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Are non-invasive fibrosis markers for chronic hepatitis B reliable in sub-Saharan Africa?

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Abstract

Background: In the absence of liver biopsy, the World Health Organization recommends non-invasive tests, such as aspartate aminotransferase to platelet ratio index and FIB-4, to assess liver fibrosis in patients with chronic hepatitis B. However, these tests are not well validated in sub-Saharan Africa. Recently, a new marker, gamma-glutamyl transpeptidase to platelet ratio, was found to be more accurate in an African setting, but this needs confirmation in other cohorts.

Methods: A treatment program for chronic hepatitis B was initiated in Addis Ababa, Ethiopia, in 2015. Non-invasive tests were compared with transient elastography (Fibroscan 402, Echosense, France) using the following thresholds: no fibrosis (≤7.9 kPa), significant fibrosis (>7.9 kPa) and cirrhosis (>11.7 kPa). The diagnostic accuracy was estimated by calculating the area under the receiver operating characteristics curve.

Results: Of 582 treatment-naïve patients, 141 (24.2%) had significant fibrosis and 90 (15.5%) had cirrhosis. The area under the receiver operating characteristics curve of aspartate aminotransferase to platelet ratio index, FIB-4 and gamma-glutamyl transpeptidase to platelet ratio was high both to diagnose significant fibrosis (0.79 [95% CI 0.75-0.84], 0.79 [95% CI 0.75-0.84], 0.80 [95% CI 0.75-0.85]) and cirrhosis (0.86 [95% CI 0.81-0.91], 0.86 [95% CI 0.81-0.91], 0.87 [95% CI 0.82-0.91]). The specificity was high for all tests (94%-100%); however, the sensitivity was poor both to detect fibrosis (10%-45%) and cirrhosis (10%-36%).

Conclusions: Aspartate aminotransferase to platelet ratio index, FIB-4 and gamma-glutamyl transpeptidase to platelet ratio had good diagnostic properties to detect liver fibrosis and cirrhosis in patients with chronic hepatitis B in East Africa. However, the sensitivity was low, and only 10% of patients with cirrhosis were detected using aspartate aminotransferase to platelet ratio index at the World Health Organization recommended threshold.

KEYWORDS

hepatitis B virus, liver fibrosis, non-invasive tests, sub-Saharan Africa

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristics curve; CHB, chronic hepatitis B; GGT, gamma-glutamyl transpeptidase; GPR, gamma-glutamyl transpeptidase to platelet ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NITs, non-invasive tests; TE, transient elastography; WHO, World Health Organization.

Trial registration number: NCT02344498 (ClinicalTrials.gov identifier).

1 | INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem, despite the availability of effective vaccine prophylaxis. It is estimated that one-third of the world's population have been infected with HBV at some point in their lives, of whom 240 million people are chronically infected. Approximately 15%-25% of adults who were infected with HBV in childhood go on to develop its main complications, cirrhosis and/or hepatocellular carcinoma (HCC), and an estimated 686 000 deaths each year can be attributed to chronic hepatitis B (CHB).[1–3]

International liver societies have issued guidelines for the treatment of CHB,[4–6] but the optimal timing of treatment is still debated. In general, treatment is recommended to persons with CHB who have high viral replication and moderate to severe liver inflammation and/or fibrosis, as these patients are at high risk of disease progression to cirrhosis and HCC.[7,8] The benefit of treatment for those with mild inflammation or fibrosis is less certain. Since the risk of complications increases dramatically once cirrhosis develops, it is of particular importance to detect patients with early cirrhosis.[9–11]

Assessment of liver fibrosis is a major challenge in the management of patients with CHB. Liver biopsy has traditionally been considered the gold standard; however, it is an invasive procedure with certain risks and limitations, and lack of trained personnel restricts its use in low- and middle-income countries.[12] Transient elastography (TE) is a non-invasive alternative to liver biopsy, and Fibroscan has been most widely evaluated. Numerous studies have shown good agreement with liver biopsy in patients with various liver diseases, including hepatitis B, hepatitis C and alcoholic liver disease.[13–19] Indeed, in a large meta-analysis of patients with CHB, TE showed excellent diagnostic accuracy for quantifying liver fibrosis and cirrhosis.[20] Furthermore, TE has been shown to be a prognostic indicator, independent of liver biopsy, of liver-related complications such as hepatic decompensation, HCC and death.[21] Unfortunately, the cost of the Fibroscan machine has until now limited its availability in resource-limited settings.

In settings without access to liver biopsy or Fibroscan, the World Health Organization (WHO) recommends to use non-invasive tests (NITs) based on simple and available laboratory methods, in the assessment of liver fibrosis. APRI (aspartate aminotransferase [AST] to platelet ratio index) was nominated as the preferred NIT in the recently launched WHO guidelines for management of CHB in resource-limited settings.[22] However, APRI and other NITs have not been sufficiently validated in sub-Saharan Africa, and it is not given that indices based on platelets will perform well on this continent, where thrombocytopenia is a frequent manifestation of endemic tropical diseases such as malaria and schistosomiasis.[23] To date, only three studies have been published from patients with CHB mono-infection in sub-Saharan Africa.[24–26] Indeed, in the largest of the three, the performance of APRI and FIB-4 was only moderate compared to liver biopsy, although a novel fibrosis marker, GPR (gamma-glutamyl transpeptidase [GGT] to platelet ratio) appeared to perform better in this setting.[24]

The WHO has recognised the lack of evidence for the use of NITs in sub-Saharan Africa, and has called for further validation studies in African CHB patients.[22] In the present study, we assessed the performance of APRI, FIB-4 and GPR in one of the largest CHB cohorts in sub-Saharan Africa, aiming to provide local data and guide evidence-based practice on the continent.

Key points

- The World Health Organization recommends non-invasive tests to assess liver fibrosis in patients with chronic hepatitis B, but these tests are not validated in sub-Saharan Africa.
- We compared the performance of APRI, FIB-4 and the novel marker GPR with Fibroscan in a large hepatitis B cohort in Ethiopia.
- Although the area under the receiver operating characteristics curve (AUROC) was high for all tests, the sensitivity to detect patients in need of antiviral therapy was poor.
- Our study supports the use of these simple and affordable tests in sub-Saharan Africa, but suggests that decision thresholds might need modification in this setting.

2 | MATERIALS AND METHODS

2.1 | Study setting and participants

Ethiopia is a low-income country located in the eastern part of Africa with a high to intermediate prevalence of CHB. Based on different institution based studies, the prevalence of HBsAg has been estimated to be around 8%-12%, with a higher prevalence in cities.[27–29] St. Paul's Hospital Millennium Medical College is a tertiary hospital which provides medical care for patients referred from all over the country. A prospective cohort study was initiated in this hospital in February 2015 in order to study the feasibility and efficacy of modern CHB treatment in a resource-limited setting. Adult patients (≥18 years) diagnosed with CHB who were willing to attend regular follow-up were included in the cohort.

Nested in this ongoing cohort study we aimed to compare non-invasive fibrosis markers with TE results. Individuals with the following conditions were excluded from the present analysis: pregnancy, HIV co-infection, concomitant tuberculosis, self-reported alcohol consumption >20 g/day, ALT elevated more than 10 times ULN, and prior or current HBV antiviral therapy. Ethical clearance was obtained from the Regional Committee for Medical and Health Research Ethics in Norway and the National Research Ethics Review Committee in Ethiopia, as well as pertinent institutional ethical review boards. All patients gave written informed consent to participate in the study.

2.2 | Laboratory analyses

HBV infection was confirmed with a WHO validated HBsAg rapid test kit (Determine, Alere, Ireland) at enrolment, and HBsAg positivity for at least 6 months was the diagnostic criteria for CHB. All patients

underwent a baseline examination including the following blood tests: complete blood count (HumaCount 30, Human, Germany), standard biochemistry (Humalyzer 3000, Human, Germany), and serology (HBsAg/anti-HIV/anti-HCV, Elisys Uno, Human, Germany). The upper limit of normal (ULN) for GGT was 61 IU/L and for AST 40 IU/L.

APRI, FIB-4 and GPR were calculated using the following formulas:

- APRI: (AST [IU/L]/ULN of AST)/platelet count (10^9/L) × 100[30]
- FIB-4: (age [years] × AST [IU/L])/(platelet count [10^9/L] × (ALT [IU/L])$^{1/2}$)[31]
- GPR: (GGT [IU/L]/ULN of GGT)/platelet count (10^9/L) × 100[24]

2.3 | Transient elastography

For fibrosis assessment, transient elastography was employed (Fibroscan 402, Echosense, France). Patients were instructed to fast for at least 2 hours prior to the examination, and the procedure was performed by an experienced operator per the manufacturer's instructions. The median of 10 readings was employed, and the result was discarded if the interquartile range (IQR) divided by the median exceeded 30%.

2.4 | Statistical analysis

Based on a previous meta-analysis, we used a Fibroscan threshold of 7.9 kPa to define significant fibrosis (Metavir score ≥F2) and 11.7 kPa to define cirrhosis (Metavir score F4).[20] Non-invasive markers were compared with Fibroscan values, and their diagnostic accuracy were estimated by calculating the area under the receiver operating curve (AUROC). We used the method described by DeLong et al. to compare AUROC of the different NITs.[32] The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were calculated based on established thresholds:

- APRI: 0.5 and 1.5 to distinguish F0-1 and F2-4; 1.0 and 2.0 to distinguish F0-3 and F4[30]
- FIB-4: 1.45 and 3.25 to distinguish F0-2 and F3-4[31]
- GPR: 0.32 to distinguish F0-1 and F2-4; 0.56 to distinguish F0-3 and F4[24]

SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA) was used to analyse the data, except comparison of AUROC between tests which was done with MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium). All tests were two-sided and level of significance was set at $P<.05$. Results were reported in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD).[33]

3 | RESULTS

3.1 | Patient characteristics

Out of 1101 non-pregnant, treatment-naive adults who enroled in care between February 9 and December 10, 2015, 1051 (95.5%) had a valid Fibroscan result. Among 50 individuals with an invalid or indeterminate Fibroscan result, 13 had ascites and 19 were overweight or obese (body mass index>25 kg/m^2). Since GGT was not part of the diagnostic workup in the early phase of the project, 469 patients had an incomplete laboratory profile.

The remaining 582 patients were included in the present analysis. Of these, 351 (60.3%) were male, median age was 31 years (IQR 27-39) and median Fibroscan result was 5.8 kPa (IQR 4.6-7.7). One-hundred-and-forty-one patients (24.2%) had significant fibrosis, of whom 90 (15.5%) had cirrhosis. Summary statistics of baseline characteristics are shown in Table 1.

3.2 | Performance of non-invasive tests

The different non-invasive markers of liver fibrosis were compared with transient elastography. Figure 1 shows box plots for APRI, FIB-4 and GPR compared with Fibroscan fibrosis categories.

There was no significant difference between the various NITs for the detection of significant fibrosis (Fibroscan>7.9 kPa): the AUROC of APRI was 0.79 (95% confidence interval [CI] 0.75-0.84), the AUROC of FIB-4 was 0.79 (95% CI 0.75-0.84) and the AUROC of GPR was 0.80 (95% CI 0.75-0.85). For the detection of cirrhosis (Fibroscan>11.7 kPa) all NITs had a higher AUROC, but without any significant difference between the tests: the AUROC of APRI was 0.86 (95% CI 0.81-0.91), the AUROC of FIB-4 was 0.86 (95% CI 0.81-0.91) and the AUROC of GPR was 0.87 (95% CI 0.82-0.91), respectively. The AUROC analyses are shown in Figure 2.

GPR was not significantly better than the WHO recommended non-invasive tests, neither for detection of fibrosis (GPR vs APRI, $P=.75$; GPR vs FIB-4, $P=.80$) or cirrhosis (GPR vs APRI, $P=.84$; GPR vs FIB-4, $P=.79$). Summary performance of the various NITs are described in Table 2.

The sensitivities of the conventional NITs were low, both to detect fibrosis and cirrhosis. For APRI the higher threshold yielded a sensitivity of merely 10%, although the specificity was high at nearly 100%. GPR had a better performance with a sensitivity of 36% and a specificity of 98% using the higher threshold.

TABLE 1 Baseline characteristics of 582 Ethiopian patients with chronic hepatitis B

Characteristics	Median (IQR)
Age (years)	31 (27-39)
Fasting TE value (kPa)	5.8 (4.6-7.7)
Platelet count (10^9/L)	278 (230-328)
ALT (IU/L)	26 (19-37)
AST (IU/L)	25 (20-35)
Bilirubin (mg/dL)	0.6 (0.4-0.8)
GGT (IU/L)	20 (16-32)
Viral load (IU/mL)	1494 (351-16,273)

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; IQR, interquartile range; TE, transient elastography.

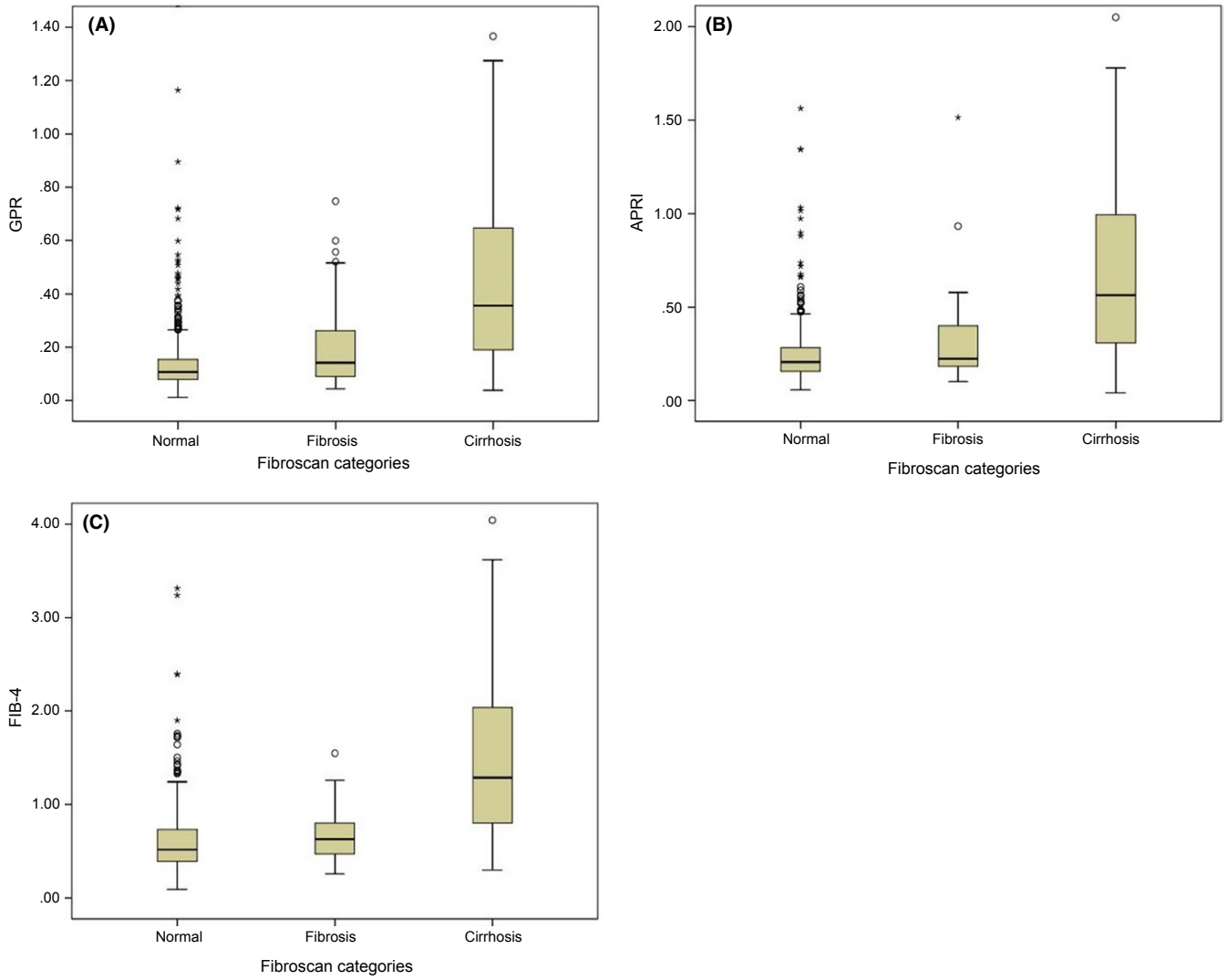

FIGURE 1 Box plots of (A) GPR, (B) APRI, and (C) FIB-4 compared to the degree of fibrosis in a cohort of patients with chronic hepatitis B in Ethiopia. Fibroscan categories were: normal (≤7.9 kPa), fibrosis (8.0-11.7 kPa), cirrhosis (>11.7 kPa)

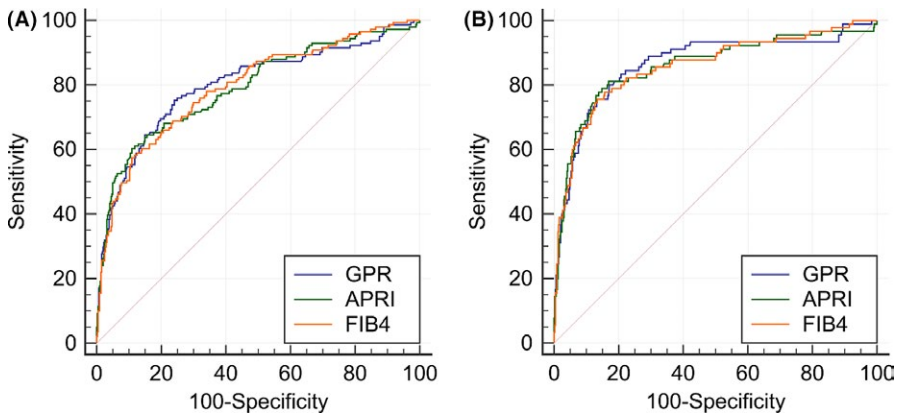

FIGURE 2 Receiver operating curves for APRI, FIB-4 and GPR to detect (A) significant fibrosis (Fibroscan >7.9 kPa) and (B) cirrhosis (Fibroscan >11.7 kPa) in patients with chronic hepatitis B in Ethiopia

4 | DISCUSSION

In this study both APRI, FIB-4 and GPR had a high AUROC to detect significant fibrosis and cirrhosis in Ethiopian CHB patients. Our results were slightly better than those found in a recent meta-analysis of studies from Europe, Australia and Asia, where the summary AUROC of APRI was 0.74 for fibrosis and 0.73 for cirrhosis, and the summary AUROC for FIB-4 was 0.78 for fibrosis and 0.82 for cirrhosis.[34]

TABLE 2 Diagnostic performance of non-invasive markers to detect significant fibrosis (Fibroscan >7.9 kPa) and cirrhosis (Fibroscan >11.7 kPa) in Ethiopian patients with chronic hepatitis B

	Normal vs significant fibrosis		Non-cirrhosis vs cirrhosis	
GPR				
AUROC (95% CI)	0.80 (0.75-0.85)		0.87 (0.82-0.91)	
Cut-off values	0.32		0.56	
Sensitivity/specificity	45/94		36/98	
Correctly classified (%)	82		88	
PPV/NPV	69/84		76/89	
Positive/negative LR	7.5/0.6		18/0.7	
APRI				
AUROC (95% CI)	0.79 (0.75-0.84)		0.86 (0.81-0.91)	
Cut-off values	0.5	1.5	1	2
Sens./Specificity	48/95	10/100	29/98	10/100
Correctly classified (%)	84	79	88	86
PPV/NPV	75/85	88/78	77/88	90/86
Positive/negative LR	9.6/0.5	22/0.9	15/0.7	49/0.9
FIB-4				
AUROC (95% CI)	0.79 (0.75-0.84)		0.86 (0.81-0.91)	
Cut-off values	1.45		3.25	
Sens./Specificity	32/97		16/99	
Correctly classified (%)	81		86	
PPV/NPV	76/82		82/87	
Positive/negative LR	11/0.7		26/0.8	

APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GPR, gamma-glutamyl transpeptidase to platelet ratio; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

The performance of APRI and FIB-4 in studies from CHB patients in sub-Saharan Africa has been less favourable. In a study from Burkina Faso the AUROC of APRI to predict significant fibrosis and cirrhosis was 0.61 and 0.50, respectively, the latter being identical to chance. FIB-4 had a better performance, the AUROC was 0.71 for fibrosis and 0.74 for cirrhosis.[25] In a study from the Gambia and Senegal the performance of NITs was also inferior to the findings in our study: the AUROC of APRI was 0.62-0.66 for fibrosis and 0.70 for cirrhosis, whereas the AUROC for FIB-4 was 0.57-0.66 for fibrosis and 0.73 for cirrhosis, respectively.[24] Although our results suggest that APRI and FIB-4 have good diagnostic properties in African CHB monoinfected patients, further studies from the continent are needed before strong conclusions can be drawn.

In spite of the high AUROC for APRI and FIB-4 in our study, the sensitivity using existing thresholds was poor. Indeed, APRI detected only 10% of patients with significant fibrosis or cirrhosis using the higher thresholds recommended by the WHO. In clinical practice, this means that 90% of patients with cirrhosis will be erroneously labelled as non-cirrhotic and not receive appropriate treatment and follow-up. Similarly, 90% of patients with significant fibrosis, who should commence treatment in order to avoid progressive liver disease, will pass unnoticed using the recommended APRI threshold. A similar trend was observed in the study by Lemoine et al. from West Africa: APRI had a sensitivity of 0% to detect significant fibrosis in Senegal, whereas the sensitivity was 9% to detect significant fibrosis and 25% to detect cirrhosis in Gambia.[24] Taken together with our findings, these data suggest that established thresholds, mainly derived from European and Asian patient cohorts, might need modification when employed in Africa.

The new fibrosis marker GPR was better than APRI and FIB-4 in the study by Lemoine et al.[24] However, since only patients with suspected advanced liver disease were included in the study, the results might not be representative of all patients with chronic HBV infection. Furthermore, the study was carried out in a predominantly Muslim community where alcohol consumption, which might affect GGT levels, is lower than in many other areas in Africa. In our study the AUROC of GPR was not significantly better than the traditional markers; however, GPR had a more favourable sensitivity: 45% for significant fibrosis and 36% for cirrhosis.

The GPR has not been assessed in other African CHB monoinfected patient cohorts, but a few studies have been published from other parts of the world. In a recent study from China the AUROC of GPR to predict significant fibrosis (0.72) was significantly lower than APRI (0.78) and comparable to FIB-4 (0.70). To predict cirrhosis, the AUROC of GPR (0.78) was also inferior to APRI (0.83) and similar to FIB-4 (0.75).[35] Furthermore, in a recent small study from Brazil, there

was no apparent advantage of GPR over the traditional markers: the AUROC of GPR, APRI and FIB-4 to detect significant fibrosis was 0.73, 0.80 and 0.79, respectively. Even to detect cirrhosis GPR had no apparent advantage; the AUROC of GPR, APRI and FIB-4 was 0.84, 0.80 and 0.83, respectively.[36] Although our study and the studies from China and Brazil did not reproduce the good performance of GPR from the validation study, further studies from African cohorts should be undertaken to determine whether GPR adds anything to the traditional markers in this setting.

Several African countries, including Ethiopia, are developing national guidelines for treatment and care of CHB. The Ethiopian guidelines recommend the use of APRI to detect patients in need of treatment.[37] Our study supports the use of APRI given its simplicity and high AUROC; however, the threshold recommended by the WHO renders very few patients eligible for treatment. In our study the majority of patients were HBeAg negative and had normal transaminases. Consequently, their APRI (and FIB-4) would be lower than in many Asian cohorts, where a larger proportion are HBeAg positive and have higher transaminases.[38,39] This might explain the low sensitivity found in our study and other African cohorts.

The main limitation of our study was that we used transient elastography as the gold standard instead of liver biopsy. However, previous studies have found good agreement between TE and liver biopsy in patients with CHB. A meta-analysis of 18 studies and 2772 CHB patients from Europe and Asia found that TE can be performed with good diagnostic accuracy for quantifying liver fibrosis: the AUROC was 0.86 to detect significant fibrosis and 0.93 to detect cirrhosis.[20] Studies from sub-Saharan Africa have also found a good agreement between TE and liver biopsy. In West Africa the AUROC was 0.61-0.85 for significant fibrosis, and 0.98 for cirrhosis,[24] whereas in Burkina Faso the AUROC was 0.87 for significant fibrosis and 0.88 for cirrhosis.[25]

Although the use of liver biopsy is considered a gold standard for assessment of liver fibrosis, even this method has its limitations. First, since a single biopsy only assesses about 1/50,000 of the liver there is a risk of sampling error, and studies have shown that the degree of fibrosis can vary significantly in different liver biopsies from the same patient.[40] Furthermore, the interpretation of histology is to a certain degree a subjective exercise, and there is a significant inter-observer variability. Indeed, a study from North America compared hepatopathologists with general pathologists, and found that only 49.9% of the readings agreed with regard to Metavir fibrosis stage.[41] Fibroscan, on the contrary, assesses a larger portion of the liver and is less user dependent. Although TE can overestimate liver fibrosis in certain situations, such as patients with hepatic flares or after a meal,[42,43] we minimised this problem by instructing patients to fast for minimum 2 hours before the examination, and excluding patients with grossly elevated ALT or liver stasis.

In summary, we found that both APRI, FIB-4 and GPR had good diagnostic properties in Ethiopian CHB patients. However, the sensitivities of all tests were poor, and the WHO recommended threshold for APRI would only detect 10% of patients with cirrhosis. Our study supports the use of these simple and affordable NITs in sub-Saharan Africa, but further studies should be undertaken in African CHB patients to assess whether the thresholds need modification in this setting.

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CONFLICTS OF INTEREST

We declare that we have no conflicts of interest.

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