

The Roles of Fibrosis Index Based on Four Factors and Aspartate Transaminase-to-Platelet Ratio Index Scoring Systems as an Alternative to Transient Elastography Liver Stiffness in Liver Fibrosis Staging in Human Immunodeficiency Virus and Hepatitis C Virus Co-Infected Patients

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Abstract

Background: Liver biopsy used to be the gold standard to assess liver fibrosis in patients infected with hepatitis C virus (HCV). Nonetheless, due to its invasive nature, techniques such as transient elastography liver stiffness (TE-LS), fibrosis index based on four factors (FIB-4) and aspartate transaminase-to-platelet ratio index (APRI) scores are currently being used. FIB-4 and APRI scores have the advantage of low cost and are readily available, compared with TE-LS. Herein, we evaluated the diagnostic performance of these scoring systems as compared to TE-LS in assessing liver fibrosis in patients with human immunodeficiency virus (HIV) and HCV co-infection.

Methods: The medical records of patients with HIV and HCV co-infection who had TE-LS done at our facility between August 1, 2013 and January 1, 2020 were extracted and analyzed. Exclusion criteria include: 1) patients co-infected with hepatitis B virus; 2) invalid TE-LS assessment; 3) have \geq 10th upper limit of normal (ULN) alanine aminotransferase (ALT) levels; and 4) excessive alcohol use. Patient demographics, medical history, biochemical and clinical data were retrieved. For each patient, we calculated the FIB-4 and APRI score. Descriptive analysis was performed and correlation of FIB-4 and APRI with TE-LS was assessed with GraphPad Prism statistical software.

Results: Five hundred forty-seven patients underwent TE-LS during the study period. After excluding those without complete laboratory parameters, the total study population was 344. Their age was 56 ± 10.4 years and 234 (68%) were male. The average aspartate aminotransferase (AST) and ALT were 27.95 and 30.73. The average platelet count was 224 and the average TE-LS was 7.29. Fourteen patients (4.1%) had TE-LS values between 9 and 11.9 kPa and were classified as F3, while 29 (8.5%) had TE-LS \geq 12 kPa and were classified as F4. With the correlation analysis, both APRI (correlation coefficient, $r = 0.1097$, 95% confidence interval (CI) 0.0403 - 0.2130; $P = 0.042$) and FIB-4 ($r = 0.0424$, 95% CI -0.0634 - 0.1474; $P = 0.4335$) were not correlated with TE-LS stages of fibrosis.

Conclusion: In our cohort, we failed to demonstrate that APRI and FIB-4 are reliable alternatives for screening liver fibrosis in patients with HIV and HCV co-infection. Nonetheless, APRI score still has a potential role as a screening tool instead of TE-LS measurement, which is costly and not readily available. It will be important to corroborate these findings in another large cohort, since this may have an important impact on patient management.

Keywords: Liver fibrosis; APRI; FIB-4; Transient elastography; HIV; HCV

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Introduction

Liver biopsy has been established as the gold standard to assess stages of fibrosis prior to treatment of chronic hepatitis C (CHC). Nonetheless, it has been replaced by non-invasive techniques such as transient elastography liver stiffness (TE-LS). Moreover, aspartate transaminase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) have also emerged as scoring systems to predict the stages of fibrosis and/or cirrhosis [1, 2]. The disadvantages of TE-LS are its lack of availability, and the patient having to schedule an

extra visit prior to starting treatment for CHC. APRI and FIB-4 biochemical scorings are derived from aspartate transferase (AST), alanine transferase (ALT) and platelets. They are frequently used in non-human immunodeficiency virus (HIV)-infected individuals and could give valuable information at no extra cost [2]. In our study, we aimed to assess the diagnostic performance of these scoring systems compared to TE-LS in detecting liver fibrosis particularly in person living with HIV co-infected with hepatitis C virus (HCV).

HIV and HCV co-infection is common due to their similar modes of transmission. A recent study supported by the World Health organization (WHO) states that an estimated 2.3 million individuals infected with HIV are co-infected with HCV globally [3]. The CDC goes on to state that co-infection prevalence varies depending on the risk group, the most common being injection-drug users [4].

Certain aspects of hepatitis C infection may be different in HIV co-infected individuals, for example, some studies have shown that HCV RNA levels are elevated and increase with time in individuals co-infected with HIV and HCV, as compared with individuals who are infected with HCV alone [5]. Others show weak cellular immune responses to HCV antigens in individuals with HIV [6]. Regardless of the exact pathogenesis, patients with HIV and HCV co-infection have been reported to have expedite rates of fibrosis and rapid progression to liver cirrhosis and ultimately hepatocellular carcinoma [7]. Hence, it is paramount to identify and evaluate liver disease severity in these patients for early and optimal treatment.

Materials and Methods

Subjects

The records of all patients with HIV and HCV co-infection who had TE-LS done at our facility between October 2013 and January 2020 were retrieved and analyzed. METAVIR classification score, developed by Bedossa and Poynard [8], was used for analysis of the stages of fibrosis. With the TE-LS measurements, the stages of fibrosis in our study was defined as F0-1 if TE-LS values < 7 kPa, F2 (TE-LS values between 7 and 8.9 kPa), F3 (TE-LS values between 9 and 11.9 kPa) and F4 (TE-LS values \geq 12 kPa).

There were 547 patients during the study period and after excluding those without complete laboratory parameters (203 patients), the total study population was 344. We excluded patients who had: 1) hepatitis B virus co-infection; 2) invalid TE-LS assessment, defined as an interquartile range of > 30% in at least 10 validated measurements and a low success rate of \leq 60%; 3) ALT and AST levels \geq 10th upper limit of normal (ULN); and 4) excessive alcohol use. The database that we retrieved included patients' demographics characteristics, medical history including medications, biochemical and clinical data.

Ethical issues and informed consent

The study protocol has been approved by the Ethical Review

Board of Saint Michael's Medical Center, New York Medical College. All procedures of the present study were conducted in compliance with the ethical standards of Saint Michael's Medical Center as well as Helsinki declaration for research on human beings. A waiver of HIPAA privacy authorization has also been obtained through the ethical review board.

Laboratory methods

The laboratory parameters including liver function tests (AST and ALT) as well as hematological parameters (platelet count) were obtained using commercially available assays. The reference range for platelets count was $150 - 400 \times 10^9/L$, whereas for both ALT and AST in our study, the ULN was 40 IU/L. We further calculated the APRI and FIB-4 scores for each patient using the following formula: FIB-4 = (age \times AST/platelet count ($10^9/L$) \times \sqrt{ALT}); APRI = ((AST level/ULN)/platelets ($10^9/L$)) \times 100 [9, 10].

Statistical analysis

We analyzed the patients' demographics characteristics, clinical and biochemical data. Descriptive data were represented by percentages, mean \pm standard deviation, medians and numbers. Continuous variables analysis was performed with Mann-Whitney test and *t*-test for non-normal and normal distribution, respectively. As for categorical variables, Chi-square (χ^2) or Fisher exact test was used. We did a correlation analysis to assess the potential utility of FIB-4 and APRI scores in determining degree of liver fibrosis with TE-LS measurements as standard.

We did all data analysis using statistical software Graph-Pad Prism version 9.0.2. Statistical significance was achieved if the null hypothesis could be rejected at $P < 0.05$ with 95% confidence interval (CI). We further explored the diagnostic performances of FIB-4 and APRI scoring system versus TE-LS measurements by using the sensitivity analysis. Area under the receiver operating characteristic (ROC) curve (AUC), sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were analyzed separately to provide information on the potential diagnostic performances of FIB-4 and APRI scores as well as to compare these two tests with TE-LS measurements.

Results

In total, 344 patients with both CHC and HIV were evaluated during the study period. The average age was 56 ± 10.4 years and 234 (68%) were male. The median \pm interquartile range of AST and ALT were 23 ± 11 and 21 ± 16.75 U/L, respectively. The median \pm interquartile range of platelet count was $216 \pm 83 \times 10^3/UL$ and median \pm interquartile range of TE-LS was 5.4 ± 2.6 . The median \pm interquartile range of APRI and FIB-4 score were 0.26 ± 0.17 and 1.31 ± 0.91 , respectively. Based on the TE-LS measurements, the stages of liver fibrosis were

Table 1. Baseline and Clinical Characteristics of the Study Population (n = 344)

Characteristics	
Baseline characteristics	
Age (average \pm SD)	56.16 \pm 10.46
Gender	
Male	234
Female	100
Not disclosed	10
Clinical characteristics	
Alanine aminotransferase (normal range 9 - 46 U/L) (median \pm interquartile range)	21 \pm 16.75
Aspartate aminotransferase (normal range 10 - 36 U/L) (median \pm interquartile range)	23 \pm 11
Platelets (normal range 150 - 450 \times 10 ³ / μ L) (median \pm interquartile range)	216 \pm 83
TE-LS (median \pm interquartile range)	5.4 \pm 2.6
Stages of liver cirrhosis according to TE-LS, n/N (%)	
F0-1 (< 7 kPa)	285/344 (82.8%)
F2 (7 - 8.9 kPa)	16/344 (4.7%)
F3 (9 - 11.9 kPa)	14/344 (4.1%)
F4 (\geq 12 kPa)	29/344 (8.4%)
APRI (median \pm interquartile range)	
F0-1	0.26 \pm 0.15
F2	0.25 \pm 0.17
F3	0.32 \pm 0.32
F4	0.54 \pm 0.62
FIB-4 (median \pm interquartile range)	
F0-1	1.27 \pm 0.86
F2	1.26 \pm 1.37
F3	1.67 \pm 1.29
F4	2.51 \pm 2.08

SD: standard deviation; TE-LS: transient elastography liver stiffness; APRI: aspartate transaminase-to-platelet ratio index; FIB-4: fibrosis index based on four factors.

determined for all study patients. F0-1 was observed in 285 (82.8%), F2 in 16 (4.7%), F3 in 14 (4.1%), and F4 in 29 (8.5%) (Table 1). Both APRI (r = 0.1097, 95% CI 0.0403 - 0.2130; P = 0.042) and FIB-4 (r = 0.0424, 95% CI -0.0634 - 0.1474; P = 0.4335) score in our cohort of patients with HIV and HCV co-infection were not correlated with the fibrosis stages determined with TE-LS.

Due to the small sample size, we could not predict the optimal APRI and FIB-4 score in predicting the patients in F2, F3 and F4 with fibrosis/cirrhosis. Nevertheless, we used arbitrary optimal APRI score to try to predict patients in F2, F3 and F4 as one group. With the arbitrary optimal APRI score \geq 0.5 to predict patients in F2, F3 and F4 as one group indicating fibrosis/cirrhosis gave rise to sensitivity 36%, specificity 91%, PPV 46%, and NPV 87% (Table 2). The arbitrary optimal FIB-4 score to predict patients in F2, F3 and F4 as one group, on the other hand, was calculated as \geq 1.45, giving sensitivity 64%, specificity 62%, PPV 26%, and NPV 89%

(Table 3).

The combination of optimal values (\geq 1.45 and \geq 0.5, respectively) for FIB-4 and APRI as one score predicted patients in F2, F3 and F4 with sensitivity 50%, specificity 88%, PPV 47%, and NPV 89%. From our study, APRI score alone seemed to adequate in ruling out non-cirrhotic patients with

Table 2. APRI Cutoff < 0.5 (No Cirrhosis) and \geq 0.5 (Significant Fibrosis)

Sensitivity	35.59%
Specificity	91.23%
PPV	45.65%
NPV	87.25%
AUC	0.2218

APRI: aspartate transaminase-to-platelet ratio index; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

Table 3. FIB-4 Cutoff < 1.45 (No Cirrhosis) and \geq 1.45 (Significant Fibrosis)

Sensitivity	64.41%
Specificity	62.46%
PPV	26.21%
NPV	89.45%
AUC	0.5098

FIB-4: fibrosis index based on four factors; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

high specificity, whereas the APRI/FIB-4 combination does not affect sensitivity/specificity and its ability to predict ability fibrosis or cirrhosis (F2/F3/F4) in patients (Table 4).

Discussion

Measuring liver fibrosis prior to treating CHC is crucial for the follow-up of patients after HCV is treated. It is important to continue follow-up of those with significant fibrosis (defined by METAVIR scale with fibrosis stage 2 or higher) in order to ensure resolution of liver disease or worsening in certain cases that would require hepatocellular carcinoma bi-annual screening [8]. TE-LS however is not widely available, so we wanted to see if we can replace TE-LS with APRI and FIB4 scores as the test of choice to diagnose liver fibrosis [11]. There is no absolute contraindication for TE-LS, but the diagnostic accuracy is compromised in many circumstances such as ascites, acute hepatitis, right heart failure, pregnancy, the presence of a pacemaker or automated implantable cardiac defibrillator (AICD) [12, 13]. To the best of our knowledge, there are still limited studies comparing the accuracy of both FIB-4 and APRI scores with TE-LS in diagnosing fibrosis in patients with HIV and HCV co-infection.

In our study, we found that APRI was a good predictor of F2/3/F4 (significant fibrosis) and might be more adequate in ruling out non-cirrhotic patients, while FIB-4 was not helpful. The AUC was 0.2218 and 0.5098 for APRI and FIB-4 scores, respectively. The threshold for APRI at > 0.5 was 35.59% sensitive and 91.23% specific in detecting F2/3/F4 patients. The PPV of this threshold was 45.65%, with a NPV of 87.25%. A threshold for FIB-4 of > 1.45 was 64.41% sensitive and 62.46% specific in diagnosis F2/3/F4 patients. The PPV of this threshold was 26.21% and the NPV was 89.45%. This indicates that APRI may be a better screening test at ruling out patients without significant cirrhosis.

Separately, we combined both APRI and FIB-4 with threshold values of 0.5 and 1.45 respectively. The AUC was 0.2183. At the threshold set for the combination of the scores, the combined score was 50% sensitive and 88.44% specific in detecting F2/3/4 patients. The PPV was 47.73% and NPV was 98.34%. While the APRI score is adequate to rule out patients without significant fibrosis, the APRI/FIB-4 combination did not significantly affect sensitivity, specificity and the predictive ability in determining patients with significant fibrosis.

In the study done by Papadopoulos et al, F3/F4 patients

Table 4. FIB-4 \geq 1.45 (Significant Fibrosis) and APRI \geq 0.5 (Significant Fibrosis)

Sensitivity	50.00%
Specificity	88.44%
PPV	47.73%
NPV	89.34%
AUC	0.2183

FIB-4: fibrosis index based on four factors; APRI: aspartate transaminase-to-platelet ratio index; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

who had APRI threshold value of > 0.64 were 72% sensitive and 83% specific, with PPV 88% and NPV 63%, suggesting that APRI score can be a good tool for indicating significant fibrosis. The FIB-4 score with a threshold value of 1.46 was 81.5% sensitive and 79% specific in the diagnosis of F3/F4 patients but was less effective than APRI at indicating significant fibrosis in these patients (PPV 85.5%) [14]. Comparing the findings to the present study, they seem to be similar in regard to APRI being a better screening tool when compared to FIB-4.

The invasive technique of liver biopsy was previously considered to be the gold standard test, but is no longer used routinely in patients with liver fibrosis. TE-LS is a reliable non-invasive means of detecting fibrosis in patients with HCV [15, 16]. A limitation of our study is the fewer number of patients with significant fibrosis (fibrosis stage 2 or greater), which may lead to insignificant statistical findings that we obtained by comparing APRI and FIB-4 with TE-LS in correctly identifying fibrosis in patients with HIV co-infected with HCV. Another limitation of our study is that we looked at patients retrospectively, but we only used appropriately documented cases from electronic medical records which met our exclusion and inclusion criteria. Our cutoff values could be applicable to patients with significant fibrosis, but our study is limited by the small sample size.

Conclusion

In conclusion, our results failed to demonstrate that APRI and FIB-4 are reliable alternatives for screening liver fibrosis in patients with HIV and HCV co-infection based on the low sensitivity, specificity and PPV. Nonetheless, APRI score still has a potential role as a screening tool instead of TE-LS measurement, which is costly and not readily available. The use of the combination of APRI/FIB-4 scores with cutoff thresholds of 0.5 and 1.45 respectively as proposed was not a good test in predicting patients with significant fibrosis, particularly in our study cohorts with HIV and HCV co-infection. Ultimately these patients would need a TE-LS to confirm fibrosis. Larger studies are needed to corroborate our findings.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

SA, DR and KHC contributed to the conception and design, acquisition, analysis and interpretation of data, as well as participate in drafting and revision of the manuscript. KT, AM, MM and SL actively participate in analysis of data, drafting and revision of manuscript. JS contributed to idea design, data analysis and critically revised the manuscript and as well as approved the final submission of manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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