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Evaluation of Non-Invasive Markers of Liver Fibrosis in Chronic Hepatitis B Patients in a Sub-Saharan African Setting: Transient Elastography versus APRI, FIB4, GTT/Platelet Scores

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Abstract

Background: Non-invasive markers which use routine laboratory tests are less expensive and highly needed to assess and stage liver fibrosis in chronic hepatitis B patients in Sub-Saharan Africa. We aimed at evaluating liver fibrosis, using the Aspartate aminotransferase to Platelet Ratio Index (APRI), Fibrosis Index Based on 4 factors (FIB4), and Gamma-glutamyl transpeptidase to Platelet Ratio (GPR) in chronic hepatitis B patients with transient elastography as the reference so as to choose an alternative to transient elastography. **Method:** We carried out a cross-sectional study using the records of patients who attended the Douala General Hospital and Marie O Polyclinic Douala from 2012 to 2017. Non-invasive tests were compared with Transient Elastography. The Spearman coefficient was used to determine correlation. The sensitivity, specificity, positive predictive values and negative predictive values were used to get the optimal cut-off values. The diagnostic accuracy was estimated by calculating the area under the Receiver Operating Characteristic Curve (ROC). $P < 0.05$ was considered statistically significant. **Results:** Of the 243 patient records studied, the median age or interquartile range

(IQR) was 35 (29 - 42) years with a male predominance of 73.7%. More than 60% of the study population had normal transaminases. Significant fibrosis was found in 88 (36.2%) patients and 32 (13.7%) patients had cirrhosis. APRI had the best cut-off values and highest area under the ROC Curve, for significant fibrosis and cirrhosis with 0.55 (0.823 95% CI [0.769 - 0.869], P < 0.001) and 0.65 (0.84 95% CI [0.788 - 0.884], P < 0.005) respectively. **Conclusion:** APRI, had the best diagnostic properties to detect liver fibrosis and cirrhosis in patients with Chronic Hepatitis B in Douala. The cut-off values are 0.55 and 0.65 for significant fibrosis and cirrhosis respectively.

Keywords

Chronic Hepatitis B, Liver Fibrosis, Non-Invasive Tests, Cross Sectional, Douala

1. Introduction

Hepatitis B virus (HBV) infection poses a major burden to health worldwide [1]. Out of every three persons in the world, at least one has been infected and lives with the virus [2]. About 240 million people are chronically infected worldwide of whom 30% - 45% will develop cirrhosis and/or hepatocellular carcinoma (HCC) [3]. It is estimated that 780,000 people die annually from HBV infection; 650,000 are attributed to chronic HBV [2] [3]. In Sub-Saharan Africa and East Asia, at least 5% of the adult population is chronically infected [4]. The prevalence of HBV in Cameroon is about 11.2% with more than 8% chronically infected [5].

Liver fibrosis which results in the distortion of the hepatic architecture and is a precursor of cirrhosis is the most common complication of chronic Hepatitis B [6] [7]. Severe fibrosis and cirrhosis can also increase the incidence and mortality of HCC [8]. Early detection and staging of liver fibrosis are important to determine prognosis and prioritize treatment, thus reducing or preventing its progression to cirrhosis and/or hepatocellular carcinoma [9]. Liver biopsy has been traditionally considered the gold standard for assessing the degree of liver fibrosis [10]. However, its high cost, invasiveness, sampling errors, patient discomfort, and risk of complications leading to poor patient compliance, as well as a need for expert histological interpretation raise questions regarding its suitability for use in low-income countries [4] [11] [12].

Several non-invasive markers have been validated since 2001 [13]. Transient Elastography a non-invasive alternative to liver biopsy has shown excellent diagnostic accuracy for predicting significant fibrosis and cirrhosis [14] [15]. Unfortunately, the unavailability, procedures involved in the performance and the cost of Transient Elastography make its use limited in our setting.

The World Health Organization (WHO) has recommended the use of non-invasive tests based on simple and available laboratory methods, in the assess-

ment of liver fibrosis [16]. The recent WHO HBV guidelines recommend APRI as the preferred non-invasive test to assess liver fibrosis in resource-limited settings [16]. However, APRI and other Non-Invasive Tests like FIB4 and GPR have been evaluated with good diagnostic accuracy [9]. Unfortunately, data is still sparse in our setting. The main objective of this study was to evaluate liver fibrosis, using APRI, FIB4 and GPR scores in chronic Hepatitis B patients with Transient Elastography as the reference to choose an alternative to Transient Elastography. We hope to provide data that will assist in the early detection and staging of fibrosis, the timely intervention and follow-up of the patients thus reducing the burden of HBV infection.

2. Methodology

2.1. Study Design and Setting

We conducted a 5 year (2012-2017) cross-sectional study at the Douala General Hospital (DGH) and Polyclinique Marie O (PMO) Douala from 1st January to 31st March 2018. The DGH is a tertiary referral health facility serving the entire country and neighboring countries with a capacity of 320 beds. It has a treatment center for hepatitis and also serves as a teaching hospital. PMO is a private clinic in Douala where the management of hepatitis B is carried out as in the DGH. Its particularity is that, it has a Transient Elastography (fibroscan®) machine unlike the DGH and most hospitals in Douala.

2.2. Data Collection

Patients were recruited from among those followed up at the aforementioned clinic (PMO and DGH), in whom chronic hepatitis B had been confirmed by the persistence of HB surface antigen for more than six months. Their records from 2012-2017 were reviewed. The study period was from 1st January to 31st March 2018. Included in the study were chronic hepatitis B patients with results of transient elastography, AST, ALT and platelets counts in their files. Excluded were patients with other well-defined liver diseases (e.g. Alcoholic liver disease, non-alcoholic fatty liver disease, acute liver failure, Wilson's disease), HCC and other cancers, co-infections with HIV and HCV, decompensated liver cirrhosis, pregnant women, patients on immunosuppressive therapy and HBV treatment. A data collection form was used to enter 1) Sociodemographic data; age, gender, occupation, 2) Clinical characteristics; comorbidities, risk factors (factors considered susceptible to favor hepatitis B contamination through the parenteral route; these included previous surgery, dental care and scarification, as these practices in our context are often done with non-sterile instruments), clinical presentation at time of diagnosis, 3) Laboratory investigations; general laboratory investigations, liver enzymes and functions, viral markers, virologic activity and Transient elastography results. The clinical, laboratory and TE data were all collected at a single point in time upon presentation.

BMI was classified according to literature: undernourished as less than 18, normal between 18 and 25, overweight between 25 and 30, and obesity as greater

than 30.

These laboratory investigations were done in the fully functional laboratories of DGH and PMO with the same protocols. Baseline diagnosis of hepatitis B in the patients included in the study was based on the results of HBs testing: first with rapid DETERMINE testing, then confirmed with ELISA.

HBV DNA quantification was done using COBAST TaqMan HBV test with high pure extraction (Roche Diagnostics) on the patient's plasma as per the manufacturer's protocol. This is a real-time PCR assay based on a dual-labeled hybridization probe targeting the pre-core and core regions.

2.3. Assessment and Classification of Liver Fibrosis

Liver fibrosis was assessed by Fibrotest, Fibrometer and Transient Elastography. Fibrotest and Fibrometer are not done in Cameroon. Transient elastography is done in PMO by the same operator. This is done using a Fibroscan® device (FS 502, Echosens) on a fasting patient for at least 2 hours. The median of 10 - 15 readings was employed and results were expressed in kilopascals (kPa). These results were then correlated with the METAVIR scoring system with Significant Fibrosis (METAVIR score ≥ F2) = 7.2 kPa and Cirrhosis (METAVIR F4) = 11 kPa [17] [18] [19].

Transient elastography is a technique that helps determine two physical parameters within the liver: its stiffness expressed in kilopascals (kPa) and the ultrasonic attenuation expressed in decibels per meter (dB/m). The results obtained correspond to the median value of 10 validated measurements ranging from 2.5 to 75 kPa. A value less than 7 kPa was considered as non-significant fibrosis, where a value ranging between 7 and 15 kPa defined significant fibrosis, and a value greater or equal to 15 kPa defined cirrhosis. We considered the interquartile range (IQR) which assesses the variability of validated measures (which should be lower than 30% of the median). Both the M and the XL probes were used.

For the APRI score the following formula and cut-off values according to the literature are (AST [IU/L]/ULN of AST)/platelet count (10^9/L) × 100, with significant fibrosis considered as a score greater than or equal to 1.5 and cirrhosis considered as a score greater than or equal to 2 [20].

For the FIB4 score the following formula and cut-off values according to the literature are (age [years] × AST [IU/L])/(platelet count [10^9/L] × (ALT [IU/L]) 1/2), with significant fibrosis considered as a score greater than or equal to 1.45 and cirrhosis considered as a score greater than or equal to 3.25 [9].

For the GPR score the following formula and cut off values according to the literature are (GGT (IU/L)/ULN of GGT)/platelet count (10^9/L) × 100, with significant fibrosis considered as a score greater than or equal to 0.32 and cirrhosis considered as a score greater than or equal to 0.56 [14].

2.4. Statistical Analysis

Data was entered in CsPro (Census and Survey Processing System) and analyzed using SPSS Version 23.0 and Medical statistical software version 14. Microsoft

Excel 2016 was used to draw figures.

The scores of the non-invasive tests were calculated from their respective formulae and correlated with the METAVIR score (significant fibrosis METAVIR ≥ F2 and Cirrhosis F4). Frequencies and percentages were computed for categorical variables. Mean (or Median) and standard deviation (or Interquartile range) were computed for continuous variables. Cross tables were drawn to determine the test characteristics (sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios) for APRI, FIB4 and GPR.

The correlations between Transient Elastography scores and non-invasive scores (APRI, FIB4, GPR) were analyzed using the Spearman test.

The sensitivity, specificity, and positive and negative predictive values were used to get the optimal cut-off values of the non-invasive markers for significant fibrosis and cirrhosis.

The diagnostic accuracy of the non-invasive markers was estimated by calculating the Area under the Receiver Operating Characteristic Curve (AUROC). Threshold values were chosen to optimize specificity for the diagnosis of significant fibrosis and cirrhosis.

Statistical significance was set at a P-value < 0.05.

3. Results

3.1. Study Population

A total of 1827 patient records with CHB were reviewed. After excluding patients with co-infections, signs of decompensated cirrhosis, HCC and incomplete files, 243 patient files were studied. Figure 1 summarizes the flow chart of the study population.

3.2. Baseline Characteristics of the Study Population

The median (IQR) age of the study population was 35 (29 - 42) years with the majority being 30 - 40 years old. There was a male predominance of 73.7% (179/243). The majority of the patients 53.3% were employed. 2.1% of the patients were diabetic, 32.5% were overweight and 12.7% were obese. The most recorded risk factor was scarification (36.6%). More than 60% of the patients had normal transaminases. Significant fibrosis and cirrhosis were detected in 88 (36.2%) and 32 (13.7%) of the patients respectively, as shown in Table 1 which summarizes the baseline characteristics of the patients.

3.3. Correlation of APRI, FIB4 and GPR with Transient Elastography

The medians of APRI, FIB4 and GPR were shown to increase with stages of fibrosis Figures 2(a)-(c). There was a positive, moderate and statistically significant correlation between APRI and FIB4 with TE. ($r = 0.592$; $P < 0.001$, $r = 0.503$; $P < 0.001$) respectively. There was a positive but weak correlation between GPR and TE ($r = 0.391$; $P < 0.001$), as shown in Figures 3(a)-(c).

Table 1. Baseline characteristics of the study population.

Characteristics	Value
Median (IQR) age	35 (29 - 42)
Age groups	**N (%)**
<30	69 (28.4)
[30 - 40[	99 (40.7)
[40 - 50[	46 (18.9)
[50 - 60[	22 (9.1)
[60 - 70[	4 (1.7)
≥70	3 (1.3)
Gender	**N (%)**
Male	179 (73.8)
Female	64 (26.2)
Diabetes N (%)	**5 (2.1)**
BMI	**N (%)**
Undernourished	3 (1.2)
Normal	86 (35.5)
Overweight	79 (32.5)
Obese	31 (12.7)
Occupation	**N (%)**
Unemployed	43 (17.7)
Employed	130 (53.5)
Self employed	70 (28.8)
Mode of payment	**N (%)**
Cash	173 (71.2)
Insurance	70 (28.8)
Risk factors	**N (%)**
Scarification	89 (36.6)
Dental care	43 (17.7)
Previous surgery	31 (12.8)
Laboratory Characteristics	**N (%)**
Platelets (g/l)	
<150	65 (26.7)
≥150	178 (73.3)
ALT (IU/l)	
<40	147 (60.5)
≥40	96 (39.5)

Continued

AST (IU/l)	
<40	152 (62.6)
≥40	91 (37.4)
GTT (IU/l)	
<61	127 (52.3)
≥61	104 (42.8)
HBeAg negative	225 (92.6)
HBV DNA (IU/l)	
<2000	151 (62.1)
2000 - 20,000	56 (23.1)
>20,000	36 (14.8)
QHBsAg	
<100	4 (1.6)
100 - 1000	27 (11.1)
>1000	159 (65.4)

AST: Aspartate aminotransterase, ALT: Alanine aminotransferase, HBV DNA: Hepatitis B virus deoxy ribonucleic acid. Results are presented as counts (percentage) or otherwise stated.

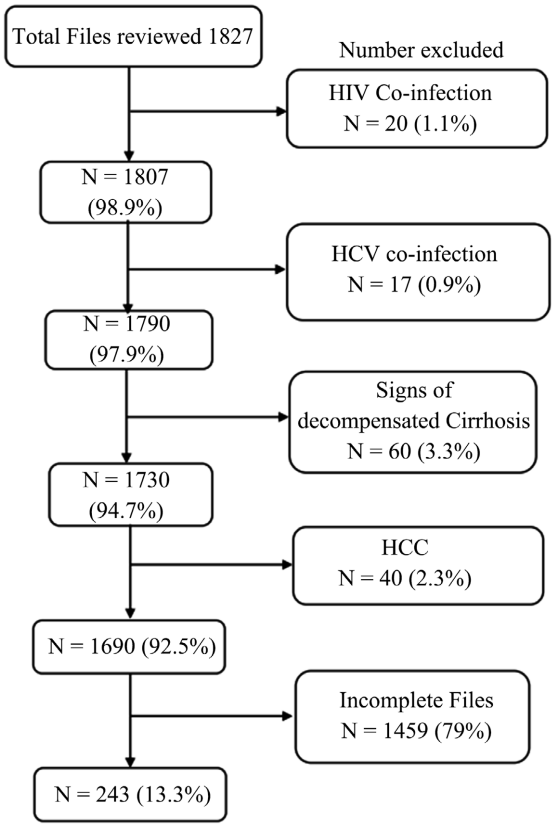
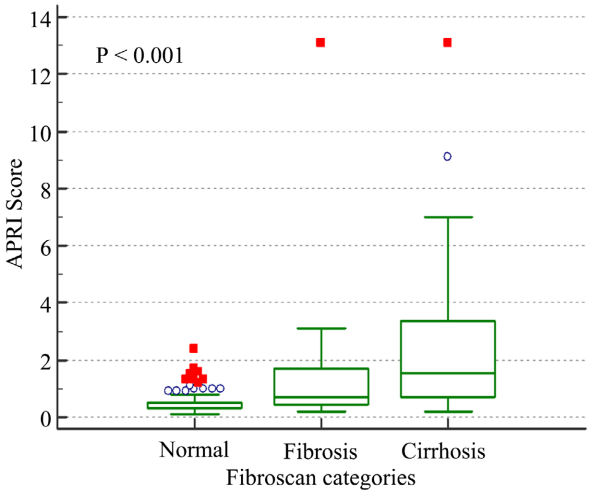


Figure 1. Flow chart of study population.



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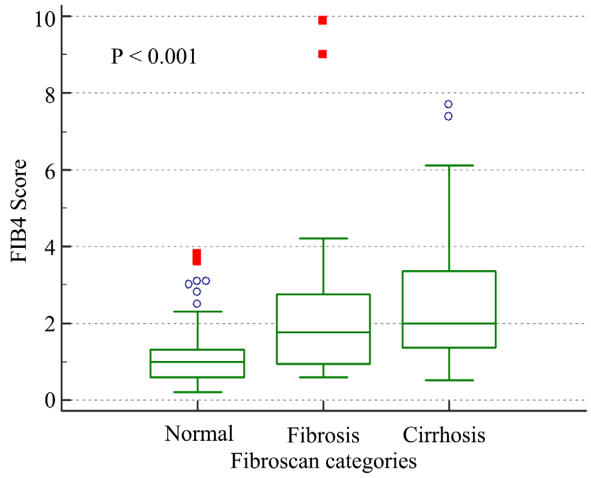

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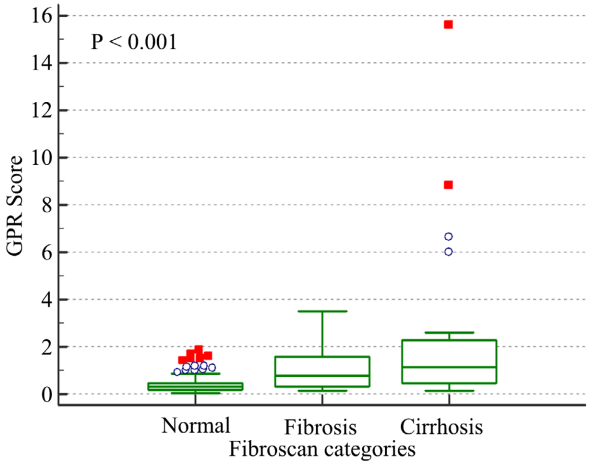

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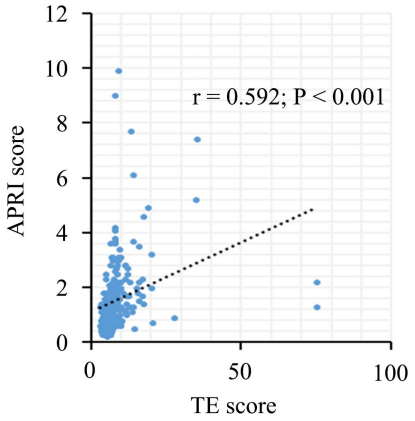
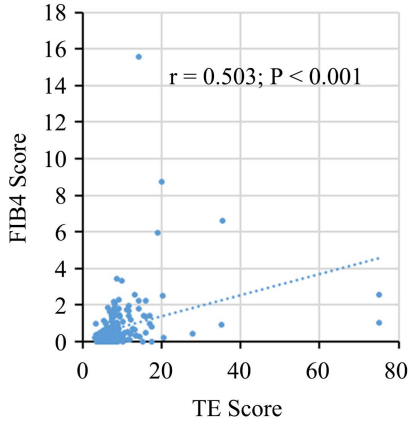
Figure 2. (a)-(c) Box plots of APRI, FIB4 and GPR respectively compared to the degree of fibrosis. The top and bottom of the whiskers represent the minimum and maximum values respectively. The top and bottom of the boxes represent the first and third quartiles and the horizontal lines across the boxes represent the median values.



(a)



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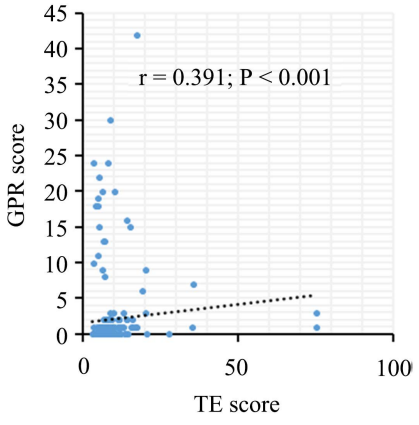


(c)

Figure 3. (a)-(c) Correlation between Transient Elastography and APRI, FIB4 and GPR respectively.

3.4. Classification of the Degree of Fibrosis by Non-Invasive Markers

Significant fibrosis detected by Transient Elastography, APRI, FIB4 and GPR was 36.2%, 14.8%, 35.4% and 67.1% respectively. Meanwhile, these methods detected cirrhosis, at 13.2%, 9.1%, 7%, and 33.8% respectively (Table 2).

Table 2. Classification of the degree of fibrosis by non-invasive markers.

Criteria	Score	Cut off	Count (%)
Significant Fibrosis (Metavir ≥ F2)	TE	≥7.2	88 (36.2)
	APRI	≥1.5	36 (14.8)
	FIB4	≥1.45	86 (35.4)
	GPR	≥0.32	155 (67.1)
Cirrhosis (MetavirF4)	TE	≥11	32 (13.2)
	APRI	≥2	22 (9.1)
	FIB4	≥3.25	17 (7)
	GPR	≥0.56	78 (33.8)

TE: Transient Elastography, APRI: Aspartate aminotransferase to platelet ratio index, FIB4: Fibrosis based on 4 factors, GPR: Gammaglutamyl transpeptidase to platelet ratio index.

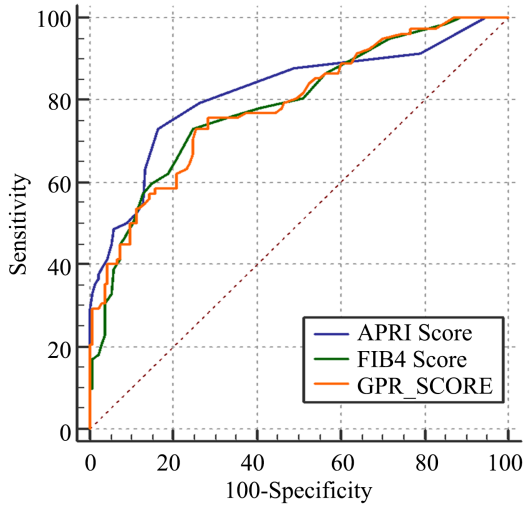
3.5. Diagnostic Performance of Non-Invasive Tests at Cut off Values Based on the Area under the Receiver Operating Characteristic Curve (AUROC)

Based on ROC analysis we obtained optimal cut-off values to diagnose significant fibrosis and cirrhosis. Figure 4(a), shows the AUROC of APRI (0.823), FIB4 (0.785) and GPR (0.787) for significant fibrosis and APRI (0.84), FIB4 (0.761) and GPR (0.780) for cirrhosis (Figure 4(b)).

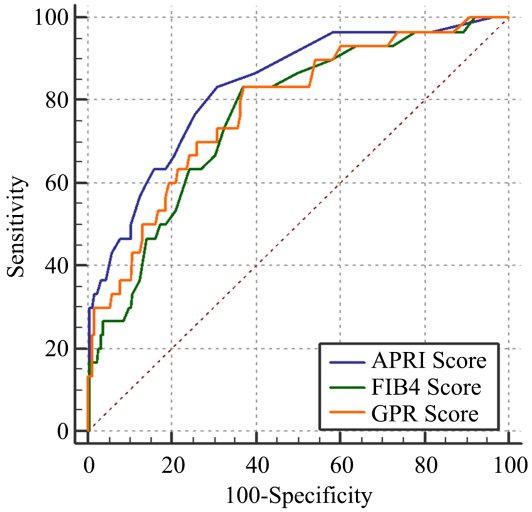
Table 3 presents the optimal cut-off values of APRI, FIB4 and GPR. For significant fibrosis we had as cut-offs 0.55, 1.25, 0.44 and for cirrhosis; 0.65, 1.35, 0.46 for APRI, FIB4 and GPR respectively.

4. Discussion

The assessment of the degree of liver fibrosis by using APRI, FIB4 and GPR and the progression of CHB is important in determining the treatment strategy and prognosis of CHB patients [21] [22]. We aimed at evaluating liver fibrosis using APRI, FIB4 and GPR scores with Transient Elastography as the reference in CHB patients, to choose a cheaper alternative to Transient Elastography. From our study, we observed that 92.6% of the study population was HBeAg negative. More than 60% had normal transaminases and 62.1% had HBV DNA < 2000 IU/l. Transient Elastography detected 36.2% of the study population with significant fibrosis and 13.2% with cirrhosis. APRI, FIB4 and GPR detected 14.8%, 35.4% and 67.1% with significant fibrosis and 9.1%, 7%, and 33.8% with cirrhosis respectively. APRI, FIB4, and GPR scores were shown to increase with fibrosis stages There was a positive and statistically significant correlation between Transient Elastography and all the non-invasive markers; APRI ($r = 0.592$; $P < 0.001$), FIB4 ($r = 0.503$; $P < 0.001$) and GPR ($r = 0.391$; $P < 0.001$). For the diagnostic performance of APRI, FIB4 and GPR for significant fibrosis and cirrhosis, APRI had the best diagnostic properties with corresponding cut-off values and



(a)



(b)

Figure 4. (a) and (b) AUROC of APRI, FIB4 and GPR to detect (a) significant fibrosis and (b) cirrhosis.

Table 3. Optimal cut off values and characteristics based on our ROC analysis.

Score	Criteria	Optimal Cut off	Sensitivity	specificity	PPV	NPV	AUC	95% CI
APRI	Significant Fibrosis	0.55	73.86	80	50.66	49.99	0.823	0.769 - 0.869
	Cirrhosis	0.65	78.12	74.41	31.64	95.73	0.84	0.788 - 0.884
FIB4	Significant Fibrosis	1.25	73.86	70.97	53.68	47.01	0.785	0.723 - 0.835
	Cirrhosis	1.35	84.37	60.66	60.82	39.58	0.761	0.702 - 0.813
GPR	Significant Fibrosis	0.44	73.17	74.44	52.24	48.40	0.787	0.726 - 0.84
	Cirrhosis	0.46	83.33	62.70	59.72	40.95	0.780	0.719 - 0.834

APRI: Aspartate aminotransferase to platelet ratio index, FIB4: Fibrosis based on 4 factors, GPR: Gammaglutamyl transpeptidase to platelet ratio index, PPV: positive predictive value, NPV: negative predictive value, AUC: Area under the curve, CI: Confidence interval.

AUROC of 0.55 (0.823 95% CI [0.769 - 0.869] P < 0.001) for significant fibrosis and 0.65 (0.84 95% CI [0.788 - 0.884], P < 0.005) for cirrhosis.

The best diagnostic properties of APRI in our studies could be compared with those in studies from Ethiopia [9], Brazil [23], and China [24] with high AUROC of APRI (0.79 - 0.86), which are slightly better than those from Europe, Australia and Asia [25] with the summary AUROC of APRI being 0.74 for significant fibrosis and 0.73 for cirrhosis. However, contrary to our findings, African studies from Burkina-Faso [26], Gambia and Senegal [14] have reported lower values between 0.50 - 0.66. This difference could be attributed to the fact that these studies employed strict exclusion criteria, excluding patients with excessive alcohol consumption, Hepatitis D virus infection who were otherwise included in our study.

Despite the highest AUROC of APRI in our study, the sensitivities were very low. Using the WHO cut-off values, APRI detected 14.8% and 9.1% of patients with significant fibrosis and cirrhosis. In clinical practice, this implies 85.2% of patients with significant fibrosis, who should commence treatment in order to avoid progressive liver disease will go unnoticed and 90.9% will be erroneously labeled as non-cirrhotic and not receive appropriate treatment and follow-up. This is consistent with the low sensitivities recorded in Ethiopia [5]; 10% for significant fibrosis and cirrhosis, Senegal and Gambia [13]; 0% for significant fibrosis in Senegal, and 9% in Gambia with 25% for cirrhosis. This raises questions as to whether the WHO thresholds will need to be modified in Africa given the fact that most of the populations in Africa are inactive carriers of Hepatitis B with normal transaminases.

With these low sensitivities, we sought to determine new cut-off values with better sensitivities and specificities of APRI, FIB4 and GPR in CHB patients. Based on our ROC analysis, the optimal cut-offs were; 0.55 and 0.65 for APRI, 1.25 and 1.35 for FIB4, 0.44 and 0.46 for GPR, for diagnosing significant fibrosis and cirrhosis respectively. These values were all lower than the proposed thresholds.

When the new cut-offs were used, APRI had a higher sensitivity (73.86% vs 14.8%) and relatively lower specificity (80% vs 98.1%) for significant fibrosis and a sensitivity of 78.12% vs 9.1% and specificity of 74.41% vs 95.73% for cirrhosis. FIB4 had a sensitivity of 73.86% vs 36.6% and a specificity of 70.97% vs 78.71% for significant Fibrosis and cirrhosis; a sensitivity of 84.37% vs 7% and specificity of 60.66 vs 95.73%. GPR provided 73.17% vs 67.1% sensitivity and 74.44% vs 47.37% specificity for significant fibrosis and 83.33% vs 33.8% sensitivity and 62.70% vs 69.19% specificity for cirrhosis.

From the above, it is worth noting that the sensitivities are better with our new cut-off values with relatively low specificities compared to the WHO thresholds. In clinical practice therefore, the cut-offs with high specificities (fewer false positive results) could be used to diagnose persons with significant fibrosis and cirrhosis and the cut-offs with high sensitivity (fewer false negative results)

could be used to rule out or screen the presence of significant fibrosis and cirrhosis.

This study had the following limitations: We used Transient elastography as the reference instead of liver biopsy which is the usual gold standard. It was a retrospective study susceptible to missing data. The study was carried out in one town in Cameroon which may not be representative of the entire population. Thus, a larger sample, the prospective and multicentered study will be necessary to validate the new cut-offs of APRI, FIB4 and GPR. That notwithstanding, this is one of the very few studies carried out in sub-Saharan Africa on the evaluation of non-invasive markers of liver fibrosis in CHB that has proposed cut-off values from the WHO traditional cut-off values.

5. Conclusion

APRI had the best diagnostic properties to detect liver fibrosis and cirrhosis in patients with CHB attending a hospital in Douala. This study supports the call of the WHO on the use of APRI in low-income settings based on its simplicity, availability in primary care, affordability and highest AUROC in our study. However, the WHO cut-offs might be higher. Our proposed cut-offs will need further validation for the use in Sub-Saharan Africa.

Acknowledgements

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Ethics Approval and Consent to Participate

We conducted this study in strict compliance with the fundamental principles of medical research:

- The principle of the interest and benefit of research
- The principle of research safety
- Confidentiality.

Informed Consent

Informed consent was obtained from all subjects and/or their legal guardian(s).

In this study all methods were carried out in accordance with relevant guidelines and regulations

Availability of Data and Materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Author Contribution

SAFBE, TWBN, ANN and CKS conceived the study. SAFBE, TWBN, ANN,

GGAG, GRDS, CKS, AM and DNN collected the data. SAFBE, TWBN, ANN and HNL analyzed the data and drafted the manuscript. SAFBE, TWBN, ANN, DNN, FAA, CT, and HNL proofread and corrected the manuscript. All authors agreed with the final manuscript to be submitted for publication.

The study was approved by the institutional review board of the Faculty of Health Sciences of the University of Buea-Cameroon 2018/140/UB/SG/IRB/FHS and the Douala General Hospital No 017AR/MISANTE/HGD/DM/01/18.

Conflicts of Interest

Not applicable.

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