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Non-invasive assessment of hepatic fibrosis among patients with chronic hepatitis B virus infection in three tertiary hospitals in Nigeria

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Abstract

Objective: This study aimed to assess hepatic fibrosis, using noninvasive tests, among patients with chronic hepatitis B virus infection in Nigeria.

Methods: The study was a retrospective cross-sectional, hospital-based, multicentered study. The data of adult Nigerians who were aged 18 years and above who had been diagnosed with chronic hepatitis B infection and were not on treatment were extracted from three tertiary health institutions across Nigeria. Sociodemographic and relevant clinical data were obtained from the case notes of the patients. Fibrosis-4 and aspartate aminotransferase platelet ratio index scores were calculated to determine the presence and severity of liver fibrosis in the patients. The data obtained were analyzed using Statistical Package for the Social Sciences (version 25.0). A *p*-value of less than 0.05 was considered as statistically significant.

Results: The data of a total of 234 patients were extracted for this study from across 3 tertiary hospitals in Nigeria. There were 132 (56.4%) males and 102 (43.6%) females in a ratio of 1.29:1 with a mean age of 37.92 ± 12.34 years. The fibrosis-4 score of the patients showed that 62.8% had "Normal/Mild Fibrosis," 25.6% had "Moderate Fibrosis," and 11.5% had "Severe Fibrosis/Cirrhosis." The aspartate aminotransferase platelet ratio index score of the patients showed that 64.1% had "No Fibrosis," 20.9% had "Mild Fibrosis," 6.4% had "Moderate Fibrosis," and 8.5% had "Severe Fibrosis/Cirrhosis." The median fibrosis-4 score of the patients was 1.18 (0.77–1.74), while the median aspartate aminotransferase platelet ratio index score was 0.40 (0.26–0.69). Liver ultrasonography detected cirrhosis in 8.5% of the patients. All the patients were not yet on treatment for hepatitis B infection.

Conclusion: The prevalence of hepatic fibrosis is high among patients with chronic hepatitis B virus infection in Nigeria and a large number of these patients were not yet on therapy. Noninvasive assessment of hepatic fibrosis should be considered as a critical part of the work-up of patients with chronic hepatitis B infection.

Keywords

Chronic hepatitis B, liver fibrosis, noninvasive tests, Nigeria

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Introduction

Chronic hepatitis B virus (HBV) infection is a major cause of liver morbidity and mortality worldwide.[1] According to the World Health Organization (WHO), about 2 billion people (one-third of the world population) globally have evidence of previous exposure to HBV and as at 2019 about 296 million people were chronically infected with the virus.[2,3] About 1.5 million new infections of HBV occurs each year with about 820,000 deaths annually, largely from fulminant hepatitis, decompensated liver cirrhosis and hepatocellular carcinoma.[2]

HBV infection is highly endemic in sub-Saharan Africa and southeast Asia with endemicity of over 8% prevalence rate.[3,4] Nigeria is one of the countries of the world with a high prevalence of HBV infection with over 70% of the population showing evidence of previous exposure to the virus and 7.3% to 24% of the populace having serological evidence of current infection (average 8.1%).[5,6] Approximately 20 million Nigerians are chronically infected with HBV.[7] It is the commonest cause of liver disease in Nigeria and it is the main etiological agent for hepatocellular carcinoma in Nigeria.[8,9]

Most patients with chronic HBV infection usually do not have symptoms of liver disease until liver failure or liver cancer has developed; hence, the need for routine screening for early detection of the disease, close monitoring for disease progression and commencement of therapy once indicated.[1] Assessment of liver fibrosis is essential in patients with chronic HBV infection for early identification of patients who should receive treatment in order to prevent progression of the disease.[10,11]

Noninvasive measures of assessment of liver fibrosis are now generally more preferred to liver biopsy which is an invasive procedure with potential risk of development of severe complications.[11] Noninvasive assessment of liver fibrosis can aid clinical decision-making on antiviral treatment, monitoring disease progression, treatment response, and to determine the overall prognosis. Noninvasive tests are now being incorporated into various international guidelines for HBV management and relied upon regularly to inform clinical judgment.[10]

Various serum biomarkers and imaging techniques have been developed to assess hepatic fibrosis noninvasively. Examples of tools using serum biomarkers include aspartate aminotransferase platelet ratio index (APRI) score, fibrosis-4 (FIB-4) index, Forns index, HepaScore, FibroMeter, FibroTest, Zeng index, and Hui index.[11] Imaging techniques include liver ultrasound scan, transient elastography, computed tomography, and magnetic resonance imaging scans.[10] FIB-4 index and APRI score are both well validated and are widely used as noninvasive tools for assessing hepatic fibrosis, and they were used for this study.[12–15]

Only a very few small-scale studies have been done on this subject in Nigeria, hence this study.[16,17] This study aimed to assess the presence and severity of hepatic fibrosis among treatment-naïve patients with chronic HBV infection in three tertiary hospitals in Nigeria using FIB-4 scoring and APRI scoring.

Methods

Study location

The study was conducted at three tertiary hospitals across Nigeria namely: Federal Teaching Hospital Ido-Ekiti (FETHI), Ekiti State in the southwestern geopolitical zone of Nigeria; Federal Teaching Hospital Lokoja (FTHL), Kogi State in the north central geopolitical zone of Nigeria; and University of Abuja Teaching Hospital (UATH) Gwagwalada, Abuja in the north central geopolitical zone of Nigeria. The three tertiary hospitals provide general and specialist care services for both in-patient and out-patient clients. Various laboratory services are also available in the hospitals. The study was carried out at the gastroenterology/hepatology specialist clinics of the participating hospitals.

Study design

The study was a retrospective cross-sectional, hospital-based, multicentered study.

Study population

The study population comprised of adult Nigerians who were aged 18 years and above who had been diagnosed with chronic hepatitis B infection.

Diagnostic criteria for chronic hepatitis B infection

Simultaneous presence of three viral markers: positive hepatitis B surface antigen (HBsAg), negative hepatitis B surface antibody (HBsAb), and positive hepatitis B core antibody (HBcAb IgG).[1]

Inclusion criteria

Adult Nigerians aged 18 years and above.

Individuals who had been diagnosed with chronic hepatitis B infection and have not received treatment.

Patients with complete clinico-laboratory data.

Exclusion criteria

Individuals less than 18 years of age.

Individuals with chronic hepatitis B infection who have received treatment.

Patients with incomplete/insufficient clinico-laboratory data.

Individuals who had been diagnosed with hepatocellular carcinoma.

Individuals who have HIV/HBV co-infection.

Individuals who had been diagnosed with other causes of chronic liver disease such as hepatitis C infection, nonalcoholic fatty liver disease, chronic alcoholics with alcoholic liver disease.

Study duration

Data was collected over a 6-month period from July 1, 2023 to December 31, 2023.

Sample size estimation

The sample size estimation was based on the available most recent national prevalence of chronic hepatitis B infection in Nigeria (8.1%).[6] In order to determine the accurate sample size that would be needed for significant statistical deductions, the Fisher's formula was used.[18]

$$n = \frac{Z^2 pq}{d^2}$$

where
n = the desired sample size (where population >10,000)
z = standard normal deviation, usually set at 1.96 which corresponds to 95% confidence level
p = the best estimated prevalence in the target population (8.1%).[6]
(National prevalence of chronic hepatitis B infection in Nigeria)
$q = 1 - p$
d = degree of accuracy desired set at 0.05

$$n = \frac{1.96^2 \times 0.081 \times 0.919}{0.05 \times 0.05} = 114.3$$

The estimated sample size was approximately 115; therefore, a minimum of 115 patients needed to be recruited into the study. However, the data of a total of 234 patients with chronic hepatitis B infection were used from the 3 tertiary health institutions that took part in the study. This large data of patients greatly increased the power of this study and would make the findings very reliable. This is the largest study till date on this subject in Nigeria.

Selection procedure

The clinic record was used to obtain the list of the patients, and their respective case note numbers, who are attending the Gastroenterology/Hepatology specialist clinic for chronic hepatitis B infection. Their case notes were subsequently retrieved from the Records Office.

The authors at the various participating institutions applied the study criteria in selecting the patients into the study. Patients that did not fulfill the study criteria were excluded from the study.

Sampling technique

Selection of patients' case notes for the study was by convenience sampling technique: successive selection of case notes of patients who fulfilled the study inclusion criteria.

Data collection

A well-structured Data Collection Instrument was used to obtain the relevant sociodemographic (age, gender, occupation, marital status, religion, tribe, and any history of cigarette smoking, alcohol use, substance abuse, and use of herbs) and clinico-laboratory data from the patients' case notes including the results of Hepatitis B Panel (HBsAg, HBsAb, hepatitis B envelope antigen (HBeAg), hepatitis B envelope antibody (HBeAb), HBcAb (IgM and IgG)), Anti-HCV, HIV, Liver function test, and Full blood count. The data collection instrument was pretested with the data of 10 (4.3%) study subjects and necessary adjustments were made before the final version was used for the study. Also, in order to ensure high data quality, the authors who had undergone a 2-day training session on the use of the data collection instrument were responsible for retrieving the data. The training was conducted collectively virtually in order to ensure uniform and standardized data retrieval across the three tertiary hospitals participating in the study.

Laboratory investigations

Full blood count. This was determined with an automated analyzer: H18 LIGHT Blood Cell Analyzer v11.00 (manufactured by SFRI Sarl Medical Diagnostics, Berganton, France).

Serological screening: This was performed with Rapid Test Kits for Hepatitis C virus antibodies and human immunodeficiency virus antibodies. Serum samples were tested for HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb (IgM and IgG) by Enzyme Linked Immunosorbent Assay (ELISA) method following standard operating procedures.

Liver function test. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by the Reitman–Frankel Colorimetric method.[19]

The above testing methods were similarly performed in all the three participating tertiary hospitals in this study, and they were performed within the 6-month period during which this study was conducted (July 1, 2023 to December 31, 2023).

Noninvasive tests of hepatic fibrosis

FIB-4 and APRI scores were calculated using a validated App (MDCalc®) which has FIB-4 calculator and APRI calculator by inputting the required parameters.[20] For FIB-4 score, age (years), AST (IU/L), ALT (IU/L), and platelet count ($\times 10^9$/L) are the required parameters while for APRI score; AST (IU/L) and platelet count ($\times 10^9$/L) are the required parameters.

$$\text{FIB}-4\ \text{formula}: \left(\text{age}\left(\text{years}\right)\times \text{AST}\left(\text{IU}/\text{L}\right)\right)\div \text{platelet count}\left(10^9/\text{L}\right)\times\sqrt{\text{ALT}}\left(\text{IU}/\text{L}\right)$$

Interpretation[20]:
<1.45 (normal/mild fibrosis)
1.45–3.25 (moderate fibrosis)
>3.25 (severe fibrosis/cirrhosis).

$$\text{APRI formula}: \left(\text{AST}\left(\text{IU}/\text{L}\right)\div 40\left(\text{ULN}\right)\right)\div \text{platelet count}\left(10^9/\text{L}\right)\times 100$$

Interpretation[20]:
<0.5 (no fibrosis)
0.5–1 (mild fibrosis)
1–2 (moderate fibrosis)
>2 (severe fibrosis/cirrhosis).

Data analysis

The data obtained was analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 computer software package (SPSS Chicago, Inc., Chicago, IL, USA).[21] We assessed the presence, severity, and predictors of hepatic fibrosis among patients with chronic HBV infection in Nigeria using FIB-4 scoring and APRI scoring.

Initial checks ensured data completeness and assessed the normality of sample distribution through Kolmogorov–Smirnov tests and Q-Q plots. A Kolmogorov–Smirnov test with a p-value <0.05 indicated significant deviation from normal distribution, while Q-Q plots with points aligning closely to the diagonal line indicated normality. Descriptive statistics were done for both continuous and categorical data. Continuous variables (laboratory parameters) with normally distributed data were presented as means (±standard deviation (SD)), while those that deviated from normal were presented as medians (interquartile range). Categorical variables (sociodemographic characteristics) were summarized in frequency tables as proportions and percentages. The distribution of the study participants across the three study locations was presented in a pie chart.

Appropriate parametric tests such as the Student's t-test were used for analyzing continuous variables, while nonparametric tests such as the chi-square (χ^2) test were used for the analysis of qualitative variables and to determine statistical significance. Bivariate analyses were conducted to compare the laboratory parameters between patients with and without significant liver fibrosis, utilizing an independent t-test or Mann–Whitney U-test as appropriate. Multivariate analysis was then carried out to identify sociodemographic predictors of hepatic fibrosis among patients. This involved employing a binary logistic regression with backward stepwise selection to identify predictor variables. The results, including statistical measures such as adjusted odds ratios, p-values, and confidence intervals (CIs), were presented in tables to communicate the significance and strength of the observed relationships. A p-value of <0.05 was considered statistically significant.

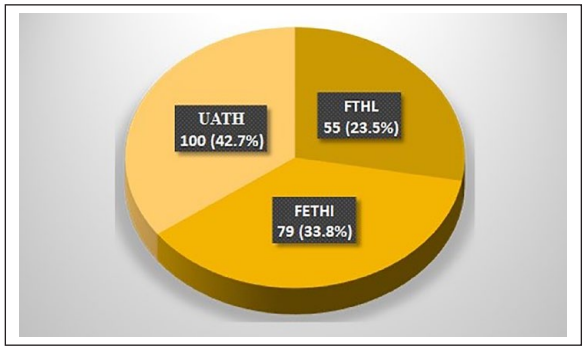

Figure 1. Distribution of the study participants across the three study locations.

Ethical considerations

The study was done in accordance with the ethical guidelines of the International Committee of Medical Journal Editors Recommendations. Informed consent was not required and was not obtained for the study. The identity of the study subjects was not disclosed, and all the information obtained from the patients' case notes were kept confidential. Ethical approval for this study was obtained from the Human Research and Ethics Committee of FETHI (Approval Number: ERC/2022/09/20/849A), Health Research Ethics Committee of UATH Gwagwalada (Approval Number: UATH/HREC/PR/279) and Health Research Ethics Committee of FTHL (Approval Number: FMCL/HREC/Vol.1/2023/176).

Results

The data of a total of 234 patients were extracted for this study from across 3 Tertiary Hospitals in Nigeria namely FETHI (79, 33.8%), UATH Gwagwalada (100, 42.7%), and FTHL (55, 23.5%) (Figure 1).

There were 132 (56.4%) males and 102 (43.6%) females in a ratio of 1.29:1. Majority (72.6%) of the patients were less than 45 years, while only 3.4% were above 64 years with

Table 1. Sociodemographic characteristics of the patients.

Variable	Frequency ($n = 234$)	Percentage
Age group		
Less than 45 years	170	72.6
45–64 Years	56	23.9
65 Years and above	8	3.4
Gender		
Male	132	56.4
Female	102	43.6
Occupation		
Student	49	20.9
Unemployed	11	4.7
Civil servant	85	36.3
Trader	30	12.8
Farmer	5	2.1
Artisan	6	2.6
Private business	17	7.3
Retiree	31	13.2
Marital status		
Single	72	30.8
Married	156	66.7
Divorced/separated	3	1.3
Widowed	3	1.3
Religion		
Christianity	168	71.8
Islam	66	28.2
Tribe		
Yoruba	123	52.6
Hausa	9	3.8
Igbo	14	6.0
Others	88	37.6
Comorbidity		
None	172	73.5
Hypertension	24	10.3
Diabetes mellitus	4	1.7
Renal disease	2	0.9
Others	32	13.7
History of cigarette smoking		
Yes	6	2.6
No	228	97.4
History of alcohol use		
Yes	28	12.0
No	206	88.0
History of substance abuse		
Yes	1	0.4
No	233	99.6
History of use of herbs		
Yes	73	31.2
No	161	68.8

a mean age of 37.92 ± 12.35 years. The sociodemographic distribution of the patients is shown in Table 1.

The FIB-4 score of the patients showed that 62.8% had "Normal/Mild Fibrosis," 25.6% had "Moderate Fibrosis," and 11.5% had "Severe Fibrosis/Cirrhosis." The APRI score

Table 2. Noninvasive hepatic fibrosis assessment and selected characteristics of the patients.

Variable	Frequency ($n = 234$)	Percentage
HBeAg		
Positive	28	12.0
Negative	206	88.0
Liver USS		
Normal	169	72.2
Cirrhosis	20	8.5
Hepatomegaly	34	14.5
Hepatic steatosis	11	4.7
AST/ALT ratio		
<1	57	24.4
>1	177	75.6
Albumin/globulin ratio		
>1	200	85.5
<1	34	14.5
APRI score		
<0.5 (No fibrosis)	150	64.1
0.5–1 (Mild fibrosis)	49	20.9
1–2 (Moderate fibrosis)	15	6.4
>2 (Severe fibrosis/cirrhosis)	20	8.5
FIB-4 score		
<1.45 (Normal/mild fibrosis)	149	62.8
1.45–3.25 (Moderate fibrosis	60	25.6
>3.25 (Severe fibrosis/cirrhosis)	27	11.5

ALT: alanine aminotransferase; APRI: aspartate aminotransferase platelet ratio index; AST: aspartate aminotransferase; FIB-4: fibrosis-4; HBeAg: hepatitis B envelope antigen; USS: ultrasound.

of the patients showed that 64.1% had "No Fibrosis," 20.9% had "Mild Fibrosis," 6.4% had "Moderate Fibrosis," and 8.5% had "Severe Fibrosis/Cirrhosis" (Table 2).

The median FIB-4 score of the patients was 1.18 (0.77–1.74), while the median APRI score was 0.40 (0.26–0.69). The laboratory parameters of the patients are shown in Table 3.

Table 4 shows the comparison of the prevalence of fibrosis among the study participants using FIB-4 scoring and APRI scoring. Seventeen (7.26%) patients were detected to have cirrhosis by both the FIB-4 scoring and APRI scoring when applied together, that is, both scoring tests are in agreement that these patients have cirrhosis. The other comparisons are as shown in Table 4.

Comparison of liver ultrasonography findings with FIB-4 scoring and APRI scoring is shown in Table 5. Twenty (8.5%) patients were detected to have cirrhosis by ultrasonography, 15 (6.4%) and 2 (0.8%) of these same patients were detected to have cirrhosis and moderate fibrosis, respectively, by FIB-4 scoring, while 13 (5.5%) and 3 (1.28%) of them were detected to have cirrhosis and moderate fibrosis, respectively, by APRI scoring. The other comparisons are as shown in Table 5.

Table 6 shows the differences in the laboratory parameters of patients with or without significant liver fibrosis. There was

Table 3. Laboratory parameters of the patients.

Variables	Total bilirubin[a]	Conjugated bilirubin[a]	ALT[a]	AST[a]	AST/ALT ratio[a]	ALP[a]	Protein[b]	Albumin[b]	Globulin[b]	Albumin/ globulin ratio[b]
Mean/ median	9.00	3.70	23.00	28.00	1.33	133.95	69.83	40.46	29.36	1.48
SD/IQR	6.60–14.85	2.50–6.20	16.00–35.25	20.00–43.25	1.00–1.74	62.75–198.75	±9.14	±7.73	±7.67	±0.51

Variables	PCV[b]	WBC[a]	Platelet count[b]	PT[a]	INR[a]	FIB-4 score[a]	APRI score[a]
Mean/ median	38.63	5.20	202.67	14.20	1.10	1.18	0.40
SD/IQR	±5.17	4.4–6.3	±77.69	12.00–16.90	1.00–1.20	0.77–1.74	0.26–0.69

[a]Median (IQR) was used for variables that do not follow a normal distribution.
[b]Mean (sSD) was used for variables with normally distributed data.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; APRI: aspartate aminotransferase platelet ratio index; AST: aspartate aminotransferase; FIB-4: fibrosis-4; INR: international normalized ratio; IQR: interquartile range; PCV: packed cell volume; PT: prothrombin time; WBC: white blood cells.

Table 4. Comparison of the prevalence of fibrosis using FIB-4 scoring and APRI scoring.

Variable	FIB-4 score			
	Normal/mild fibrosis (%), *n* = 147 (62.8)	Moderate fibrosis (%), *n* = 60 (25.6)	Severe fibrosis/cirrhosis (%), *n* = 27 (11.5)	Total (%), *n* = 234 (100)
APRI score				
No fibrosis	122 (52.1)	27 (11.5)	1 (0.4)	150 (64.1)
Mild fibrosis	23 (9.8)	23 (9.8)	3 (1.3)	49 (20.94)
Moderate fibrosis	2 (0.8)	7 (2.9)	6 (2.5)	15 (6.4)
Severe fibrosis/cirrhosis	0 (0.0)	3 (1.3)	17 (7.2)	20 (8.5)

APRI: aspartate aminotransferase platelet ratio index; FIB-4: fibrosis-4.

Table 5. Comparison of FIB-4 scoring and APRI scoring with liver ultrasonographic findings.

Variables	Liver ultrasonography				
	Normal, *n* = 169 (72.2%)	Hepatomegaly, *n* = 34 (14.52%)	Steatosis, *n* = 11 (4.7%)	Cirrhosis, *n* = 20 (8.5%)	Total, *n* = 234 (100%)
FIB-4 score					
Normal/mild fibrosis (<1.45)	128 (54.7)	10 (4.7)	6 (2.5)	3 (1.3)	147 (62.8)
Moderate fibrosis (1.45–3.25)	37 (15.8)	18 (7.7)	3 (1.3)	2 (0.8)	60 (25.6)
Severe fibrosis/cirrhosis (>3.25)	4 (1.7)	6 (2.5)	2 (0.8)	15 (6.4)	27 (11.5)
APRI score					
No fibrosis (<0.5)	125 (53.4)	15 (6.4)	8 (3.4)	2 (0.8)	150 (64.1)
Mild fibrosis (0.5–1)	34 (14.5)	12 (5.1)	1 (0.4)	2 (0.8)	49 (20.9)
Moderate fibrosis (1–2)	6 (2.5)	6 (2.5)	0 (0)	3 (1.3)	15 (6.4)
Severe fibrosis/cirrhosis (>2)	4 (1.7)	1 (0.4)	2 (0.8)	13 (5.5)	20 (8.5)

APRI: aspartate aminotransferase platelet ratio index; FIB-4: fibrosis-4.

a significant difference in the mean platelet count, protein, and albumin between patients with normal liver/mild fibrosis, and those with moderate-to-severe fibrosis at *p*-values of <0.001, 0.001, and <0.001, respectively. Similarly, there was a significant difference in the median international normalized ratio, total bilirubin, conjugated bilirubin, ALT, and AST between patients with normal liver/mild fibrosis and those with moderate-to-severe fibrosis at a *p*-value of 0.021, 0.008, 0.029, 0.006, and <0.001, respectively. There was no statistically significant difference between the packed cell volume, white blood cells, prothrombin time, alkaline phosphatase (ALP), globulin, and HBeAg status.

Selected predictors of hepatic fibrosis among the study participants are shown in Table 7. The odds of having

Table 6. Differences in the laboratory parameters of patients with or without significant liver fibrosis.

Variable	FIB-4 score			*p*-Value
	Normal/mild fibrosis, *n* = 147	Moderate to severe, *n* = 87	Test	
Mean PCV[a]	38.95 ± 4.89	38.09 ± 5.60	*t* = 1.230	0.220
Mean WBC[b]	5.2 (4.4–6.3)	5.2 (4.4–6.3)	*M* = 6384.0	0.983
Platelet count[a]	225.20 ± 72.87	164.59 ± 70.75	*t* = 6.215	<0.001
PT[b]	14.0 (12.0–16.0)	14.8 (12.2–18.8)	*M* = 85.5	0.247
INR[b]	1.1 (1.0–1.2)	1.1 (1.0–1.3)	*M* = 2184.0	0.021
Total bilirubin[b]	8.5 (6.1–13.1)	9.7 (7.4–19.7)	*M* = 5071.5	0.008
Conjugated bilirubin[b]	3.5 (2.5–5.2)	4.0 (3.0–9.3)	*M* = 5299.5	0.029
ALT[b]	20.0 (16.0–30.0)	27.0 (16.0–56.0)	*M* = 5033.0	0.006
AST[b]	23.0 (17.0–32.0)	42.0 (28.0–97.0)	*M* = 2840.0	<0.001
ALP[b]	124.0 (49.0–188.0)	139.0 (85.0–221.0)	*M* = 5631.0	0.127
Protein[a]	71.37 ± 7.87	67.24 ± .51	*t* = 3.412	0.001
Albumin[a]	42.04 ± 5.99	37.81 ± 9.45	*t* = 4.187	<0.001
Globulin[a]	29.33 ± .62	29.41 ± .81	*t* = −0.075	0.940
HBeAg				
Positive	14 (6.0)	14 (6.0)	OR	0.135
Negative	133 (56.8)	73 (31.2)		

[a]Mean (sSD) was used for variables with normally distributed data.
[b]Median (interquartile range) was used for variables that do not follow a normal distribution.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FIB-4: fibrosis-4; HBeAg: hepatitis B envelope antigen; INR: international normalized ratio; PCV: packed cell volume; PT: prothrombin time; WBC: white blood cells.

Table 7. Predictors of hepatic fibrosis among the study participants.

Variable	FIB-4 score			*p*-Value
	Normal/mild fibrosis (%), *n* = 147 (62.8)	Moderate-to-severe fibrosis, *n* = 87 (37.2)	AOR (95% cCI)	
Study center				
FETHI (Ref.)	50 (21.4)	29 (12.5)	1	
FTHL	28 (11.9)	27 (11.5)	1.29 (0.69, 2.41)	0.422
UATH	69 (29.5)	31 (13.2)	2.14 (1.09, 4.22)	0.027
Age group				
Less than 45 years (Ref.)	122 (52.1)	48 (20.5)	1	
45–64 Years	24 (10.2)	32 (13.7)	0.05 (0.01, 0.47)	0.008
65 Years and above	1 (0.4)	7 (3.0)	0.19 (0.02, 1.65)	0.133
Gender				
Male (Ref.)	73 (31.2)	59 (25.2)	1	
Female	74 (31.6)	28 (12.0)	0.47 (0.27, 0.81)	0.007

FETHI: Federal Teaching Hospital Ido-Ekiti; FIB-4: fibrosis-4; FTHL: Federal Teaching Hospital Lokoja; UATH: University of Abuja Teaching Hospital.

moderate-to-severe fibrosis was 2.14 times (95% CI: 1.09, 4.22) more likely among patients seen at UATH compared to those seen at FETHI at a *p*-value of 0.027. The odds of having moderate-to-severe fibrosis was 0.05 times (95% CI: 0.01, 0.47) less likely among patients aged 45–64 years compared to those less than 45 years at *p*-values 0.008. Females were 0.47 times (95% CI: 0.27, 0.81) less likely than males to have moderate-to-severe fibrosis at a *p*-value of 0.007.

Discussion

This multicentered study was conducted across three tertiary hospitals in Nigeria namely FETHI, FTHL, and UATH Gwagwalada. The study examined the presence of hepatic fibrosis among patients with chronic HBV infection using noninvasive assessment tools, primarily FIB-4 Scoring and APRI scoring.

The mean age of the participants in this study (37.9 years) was higher than that reported by Ameh et al.[16] in Jos (36.3 years) and that by Lakoh et al.[22] in Sierra Leone (32.6 years) but less than that by Wang et al.[23] in China (39.6 years). There were more males than females in this study. This is in keeping with the gender distribution of other similar studies on chronic hepatitis B infection in Africa and globally.[16,17,22–25]

In this study, based on the FIB-4 score the prevalence of hepatic fibrosis is high: severe fibrosis/cirrhosis (11.5%) and moderate fibrosis (25.6%). The median FIB-4 score was 1.18 and the median APRI score was 0.40. These values are higher than that reported by Lakoh et al.[22] (0.80 and 0.37, respectively) and that reported by Johannessen et al.[25] (0.82 and 0.30, respectively) in a systematic literature review on chronic HBV in Africa. Ameh et al.[16] also reported a high prevalence of significant fibrosis (31.1%) and cirrhosis (12.1%) among their patients. Thus, the results of our study are in keeping with the findings of similar studies and it supports the fact that there is significant fibrosis among chronic HBV patients who are resident in areas with high endemicity for HBV infection.[25]

In this study, FIB-4 scoring detected more patients with severe fibrosis/cirrhosis (cut-off >3.25) than APRI scoring (cut-off >2) and FIB-4 scoring also detected more patients with moderate fibrosis than APRI scoring. Furthermore, when FIB-4 scoring and APRI scoring were compared with liver ultrasonography, FIB-4 scoring correlated better than APRI scoring in detecting cirrhosis. Kooffreh-Ada et al.[26] in Calabar concluded in their study on comparative analysis of the APRI and FIB-4 score in evaluating the severity of chronic liver disease in a low- and middle-income setting that FIB-4 score correlated better than APRI score. Zhang et al.[15] in China also concluded in their study that both FIB-4 and APRI are useful for diagnosis of fibrosis and that both FIB-4 and APRI have similar diagnostic accuracy in predicting significant and severe fibrosis, while FIB-4 is superior to APRI in predicting cirrhosis. Li et al.[14] in a meta-analysis to determine the diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis in China also concluded that the FIB-4 index is valuable for detecting significant fibrosis and cirrhosis in HBV-infected patients. Based on these findings, therefore, using the cut-off >2 for APRI scoring for detecting severe fibrosis/cirrhosis will have great implications when deciding on initiation of therapy among patients with chronic HBV infection particularly in high endemic environments.

The indications for treatment in chronic HBV infection are generally based mainly on the combination of four criteria: serum HBV DNA levels, serum ALT levels, HBeAg status, and severity of liver disease (assessed by clinical evaluation, liver biopsy, or noninvasive methods).[27,28] Liver biopsy is not always available and not readily acceptable; hence, the need to assess the severity of liver disease through noninvasive methods. Indications for treatment also takes into account other factors such as age, health status, family history of hepatocellular carcinoma (HCC) or cirrhosis, and extrahepatic manifestations.[27,28] The WHO in 2015 published the guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection and recommends as a priority that all adults, adolescents, and children with chronic hepatitis B infection and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status, or HBV DNA levels.[20]

The Federal Ministry of Health (FMOH) of Nigeria published in 2016 the national guidelines for the prevention, care, and treatment of viral hepatitis B and C in Nigeria and also recommends treatment as a priority for adult patients with chronic HBV infection with APRI score >2 just as the WHO recommendation.[29] This guideline has now been recently updated in November 2023 to prioritize treatment for adult patients with chronic HBV infection with APRI score $\geqslant 1$ or FIB-4 score $\geqslant 3.25$.[30] This became necessary based on the burden of evidence that the use of APRI score of >2 in a high endemic environment for HBV will miss out many patients with severe fibrosis/cirrhosis.[25]

The Society for Gastroenterology and Hepatology in Nigeria in 2015 published the guideline for the management of chronic hepatitis B and C in Nigeria which was revised in 2021, and in both editions, the society recommends treatment for adult patients with chronic HBV infection with APRI score >2.[6,31] There is a need for the society to review this position. No definitive cut-off was provided for the FIB-4 score.

The European Association for the Study of the Liver in her 2017 Clinical Practice Guidelines on the management of HBV infection supports the use of noninvasive methods for the assessment of the severity of liver disease, the use of transient elastography was preferred and deemed to offer a higher diagnostic accuracy than the serum biomarkers, thus no cut-off values were stated for APRI score or FIB-4 score for use in determining initiation of treatment in patients with chronic HBV infection.[32]

The Asian Pacific Association for the Study of Liver in 2015 published the clinical practice guidelines on the management of hepatitis B and recommends the initiation of therapy in adult patients with chronic HBV infection with APRI score $\geqslant 1.5$.[27]

The American Association for the Study of Liver Diseases published an update on the prevention, diagnosis, and treatment of chronic hepatitis B in 2018 and supports the use of noninvasive methods for the assessment of the severity of liver disease including the use of serum biomarkers such as FIB-4 score and FibroTest, but the use of transient elastography was preferred.[28] If these noninvasive tests indicate significant fibrosis ($\geqslant$F2), treatment is recommended.

Regardless of the treatment guideline used, all patients with chronic HBV infection with severe fibrosis or cirrhosis qualify for treatment. In this study, based on FIB-4 score of >3.25 (severe fibrosis/cirrhosis), 27 (11.5%) patients ought

to be on treatment but were not receiving treatment. Also based on APRI score of >2 (severe fibrosis/cirrhosis), 20 (8.5%) patients ought to be on treatment but were not receiving treatment. Hence, this study has revealed that a large number of patients with chronic HBV infection who ought to be on treatment are not on treatment and are at a high risk of progressive liver disease and development of decompensated cirrhosis and hepatocellular carcinoma.

These patients were missed out and not commenced on therapy probably because they were not evaluated for hepatic fibrosis. This is an important finding from this study. Perhaps if they had been assessed for hepatic fibrosis, they would have been identified has having significant fibrosis and then commenced on treatment. This shows the importance of routinely evaluating patients for hepatic fibrosis using noninvasive testing tools since liver biopsy may not be an acceptable procedure to many patients.

If an APRI score of >1 is used to determine initiation of therapy based on the current 2023 recommendation of the FMOH of Nigeria, then 35 patients instead of 20 would qualify to be on treatment. This current treatment guideline would enable the initiation of therapy in more patients with chronic HBV infection and consequently limit progressive liver disease and the development of adverse sequelae.

Johannessen et al.[25] in a systematic review and individual-patient data meta-analysis of noninvasive fibrosis markers for chronic hepatitis B in Africa concluded that the WHO-recommended APRI threshold of >2.0 is inappropriately high in sub-Saharan Africa and thus suggested that the cut-off value for hyperendemic environment such as sub-Saharan Africa should be lower. APRI, FIB-4, and most other liver fibrosis markers were developed and validated in Caucasian and Asian cohorts and not in Africa.[12]

In 2024, the WHO is planning to publish consolidated guidelines on hepatitis prevention, diagnosis, treatment, and care which will focus among other things on expanded treatment eligibility in adults, adolescents, and children, and thresholds for use of noninvasive tests for staging liver disease.[33] It is hoped that the cut-off for APRI score for initiation of treatment would be reduced and that cut-off values would be made available for other noninvasive tests such as the FIB-4 score.

Apart from chronic HBV infection, other factors may be responsible for the development of hepatic fibrosis and when they are present, they can accelerate the rate of progression of the fibrosis in such patients. These factors include age, gender, intake of alcohol, herbs, cigarette smoking, and comorbidities such as obesity, diabetes mellitus, and nonalcoholic fatty liver disease/metabolic dysfunction associated steatotic liver disease (NAFLD/MASLD).[27,32] In this study, advanced age and male gender significantly increased the risk of hepatic fibrosis in the patients.

This study has provided much needed information and scientific data that would be useful for updating current treatment guidelines for the management of patients with chronic HBV infection. The findings from this study are poised to improve clinical practice as well as to stimulate further interest and research on this topic.

Limitations

This was a retrospective study, a prospective longitudinal study would have provided more information about the changes with time in the status of the hepatic fibrosis in these patients with or without therapy by regular monitoring with these noninvasive tests of hepatic fibrosis, this would have increased the power of this study. Another limitation of this study is that the APRI scores and FIB-4 scores were not compared with a reference gold standard for fibrosis/cirrhosis such as liver biopsy histology or Fibroscan (transient elastography).

Conclusion

This study has shown that the prevalence of hepatic fibrosis is high among patients with chronic HBV infection in Nigeria which is a high endemic nation for HBV. Furthermore, this study showed that a large number of these patients had significant fibrosis and ought to be on therapy. They were not yet on therapy probably because they were not evaluated for hepatic fibrosis.

Noninvasive assessment of hepatic fibrosis should be a critical part of the work-up of patients with chronic hepatitis B infection as an alternative to liver biopsy which may not be acceptable to patients due to its invasiveness. FIB-4 and APRI scorings are simple, well validated tools that can be used routinely in the clinical setting for the assessment of hepatic fibrosis.

Early identification of patients with significant fibrosis and commencement of therapy can prevent the development of complications such as liver failure and hepatocellular carcinoma.

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Author contributions

All the authors contributed sufficiently toward this research work, and the publication is approved by all the authors. Each of the authors fulfilled the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE). OOO, ALO, UBI, and JOS conceived and designed the study. Data collection was carried out by OOO, ALO, UBI, AOE, and OOA. OOO, ALO, UBI, OOG, IIM, and JOS were responsible for data analysis and interpretation. OOO, ALO, UBI, OOG, IIM, and OOA wrote the first draft of the article. OOO, ALO, UBI, OOG, IIM, AOE, JOS, and OOA contributed to subsequent drafts and were involved in the critical revision of the article for important intellectual content. All authors approved the final version of the article

to be published. OOO is guarantor for this article, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Ethics approval

Ethical approval for this study was obtained from: Human Research and Ethics Committee of Federal Teaching Hospital Ido-Ekiti (Approval Number: ERC/2022/09/20/849A). Health Research Ethics Committee of University of Abuja Teaching Hospital Gwagwalada (Approval Number UATH/HREC/PR/279). Health Research Ethics Committee of Federal Teaching Hospital Lokoja (Approval Number: FMCL/HREC/Vol.1/2023/176).

Informed consent

Not applicable because this was a retrospective study, and there was no contact with the patients. All the data for the study were obtained from the case notes of the patients.

Trial registration

Not applicable.

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