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Prevalence and factors associated with significant liver fibrosis assessed by transient elastometry in HIV/hepatitis C virus-coinfected patients

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SUMMARY. Transient elastometry (TE) could provide a more accurate evaluation of the frequency and risk factors of liver fibrosis in hepatitis C virus (HCV) infection than that based on biopsy. The aim of this study was to assess the prevalence of and factors associated with significant liver fibrosis in a large population of HIV/HCV-coinfected patients. HIV/HCV-coinfected patients, who had participated in a cross-sectional, multicenter, retrospective study of liver fibrosis using noninvasive markers and in whom a determination of liver stiffness (LS) by TE was available, were included in this analysis. Factors potentially associated with significant fibrosis (LS ≥ 9 kPa) were analyzed. One thousand three hundred and ten patients fulfilled the inclusion criteria, 526 (40%) of them showed LS ≥ 9 kPa and 316 (24%) cirrhosis (LS ≥ 14 kPa). The factors independently associated with significant fibrosis [adjusted odds ratio (95% confidence interval, *P* value) were the following: older age [1.04 (1.01–1.07), 0.002], daily alcohol intake > 50 g/day [1.58 (1.10–2.27), 0.013] and the length of HCV infection [1.03 (1.00–1.06), 0.023]]. A CD4 cell count lower than < 200 per mm^3 [1.67 (0.99–2.81), 0.053] and HCV genotype 4 [0.66 (0.42–1.02), 0.066] were marginally associated with LS ≥ 9 kPa. In conclusion, the prevalence of cirrhosis in HIV/HCV-coinfected patients seems to be higher than previously reported in studies based on liver biopsy. Older age, alcohol consumption and lower CD4 cell counts are related with significant fibrosis. The latter association supports an earlier starting of antiretroviral therapy in this setting.

Keywords: hepatitis C, HIV, liver fibrosis, transient elastometry

The vast majority of studies on the prevalence and factors associated with liver fibrosis in patients with HIV and hepatitis C virus (HCV) co-infection have been based on liver biopsy [1–9]. Liver biopsy is the gold standard for the diagnosis of liver fibrosis. However, biopsy is an invasive procedure, which entails a non-negligible risk of serious complications. Because of this, liver biopsy is only accepted by a part of patients, usually those who are more adherent with medical recommendations. In addition, biopsy is mainly considered in patients in whom therapy against HCV is planned. Finally, patients with advanced liver disease are often managed without this procedure, because clotting disorders may prevent percutaneous biopsy. Due to the former reasons, populations included in studies on liver fibrosis based on biopsy are biased and the sample size is usually reduced. Besides, liver biopsy results are limited by sampling error and intra-observer variation [10]. All these drawbacks reduce the reliability of results on the prevalence of liver fibrosis and the risk factors thereof obtained in studies carried out using liver biopsy in HIV/HCV-coinfected patients.

Transient elastometry (TE) (FibroScan™; Echosens, Paris, France) is a noninvasive procedure to assess liver fibrosis by measuring liver stiffness (LS). TE has been shown to accurately predict significant fibrosis and cirrhosis in HCV-infected patients, with and without HIV coinfection [11–13]. TE assesses a volume about 100-fold bigger than a biopsy specimen, therefore being more representative of hepatic parenchyma [11]. In addition, this procedure is well accepted by the patient, and it can be performed in most HCV carriers, regardless of the stage of liver disease. Thus, TE allows appraising liver fibrosis in populations with larger number of patients and lesser selection bias than liver biopsy. Because of this, studies which assess the degree of

Abbreviations: APRI, AST to platelet ratio index; HCV, hepatitis C virus; LS, liver stiffness; TE, transient elastometry.

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liver fibrosis and risk factors for advanced disease using TE are required.

The aim of the present study was to analyze the prevalence of and the factors associated with significant liver fibrosis, using TE, in HIV/HCV-coinfected patients in Spain.

PATIENTS AND METHODS

Study design and patients

The GRAFIHCO study was a cross-sectional multicenter retrospective survey, carried out from January 2007 to February 2008. It was aimed to assess the prevalence of significant fibrosis, as measured by the AST to platelet ratio index (APRI) and the Forns index in a large population of HIV/HCV-coinfected patients in Spain [14]. The study included 8829 HIV/HCV-coinfected patients followed in 95 health care facilities from Spain, with at least one visit in the previous year and available data to calculate the APRI and Forns indices (age, AST, GGT, platelet count and total cholesterol). Demographics, clinical and laboratory data regarding the last visit of every patient were obtained from databases and clinical records at each centre and entered in a common online case report form. TE had been carried out in some of these patients. The decision to perform such examination in a subject was based on the availability of the procedure at a center and, ultimately, on the discretion of the physician in charge. Data on TE were also recorded in the common database.

Patients enrolled in the GRAFIHCO study, who fulfilled the following criteria were included in the subanalysis: (i) older than 18 years; (ii) positive serum HCV-RNA; (iii) negative serum HBsAg and (iv) a determination of LS, carried out by TE within 1 year before or after the clinical and biological evaluation, was available. Thus, subjects recruited in 58 institutions were included in this substudy.

Measurements of liver fibrosis

All patients underwent an assessment of LS by TE. Examinations were carried out according to the recommendations of the manufacturer. Measurements were performed by one person in each center. Patients showing LS values equal to or higher than 9 kPa were considered to bear significant liver fibrosis. This cut-off point had previously yielded a positive predictive value of 87% for Metavir fibrosis index $F \geq 2$ [15], a negative predictive value for $F \geq 2$ of 74%, as well as a negative predictive value for $F \geq 1$ of 100% [16]. Liver cirrhosis was diagnosed in patients with LS values equal to or higher than 14.6 kPa. This cut-off value has shown positive and negative predictive values of 86% and 94%, respectively [13].

Statistical analysis

The main outcome variable was the presence of significant liver fibrosis. We estimated the percentage of patients (95% confidence intervals [CI]) showing this main variable. We also analyzed the following factors as potentially associated with significant fibrosis: gender, age, risk factor for HCV infection, alcohol intake, cannabis use, tobacco smoking, HCV genotype, plasma HCV viral load, age at HCV infection, length of HCV infection, antiretroviral therapy use at the time of the study, years on antiretroviral therapy, CD4 cell count at the time of the study, nadir CD4 cell count and plasma HIV-viral load. A second sensitivity analysis, using a cut-off point of 7.2 kPa, another value proposed for discriminating significant liver fibrosis in HIV/HCV-coinfected patients [13], was also carried out.

The Student's *t*-test was used for comparisons of continuous variables between patients with and without significant fibrosis, if a normal distribution was followed in both groups, otherwise the Mann–Whitney *U*-test was used. Categorical variables were compared with the χ^2 test or Fisher's test, if the expected frequency of a cell was lower than five.

The variables associated with significant fibrosis with a $P < 0.2$ in the univariate analysis were entered in a multivariate analysis, using logistic regression models. The Hosmer–Lemeshow test was used to calculate the goodness of fit of the models. The adjusted odds ratio (AOR) and the respective 95% CI for each covariate were calculated.

The statistical analysis was carried out using the SPSS 14 Statistical Software Package (SPSS; Chicago, IL, USA).

Ethical aspects

The study was carried out according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Hospital Germans Trias i Pujol.

RESULTS

Characteristics of study population

One thousand three hundred and ten patients fulfilled the inclusion criteria. The median (quartile 1–quartile 3) (Q1–Q3) time elapsed from clinical and biological evaluation to TE examination was 32 (0–117) days. One thousand two hundred and nineteen patients (93%) attended hospitals and the remaining were in prison. The median (Q1–Q3) LS was 7.90 (5.60–13.40) kPa and the range 2.40–75 kPa. Other significant features of the population analyzed are displayed in Table 1.

Prevalence of significant fibrosis and cirrhosis

Five hundred and twenty-six patients (40%; 95% CI: 37–43%) had significant fibrosis, as defined by an LS value equal to or > 9 kPa. Three hundred and sixteen patients (24%; 95% CI: 22–27%) had liver cirrhosis. The proportions of patients with different degrees of LS stratified according to significant cut-off points are shown in Fig. 1.

Table 1 Features of the population studied (n = 1310)

Variable	Value*
Male gender	997 (76)
Age (years)†	43 (39–46)
IDU‡ as risk factor for HCV infection	1107 (84)
Alcohol intake > 50 per day	270 (21)
Tobacco smokers	892 (68)
Cannabis users	352 (27)
CD4 cell count at LS measurement†	498 (329–750)
Nadir CD4 cell/mm^3†	180 (76–304)
Undetectable HIV viremia	999 (76)
Receiving antiretroviral therapy	1177 (90)
Years on antiretroviral therapy†	9 (6–12)
Age at HCV§ infection†	29 (23–35)
Duration of HCV infection (years)†	13 (8–18)
HCV genotype	
1	740 (57)
2	29 (2)
3	285 (22)
4	190 (15)
Log plasma HCV load†	6.04 (5.63–6.61)
AST†¶	47 (33–77)
ALT†**	53 (35–86)
GGT†,††	79 (42–154)
Total bilirubin†	0.68 (0.49–1.07)

*Unless something else is specified, values are no. (%).
†Median (quartile 1–quartile 3). ‡Intravenous drug using. §Hepatitis C virus. ¶Aspartate aminotransferase. **Alanine aminotransferase. ††Gamma glutamyl transpeptidase.

Factors associated with significant fibrosis

Older age, male gender, alcohol consumption, intravenous drug use as route of HCV infection, being on antiretroviral therapy, lower nadir CD4 cell count, lower CD4 cell count at the time of the study, longer length of HCV infection and infection with HCV genotype 4 were associated with the presence of significant fibrosis, defined as LS equal to or higher than 9 kPa (Table 2). In the multivariate analysis, age, alcohol intake and the length of HCV infection were independently associated with the presence of significant liver fibrosis (Table 2).

The sensitivity analysis using LS equal to or higher than 7.2 kPa as outcome variable yielded results quite similar. Thus, the following factors turned out to be associated with LS equal to or above this cut-off point in the multivariate analysis: male sex [adjusted odd ratio (AOR): 1.71; 95% CI: 1.27–2.30; $P < 0.001$]; older age (AOR:1,04; 95% CI: 1.02–1.07; $P < 0.001$); alcohol intake higher than 50 g/day (AOR: 1.55; 95% CI: 1.33–2.17; $P = 0.007$); longer length of HCV infection (AOR: 1.03; 95% CI: 1.01–1.05; $P = 0.003$); CD4 cell count lower than 200 cells/mm^3 (AOR: 1.67; 95% CI: 1.03–2.71; $P = 0.038$) and infection with HCV genotype 4 (AOR: 0.53; 95% CI: 0.37–0.75; $P = 0.003$).

DISCUSSION

The prevalence of liver cirrhosis observed in this large population of HIV/HCV-coinfected patients is higher than that previously reported in studies based on liver biopsy in this setting [4,5,8,9]. Likewise, data from this study show that older age, alcohol consumption, longer duration of HCV infection and lower CD4 cell counts are associated with significant liver fibrosis measured by TE in HIV/HCV-coinfected patients. Remarkably, HCV genotype 4 infection also tended to be associated with a higher degree of fibrosis than the remaining genotypes.

Liver cirrhosis was found in 5–14% of patients with HIV/HCV coinfection in studies in which liver biopsy was carried out [2,4,5,8,9]. However, in an analysis of the prevalence of cirrhosis in HIV-infected patients using TE, it was observed in 19% (95% CI: 16–22%) of patients [17], a figure closer to 24% detected in this study. This finding could have two possible explanations. The cut-off point used here to discriminate cirrhosis had a very high negative predictive value, but the positive predictive value was 86%, if biopsy is considered as the reference [13]. Accordingly, we cannot rule out that some patients with precirrhotic liver disease have been classified as having cirrhosis. On the other hand, as the decision to perform TE depended in part on the discretion of the physician caring for a patient, it is conceivable that patients with more advanced liver disease are over-represented in this study. However, two facts make us believe that the figure reported herein on the prevalence of cirrhosis in HIV/HCV-coinfected patients is more reliable than that coming from biopsy-based studies. Firstly, there was no restriction to measure liver fibrosis in any patient due to stage of liver disease, indication of therapy against HCV or adherence to the scheduled care program, as commonly happens with biopsy. In addition, our results are similar to those obtained in another center, where all HIV/HCV-coinfected patients underwent a TE examination [17]. Because of this, we think the actual prevalence of cirrhosis in HIV/HCV-coinfected patients is closer to that reported herein than to the rates observed in previous studies which used liver biopsy.

Comparisons of the prevalence of significant fibrosis observed here with that of $F \geq 2$ in studies based on biopsy are difficult to draw. Indeed, the positive and negative predictive values of the cut-off value of 9 kPa are 87% and 74%, respectively, for Metavir fibrosis index $F \geq 2$, in comparison to biopsy [16]. Thus, a number of patients having $F \geq 2$ might have been classified as without significant fibrosis in this study. Due to this, the prevalence of significant fibrosis observed here has been lower than that of $F \geq 2$ according to the Metavir or Scheuer indices in the studies with the largest sample size of HIV/HCV-coinfected patients [4,8]. The

Table 2 Association between significant fibrosis (LS*≥ 9 kPa) and other parameters

Variable no. (%)	LS ≥ 9 kPa *n* = 526	LS < 9 kPa *n* = 784	*P* univariate	Adjusted OR (95% CI)	*P* multivariate
Male gender	428 (81)	569 (73)	< 0.001	1.24 (0.86–1.79)	0.242
Age (years)†	44 (40–47)	42 (38–45)	< 0.001	1.04 (1.01–1.07)	0.002
Alcohol intake > 50 g/day	136 (26)	134 (17)	< 0.001	1.58 (1.10–2.27)	0.013
Cannabis use	129 (26)	223 (30)	0.121	1.30 (0.90–1.83)	0.135
Tobacco smoking	351 (69)	541 (70)	0.557	–	–
Risk factor IDU‡	458 (87)	649 (83)	0.043	1.28 (0.81–2.02)	0.287
On ART§	487 (93)	690 (88)	0.010	1.36 (0.54–3.42)	0.508
Years on ART†	10 (6–13)	9 (5–12)	0.150	1.01 (0.98–1.05)	0.476
Nadir CD4†	152 (65–287)	192 (84–311)	0.001	1.00 (0.99–1.00)	0.555
CD4 < 200 per mm^3	63 (12)	57 (7)	0.004	1.67 (0.99–2.81)	0.053
HIV plasma load BDL¶	414 (79)	585 (75)	0.101	1.01 (0.68–1.52)	0.947
Age at HCV infection†	29 (23–35)	29 (23–35)	0.547	–	–
Years of HCV** infection†	14 (10–20)	13 (8–17)	0.008	1.03 (1.00–1.06)	0.023
HCV genotype 4	60 (11)	130 (17)	0.011	0.66 (0.42–1.02)	0.066
Log HCV-RNA (IU/mL)†	6.11 (5.69–6.62)	5.98 (5.55–6.61)	0.116	1.00 (1.00–1.00)	0.456

*Liver stiffness. †Values are median (quartile 1–quartile 3). ‡Intravenous drug user. §Antiretroviral therapy. ¶Below the detection level. **Hepatitis C virus.

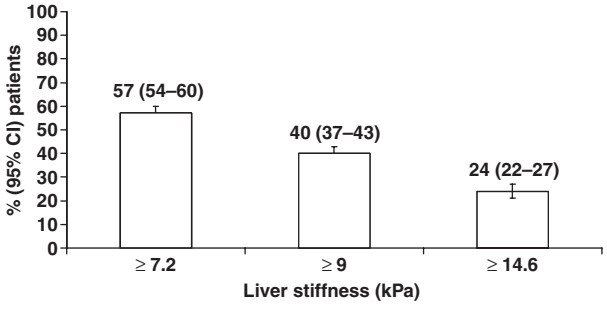

Fig. 1 Proportion of patients with different levels of liver stiffness, stratified according to significant cut-off values.

figures reported in these studies were 57% and 58%, almost identical to the proportion of patients we observed with LS equal to or > 7.2 kPa, a cut-off with positive and negative predictive values of 86% and 68%, respectively [13]. In spite of this fact, we considered only the patients with LS ≥ 9 kPa as having significant fibrosis in the primary analysis of factors associated with this variable, because this cut-off yields better diagnostic performance [13,16], and thus the results would be more accurate.

Most factors associated with LS ≥ 9 kPa in this work are consistent with those found in previous studies in HCV-monoinfected patients based on liver biopsy. Thus, alcohol, male sex, older age at biopsy and longer duration of infection are well-known factors associated with fibrosis progression in this setting [18]. Nonetheless, while alcohol consumption has been found to be related with advanced stages of liver fibrosis in several studies conducted in HIV/HCV-coinfected patients [2,4,5], male sex, older age and longer duration have usually not been so [1–9]. It is likely that lower sample size in studies based on biopsy may account for the discrepancy between the results presented herein and those in such studies.

The association between lower CD4 cell counts and significant liver fibrosis is also consistent with the finding of a worse clinical progression of liver disease in patients with deeper immunosupression [19–21]. This finding supports the recommendation included in some clinical practise guidelines regarding an earlier starting of antiretroviral therapy in patients with HIV/HCV coinfection, in order to prevent rapid liver disease progression [22,23]. Likewise, it is also in keeping with the positive impact of CD4 gain following antiretroviral treatment on the clinical course of hepatitis C in HIV-infected subjects reported previously [24]. The fact that antiretroviral therapy was not associated with lower degree of fibrosis might be surprising. However, this study is not appropriate to assess the influence of this treatment on the progression. Indeed, the vast majority of patients in this study were on antiretroviral therapy. Moreover, because of the above-stated reasons, many physicians in our area could have given priority to the treatment of HIV/HCV-coinfected patients with severe fibrosis. This would have led to a higher frequency of advanced liver disease among antiretroviral treatment recipients.

The role of HCV genotype in liver fibrosis progression is unclear. Thus, HCV genotype 3 has been suspected to be associated with more rapid fibrosis progression, because this genotype causes characteristically higher degrees of liver steatosis, a well-known promoter of fibrogenesis [18].

However, to our knowledge, an association between infection with HCV genotype 4 and less severe fibrosis has not been previously reported. In this study, genotype 4 was associated with lack of significant fibrosis in univariate analysis, and this association tended to be maintained in the logistic regression analysis. When the dependent variable was LS ≥ 7.2 kPa, this association was maintained in the multivariate study. This finding should be confirmed by other studies and, if so, further research will be needed in order to clarify the mechanism of this intriguing association.

The retrospective design of this study is a limitation. In addition, the study did not include an analysis of the association of a specific antiretroviral drug or drug families and significant fibrosis, because a complete history of prior prescriptions was not recorded in the case report form. However, retrospective cross-sectional studies are a deficient way to analyze this topic. As a consequence, the results reported in these studies have been very controversial, showing a relationship between less advanced fibrosis and protease inhibitors in some cases [4,8], with non-nucleoside retrotranscriptase inhibitors in others [9], and no relationship at all in other cases [5,7]. Large sample size and less selection bias than in studies based on biopsy are strengths that counterbalance the former limitations. The consistency of results regarding factors associated with significant fibrosis with those found in HCV-monoinfected patients suggest that the above-mentioned limitations should have no impact on our results.

In summary, when TE is used, the frequency of liver cirrhosis in HIV/HCV-coinfected patients is higher than previously reported. This supports the routine use of this procedure to assess liver fibrosis in these patients. Factors previously reported in HCV-monoinfected patients are associated with advanced liver fibrosis. In addition, patients with lower CD4 cell count show more commonly significant fibrosis than those with less deep immunosupression, suggesting that antiretroviral therapy should be started in this setting before immune suppression appears.

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APPENDIX

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