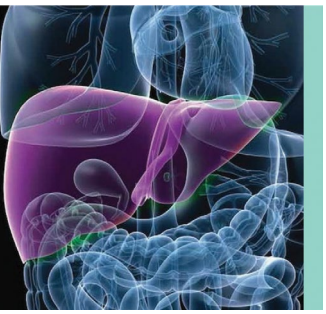

Assessment of Noninvasive Markers of Liver Fibrosis in Patients With Chronic Hepatitis C in Ethiopia

Hailemichael Desalegn, M.D., Yemisrach Chanie, M.D.,* Paulos Shume, M.D.,* Miftah Delil, M.D.,* Neil Gupta, M.D.,† and Asgeir Johannessen, M.D., Ph.D.‡,§*

BACKGROUND

Of an estimated 71 million individuals with chronic hepatitis C virus (HCV) infection worldwide, 10 to 15 million are estimated to live in sub-Saharan Africa (SSA).[1] Despite recommendations for a "treat-all" public health approach to reach elimination by 2030,[2,3] national treatment programs in many African countries and other resource-constrained settings still might have to prioritize HCV treatment for individuals with advanced liver fibrosis and cirrhosis.

In settings with limited resources, there is little or no access to liver biopsy and transient elastography (TE) to determine fibrosis stage. Noninvasive tests, such as the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) score, have demonstrated acceptable sensitivity and specificity to detect advanced fibrosis and cirrhosis in chronic hepatitis C (CHC).[4] However, there are limited data on the performance of these tests in SSA, where endemic conditions such as malaria, schistosomiasis, and human immunodeficiency

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CHC, chronic hepatitis C; CI, confidence interval; DAA, direct-acting antiviral; FIB-4, Fibrosis-4; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NPV, negative predictive value; PPV, positive predictive value; SSA, sub-Saharan Africa; TE, transient elastography.

From the *Medical Department, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia; †Division of Global Health Equity, Brigham & Women's Hospital, Boston, MA; ‡Centre for Imported and Tropical Diseases, Oslo University Hospital Ullevål, Oslo, Norway; and §Department of Infectious Diseases, Vestfold Hospital Trust, Tønsberg, Norway.

Potential conflict of interest: N.G. received grants from Gilead.

Received July 28, 2020; accepted September 12, 2020.

View this article online at wileyonlinelibrary.com

virus (HIV) conferring thrombocytopenia might interfere with the performance of such tests.[5] In this study, we prospectively evaluated the performance of APRI and FIB-4 compared with TE in patients with CHC at a referral hospital in Ethiopia.

METHODS

Study Setting and Participants

Ethiopia is a low-income country in east Africa with a total population of 114 million, making it the second most populous country in SSA.[6] This study was nested in a prospective observational treatment study for patients with CHC presenting to St. Paul's Hospital Millennium Medical College in Addis Ababa, Ethiopia, between August 2018 and July 2019. Inclusion and exclusion criteria are depicted in Table 1. Data collected about the study participants and relevant laboratory procedures are summarized in Table 2. Written informed consent was obtained from all participants, and the study protocol was approved by the St. Paul's Hospital Millennium Medical College Institutional Review Board.

Liver Fibrosis Assessment

TE was used to assess liver fibrosis stage in all participants. The procedure was done by local clinical staff with certified training in TE. Patients were instructed to fast for a minimum of 2 hours prior to the examination. The median of 10 readings was used, and the result was discarded if the interquartile range (IQR) divided by the median exceeded 30%, as recommended by the manufacturer. The following cutoffs were used to define stages of fibrosis: no fibrosis (≤7.9 kPa), significant fibrosis (>7.9 kPa), and cirrhosis (>11.7 kPa).[7]

APRI and FIB-4 were derived from standard blood test results by the following formulas, using 40 U/L as the upper limit of normal for AST[8,9]:

- APRI: (AST [U/L]/upper limit of normal for AST)/platelet count (10^9/L) × 100
- FIB-4: (age [years] × AST [U/L])/(platelet count [10^9/L] × (ALT [U/L])^{½})

TABLE 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	Exclusion Criteria
• 18 years of age or older • Anti-HCV positive • HCV RNA positive	• Previous HCV therapy • Hepatocellular carcinoma • Other comorbidity that could interfere with HCV therapy

Statistical Analysis

Individuals with ascites were excluded from the analysis because TE is erratic in these patients. Baseline data were summarized using descriptive statistics. Chi-square test was used to compare groups with categorical variables. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and area under the receiver operating characteristic curve (AUROC) of APRI and FIB-4 were calculated using TE as the gold standard. SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The level of significance was set at $P < 0.05$.

RESULTS

Eighty patients with CHC were enrolled, of whom 51 (64%) were women and the median age was 50 (IQR 38-57) years. Two patients (3%) had coinfection with hepatitis B and three (4%) with HIV. The median (IQR) alanine aminotransferase (ALT), AST, platelet count, and HCV viral load were 44 (28-74) U/L, 46 (29-80) U/L, 178 × 10^9/L (122-232 × 10^9/L), and 762,000 (198,000-2,730,000 IU/mL), respectively. The median (IQR) values for APRI and FIB-4 were 0.62 (0.35-1.50) and 2.04 (1.22-3.79), respectively. Fifty-three patients (66%) had significant fibrosis, and 40 (50%) had cirrhosis by TE. None of the patients were pregnant or had signs of congestive heart failure, conditions known to interfere with elastography measurements. Characteristics of the study participants are summarized in Table 3.

The test characteristics of APRI and FIB-4 compared with TE are given in Table 4. Although the sensitivity of APRI was poor using the higher thresholds, a reasonably fair precision was found using the lower thresholds (0.5 for significant fibrosis and 1.0 for cirrhosis). For FIB-4, the lower threshold (1.45) yielded a poor specificity at only 52% to detect significant fibrosis, whereas the higher threshold (3.25) had a poor sensitivity at only 55% to detect cirrhosis. The AUROC analyses are shown in Fig. 1.

In a sensitivity analysis, we excluded patients coinfected with HBV or HIV; however, the test characteristics of APRI and FIB-4 were unchanged (data not shown).

DISCUSSION

In this study, we found that the APRI score had good performance for the detection of both fibrosis and cirrhosis in

TABLE 2. DATA COLLECTION AND LABORATORY METHODS

Medical history and physical examination
- Sociodemographic data
- Symptoms and signs of liver disease

Blood samples
- Hematology (HumaCount 30; Human, Germany)
- Biochemistry (Humalyzer 3000; Human)
- Serology
  - Anti-HCV (Elisys Uno; Human)
  - Hepatitis B surface antigen (determine rapid diagnostic test; Alere, Waltham, MA, USA)
  - Anti-HIV (KHB HIV 1+2 rapid diagnostic test; Shanghai Kehua Bio-engineering, Shanghai, China)
- HCV RNA and genotype (Abbott Real-Time HCV assay; Abbott Molecular, Des Moines, IA, USA)

Imaging
- Abdominal ultrasound
- TE (FibroScan 402; Echosens, France)

TABLE 3. BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS (N = 80)

Characteristics	n	%
Women	51	64
Age (years)		
<40	21	26
40-54	32	40
≥55	27	34
ALT (U/L)*		
<40	35	44
40-79	29	37
≥80	15	19
AST (U/L)*		
<40	35	44
40-79	25	32
≥80	19	24
Platelets ($\times 10^9$/L)*		
<110	14	18
150-300	36	46
≥300	29	37
HCV viral load (IU/mL)†		
<800,000	39	51
≥800,000	37	49
HCV genotype†		
1	20	26
2	5	7
4	40	53
5	2	3
Indeterminate	9	12
TE (kPa)		
≤7.9	27	34
8.0-11.7	13	16
>11.7	40	50
Coinfections‡		
Hepatitis B	2	3
HIV	3	4
APRI, median (IQR)*	0.62	0.35-1.50
FIB-4, median (IQR)*	3.06	1.22-3.79

*Missing one value.
†Missing four values.
‡Missing two values.

TABLE 4. DIAGNOSTIC PERFORMANCE OF APRI AND FIB-4 COMPARED WITH TE TO DETECT SIGNIFICANT FIBROSIS (FIBROSCAN > 7.9 KPA) AND CIRRHOSIS (FIBROSCAN > 11.7 KPA)

	Normal Versus Significant Fibrosis		Noncirrhosis Versus Cirrhosis	
APRI				
AUROC (95% CI)	0.84 (0.76-0.93)		0.90 (0.83-0.97)	
Cutoff values	0.5	1.5	1	2
Sensitivity/Specificity	75/78	39/100	75/95	30/100
PPV/NPV	87/62	100/46	94/79	100/58
FIB-4				
AUROC (95% CI)	0.79 (0.69-0.89)		0.87 (0.80-0.95)	
Cutoff values	1.45		3.25	
Sensitivity/Specificity	77/52		55/97	
PPV/NPV	76/54		96/68	

CHC, with acceptable test characteristics at a cutoff of 0.5 for significant fibrosis (sensitivity 75% and specificity 78%) and 1.0 for cirrhosis (sensitivity 75% and specificity 95%). The APRI score appeared to be slightly more reliable than the FIB-4 score for the detection of both significant fibrosis and cirrhosis. To our knowledge, this is the first prospective study to report the performance of commonly used noninvasive fibrosis tests in patients with chronic HCV infection in SSA.

Our results strongly suggest that the higher cutoffs recommended by the World Health Organization are not appropriate for CHC care in Ethiopia and possibly other SSA countries. It is unclear why the APRI cutoff needs adjustment in African viral hepatitis cohorts,[10-12] but biological differences cannot be excluded because the validation of APRI and FIB-4 has been carried out mainly among Caucasian and Asian patients.[4]

Our findings have certain implications for HCV treatment initiation in resource-limited settings to reduce CHC-related mortality and advance progress toward hepatitis elimination.[2,3] For national hepatitis treatment programs that currently have limited access to direct-acting antivirals (DAAs), rapid assessment of fibrosis stage using APRI may be a valid measure to prioritize treatment for patients with cirrhosis. In most settings in SSA where publicly provided or subsidized treatment programs do not exist, DAA access is primarily through private pharmacies, and costs are fully out of pocket for patients. Reliable assessment of fibrosis stage with noninvasive tests may provide additional guidance to providers and patients as to the relative urgency of DAA treatment.

Our study had certain limitations. First, the sample size was relatively small. These study results should be

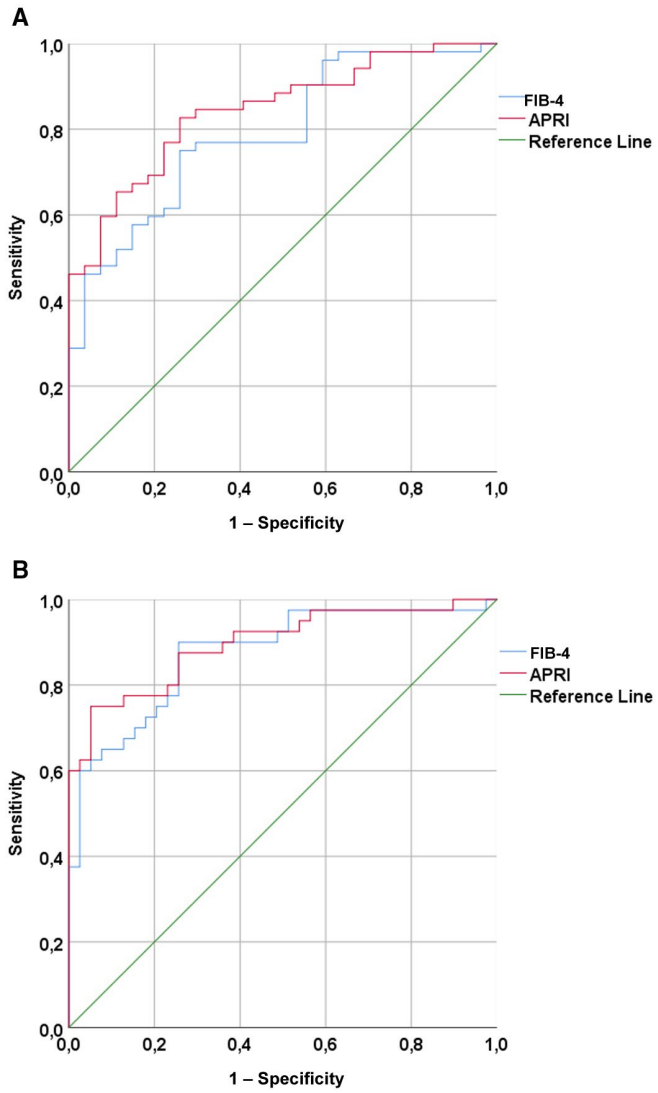

FIG 1 Receiver operating curves for APRI and FIB-4 to detect (A) significant fibrosis (FibroScan > 7.9 kPa) and (B) cirrhosis (FibroScan > 11.7 kPa) in patients with CHC in Ethiopia.

confirmed in larger CHC cohorts in SSA. Second, there were few patients with coinfections with HIV or hepatitis B, and few patients were from malaria- and schistosomiasis-endemic regions, which may limit the generalizability to other geographical areas in SSA.

CONCLUSION

We found that APRI and FIB-4 had good diagnostic properties in Ethiopian patients with CHC. APRI at a cutoff of 0.5 to detect significant fibrosis and 1.0 to detect cirrhosis appeared to have reasonable test performance to be used in clinical practice in the absence of TE or liver biopsy.

ETHICS, CONSENT, AND PERMISSIONS

The study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the St. Paul's Hospital Millennium Medical College Institutional Review Board. Written informed consent was obtained from all study subjects. Consent for publication was not applicable.

AVAILABILITY OF DATA AND MATERIALS

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

Acknowledgments: We are indebted to the patients who participated in this study. We also acknowledge the hospital administration for support during the program and the nursing staff of the liver clinic for their help in recruitment and follow-up of patients.

CORRESPONDENCE

Asgeir Johannessen, Department of Infectious Diseases, Vestfold Hospital Trust, PO Box 2168, 3103 Tønsberg, Norway. E-mail: uxasoh@siv.no

REFERENCES

1) Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161-176.

2) World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Geneva: WHO; 2016.

3) Sonderup MW, Afihene M, Ally R, et al. Hepatitis C in sub-Saharan Africa: the current status and recommendations for achieving elimination by 2030. Lancet Gastroenterol Hepatol 2017;2:910-919.

4) European Association for the Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-264.

5) Johannessen A, Lemoine M. Is AST-to-platelet ratio index a reliable tool in HIV patients in Africa? Liver Int 2015;35:2059.

6) World Population Review. Ethiopia Population 2020 (Live). Available from: https://worldpopulationreview.com/countries/ethiopia-population/. Published June 12, 2020.

7) Chon YE, Choi EH, Song KJ, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One 2012;7:e44930.

8) Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.

9) Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-1325.

10) Desalegn H, Aberra H, Berhe N, et al. Are noninvasive fibrosis markers for chronic hepatitis B reliable in sub-Saharan Africa? Liver Int 2017;37:1461-1467.

11) **Lemoine** M, **Shimakawa** Y, Nayagam S, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. Gut 2016;65:1369-1376.

12) Aberra H, Desalegn H, Berhe N, et al. The WHO guidelines for chronic hepatitis B fail to detect half of the patients in need of treatment in Ethiopia. J Hepatol 2019;70:1065-1071.