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Stratification of the Degree of Hepatic Involvement in HIV-HCV Coinfection Using Two Biomarkers: APRI and FIB-4

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Abstract

Hepatitis C infection in people living with Human Immunodeficiency Virus (HIV) poses management challenges. Of the world's population, 3% are estimated to have chronic Hepatitis C Virus (HCV) infection, which is responsible for about 70% of cases of chronic hepatitis (accelerated chronicity in the presence of HIV and for such major complications as cirrhosis and hepatocellular carcinoma. The fibrosis 4 (FIB-4) and Aspartate aminotransferase/platelet ratio index (APRI) scores are simple, inexpensive tests accessible to most people, and their performance has not yet been studied in Côte d'Ivoire. **Objective:** To prospectively evaluate the diagnostic performance of APRI and FIB-4 scores in liver damage in those co-infected with HIV/HCV in Côte d'Ivoire. **Methods:** This study was conducted over three months. The patients came from national blood transfusion center of the cities of Man and Daloa. The criteria for selecting respondents were at least 18 years of age and a positive test for HIV and HCV. APRI and FIB-4 scores were calculated for each patient from biological data obtained by COBAS C311 (Roche Hitachi, Japan). Statistical analyses were performed using GraphPad and MED-CALC software. **Results:** Our study involved 30 patients (men) of middle age (25 - 52 years), with extremes ranging from 0.67 to 8 for APRI and 0.201 to 22 for FIB-4. A predictive APRI and FIB4 score of significant hepatic fibrosis was observed in 23% of patients; however, 46% and 54% of patients for the APRI and FIB-4 score, respectively, would not have significant fibrosis. An APRI and FIB4 score not included in the classification limits of the type of fibrosis hepatitis was observed in 31% and 23% of patients, respectively. **Conclusion:** The performance of the APRI and FIB-4 biological scores analyzed according to the interpretation of their cut-off values would enable classifying about

70% and 77%, respectively, of the patient population in the stages of hepatitis C fibrosis.

Keywords

Co-Infected Patients, HIV, HCV, APRI and FIB-4

1. Introduction

HIV/Hepatitis C co-infections are common and represent major public health problems. It is estimated that HIV and HCV co-infection affects between 2 and 3 million people worldwide [1]. In Côte d'Ivoire, HCV infection is estimated at 5% and HIV infection at 3% [2]. Mortality attributable to hepatitis C virus infection, which is higher than that of HIV in general, is a major cause of death in co-infected people [3]. The effectiveness of HCV transmission increases in the presence of HIV infection. For example, people living without treatment for HIV are less likely to spontaneously eliminate HCV infection, and they experience a more rapid progression of HCV disease [1]. The silent course of liver disease and the high frequency of transition to chronicity explain the existence of a large reservoir of infected subjects. Hepatitis viruses play little role in HIV evolution, but they aggravate the natural history of chronic hepatitis, including the risk of cirrhosis and hepatocellular carcinoma, the latter occurring more frequently in co-infected HIV/HCV patients [4]. The assessment of fibrosis during chronic viral hepatitis C represents an important step in its management, in this case in people living with HIV in whom this progression is accelerated. Indeed, this evaluation will make it possible, on the one hand, to classify the liver disease severity and, on the other, to pose the therapeutic indication [5]. A few years ago, the historical reference examination for the analysis of hepatic fibrosis was the puncture liver biopsy [6]. However, due to its limitations, in particular its invasive nature and its inaccessibility for most patients from developing countries, several non-invasive tests have been developed. These tests include fibrosis tests based on scores from blood tests, which are presented as an alternative to the histological analysis of liver biopsy, an invasive examination requiring hospitalization, and above all are very expensive for patients in developing countries.

Aspartate aminotransferase/platelet ratio index (APRI) and fibrosis 4 (FIB-4) scores are simple and inexpensive blood tests based on aspartate aminotransferase and alanine aminotransferase to diagnose different stages of liver fibrosis [7] [8]. They showed that a gradual increase in aspartate aminotransferase (AST) levels and a decrease in platelet levels are significantly correlated with the severity of hepatic fibrosis. These tests are among those widely utilized to stage hepatic fibrosis during chronic viral hepatitis C or hepatic B [9]-[16]. The present study, which is the first prospective of its kind, aims to use non-invasive biomarkers FIB-4 and APRI scores and the AST/alanine aminotransferase (ALT) ratio in the process of diagnosing chronic liver damage in co-infected HIV/HCV

patients living in rural localities in the west of Côte d'Ivoire.

2. Materials and Methods

2.1. Patients and Inclusion Criterion

The qualitative method of semi-directive interviewing was used to interview patients with hepatitis C and human immunodeficiency virus coinfection in Blood Transfusion Centres (CTS) in the cities of Man and Daloa located in the west of Côte d'Ivoire. The study proceeded from September 2019 to November 2019 in the sampling and collection units of the CTS in both sites. The study consisted of collecting, using a maintenance questionnaire, the lifestyle, the diagnostic and therapeutic routes, the knowledge, representations and experiences of the disease.

The criteria for selecting respondents were to be at least 18 years of age and have a positive test for HIV and HCV. They were registered with the agreement of the respondents who gave their informed consent and were assured of respect for the anonymity and confidentiality of the collected information.

2.2. Data Analysis

For each patient, socio-demographic data were collected (sex, age, place of residence, occupation, marital status, personal history of high blood pressure, diabetes, smoking, alcoholism, and medication). Serological tests for confirmation of HIV and HCV presence were performed in patients included in the study by using Alere Medical's DETERMINE HIV 1/2 and Chembio HIV 1/2 STAT-PAK rapid *in vitro* diagnostic and COBAS 6000 (Roche Hitachi, Japan), respectively.

2.3. Biology and Immunological Tests

The enzymatic activity of the biochemical parameters, which were ALT, AST and PAL, was determined using the automata COBAS C311 (Roche Hitachi, Japan) available at the Institut Pasteur Côte d'Ivoire. The normal values taken were according to the normal laboratory limit, respectively, of 8 - 45 UI/L, 8 - 40 UI/L, and 40 - 129 UI/L. The platelet level of each patient was determined from the blood count (NFS) on the Sysmex. Normal values were 150 - 400 10^3/µL. Immunology was represented by the CD4 level of each patient, with a normal level taken between 33% - 50%.

2.4. Aspartate Aminotransferase (AST)/Platelet Ratio Index (APRI) and Fibrosis 4 (FIB-4) Indices

APRI and FIB-4 scores were determined using biochemistry parameters [7] [8] Table 1

The score corresponding to the diagnosis of significant fibrosis is shown in Table 2. An APRI score ≤ 0.5 corresponded to minimal fibrosis; a score ≥ 1.5 corresponded to cirrhosis. A FIB-4 ≤ score of 1.45 corresponded to minimal fibrosis; a score ≥ 3.25 corresponded to cirrhosis. The ratio of the AST values to the ALT is defined the AST/ALT Score Ratio (RAA).

Table 1. Score of fibrosis tests formula.

Fibrosis test	Calculation
APRI	([AST (IU/L]/platelet count [10^9/L]) × 100
FIB-4	Age (years) × AST [U/L]/(platelet count [10^9/L] × (ALT [U/L])$^{1/2}$
RAA	AST (U/L)/ALT(U/L)

APRI: Aspartate aminotransferase to Platelet Ratio Index, FIB-4: Fibrosis 4, RAA: Ratio aspartate aminotransferase (AST)/ alanine aminotransferase (ALT).

Table 2. Thresholds are used for each test in the diagnosis of significant fibrosis.

	Non-significant fibrosis	Significant fibrosis
APRI	<0.5	>1.5
FIB-4	<1.45	≥3.25
RAA	<1	>1

2.5. Statistical Analysis

Population characteristics are expressed in percentages or means, standard deviations and intervals. For each biological data, two groups were determined: normal and abnormal values. The Spearman's nonparametric test studied the correlations between quantitative variables. A $p < 0.05$ value is considered statistically significant. Variables with too low an event rate (numbers less than 3) were not taken into account in the statistical analysis. The statistics software GraphPad and MED-CALC entered and interpreted the data.

3. Results

The socio-demographic, epidemiological and biological average characteristics of the patients in the study are presented in Table 3. Over a period of 3 months, 30 patients were included prospectively. Of the patients, 100% lived in rural areas, the majority of whom (61%) were unemployed and had no medical history (77%). The average age was 37 ± 7.67 years.

3.1. Biology Parameters and Liver Fibrosis Biomarkers APRI and FIB-4

Biology results were presented in Table 4. The study population is HIV and HVC-positive, which is the main criterion for participating in the study. Transaminase mean values were 39.76 IU/L ± 396 IU/L for ALT and 44.56 IU/L ± 401 IU/L for AST. AST levels ranged from 14 to 199.01, and ALAT values ranged from 13 to 228. Of the population study, 85% have ALT normal value against 15% with abnormal value. This result is similar to AST with 75% of patients that have AST normal values while 25% of this population have AST values higher than normal. About 54% had platelet levels normal while 46% have platelet values below normal with a maximum of 205 10^3/µL. Regarding CD4, values ranged from 12 to 46, with 46% of the population having normal values and 54% with values higher than normal.

Table 3. Epidemiological and socio-demographic characteristics.

Epidemiological data	Patient outcome (%) or Mean (SD)
Rural areas	100%
Age (mean ± SD) (years)	37 ± 7.7
occupational status	39%
Personal and medical history	23%
Concept of transfusion	8%
Use of non-sterile objects	54%
Familial viral hepatitis	15%
Surgery	8%
Extrahepatic pathology	8%
Hepatitis B vaccine	15%

Table 4. Biological parameters.

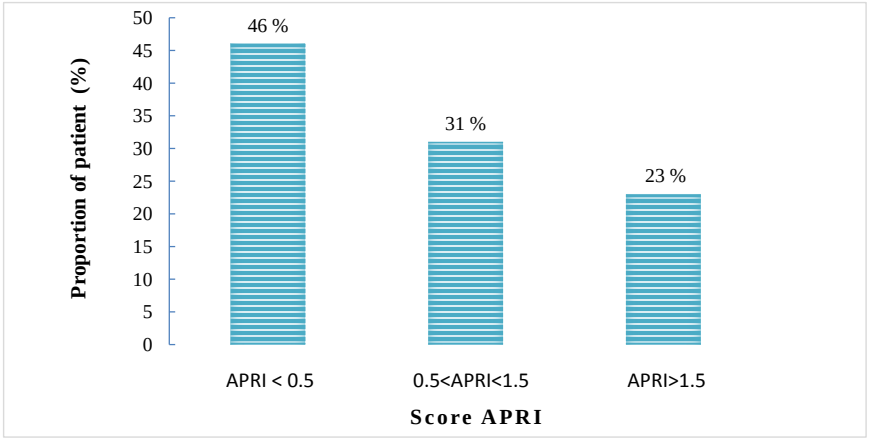
Biological data (Value range)	**Mini. - Max**	**Normal values (%)**	**Anormal values (%)**	**Patient Outcomes** (mean ± SD)
HIV				**100% (+)**
HCV				**100% (+)**
ALT (**8 - 40 UI/L**)	13 - 228	85%	15%	39.76 ± 396
AST (**8 - 45 UI/L**)	14 - 199.01	75%	25%	44.56 ± 401
PAL (**40 - 129 UI/L**	57 - 119	100%	-	85 ± 19
PLATELETS (**150 - 400** 10^3**/µL**)	70 - 205	54%	46%	152 ± 42
CD4 (**33 - 50%**)	12 - 46	46%	54%	28 ± 11

HIV human immunodeficient virus, HCV hepatitis C virus, AST aspartate aminotransferase, ALT alanine aminotransferase, Lymphocytes T CD4.

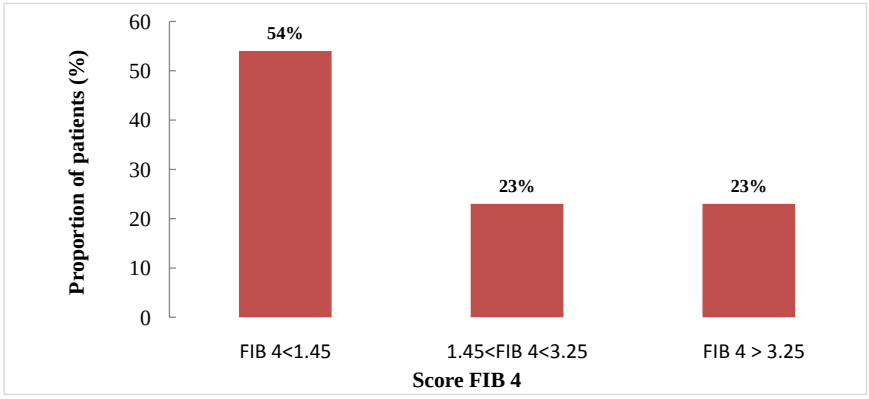
APRI and FIB-4 scores and the proportion of the population were presented in Table 5 and Figure 1. The scores range from 0.20 to 3.62 for APRI with an average of 0.92, and from 0.67 to 5.12 for FIB-4 with an average of 1.99. According to the results, about 46% of the study population had APRI score below 0.5 with minimal fibrosis, while 23% had a score above 1.5 with significant fibrosis, and 31% was in the intermediate zone (Figure 1). Concerning FIB-4, about 54% of the study population was observed to have a score below 1.45, corresponding to minimal fibrosis while 23% had a score above 3.25 with significative fibrosis, and 23% was in the intermediate zone. Finally, the AST/ALT ratio (RAA) > 1 concerned 84% of patients with significative fibrosis (Table 5).

Table 5. Average value of biological scores and stages of liver fibrosis according to their interpretation.

Parameters	Min - Max	Average	Minimal fibrosis	Significative fibrosis	Not determined
APRI	0.20 - 3.62	0.92	46%	23%	31%
FIB-4	0.67 - 5.12	1.99	54%	23%	23%
Ratio AST/ALT	0.82 - 1.86	1.30	16%	84%	-



(a)



(b)

Figure 1. Distribution according to APRI (a) FIB-4 (b) score classification value.

3.2. Correlation of Biochemical Parameters and APRI and FIB4 Score

Table 6 and Table 7 showed a correlation between scores and biochemical parameters and APRI and FIB-4 score significance between biochemical parameters, respectively. Spearman's correlation analysis showed no significant difference between the APRI score and the age and between the CD4 and PAL rates of patients. In addition, there was no significant difference between the APRI and RAA scores (95% CI p-value > 0.05). However, the results showed that the value of ALT, AST, RAA and platelets were significantly correlated with the results of FIB-4 and APRI (95% CI, $p < 0.05$), Table 7.

Table 6. Correlation between scores and biochemical parameters (Spearman Correlation Matrix).

VARIABLES	AST	ALT	PAL	PLAQUET	CD4	AGE	APRI	FIB-4
AST	1	0.8281	0.3939	−0.4952	−0.4273	0.2834	0.9725	0.8996
ALT	0.8281	1	0.3241	−0.1736	−0.4237	0.1983	0.7785	0.6281
PAL	0.3939	0.3241	1	0.0166	−0.3881	0.2786	0.4518	0.4290
PLAQUET	−0.4952	−0.1736	0.0166	1	0.4000	−0.0358	−0.6245	−0.6832
CD4	−0.4273	−0.4237	−0.3881	0.4000	1	−0.5057	−0.5364	−0.6560
AGE	0.2834	0.1983	0.2786	−0.0358	−0.5057	1	0.2944	0.4559
APRI	0.9725	0.7785	0.4518	−0.6245	−0.5364	0.2944	1	0.9409
FIB-4	0.8996	0.6281	0.4290	−0.6832	−0.6560	0.4559	0.9409	1
AST/ALT	–	–	–	–	–	–	0.247	0.390

Values different from 0 at significance level alpha = 0.05.

Table 7. Significance values between score and biochemical parameters (p-values).

VARIABLES	AST	ALT	PAL	PLAQUET	CD4	AGE	APRI	FIB-4
AST	0	0.0008	0.1809	0.0884	0.1926	0.3430	0.0000	0.0000
ALT	0.0008	0	0.2757	0.5712	0.1967	0.5100	0.0026	0.0240
PAL	0.1809	0.2757	0	0.9565	0.2401	0.3513	0.1211	0.1428
PLAQUET	0.0884	0.5712	0.9565	0	0.2194	0.9131	0.0258	0.0126
CD4	0.1926	0.1967	0.2401	0.2194	0	0.1167	0.0936	0.0333
AGE	0.3430	0.5100	0.3513	0.9131	0.1167	0	0.3240	0.1174
APRI	<0.0001	0.0026	0.1211	0.0258	0.0936	0.3240	0	<0.0001
FIB-4	<0.0001	0.0240	0.1428	0.0126	0.0333	0.1174	<0.0001	0
AST/ALT	-	-	-	-	-	-	0.415	0.188

4. Discussion

4.1. Socio-Demographic Characteristics

The present study is the first prospective study of this type primarily concerning co-infected HIV/HCV patients living in rural localities where the possibilities of treatment for hepatitis diseases are very limited. Our study showed that patients were relatively young, with an average age of 37 ± 7.7, and none of the patients practice the tattoo or inject themselves with drugs. However, 53.84% of patients use non-sterile instruments (sharp or prickly metal objects, etc.), which could be the risk factor for the spread of the disease [17] [18] [19]. Additionally, the study showed that the source of income strongly influences the HIV/HCV coinfection. Patients in stable employment (government employees, 15%) are less infected while those in the informal sector (39%) and the unemployed (46%) are at higher risk. These results are similar to other work that has shown a significant link between social status such as level of education or even financial status and a high risk of HCV infection [15] [17] [18]. These results suggest that socio- de-

mographic characteristics should be considered in the search for ways to combat HIV/HCV co-infection.

4.2. Biochemical Parameters and Liver Fibrosis Biomarkers

The obtained transaminase values show that almost 25% of patients had AST levels higher than normal, and 15% are normal for ALT, while half of the patients studied (46%) had below-normal platelet levels. Nearly 84% of our study patients had an AST/ALT ratio > 1. These results show that these patients could have significant liver fibrosis similar to McPherson *et al.* [9], who showed that the increased AST/ALT ratio was associated with advanced fibrosis [9] [13]. Additionally, there is a significant correlation between transaminase values, platelet levels and our biological scores (p-value < 0.05) **Table 7**.

Regarding APRI and FIB-4 scores, our study showed that nearly 23% of patients had APRI > 1.5 and FIB-4 scores ≥ 3.25, suggestive of significant liver fibrosis with a very significant correlation between APRI and FIB-4 (p-value < 0.0001) in **Table 7**. These results are similar to those found in the literature, which show that FIB4 and APRI would give an incidence of liver fibrosis of less than 50% [12] [20]. The low FIB-4 values could be related to the small size of the sample and also the young age (37 ± 7.7) of the patients in our study [21]. Indeed, studies by Chun-han Chen *et al.* showed that the average FIB-4 index was significantly higher in elderly patients compared to younger ones [22].

For APRI < 0.5, about 46% and for FIB-4 < 1.45, more than half of the population (54%) would not have significant fibrosis. By associating the APRI cut-off points below the lower threshold value (0.50) and above the upper-value threshold value (1.50), 69% of patients could be identified correctly as without or with significant fibrosis. Although the diagnosis accuracy of the APRI remains low for diagnosing advanced fibrosis in patients in our study, nevertheless, APRI allows correct identification of 69% of population studies as without or with significant fibrosis [7] [11] [13]. Likewise, the FIB-4 breakpoints below the lower threshold value (1.45) and above the upper-value threshold value (3.25) correctly identified 77% of patients as without or with significant fibrosis. These results show that APRI was comparable to FIB-4 in predicting significant liver fibrosis in hepatitis C patients [13] [23]. However, when analyzing the threshold value of APRI > 0.5 and <1.5 and FIB-4 ≥ 1.45 and <3.25, our study showed that 31% and 23% of patients, respectively, of APRI and FIB-4 corresponding to the intermediate scores were not included in the classification limits of the type of hepatitis C fibrosis. These results, although lower than those of Sterling *et al.*, represent a good percentage of diagnosis of liver fibrosis C for patients who could avoid a liver biopsy [8]. APRI or FIB-4 score alone does not make it possible to classify patients into the different stages of liver fibrosis, whether type B or C. The combination of several methods, a large number of patients and a classification according to age may predict significant fibrosis in HIV/HCV co-infection patients.

4.3. Limits of Study

Our study has some limitations. First, we had a relatively small number of patients, and we used the retrospective method for analysis. A cohort study with independent variable analysis will be more powerful. Additionally, the study showed that APRI or FIB-4 score alone does not make it possible to classify patients into the different stages of liver fibrosis, whether type B or C. The combination of several methods, a large number of patients and a classification according to age may differentiate mild to moderate from advanced fibrosis in HIV /HCV co-infection patients.

5. Conclusion

Our study on the use of non-invasive biomarkers FIB-4 (Fibrosis 4) and APRI in the process of diagnosing chronic liver disease in HIV/HCV co-infected patients enabled us to classify approximately 70% and 77% of the population of patients with fibrotic stages of hepatitis C, respectively. It gives an opportunity to many people in rural areas to avoid liver biopsy with its disadvantages and especially it is very expensive price for these financially deprived patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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