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TOPIC HIGHLIGHT

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Liver fibrosis in human immunodeficiency virus/hepatitis C virus coinfection: Diagnostic methods and clinical impact

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Abstract

Several non-invasive surrogate methods have recently challenged the main role of liver biopsy in assessing liver fibrosis in hepatitis C virus (HCV)-monoinfected and human immunodeficiency virus (HIV)/HCV-coinfected patients, applied to avoid the well-known side effects of liver puncture. Serological tests involve the determination of biochemical markers of synthesis or degradation of fibrosis, tests not readily available in clinical practice, or combinations of routine tests used in chronic hepatitis and HIV/HCV coinfection. Several radiologic techniques have also been proposed, some of which commonly used in clinical practice. The studies performed to compare the prognostic value of non-invasive surrogate methods with that of the degree of liver fibrosis assessed on liver tissue have not as yet provided conclusive results. Each surrogate technique has shown some limitations, including the risk of over- or under-estimating the extent of liver fibrosis. The current knowledge on liver fibrosis in HIV/HCV-coinfected patients will be summarized in this review article, which is addressed in particular to physicians involved in this setting in their clinical practice.

Key words: Human immunodeficiency virus/hepatitis C virus coinfection; Liver fibrosis; Liver biopsy; Fibroscan; Liver ultrasonography

Core tip: The extent of liver fibrosis is a marker of disease progression influencing the clinical and therapeutic decisions to be made for human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients. The international guidelines suggest anti-HCV therapy for HIV/HCV-coinfected patients with histological fibrosis score $\geqslant$ 2 in the Metavir scoring system since they have an increased risk of liver failure. Due to the high clinical impact of liver fibrosis and of the well-known limitations of liver biopsy, surrogate, non-invasive technologies have been researched. The pros and cons of liver biopsy and surrogate technologies in detecting liver fibrosis in HIV/HCV-coinfected patients will be discussed in this review article.

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INTRODUCTION

Nearly 7 million people are chronically coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), *i.e.*, around 20% of the entire HIV-positive population worldwide[1-3].

HCV liver-related mortality is among the leading causes of death of HIV-positive patients, despite the introduction of new potent antiretroviral regimens that have resulted in recent years in a consistent reduction in hepatic decompensation and mortality. Liver-related mortality remains higher in HIV/HCV-coinfected patients than in those with HIV or HCV monoinfection[4], most probably because HIV infection promotes HCV replication and speeds up the progression of liver fibrosis to its more severe stages[5-7].

An accurate assessment of liver fibrosis is fundamental for monitoring the disease progression and for the therapeutic decisions to be made in HIV/HCV coinfection. According to the current international guidelines, HIV/HCV-coinfected patients with chronic hepatitis and significant fibrosis (grade F2 or more in the Metavir scoring system) should be considered for anti-HCV therapy[8,9], especially those with a controlled HIV infection[9,10].

Liver biopsy, an invasive method entailing side effects or complications in a minority of cases[11-16], remains the gold standard for a morphological assessment of chronic liver diseases, particularly in patients with chronic hepatitis of dubious etiology. However, clinicians need repeatable, non-invasive procedures to monitor liver fibrosis in patients with HIV/HCV coinfection. Two types of non-invasive procedures have been developed: The radiologic assessment of liver morphology and the comprehensive evaluation of surrogate serum markers that in any way correlate with the extent of liver fibrosis. Each technique shows some limitations, including the risk of an over- or under-estimation of the extent of liver fibrosis.

This review presents the invasive and non-invasive techniques currently available to assess liver fibrosis in HIV/HCV-coinfected patients, and offers the physicians who have these patients in care an evaluation of the pros and cons of each method[10].

HIV INFECTION AND LIVER FIBROSIS IN HCV-RELATED CHRONIC HEPATITIS: A PATHOGENETIC APPROACH

Several factors possibly accelerating the progression of HCV-related liver fibrosis to its more severe stages have been investigated, namely the direct action of HIV, immune deregulation, an alteration in the cytokine pattern towards a pro-fibrotic state, HIV-related depletion of gut $CD4^+$ cells and consequent microbial translocation, oxidative stress, and hepatocyte apoptosis[1]. It has been suggested that HIV promotes liver fibrosis by acting on CCR5 and CXCR4 co-receptors for HIV-1 on hepatocytes and other liver cells[1]. In addition, experiments using *in vitro* models have suggested that the HIV-1 viral envelope glycoprotein gp120 may directly promote hepatocyte apoptosis[17] and high viral loads by inducing transforming growth factor (TGF)-β, a cytokine that alters the immune response and promotes liver fibrosis and hepatocyte transformation towards HCC[18,19]. Alterations and immune deregulation of the cytokine network may further promote the loss of $CD4^+$ cells induced by HIV, and a deregulated $CD4^+$ cell function may lead to a reduction in the anti-fibrotic activity of natural killer cells, possibly resulting in an accelerated progression of liver fibrosis[20]. The marked deregulation of peripheral and intrahepatic cytokine networks and the altered balance between $CD4^+$ and $CD8^+$ in HIV infection may play an important role in accelerating liver fibrosis. In fact, the predominant $CD8^+$ cell response is characterized by an increased production of cytokines such as interleukin-4 (IL-4), IL-5 and TGF-α, which promote collagen deposition by fibroblasts. It has also been observed that the acceleration of liver fibrosis is more pronounced when the peripheral blood $CD4^+$ cell count is consistently decreased[21-25], an observation possibly accounting for the reduction in the secretion of interferon-gamma (a cytokine with anti-fibrotic action) by $CD8^+$ cells following a decline in the number of $CD4^+$ cells[26-28].

There is also some evidence that HIV and HCV infections may promote hepatic fibrosis through an

increase in microbial translocation. Recent studies have shown that massive $CD4^+$ cell depletion in lymphoid tissue at the gastrointestinal level leads to an increased microbial translocation through a disrupted epithelium[29,30], and microbial products, like lipopolysaccharide (LPS), enter the bloodstream[31]. Of note, experiments in animal models have shown that LPS increases hepatic fibrosis and may activate Kupffer cells to promote fibrosis[32]. A further contribution to fibrosis progression may also come from an HIV- and/or HCV-induced inflammatory activity in the liver tissue that, by increasing the susceptibility of intrahepatic lymphocytes, hepatocytes, and/or hepatic stellate cells to apoptosis, may give rise to a continuous cycle of cell death and regeneration in the lymphocytes and hepatocytes that may promote fibrogenesis[1,33].

Metabolic factors like insulin resistance and non-alcoholic liver steatosis have also been proposed as factors involved in the pathogenesis of HCV-related liver disease[34], and in turn HCV and chronic inflammation of the liver may contribute to the development of these metabolic syndromes. In addition, HIV infection also induces metabolic abnormalities, including glutathione deficiency, which could predispose T cells to apoptosis through enhanced susceptibility to oxidative stress[5,35].

In conclusion, HIV infection accelerates hepatic fibrosis progression either by its direct viral action or indirectly through a dysfunction of the immune system, favoring a pro-fibrotic cytokine pattern, an increase in bacterial translocation from the gut to the bloodstream and an enhancement of apoptosis and oxidative stress.

Liver biopsy

Liver histopathology is still considered the gold standard to assess the degree of liver fibrosis, necroinflammation and steatosis[36,37]. The degree of liver fibrosis has been used as a predictive factor of disease prognosis and a guide for treatment of HCV infection[38-44], both in HCV-monoinfected and HIV/HCV-coinfected patients. Liver biopsy, usually performed with a 1.6 mm needle, has some limitations, including sampling errors and intra/inter-observer variations (approximately 24% false-negative rate in the diagnosis of liver cirrhosis)[38,45], infrequent but potentially severe complications and the difficulty to obtain multiple determinations[12,14-16,38,46]. Safety in liver biopsy has always been considered a main issue and important improvements have been obtained over time. In 1986, a nationwide Italian survey considering 68272 percutaneous needle biopsies[14] registered a mortality rate of 9/100000. In this study, ultrasound assistance to liver biopsy was available only for a small percentage of patients and the six patients who died had liver cancer or liver cirrhosis. From then on, the routine use of ultrasound-guided liver biopsy and the improved skills of the clinicians in selecting patients have greatly reduced the incidence of complications and the mortality rate following percutaneous liver biopsy.

The transjugular liver biopsy (TJLB), proposed for patients with coagulation disorders and massive ascites, allows the procurement of a liver specimen even in patients with advanced liver diseases. TJLB is a safe technique that provides good-quality specimens with a low rate of complications[47], and is highly recommended also for patients with coagulation disorders[48]. Another main issue is the representativeness of the liver specimen, which correlates with the number of portal tracts observed at microscopy and consequently, at least in part, with its size. In a recent study, Komemushi *et al*[49] compared the weight of liver specimens obtained in ten bovine livers using either an aspiration-type semiautomatic cutting biopsy needle, or an aspiration-type semiautomatic biopsy needle without aspiration, or a normal-type semiautomatic biopsy needle. The weights of the specimens were 6.80 ± 0.615 mg, 5.62 ± 0.843 mg, and 4.19 ± 0.140 mg, respectively, suggesting that, at least in bovine livers, heavier specimens can be obtained using an aspiration-type semiautomatic cutting biopsy needle.

The liver specimen is formalin-fixed and paraffin embedded. Four microns-thick sections are stained with hematoxylin-eosin or with trichrome stain. Liver fibrosis should be evaluated using the Metavir scoring system[50] or the Ishak[51] scoring system.

Several Authors assessed the degree of fibrosis on a specimen obtained by liver biopsy to predict fibrosis progression and cirrhosis development both in HCV-monoinfected patients[52,53] and in those with HIV/HCV coinfection[54]. Comparative studies showed that HIV infection accelerates the progression of fibrosis[55-57] and that fibrosis is more severe and cirrhosis development more rapid in HIV/HCV-coinfected patients with a $CD4^+$ value < 200 cells/mm^3[58-60].

It has also been demonstrated that a high degree of liver steatosis speeds up the progression of fibrosis to its more severe forms in HIV/HCV-coinfected patients[41-43,61,62].

At present, the examination of a liver specimen is still considered the gold standard to assess liver fibrosis, necroinflammation and steatosis in chronic hepatitis of all etiologies, and to diagnose autoimmune hepatitis, primary biliary cirrhosis, diseases related to iron or copper deposits, alcoholic diseases, genetically induced liver damage and toxicity- and drug-induced liver illness.

RADIOLOGIC TECHNIQUES

Morphological procedures

Conventional ultrasound: Ultrasound (US) examination of the liver, the first non-invasive repeatable procedure used to diagnose liver cirrhosis, remains the first step in the management of chronic hepatitis. Liver fibrosis is detected through US signs such as a coarse or nodular parenchymal feature, hepatomegaly, caudate lobe hypertrophy or irregular liver edges[63]. US cannot differentiate between the different degrees of liver fibrosis, but it allows the assessment of some signs of compensated or decompensated cirrhosis such as portal vein diameter, the velocity of flow, flow

reversal, ascites and splenomegaly[64]. Hepatic surface nodularity, especially as detected by a linear probe, has been shown to be the most direct sign of advanced fibrosis[65].

Contrast-enhanced US can be used for a more accurate detection of cirrhosis[66], but it should be remembered that the "arrival time" of the contrast medium into the hepatic vein is reduced in patients with cirrhosis. In addition, contrast-enhanced US requires additional expertise and entails added costs, factors which may limit its use in routine clinical practice.

As there is a higher risk of an early development of liver cirrhosis and hepatocellular carcinoma (HCC) in HIV/HCV coinfection than in HCV monoinfection[67], conventional US is of great clinical value for an early detection of liver cirrhosis in HIV/HCV coinfection, since it is cheap, easy to perform and safe and, consequently, repeatable. It should be repeated at a 12-mo interval in HIV/HCV-coinfected patients without cirrhosis and at a 6-mo interval in those with liver cirrhosis or an advanced stage of liver disease[68].

Computed tomography: Morphological signs of liver cirrhosis and portal hypertension observed at computed tomography (CT), a technique of high sensitivity but moderate specificity, have been used to diagnose liver cirrhosis. CT allows an examination of the entire abdomen and shows high sensitivity in detecting small varices at various typical locations. Some parameters, obtained from multiple measurements during dynamically-enhanced CT studies and proposed as markers of liver fibrosis[69], have not as yet been validated in multicenter trials.

Of note, some important factors limit the use of CT to assess liver cirrhosis in clinical practice, namely, its cost and the exposure of patients to ionizing radiations and to intravenous contrast medium. As it is not routinely repeatable, it is of little use in HIV/HCV coinfection.

Magnetic resonance electrography: Magnetic resonance electrography (MRE) uses a vibration device to induce a shear wave in the liver. This process involves applying a probe to the back of the patient which generates continuous low-frequency vibrations (60 MHz). Transmitted into the body, the acoustic vibrations produce a shear-wave motion within the liver that is measured through the magnetic resonance imaging (MRI) spin echo sequence. A calculator analyzes the wave images with an inversion algorithm to obtain a quantitative image of shear stiffness (elastogram). MRE has a higher sensitivity than the elastographic methods in defining mild fibrosis and a better reproducibility. A meta-analysis of five trials comparing MRE to liver biopsies showed a sensitivity of 94% and specificity of 95% in differentiating F0-F1 from F2-F4, as well as a sensitivity of 98% and specificity of 94% in differentiating F0-F3 from F4[70]. It is also possible to use MRI techniques to quantify liver fibrosis using diffusion-weighted MRI and contrast-enhanced MRI to evaluate the slow washout of intravenous contrast in fibrotic areas[71]. The use of these techniques is limited by their high cost and by the high degree of expertise required. As they are not routinely repeatable, they are of little use in HIV/HCV coinfection.

Elastography techniques

Fibroscan (transient elastography): Transient elastography (TE, Fibroscan) is a technique used for the non-invasive assessment of liver fibrosis using a transducer on the end of a US probe that transmits 50-MHz pressure waves through the liver tissue. The velocity of the resulting "shear wave", measured by US, correlates with the liver stiffness and provides an estimate of liver fibrosis. Liver stiffness is expressed in kilopascal (kPa) and is measured on a section of liver tissue 100 times bigger than the biopsy sample, ensuring more representative information. The result is the median of at least 10 valid measurements performed in a single session. The system considers valid only the shear waves with a stable velocity. The result of liver stiffness has been correlated with the degree of fibrosis as detected by the Metavir staging system. For HCV-related chronic hepatitis a value lower than 7 kPa reflects fibrosis stage F0-F1, from 7 to 10 kPa stage F2, from 10 to 14 kPa stage F3 and over 14 kPa stage F4, a sign of liver cirrhosis. The TE technique, evaluated for different etiologies of chronic liver disease[72] has a pooled sensitivity and specificity for the diagnosis of cirrhosis of 83% and 89%, respectively. It is easy to perform, repeatable, and well tolerated, but it necessitates expensive equipment and is less reliable in detecting the intermediate levels of fibrosis. In addition, the diagnostic accuracy of transient elastography (TE) is lower in obese patients[73], but a specific probe has been developed to improve the accuracy in these cases[74]. Studies performed on patients with chronic hepatitis B or C[75] have shown that the score of liver stiffness increases in patients with elevated aspartato aminotransferase (ALT) serum levels, indicating a reduced accuracy of TE in detecting liver fibrosis in these cases. Of note, the consumption of a meal before TE can increase the scores by as much as 27%[76].

At present, TE is the procedure used most to assess liver fibrosis as it is well-validated and non-invasive both in HCV monoinfection and HIV/HCV coinfection. Its limitations, however, should be taken into consideration when interpreting the results. De Lédinghen *et al*[77] studied 72 consecutive HIV/HCV-coinfected patients who underwent both liver biopsy and liver stiffness measurement by transient elastography. Liver stiffness values ranged from 3.0 to 46.4 kPa and a value $\geqslant$ 14.5 kPa for the diagnosis of cirrhosis showed good specificity and a positive predictive value.

Acoustic radiation force impulse: This technique uses conventional US to generate a shear wave directly within the liver for the estimation of liver stiffness. The propagation velocity of the shear wave is reported in meters per second and correlates with the liver stiffness.

Due to the direct generation of shear waves within the liver, the distortion of waves induced by chest, abdominal wall and ascites is avoided. Acoustic radiation force impulse (ARFI) has an excellent accuracy in the diagnosis of liver cirrhosis, with 84% sensitivity and 92% specificity. The location of a region of interest allows ARFI to estimate liver stiffness accurately. Measurements made 1-2 cm below the liver capsule offer the best results. The region of interest in ARFI (1-2 cm) is smaller than in TE (5 cm)[78], but placing the region of interest directly in the liver tissue avoids distortions. As regards obesity, ARFI has the same limitations as Fibroscan, providing unreliable results when the body mass index (BMI) is over 30[79]. The accuracy of ARFI has been compared to that of standard TE in HIV/HCV-coinfected patients. In particular, Frulio *et al*[80] studied 46 HIV/HCV-coinfected patients who underwent both ARFI and TE within 6 mo. The agreement between the two methods was defined as very good in predicting severe fibrosis (F $\geqslant$ 3) and moderate in predicting significant fibrosis (F $\geqslant$ 2). Morphological ultrasound analysis concomitant to ARFI detected HCC in two cases, indicating that, at least in this study, ARFI was more useful than TE.

Supersonic shear wave imaging: Like ARFI, supersonic shear wave imaging (SSWI) is a real-time shear wave elastography technique that generates shear waves directly within the liver and uses the Mach cone of supersonic US waves. It uses conventional US and at the same time displays the image of the liver, measures the velocity of the shear wave and calculates hepatic stiffness. Compared to TE, SSWI shows more accuracy in assessing mild fibrotic stages and a similar performance in detecting liver cirrhosis[81]. Based on a single excitation, SSWI analyzes the transversal propagation of the wave outside the region of excitation (ROE), whereas ARFI gives a local measurement of the ROE and a qualitative measurement of liver stiffness. There are no data on the application of this technique in HIV/HCV coinfection, but it seems reasonable that, as it is similar to ARFI, it merits validation also in this setting.

SEROLOGICAL MARKERS OF LIVER FIBROSIS

The assessment of liver fibrosis and the presence of liver cirrhosis based on the results of serological biomarkers have been investigated in several studies. Overall, the association of two or more biomarkers can be considered a good indicator of the presence or absence of severe fibrosis or cirrhosis, but their use in distinguishing between the intermediate stages of fibrosis or evaluating the progression of fibrosis needs further investigation and validation. A combined use of some biomarkers and radiologic techniques might afford a more accurate assessment of liver fibrosis. Two large categories of biomarkers have been established: The direct and indirect. Indirect biomarkers are correlated with the liver function, whereas the direct biomarkers reflect the turnover of the extracellular matrix.

INDIRECT BIOMARKERS

The aspartate aminotransferase/alanine aminotransferase ratio index

The aspartate aminotransferase/alanine aminotransferase ratio (AAR) index, also called aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT) ratio, is one of the oldest markers used in clinical practice for an approximate determination of disease etiology and extent of liver fibrosis. This ratio is usually over 2.0 in alcoholic liver diseases and below 1.0 in patients with long-lasting cholestatic syndromes and in those with virus-related chronic hepatitis without cirrhosis. A significant correlation between this ratio and the presence of liver cirrhosis was documented in a retrospective study on 252 HCV-monoinfected patients, where an AST/ALT ratio of 1.0 or higher was more frequently detected in a subset of 63 patients with cirrhosis than in those without ($P < 0.001$)[82]. In this study the AAR index showed 81.3% sensitivity and 55.3% specificity in identifying cirrhotic patients, but 16 patients died within 1 year of follow-up. There are no data on the application of this index in HIV/HCV coinfection.

The aspartato aminotransferase/platelet ratio index

This test is based on the ratio between AST and platelet count: Aspartato aminotransferase/platelet ratio index (APRI) = [(AST/upper normal limit) × 100/platelet count]. APRI values increase in the case of portal hypertension because of the decline in the platelet count. APRI has been extensively validated in chronic hepatitis C. In a meta-analysis of 18 studies[83], an APRI value > 2 had a specificity of 94% for the diagnosis of cirrhosis and an APRI value > 0.5 showed a sensitivity of 81% and a specificity of 55% for the diagnosis of fibrosis (n = 28 studies). APRI has also been studied in non-alcoholic fatty liver disease (NAFLD)[84], but has not been validated for other etiologies. In a multicenter study, Castera *et al*[85] evaluated the reliability of APRI, Fibrotest, TE, and two algorithms combining TE and fibrotest (FT), or APRI and Fibrotest in a cohort of 116 HIV/HCV-coinfected patients. They observed that for F $\geqslant$ 2, both TE and FT had a better diagnostic performance than APRI ($P < 0.005$) and for F4, TE had a better performance than FT ($P = 0.005$) or APRI ($P = 0.025$). In HIV/HCV-coinfected patients, the performance of APRI and FT might be affected by HIV-induced thrombocytopenia[86] or by drug-related toxicity, *e.g.*, bilirubin elevation caused by atazanavir or gamma glutamyl transpeptidase abnormalities caused by non-nucleoside reverse transcriptase inhibitors.

FT and actitest

FT is a biomarker panel containing 5 biochemical

markers and 2 clinical parameters[87]: Alpha-2 macroglobulin, haptoglobin, total bilirubin, apolipoprotein-A, gamma glutamyl transferase (GGT), age and gender. The results of these biomarkers are combined in a formula yielding a numerical value between 0.0 and 1.0 and the resulting score correlates with the METAVIR fibrosis stages. FT was originally developed in 205 HCV-monoinfected patients and validated in 134 patients. FT was subsequently validated in numerous patients with cirrhosis of different etiologies. Poynard *et al*[88] conducted a meta-analysis of 30 studies (n = 6378 patients) including patients with chronic hepatitis C, chronic hepatitis B, alcoholic liver disease (ALD), and NAFLD. This study demonstrated that FT was moderately accurate in distinguishing between adjacent fibrosis stages in all etiologies investigated. The combination of FT with transient elastography was assessed[89] in a study on 183 HCV-monoinfected patients who underwent FT, TE and liver biopsy. When FT and TE results were concordant, liver biopsy confirmed the diagnosis of cirrhosis in 94% of patients, suggesting that the combination of these two tests can be used instead of liver biopsy in a large proportion of patients. Poynard *et al*[90] studied the progression of fibrosis in 2472 patients with chronic liver disease of various etiologies and found that FT and liver biopsy had a high degree of concordance in estimating fibrosis progression. Vermehren *et al*[91] assessed liver fibrosis using FT and TE in 202 consecutive HIV-infected patients, 35 of whom with HIV/HCV coinfection. A combination of TE and FT indicated significant fibrosis in 8% of patients (31% in HIV/HCV-coinfected and 3% in HIV-monoinfected individuals). The Actitest, an evolution of FT that considers the same panel of biotests plus the ALT values and correlates with liver necroinflammation, has been validated for the diagnosis of cirrhosis in chronic hepatitis C.

The Fibrosis 4 score

The Fibrosis 4 score (FIB4) is a biomarker panel using age, AST, platelet count and ALT [FIB4 = (age × AST)/(platelets × ALT)][92]. This marker was originally developed and validated in a study on 832 HIV/HCV-coinfected patients, where FIB4 > 3.25 had a specificity of 97% for the diagnosis of cirrhosis; the authors estimated that 71% of liver biopsies could be avoided using FIB4[93]. FIB4 was subsequently validated in 592 HCV-monoinfected patients, where a value > 3.25 correlated with cirrhosis, while a value < 1.45 had a sensitivity of 74% in excluding severe fibrosis[94].

Forns index

The Forns Index uses a panel of common parameters: Age, GGT, cholesterol and platelet count but requires a complex calculation of the score. A score lower than 4.25 has a negative predictive value of 96% for excluding significant fibrosis (≥ F2), whereas a score greater than 6.9 has a positive predictive value of 66% for significant fibrosis. This index is therefore useful to identify patients with a low risk of significant fibrosis but does not reliably predict the more advanced stages of fibrosis or liver cirrhosis. The Forns Index should not be used for patients with HCV-genotype-3 infection and liver steatosis since they frequently show a high cholesterol serum level that may affect the score. In addition, the administration of drugs reducing the plasma level of lipids may compromise the test results[95]. The Forns Index is considered useful to diagnose liver cirrhosis, but of lower efficacy in detecting advanced fibrosis. In addition, in HIV/HCV coinfection its diagnostic accuracy is affected by the $CD4^+$ cell count and ALT levels[10].

NAFLD fibrosis score, Fibroindex

The NAFLD fibrosis score is a panel of parameters comprising impaired fasting glucose (diabetes), age, AST, ALT, platelets, BMI and albumin[96]. Fibroindex[97] is a score based on the platelet count, AST and GGT. These tests, considered of some clinical value in detecting liver fibrosis in HCV monoinfection, have not yet been used in HIV/HCV coinfection.

FibroMax

The FibroMax test is a panel of 5 different hepatic tests that allows the assessment of liver fibrosis by a complex sophisticated algorithm. This procedure is based on the Fibro-test, ACTI-test, Steato-test, ASH-test and NASH-test. FibroMax, which has shown similar efficacy to that of histopathology in assessing liver fibrosis in HCV monoinfection, but being non-invasive and repeatable, it might be particularly useful for long-term management and treatment monitoring. It can also measure liver steatosis and/or steatohepatitis. There are no data, however, on its application in HIV/HCV coinfection.

DIRECT BIOMARKERS

Hyaluronic acid

Hyaluronic acid (HA) is a high molecular weight glycosaminoglycan in the extracellular matrix that is produced by hepatic stellate cells. Elevated HA levels may be due to an increased production within a fibrotic liver or to a reduced clearance. Serum HA concentration has been found to correlate with both liver inflammatory activity and the fibrotic stage. In a study on 486 HCV-monoinfected patients, those with cirrhosis had significantly higher serum HA levels than those without (382 mcg/L *vs* 110 mcg/L)[98]. In this study, an HA level < 60 mcg/L excluded cirrhosis (sensitivity 98%), while a score > 110 mcg/L showed 78% specificity for cirrhosis. HA has also been combined with indirect markers (bilirubin, GGT, alpha-2 macroglobulin), age and gender to formulate the Hepascore, a panel validated in 221 HCV-monoinfected patients[99]. Resino *et al*[100] studied HA as a possible marker of liver fibrosis in HIV/HCV coinfection in 201 patients naïve for anti-HCV therapy who underwent a liver biopsy. In this study the serum HA levels correlated with the degree of hepatic fibrosis on the liver biopsy, in particular for F4 (Metavir score).

PIIINP

PIIINP (amino-terminal propeptide of serum type Ⅲ procollagen) is a serum marker of collagen turnover indicating tissue repair and fibrosis. Although associated with liver cell necrosis and high aminotransferase serum values, it has been studied as a non-invasive marker of liver fibrosis. First studied in primary biliary cirrhosis (PBC)[101], PIIINP values were found to correlate with the histological stage of PBC and with the levels of cholestasis. In patients with chronic viral hepatitis, PIIINP was identified as an independent predictor of liver cirrhosis[102]. There are no data, however, on the application of PIIINP in HIV/HCV coinfection.

Tissue inhibitor of metalloproteinase-1

Tissue inhibitors of metalloproteinase are a family of enzymes that inactivate collagenase and metalloproteinases. The development of hepatic fibrosis causes an imbalance between collagen production and collagen degradation, which entails decreased levels of serum collagenase. The levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) were found to be higher in alcoholic patients with significant fibrosis and cirrhosis than in those with steatosis alone[103]. TIMP-1 was also studied in a cohort of 194 HCV-monoinfected patients[104] and found to significantly correlate with the stage of fibrosis. A cutoff value of 1300 ng/mL showed 75% sensitivity and 70% specificity for the diagnosis of extensive fibrosis. Of note, also in HBV-related chronic hepatitis TIMP-1 correlated significantly with both liver inflammatory activity and fibrosis[105]. Macías *et al*[106] analyzed the changes in the mediators of fibrogenesis as a non-invasive marker of liver fibrosis in HIV/HCV-coinfected patients starting MVC-based antiretroviral therapy. Twenty-four patients were enrolled and TGF-β1, matrix metalloproteinase-2 and the TIMP-1 were measured in serum samples obtained at baseline and 6 mo after starting maraviroc (MVC)-based therapy. Serum mediators of liver fibrogenesis and fibrosis did not change significantly in HIV/HCV-coinfected patients treated with MVC. Since the TGF-β1 levels have been found to increase in HIV/HCV coinfection in relation to the increase in fibrosis[103], this deterioration was considered to have been prevented by MCV therapy.

YKL-40

YKL-40 (Chondrex) is a member of the bacterial chitinase enzyme family thought to play a role in extracellular matrix remodeling. In alcoholic liver diseases, the levels of YKL-40 were found to correlate with the presence of fibrosis[107] and with a lower survival. In patients with HCV monoinfection the YKL-40 technique showed 80% sensitivity and 71% specificity in the diagnosis of cirrhosis[108]. YKL-40 was investigated in a cohort of 95 HIV/HCV-coinfected patients at the Johns Hopkins HIV Clinic to evaluate its efficacy in the assessment of liver fibrosis: Patients with a Metavir score ⩾ F3 had significantly higher serum levels of YKL and hyaluronic acid than those with a lower fibrosis score ($P < 0.05$)[109].

ASSOCIATION OF DIRECT AND INDIRECT BIOMARKERS

Hepascore

The Hepascore, also known as the FibroScore, includes specific and non-specific parameters to assess liver fibrosis: Age, sex, total bilirubin, GGT, alpha-2-macroglobulin, and hyaluronic acid serum levels; a Hepascore is generated using a very complex equation model. Values ⩽ 0.2 are negative predictive values excluding fibrosis in 98% of cases, whereas values ⩾ 0.8 are positive predictive values for cirrhosis in 62% of cases. Given the good negative predictive value of a low Hepascore, this method is useful to exclude significant fibrosis but is not indicated to predict liver cirrhosis. Calès *et al*[110] compared 5 non-specific tests, APRI, FIB-4, Fibrotest, Hepascore, FibroMeter, and 2 new specific blood tests, FibroMeter HICV (human immunodeficiency and C virus) and HICV test, in detecting liver fibrosis in 467 HIV/HCV-coinfected patients. These tests, originally designed for HCV monoinfection were found to be less effective in HIV/HCV coinfection (the Hepascore in particular), while FibroMeter HICV and HICV test proved to be acceptably reliable in identifying the different stages of fibrosis.

Enhanced liver fibrosis score

The enhanced liver fibrosis score (ELF) score was developed in a cohort of 1021 patients with chronic liver disease[111]. It combined age, HA, TIMP-1 and PIIINP. This test identified liver cirrhosis with 90% sensitivity and 69% specificity and showed high efficacy in ALD and NAFLD. The ELF score to detect liver fibrosis has also been validated in chronic hepatitis C and B[112,113]. A modified ELF (not including age) was validated as a predictor of severe fibrosis in patients with NAFLD[114]. There are no data, however, on the application of ELF in HIV/HCV coinfection.

CONCLUSION

The assessment of liver fibrosis in HIV/HCV-coinfected patients is invaluable for an accurate evaluation of the clinical condition and therapeutic decisions to be made[113-125]. In fact, the main risk for patients with chronic hepatitis is the development of liver cirrhosis and an associated HCC, clinical events entailing liver transplantation and a high mortality rate. Although liver biopsy is considered the gold standard for the assessment of liver fibrosis because it offers a direct view of the liver lesions, it is an invasive procedure with complications in a limited number of cases, although seldom life-threatening, and is not readily accepted by patients and not easily repeatable.

The use of non-invasive radiologic techniques and direct and indirect serological biomarkers to assess

liver fibrosis has gained popularity with clinicians. Non-invasive techniques have been found to be quite sensitive and specific in detecting liver cirrhosis, but less accurate in differentiating between the intermediate stages of fibrosis. Different combinations of radiologic techniques and direct and indirect serological biomarkers to assess liver stiffness are currently under evaluation.

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