

Risk factors for liver fibrosis among human immunodeficiency virus monoinfected patients using the FIB4 index in Morocco

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Received: April 13, 2013 Revised: August 31, 2013

Accepted: September 18, 2013

Published online: October 27, 2013

independent risk factors for FIB4 > 1.45.

RESULTS: A FIB4 score > 1.45 was identified in 96 among 619 (15.5%). HIV monoinfected patients followed up between September 1990 and September 2012. Multivariate analysis showed that only a viral load > 75 (OR = 2.23, 95%CI: 1.36-3.67), CD4 > 200 cells/mm³ (OR = 0.39, 95%CI: 0.21-0.72) and age at FIB4 index calculation (OR = 1.10, 95%CI: 1.07-1.13) were independently associated with the occurrence of FIB4 index (> 1.45). Gender, duration of HIV infection, glycemia, use of antiretroviral therapy and ART duration were not associated with significant fibrosis by FIB4.

CONCLUSION: FIB4 score > 1.45 was found in 15.5% of Moroccan HIV monoinfected patients. Age, HIV viremia > 75 copies/mL and CD4 count > 200 cells/mm³ are associated with liver fibrosis. Further studies are needed to explore mechanisms for fibrosis in HIV monoinfected patients.

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Key words: Human immunodeficiency virus; FIB4; Liver; Monoinfected; Risk factors

Abstract

AIM: To study the prevalence and risk factors of significant hepatic fibrosis in Moroccan human immunodeficiency virus (HIV) monoinfected patients.

METHODS: We conducted a cross-sectional study among HIV monoinfected patients (negative for hepatitis B surface antigen and hepatitis C antibody). Clinical and laboratory data were collected from the data base of the Infectious Diseases Unit in Ibn Rochd Hospital Center [age, gender, duration of HIV infection, CD4 T lymphocyte count, HIV viral load, glycemia and current or prior use of antiretroviral and antiretroviral therapy (ART) duration]. The primary outcome was a FIB4 score > 1.45. Multivariable logistic regression identified

Core tip: We evaluated, for the first time in Morocco, the prevalence and risk factors of significant hepatic fibrosis in Moroccan human immunodeficiency virus (HIV) monoinfected patients using the FIB4 score which represents a noninvasive, composite index that is a validated measure of hepatic fibrosis. FIB4 score > 1.45 was found in 15.5% of Moroccan HIV monoinfected patients. Age, HIV viremia > 75 copies/mL and CD4 count < 200 cells/mm³ are associated with liver fibrosis. Gender, duration of HIV infection, glycemia, use of antiretroviral therapy and antiretroviral therapy duration were

not associated with significant fibrosis.

Tahiri M, Sodqi M, Lahdami FEZ, Marih L, Lamdini H, Hliwa W, Lahcen AO, Badre W, Haddad F, Chakib A, Bellabah A, Alaoui R, El Filali KM. Risk factors for liver fibrosis among human immunodeficiency virus monoinfected patients using the FIB4 index in Morocco. *World J Hepatol* 2013; 5(10): 584-588 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v5/i10/584.htm> DOI: <http://dx.doi.org/10.4254/wjh.v5.i10.584>

INTRODUCTION

About 33 million people are infected with human immunodeficiency virus (HIV). Most of them live in low and middle income countries^[1]. The liver is a major target of HIV infection and a wide spectrum of liver disease can be seen in patients with HIV infection, ranging from steatosis, steato-hepatitis, non cirrhotic portal hypertension and hepatocellular carcinoma^[2]. Recent data shows that HIV *per se* (without viral hepatitis infection) can induce liver fibrosis but few studies^[3-5] have identified risk factors involved in liver fibrosis among HIV monoinfected patients.

Liver biopsy is the gold standard technique for diagnosis of liver fibrosis but it is an invasive procedure that can induce non-negligible morbidity and mortality. Thus, liver biopsy is not an acceptable technique for monitoring progression liver fibrosis and for pursuing appropriate epidemiological analysis. Many alternative biochemical markers have been introduced to avoid liver biopsy [fibrotest, actitest, aspartate aminotransferase (AST) to platelet ratio index (APRI) and FIB4]. FIB4 was previously validated as a fibrosis marker in HIV/HVC co-infection^[6] and has recently been used to determine advanced fibrosis in HIV monoinfected patients^[7].

To date, there is no data in Morocco regarding liver fibrosis in HIV monoinfected patients. To identify risk factors for liver fibrosis in Moroccan HIV monoinfected patients, we examined hypothesized risk factors: CD4 counts^[7], hypoglycemia^[8,9], antiretroviral therapy (ART) use and HIV viremia^[7,10].

MATERIALS AND METHODS

Study design and patients

We conducted a cross sectional study of patients followed in IBN ROCHD University Hospital center. We used the database "NADIS" that was launched in 2005 to describe the demographic, clinical and laboratory characteristics of Moroccan HIV infected patients. All laboratory confirmed HIV patients and Hepatitis B virus surface antigen (HBsAg) negative/anti HVC negative were enrolled in the study.

Study outcome

The major study outcome was significant fibrosis, as

determined by FIB4 index > 1.45. FIB4 score was calculated during the last consultation using the following formula: $[\text{age (year)} \times \text{AST (U/L)}] / [\text{platelet (10}^9/\text{L)} \times \text{alanine aminotransferase (ALT) (U/L)}]^{1/2}$. All participants provided informed consent prior to sample and clinical data collection. HIV RNA levels were qualified using second or third generation Quantiplex branched DNA assays (Chiran). HBsAg was tested with Austria-IL-125 RIA (ABBOTT laboratory). Hepatitis C virus (HCV) status was obtained through HCV enzyme immunoassay 2.0.

Data collection

All data were collected from "NADIS" IBN ROCHD University Center Hospital and included: age, gender, duration of HIV diagnosis, presence of diabetes mellitus (glucose level greater than 126 mg/dL or self reported), CD4 count during the last visit, HIV viral load at first and last visit, AST, ALT and platelet at the last visit, use of ART (receipt of three antiretroviral drugs from at least two different drug classes), ART duration and prior of current use of Zidovudine, Lamivudine, Efavirenz, Nevirapine, Lopinavir, Ritonavir, Emtricitabine, Stavudine, Tenofovir and Didanosine. FIB4 index was used as a categorical variable with two levels < 1.45 and > 1.45 corresponding to the recommended cutoff used to exclude the presence of advanced fibrosis^[6].

Statistical analysis

Statistical analysis was performed using SPSS Base 20 statistical software (SPSS, Inc., Chicago, IL). We included only patients in whom in the last visit AST, ALT, RNA HIV level, CD4 level and platelet count were available. Duration of HIV infection was calculated as the difference between the first and the last visit. The results were expressed as mean \pm SD. For categorical data, χ^2 test were used to assess differences between patients with and without significant fibrosis by FIB4 score (FIB4 > 1.45). For continuous data, *t* test for continuous variables was used. A two tailed *P* value of less than 0.05 was taken to indicate statistical significance. Univariate analysis was performed to study characteristics associated with FIB4 > 1.45. Variables with *P* values < 0.1 in univariate analysis were used in the multivariate regression analysis with backward variable selection.

RESULTS

Characteristics of the study population

Six hundred and nineteen patients were studied. Three hundred and fifty-four patients were female, with a mean age of 39.85 ± 9.56 years. Five hundred and twenty-three patients had a FIB4 < 1.45. 87 had a FIB4 between 1.45 and 3.25 and only 9 patients (1.45%) had a FIB4 > 3.25. Mean HIV diagnosis was 4.71 ± 3.91 . Mean antiretroviral duration was 4.45 ± 3.77 years. Thirty-six patients (5.8%) had diabetes mellitus. Five hundred and seventy were under antiretroviral therapy (92.1%).

At the time of analysis, mean AST was 24.66 ± 20.84

Table 1 Baseline subject characteristics, overall and by significant fibrosis as determined by FIB4 score

	All patients (n = 619)	Patients with FIB4 > 1.45 (n = 96)	Patients with FIB4 < 1.45 (n = 523)	P value
Male gender	42.80%	51.04%	41.30%	0.920
AGE	39.8 ± 9.5	46.5 ± 8.9	38.6 ± 9.1	< 0.001
Duration of HIV infection	4.7 ± 3.9	4.2 ± 4.2	4.7 ± 3.8	0.250
ART TTT	92.08%	90.62%	92.35%	0.540
ART duration	4.4 ± 3.7	4.5 ± 4.12	4.5 ± 3.7	0.340
AST	24.6 ± 20.8	39.6 ± 46.6	21.9 ± 8.3	0.000
ALT	21.2 ± 16.1	25.6 ± 24.9	20.7 ± 13.7	0.670
PQ	256.9 ± 33.8	170.5 ± 61.5	272.7 ± 338.0	0.003
CV	76060 ± 39663	260460 ± 765929	42212 ± 268494	0.007
CD4	602.2 ± 367.6	403.16 ± 266.5	638 ± 372	0.001
CD4 < 200	12.40%	23.95%	10.32%	0.001
CV < 75	57.20%	41.66%	60.03%	0.001
Diabetes	5.80%	8.33%	5.35%	0.240
Zidovudine	87.20%	80.20%	88.52%	0.030
Lamivudine	89.00%	85.41%	89.67%	0.210
Efavirenz	79.30%	77.08%	79.73%	0.580
Nevirapine	11.10%	10.41%	11.28%	1.000
Lopinavir	23.30%	22.91%	23.32%	1.000
Ritonavir	29.70%	30.20%	29.63%	0.900
Emtricitabine	8.10%	11.45%	7.45%	0.210
Stavudine	23.40%	29.16%	22.37%	0.150
Tenofovir	8.90%	12.50%	8.22%	0.170
Didanosine	5.30%	6.25%	5.16%	0.620

HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

and mean ALT 21.52 ± 16.10 . Mean platelet count was 256.96 ± 313.80 . Mean CD4 count was 602.24 ± 367.65 . Mean viral load was 76060.4 ± 396639 and 12.4% (77 patients) had a CD4 count below 200 cells/mm³, 57.62% (354 patients) had viral load below 75 copies/mL.

In univariate analysis, only CD4 count ($P = 0.001$), viral load > 75 copies/mL ($P = 0.007$), age ($P = 0.000$) and prior or current Zidovudine intake ($P = 0.03$) were associated with a FIB4 over 1.45. In contrast, gender, ART therapy, ART duration, diabetes and prior or current intake of Lamivudine, Efavirenz, Nevirapine, Lopinavir, Ritonavir, Emtricitabine, Stavudine, Tenofovir, Didanosine, Abacavir, Raltegravir, Indinavir and Nelfinavir were not associated with a FIB4 over 1.45.

Multivariate analysis showed that only a viral load > 75 (OR = 2.23, 95%CI: 1.36-3.67), CD4 > 200 cells/mm³ (OR = 0.39, 95%CI: 0.21-0.72) and age at FIB4 index calculation (OR = 1.10, 95%CI: 1.07-1.13) were independently associated with occurrence of a high FIB4 index (> 1.45).

DISCUSSION

Since antiretroviral therapy has been widely used, liver diseases have become a major cause of morbidity among HIV patients. The presence of viral co-infection B and C are a common cause of liver disease^[11-16]. Moreover, recent data suggest a direct role of HIV virus in hepatic fibrosis^[3-5]. Studies carried out in HIV monoinfected patients

found a mild to moderate increase in liver enzymes^[6-17].

Indirect data indicate a possible direct role of HIV virus in liver damage and fibrosis. In HIV-HVC co-infected people, slower fibrosis progression is associated with HIV suppression^[18] and liver related mortality is less in patients under ART^[19,20]. Thus, in monoinfected HIV patients, without hepatitis B or C co-infection, elevation of AST and ALT is associated with a higher HIV RNA level^[21-23].

HIV can induce liver fibrosis through interacting with many kinds of liver cells; Kupffer cells can be stimulated by lipopolysaccharide (LPS) due to increased permeability induced by HIV infection. Once stimulated, Kupffer cells produce pro-inflammatory cytokines, such as tumor necrosis factor- α , transforming growth factor β , interleukin (IL)-6 and IL-12^[24]. These cytokines are responsible for chemotaxis of monocytes and T cells to the liver^[25]. HIV can also stimulate stellate cells (HSC) through CxCR4 receptors^[26]. Activated HSC showed increased fibrogenesis and increased collagen production and alpha smooth muscle^[27] in patients with HIV-HVC co-infection.

The first interesting result of our study is the prevalence of advanced fibrosis (FIB4 > 3.25) estimated as 1.45% among Moroccan monoinfected patients. This finding disagrees with previously published studies; using the APRI index in 1845 HIV monoinfected patients, Sulkowski *et al.*^[5] found 7% significant fibrosis, as defined by APRI > 1.5^[5].

Another study, carried out in 432 monoinfected HIV patients, identified significant fibrosis by APRI in 8.3% patients^[3]. Moreover, in a recent study, 1.3% of monoinfected HIV women had a FIB4 > 3.25^[7]. Interestingly, only 1% of HIV monoinfected had significant fibrosis measured by elastometry^[4]. APRI had platelet count in the denominator, which accounts for the relatively higher frequency of liver fibrosis by APRI compared to elastometry which can be explained by the frequency of thrombocytopenia commonly found among HIV patients^[28].

Our study found that HIV viremia was a risk factor for significant liver fibrosis among HIV monoinfected patients. Previous studies identified HIV RNA as an independent factor of elevated AST and ALT in HIV monoinfected patients^[6,17].

HIV viremia was also associated with a high FIB4 index score in HIV-HVC co-infected patients^[18]. Our results are in concordance with previously published studies that used non invasive methods to assess liver fibrosis. Using the APRI index, Piazza found that detectable HIV viremia is a risk factor for liver fibrosis in HIV monoinfected patients^[10]. Another recent study found that a 1 log^[10] increase in HIV RNA was associated with a median increase in FIB4 of 12%^[29].

Another risk factor for significant hepatic fibrosis in our sample was CD4 counts. This result is also in accordance with those of Blackard who reported that CD4 T cell counts are negatively associated with FIB4. Some studies reported that AST/ALT was negatively associated with CD4 T cell counts. Other studies did not find CD4

T cell counts as an independent factor for liver fibrosis^[10].

The last risk factor for significant hepatic fibrosis in our study was age at FIB4 index calculation. This result disagrees with studies previously published in HIV monoinfected patients^[7,10,29]. This is in concordance with a study carried out by Blanco who found that old age is associated with liver fibrosis by elastometry. Also, age ≥ 40 was a high factor for liver fibrosis progression in HIV^[30]. In HIV-HVC co-infected patients, older age was found to be an independent factor for advanced liver fibrosis measured by elastometry^[31].

Another interesting result of our study is that ART use and its duration were not independently associated with liver fibrosis. This result agrees with previously published studies^[3,10,29] suggesting that liver fibrosis is not increased by long term use of highly active antiretroviral therapy in HIV monoinfected patients.

Our study has many advantages. Firstly, it is the first study carried out in Moroccan people and the design of the study is distinctive. Secondly, most of the included patients in this study received ART and the prior and current use of the most commonly prescribed HIV drug was included in the univariate analysis. Furthermore, in our sample, the impact of ART duration on liver fibrosis was also assessed, whereas other studies included mostly ART naïve patients or those receiving less than an optimally suppressive ART regime^[7,32]. On the other hand, our study has several limitations. Firstly, the cohort was recruited from a university hospital and all patients were in regular HIV care. Secondly, liver fibrosis evaluation was based on the FIB4 index that is not widely assessed in HIV monoinfected patients; FIB4 has been validated as a liver fibrosis index in HVC and HIV-HVC co-infected patients^[6,33]. It did not exclude some patients that were misclassified by FIB4. All conditions, decreasing platelet count (idiopathic thrombocytopenia) or increasing ALT or AST (drug hepatotoxicity) can lead to an imprecise FIB4 index. Thirdly, other confounding factors were not studied, such as alcohol use and other hepatotoxic drugs (*e.g.*, antibiotics, acetaminophen). Thus, our study is unable to specify the independent effect of these factors on liver fibrosis.

Our study found that 15.5% of Moroccan HIV monoinfected patients had a FIB4 > 1.45. HIV RNA load, CD4 count and age were independently associated with liver fibrosis. Longitudinal studies are required to examine the exact role of the HIV virus on liver fibrosis progression in monoinfected patients.

COMMENTS

Background

The liver is a major target of human immunodeficiency virus (HIV) infection and a wide spectrum of liver disease can be seen in patients with HIV infection, ranging from steatosis, steato-hepatitis, non cirrhotic portal hypertension and hepatocellular carcinoma. Recent data shows that HIV *per se* (without viral hepatitis infection) can induce liver fibrosis.

Research frontiers

The aim of this study is to identify risk factors involved in liver fibrosis among HIV monoinfected patients in Morocco using the FIB4 index, including the use

of antiretroviral therapy.

Innovations and breakthroughs

This study is the first one carried out in Moroccan people. Moreover, most of the included patients in this study received antiretroviral therapy and the prior and current use of the most commonly prescribed HIV drug was included in the univariate analysis.

Applications

The prevalence of advanced fibrosis (FIB4 > 3.25) is estimated to 1.45% among Moroccan HIV monoinfected patients. Thus, advanced liver fibrosis is a rare situation in HIV monoinfected patients in Morocco.

Peer review

A very interesting study with relevant findings in the noninvasive prediction of fibrosis field for monoinfected HIV patients.

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