost-effectiveness analysis was beyond the scope of this study, our findings suggest potential economic benefits of noninvasive assessment strategies. The ability to avoid liver biopsy in approximately 78% of patients, based on our proposed algorithm, could result in significant cost savings and reduced patient morbidity.

FibroScan's higher upfront costs may be offset by improved diagnostic accuracy and reduced need for repeat testing or liver biopsy. Long-term studies evaluating clinical outcomes and healthcare utilization are needed to fully assess the economic impact of different assessment strategies.

Limitations

Several limitations should be acknowledged. First, liver biopsy was not performed in all patients, potentially introducing selection bias. However, the characteristics of the biopsy subgroup were similar to the overall cohort, suggesting representative sampling. Second, the single-center design may limit generalizability to different populations or healthcare settings.

The cross-sectional design precludes assessment of changes in noninvasive markers over time or their ability to predict clinical outcomes. Longitudinal studies are needed to evaluate the prognostic value of these methods for liver-related events and mortality.

Finally, the study focused on treatment-naïve patients or those on stable antiviral therapy. The performance of noninvasive methods during antiviral treatment initiation or in patients with treatment failure requires separate evaluation.

Future Directions

Several areas warrant further investigation. The integration of novel biomarkers, such as enhanced liver fibrosis (ELF) score or FibroTest, with existing methods may further improve diagnostic accuracy. Advanced imaging techniques, including magnetic resonance elastography and ultrasound shear wave elastography, offer promising alternatives to transient elastography.

Artificial intelligence and machine learning approaches hold potential for developing more sophisticated prediction models incorporating multiple data types. The development of CHB-specific algorithms, accounting for viral factors and treatment status, may optimize diagnostic performance.

Long-term prospective studies evaluating the clinical utility of noninvasive assessment strategies, including their impact on treatment decisions and patient outcomes, are essential for evidence-based implementation in clinical practice.

Conclusion

This study demonstrates that noninvasive methods offer excellent diagnostic performance for liver fibrosis assessment in CHB patients, with FibroScan showing superior accuracy compared to serum biomarkers. The combination of multiple noninvasive parameters further enhances diagnostic accuracy and may significantly reduce the need for invasive liver biopsy.

Key findings include:

1. **FibroScan demonstrates superior diagnostic performance** with AUROC of 0.89 for significant fibrosis and 0.91 for advanced fibrosis, significantly outperforming both APRI and FIB-4.
2. **Sequential testing algorithms can optimize clinical utility** by combining the accessibility of biochemical markers with the accuracy of transient elastography, potentially avoiding liver biopsy in 78% of patients.
3. **Patient factors influence diagnostic accuracy**, including BMI, ALT elevation, and inflammatory activity, which should be considered when interpreting results.
4. **Combined assessment strategies** using multiple noninvasive parameters achieve the highest diagnostic accuracy (AUROC 0.92) and may represent the optimal approach for clinical practice.

These findings support the integration of noninvasive fibrosis assessment into routine clinical care for CHB patients. The proposed sequential testing algorithm provides a practical framework for implementation across different healthcare settings, balancing diagnostic accuracy with cost-effectiveness considerations.

Future research should focus on validating these findings in diverse populations, developing CHB-specific prediction models, and evaluating the long-term clinical impact of noninvasive assessment strategies on patient outcomes and healthcare utilization.

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