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Interest of Non-Invasive Markers (APRI, FIB-4) for Assessing Hepatic Fibrosis in Patients with Chronic Viral Hepatitis B without Cytolysis and with Low Viral Replication

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Abstract

Background and Objectives: The indication for treatment in HBsAg-positive patients with low viral load and normal transaminases requires an assessment of fibrosis. In resource-limited settings, free hepatic fibrosis evaluation tests can aid in therapeutic decision-making. Our study aims to demonstrate the utility of assessing hepatic fibrosis using non-invasive markers (APRI and FIB-4) in patients with chronic B viral hepatitis without cytolytic activity and low viral replication in our context. **Patients and Methods**: This is a retrospective cross-sectional study conducted between January 2018 and December 2021 at the University Hospital Center of Bouaké. Included were all patients aged ≥18 with normal transaminases (<40 IU/mL), low viral replication (<20,000 IU/mL), asymptomatic, and monoinfected with HBV. Patients with HIV or HCV co-infection or those who had received any antiviral treatment were excluded. FibroScan® was performed on all patients. APRI and FIB-4 scores were calculated. The diagnostic performance of fibrosis markers was analyzed using the receiver operating curve (ROC) to compare them. Sensitivity, specificity, positive and negative predictive values, and the area under the curve (AUROC) were calculated for each marker with a 95% confidence interval. A p-value <0.05 was considered significant. **Results**: Our study included 241 patients, with a mean age of 36.19 years (±10.52 years) and a male predominance of 52%. The mean FibroScan® value was 6.44 ± 2.3 kPa, and 68 patients (28.22%) had fibrosis >7 kPa. To exclude significant fibrosis (FS < 7 kPa), APRI and FIB-4 scores showed comparable performances, with sensitivity, specificity, positive predictive value, and negative predictive value of 90.17%, 36.76%, 78.39%, 59.52%, and 84.97%, 39.70%, 78.19%, 59.52%, respectively. We found

a positive correlation between FibroScan and biological fibrosis scores, with coefficients of 0.34 for APRI and 0.24 for FIB-4 (p-value < 0.05). Biological fibrosis scores had moderate performance in detecting significant fibrosis with respective AUROCs of 0.668 and 0.752 for APRI and FIB-4. **Conclusion**: A significant proportion of HBV-infected patients with normal ALT and low viral load have active liver disease. Both FIB-4 and APRI biological scores are useful in identifying individuals without significant fibrosis with a good negative predictive value (>50%).

Keywords

HBV Infection, APRI, FIB-4, Impulse Elastography, Bouaké University Hospital

1. Introduction

Chronic infection with hepatitis B virus (HBV) is a significant public health issue, affecting over 350 million people worldwide and standing as the primary cause of mortality related to chronic viral liver diseases [1]. In Côte d'Ivoire, HBV prevalence ranges from 8 to 13% in the population [2] [3]. Effective management of this infection requires a precise evaluation of the degree of hepatic fibrosis, a critical outcome in most liver conditions.

Traditionally, liver biopsy has been the gold standard for assessing hepatic fibrosis in chronic viral liver diseases. While providing a direct measurement of hepatic fibrosis, liver biopsy has limitations due to its invasiveness, sampling errors, and risks of complications [4]. Consequently, many chronic HBV patients are hesitant to undergo a liver biopsy, potentially delaying timely antiviral treatment. This has prompted the search for non-invasive methods, such as FibroScan, APRI score, FIB-4 index, etc., which have demonstrated their utility in diagnosing fibrosis in chronic HBV patients [5] [6].

FibroScan, based on transient elastography (TE), has emerged as a non-invasive method for diagnosing hepatic fibrosis. TE measures the speed of an impulse wave through homogeneous tissue, which is proportional to its elasticity, and correlated with the amount of fibrosis in the liver [7]. While FibroScan is the most reliable non-invasive tool for evaluating hepatic fibrosis, its high cost and limited availability outside of Abidjan restrict its use, especially in healthcare facilities in other parts of the country. Several studies suggest that FibroScan accurately predicts hepatic fibrosis in patients with chronic viral hepatitis C (HCV) [8] [9]. However, limited research has been conducted using FibroScan for fibrosis evaluation in patients with chronic HBV, and existing studies have primarily been conducted in European, American, and Asian countries, making generalization to African patients with chronic HBV challenging [10].

Various non-invasive methods, including serum markers like the AST-to-platelet ratio index (APRI) and FIB-4 index [11], have been proposed for non-invasive

fibrosis evaluation in chronic HBV patients. APRI and FIB-4 scores are two other non-invasive methods demonstrating high accuracy in diagnosing advanced fibrosis and cirrhosis in patients with chronic B viral hepatitis compared to liver biopsy [12]. These non-invasive fibrosis detection tests offer several advantages, such as ease of execution, widespread availability, minimal complications, outpatient applicability, no need for specialized training, and homogeneity through automated variable component measurements with automated score calculation tools (free mobile applications).

Treatment indication for HBsAg-positive patients with low viral load and normal transaminases requires fibrosis evaluation. In resource-limited areas, these free hepatic fibrosis evaluation tests can assist in therapeutic decision-making.

Our study aims to demonstrate the value of assessing hepatic fibrosis using non-invasive markers (APRI and FIB-4) in patients with chronic B viral hepatitis without cytolytic activity and low viral replication in our context.

2. Materials and Methods

This was a prospective, cross-sectional, descriptive, and analytical study focusing on the evaluation of hepatic fibrosis using non-invasive markers in patients with chronic B viral hepatitis without cytolytic activity and low viral replication in Bouaké, Côte d'Ivoire: Impulse Elastography versus APRI, FIB-4. The study spanned four years from January 2018 to December 2021.

Inclusion Criteria: *

- All patients aged at least 18 years with chronic hepatitis B (persistent HBsAg for more than 6 months), regardless of gender.
- Patients with normal transaminases (<40 IU/L).
- Patients with low B viral load (<20,000 IU/mL) or HBV DNA < 68,200 copies/mL.
- Patients who underwent a complete blood count and FibroScan in the same week.

Exclusion Criteria:

- Patients on antiviral treatment.
- Patients with hepatocellular carcinoma.
- Pregnant women.
- Organ transplant recipients.
- Patients co-infected with HBV-HDV or HIV or HCV and with another associated liver disease.

Outcome Measures:

- Chronic hepatitis B (persistent HBsAg for more than 6 months) with inactive disease, defined as viral load < 20,000 IU/mL and normal transaminases (<40 IU/L).
- Hepatic fibrosis.

In our study, we performed FibroScan and calculated APRI and FIB-4 scores for all patients. All included patients underwent examination with the FibroScan®

model 402 with the M probe. FibroScan thresholds for classifying fibrosis stages (F) from 0 to 4 were: EI ≤ 7.1 kPa = F0 − F1, EI between 7.2 to 8.1 kPa = F2, EI between 8.2 to 11 kPa = F3, and EI > 11 kPa = F4, corresponding to minimal, significant, severe fibrosis, and cirrhosis, respectively. APRI score, calculated as the ratio of AST (expressed in "times the upper normal limit") × 100/platelets (10^9/L), was interpreted as follows: APRI < 0.5 = minimal fibrosis, APRI > 1.5 = significant fibrosis. FIB-4 index, calculated as age (years) × AST (UI/L)/(platelets (10^9/L) × ALT (UI/L)), was interpreted as follows: FIB-4 < 1.45 = minimal fibrosis, FIB-4 > 3.25 = cirrhosis.

Non-invasive tests were compared with each other, and then APRI score and FIB-4 index were compared to FibroScan. Secondary outcome measures included sociodemographic data (gender, age, place of residence, education level, profession, marital status) and comorbidities (personal history of hypertension, diabetes, smoking, alcoholism, modern and/or traditional medication use).

Biological analyses were conducted in the same week as the FibroScan®, and no liver biopsy was performed.

Data Entry and Statistical Analysis:

Quantitative variables were expressed as mean ± standard deviation, and qualitative variables as percentages. The diagnostic performance of fibrosis markers was analyzed using the receiver operating curve (ROC) to compare them. Sensitivity, specificity, positive and negative predictive values, and the area under the curve (AUROC) were calculated for each marker with a 95% confidence interval. A p-value <0.05 was considered significant. Concordance between different non-invasive tests was analyzed using Pearson's correlation test. The linear correlation coefficient ranges from −1 to +1, with 0 indicating no association. A correlation coefficient (r) greater than 0 indicates a positive association, while a coefficient less than 0 indicates a negative association.Data entry was done with EXCEL 2013, and analysis was performed using the IBM SPSS Statistics 20.

Ethical Considerations: Data collection was conducted while maintaining patient anonymity, and the confidentiality of collected medical information was respected.

Conflict of Interest: No conflicts of interest were declared during the conduct of our study.

3. Results

Our study spanned from January 2018 to December 2021 and included 241 patients meeting our inclusion criteria. Patient ages ranged from 18 to 85 years, with a mean age of 36.19 ± 10.52 years. We observed a male predominance with a sex ratio of 1.07 (Table 1).

The consumption of alcohol and tobacco was noted in 37 (15.35%) and 10 (4.15%) of the patients, respectively. Family history of hepatitis B virus (HBV) was present in 34 (37%) cases. Family history of chronic liver disease was observed in 64 (26.56%) cases.

Regarding the biological assessment (Table 1), the mean values for ALT (Alanine Aminotransferase) and AST (Aspartate Aminotransferase) were 26.64 ± 12.13 IU/L and 28.11 ± 8.49 IU/L, respectively. The mean viral load of HBV was 1988.97 ± 3131.27 IU/mL.

The assessment of hepatic fibrosis in patients using FibroScan revealed non-significant fibrosis in 71.78% of cases (LSM < 7.1 kPa) (Table 1). The mean APRI score was 0.36 ± 0.19. Non-significant fibrosis accounted for 76.76% of cases. Significant fibrosis was observed in 22.83% of cases. Cirrhosis was present in 0.41% of cases (Table 1). The mean FIB-4 score was 1.04 ± 0.55. Non-significant fibrosis accounted for 74.27% of cases. Significant fibrosis was observed in 25.73% of cases (Table 1).

Table 1. Baseline characteristics of the study population

Characteristics	Total patients (n = 241)
Females	125 (51.9%)
Males	116 (48.1%)
Age (means ± SD) in years	36.19 ± 10.52
AST (IU/L)	28.11 ± 8.49
ALT (IU/L)	26.64 ± 12.13
Platelets (×10^3/mm^3)	212.6 ± 66
PCR DNA VHB	1988.97 ± 3131.27
FibroScan Score (means ± SD) en kPa	**6.44 ± 2.3 kPa**
Stages of liver fibrosis as per FibroScan, n (%)	
F0 - F1 (<7 kPa)	173 (71.78%)
F2 (7 - 8.99 kPa)	31(12.86%)
F3 (9 - 12.49 kPa)	30 (12.45%)
F4 (≥12.5 kPa)	7 (2.91%)
APRI score (mean ± SD)	**0.36 ± 0.19**
<0.5	185 (76.6%)
≥0.5 - ≤1.5	55 (22.83%)
>1.5	1 (0.41%)
FIB-4 score (mean ± SD)	**1.04 ± 0.55**
<1.45	179 (74.27%)
≥ 1.45 - ≤3.25	62 (25.73%)
>3.25	0 (0%)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; APRI: aspartate transaminase-to-platelet ratio index; FIB-4: fibrosis-4.

There were correlations between LSM and FIB-4 (r = 0.24; p = 0.000135) as well as between LSM and APRI (r = 0.34; p = 4.510 - 8) (Figure 1, Figure 2).

Evaluation of the performance of FIB-4 and APRI for the diagnosis of fibrosis (see Figure 3).

High AUROC values for APRI and FIB-4 indicated the very good performance of these tests in recognizing significant fibrosis. The ROC curve for the APRI score had an AUROC of 0.752 (CI 0.667 - 0.837), sensitivity of 90.17%, specificity of 36.76%, with a positive predictive value (PPV) of 78.39% and a negative predictive value (NPV) of 59.52%. The ROC curve for the FIB-4 index had an AUROC of 0.668 (CI 0.596 - 0.781), sensitivity 84.97%, specificity 39.70%, PPV 78.19%, and NPV 59.52%.

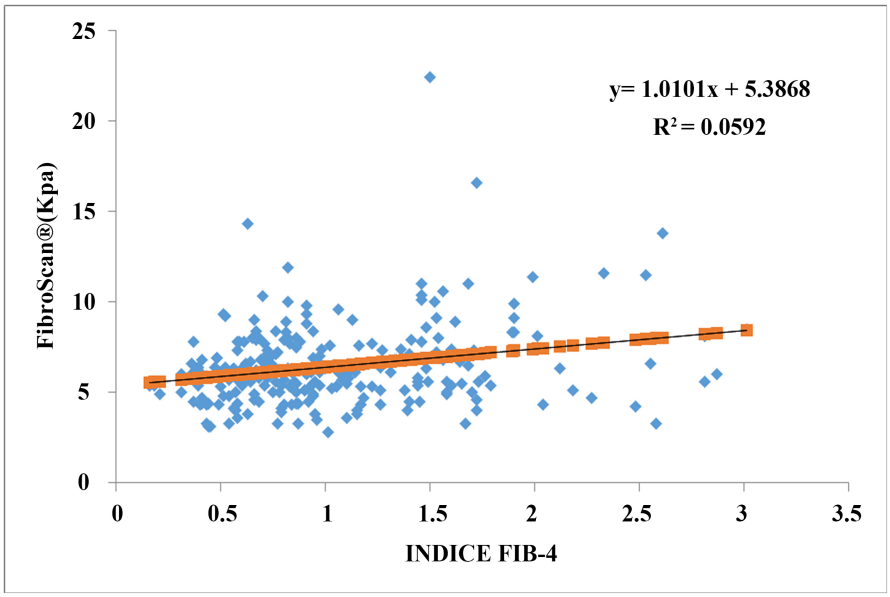

Figure 1. Impulse elastography (EI) as a function of the FIB-4 index.

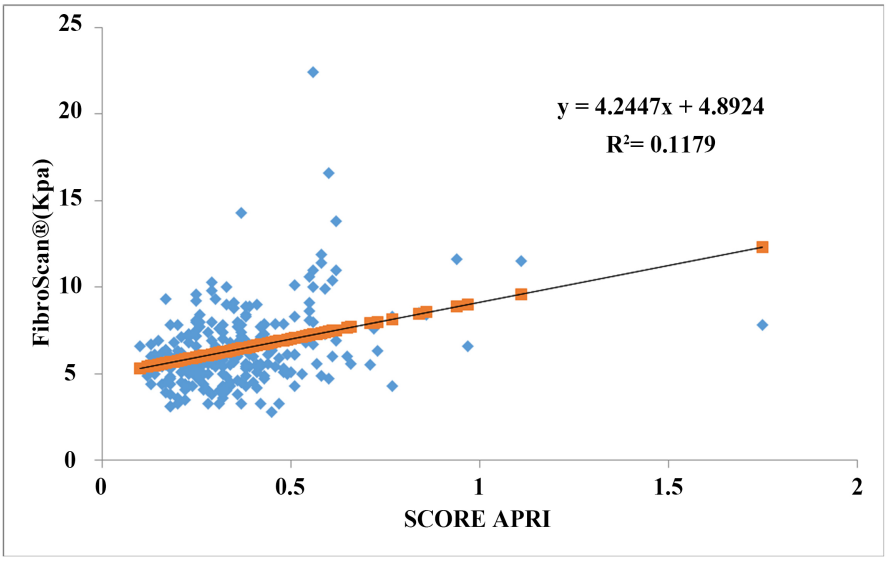

Figure 2. Impulse elastography (EI) as a function of the APRIscore.

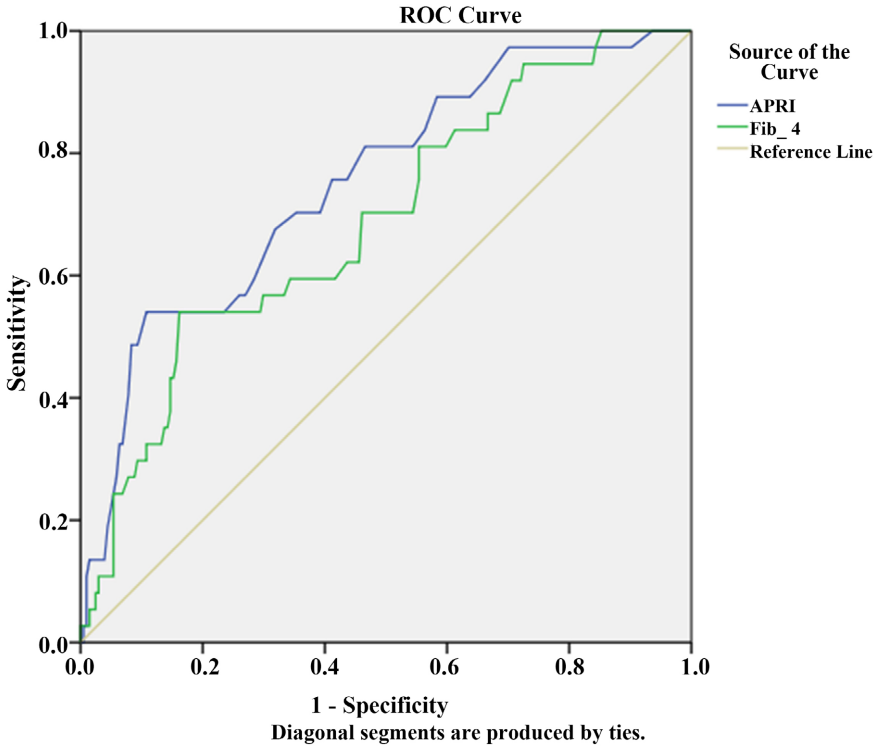

Figure 3. AUROC for APRI and FIB-4 for significant fibrosis.

4. Discussion

Chronically infected hepatitis B virus carriers with low viral replication and no cytolysis have a lower risk of progressing to fibrosis. However, few published studies have assessed the utility of non-invasive methods (APRI and FIB-4) compared to FibroScan® in patients chronically infected with HBV [13] [14] [15]. In our study, we found non-significant fibrosis in 71.78% by FibroScan. However, we found significant fibrosis in 28.22% by FibroScan. These results were similar to those of TOURE *et al*. in Senegal, who found non-significant fibrosis in 82% and significant fibrosis in 18% [16]. The prevalence of significant fibrosis in our study could be justified by the fact that transaminases, viral load, and FibroScan were not evaluated on the same day in our patients.

In our study, we found concordance between FibroScan, APRI, and FIB-4 in detecting fibrosis, with Pearson correlation analysis between FibroScan and fibrosis scores revealing coefficients of 0.34 for APRI, 0.24 for FIB-4 (with p-values < 0.05). This has been found in several African (Touré, Bagnaka) and Asian (Wang, Seo) studies [16] [17] [18] [19]. However, in the study by (Doffou) in Côte d'Ivoire, there was no correlation between FibroScan and the FIB-4 score, the APRI score [20].

In our series, the APRI and FIB-4 scores had comparable performance in ruling out significant fibrosis (LSM < 7.1 kPa), with sensitivity, specificity, PPV, and NPV of 90.17%, 36.76%, 78.39%, 59.52%, and 84.97%, 39.70%, 78.19%, 59.52%, respectively.

A study conducted in Senegal in chronically HBV-infected patients with low

viral replication by Touré *et al*. reported that the APRI and FIB-4 scores had comparable performance in ruling out significant fibrosis, with sensitivity, specificity, PPV, and NPV of 11.1%, 96.05%, 40%, 82%, and 11.11%, 90.79%, 22.22%, 81.18%, respectively [16]. In our study, we reported an area under the ROC curve of 0.668 for the FIB-4 index and 0.752 for the APRI score in predicting significant fibrosis. Therefore, moderate performance. Whereas, in a study comparing biological markers in chronic hepatitis B with normal ALT, Wang reported an area under the ROC curve of 0.81 for the FIB-4 score and 0.80 for the APRI score in predicting significant fibrosis [19]. The sensitivity, specificity, PPV, and NPV were 38%, 98%, 65%, and 84% for the APRI score and 63%, 88%, 61%, and 93% for FIB-4 [15]. Xu observed in a meta-analysis during chronic HBV infection the diagnostic accuracy of these biomarkers in predicting significant fibrosis with an area under the ROC curve of 0.77 and 0.75, respectively, for the APRI score (N = 3573) and FIB-4 (N = 1996); with a sensitivity of 65.8% and specificity of 73.6% for FIB-4 [21]. In another study, Sébastiani *et al*. studied the performance of the APRI and FIB-4 scores in 2411 patients with chronic liver disease. The results showed that in chronic HBV carriers, the APRI score had an area under the ROC curve of 0.68 with an NPV of 72% and a sensitivity of 67.9%, slightly higher than that of FIB-4, which was 0.66, 60.1%, and 65%, respectively [21] [22]. The results of these various studies indicate that both APRI and FIB-4 scores have the same efficacy in excluding significant fibrosis.

As our study shows, the APRI score and the FIB-4 index can easily rule out significant fibrosis in chronically inactive HBV carriers. However, these two scores must be interpreted with caution in patients with thrombocytopenia, as there is a risk of overestimating significant fibrosis, especially in our context of endemic malaria.

Identifying patients with significant fibrosis in the 'immune tolerance' phase based on their ALT levels is important. Due to their moderate PPV, although the FIB-4 and APRI scores are good tests to rule out significant fibrosis in chronically inactive HBV carriers, FibroScan can still be useful for patients with FIB-4 > 1.45 or APRI > 0.5; to provide a better assessment of fibrosis and thus better specify the prognosis.

5. Conclusion

Fibrosis assessment tests (APRI and FIB-4) have performance for diagnosing hepatic fibrosis in chronic carriers of the hepatitis B virus with low viral replication and no cytolysis. These methods (APRI and FIB-4) can exclude significant fibrosis. Their use would better select patients for FibroScan, thus reducing the cost of care. However, further large-scale multicenter studies should be conducted in sub-Saharan Africa to better evaluate the diagnostic performance of these methods.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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