Non-Invasive Markers of Liver Fibrosis in HCV Mono-Infected and in HIV/HCV Co-Infected Subjects

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Abstract: Non-invasive markers of liver fibrosis have been recently developed as a possible alternative to liver biopsy. The clinical management of hepatic diseases is dependent on the extent of liver fibrosis. Liver biopsy remains the gold standard but severe complications are found in about 0.5% of cases. Studies involving sequential liver biopsies are impractical, costly, and risky. Therefore non-invasive markers of liver fibrosis could be useful. These drawbacks justify an intensive research on non-invasive alternatives. Several serum markers are either directly involved in fibrosis remodelling or are indirectly associated with the presence of significant liver fibrosis. More recently, fibrosis scores calculated from statistical models have been described. This review describes the role of non-invasive markers in assessing hepatic fibrosis in both HCV mono-infected and HIV/HCV co-infected subjects.

Key Words: Liver, hepatitis C, AST, ALT.

EPIDEMIOLOGY OF HCV IN HIV INFECTED SUBJECTS

Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) are common chronic viral infections documented worldwide [1,2]. These viruses have similar routes of transmission, through blood and blood derivates, sharing of needles to inject drugs and sexual activity, enabling co-infection with these viruses a common event [3,4]. The prevalence of HIV/HCV co-infection varies widely from country to country, being mostly influenced by the prevalence of intravenous drug abusers. For instance, within European countries, high rates of HCV co-infection (up to 70%) can be observed in eastern countries like Belarus and Ukraine, where intravenous drug abuse is the main route of HIV transmission. On the contrary, in central European countries such as Belgium, Austria, or Germany, where sexual intercourse is the predominant mode of HIV transmission, HCV co-infection rates are lower, between 10-15% [5,6]. The prevalence of HCV within the HIV-infected population is far higher compared to the general population worldwide, where the global burden of hepatitis C is estimated to be roughly around 2% [7]. This highlights the importance of considering HCV infection as one of the most important co-morbidities in HIV-infected individuals.

THE NATURAL COURSE OF HEPATITIS C INFECTION IN HIV-POSITIVE PATIENTS

The fact that liver disease caused by HCV has become a major cause of morbidity and mortality among HIV-infected patients in the developed world is not solely due to the reduced incidence of opportunistic infections. More rapid progression of liver fibrosis and increased survival after HAART (which implies in longer duration of HCV infection and exposure to potential hepatotoxic drugs) are other factors involved [8-10]. In addition, HIV-infection accelerates the development of decompensated cirrhosis related to HCV with a consequent increase of both morbidity and mortality [11,12]. Cohort and *in vivo* studies have demonstrated that HIV-infection weakens the immune response against HCV. As a consequence, HIV-infection reduces the probability of spontaneous viral clearance of HCV; this finding seems to be of clinical relevance only for patients with more advanced disease such as those with a CD4 cell count < 200 cells/mm^3, who are at a significantly higher risk of developing chronic HCV-infection compared to patients with higher CD4 cell counts [13]. Data from a case report by Kim *et al*. suggested that the cellular immune response against HCV was directly related to the CD4 status [14]. Moreover, patients with CD4 cell counts < 500 cells/mmc showed a diminished capability of mounting CD8 specific immune responses [13].

The true rate of hepatic fibrosis progression in HIV/HCV co-infected subjects and the effect of HAART on such a progression are still poorly understood. In fact, most of the studies that evaluated liver fibrosis in the HIV-infected population were cross-sectional [15-19], have relied on modelled fibrosis progression rates [16,17,19,20] or did not take into account the cumulative HAART exposure [16,21,22]. Additionally, studies including paired liver biopsy have been of small sample size [23]. Therefore, the association between HAART and hepatic fibrosis remains controversial. Fibrosis progression should be ideally evaluated in studies involving sequential liver biopsies on a sufficient number of patients. However, multiple biopsies are impractical, costly and risky; as a consequence, the use of non-invasive markers of liver fibrosis may be useful for the correct management of HCV-related liver disease.

PATHOGENESIS OF LIVER FIBROSIS IN HCV-INFECTED SUBJECTS

The pathogenesis of liver fibrosis is affected by the balance between the extracellular matrix deposition and its re-

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moval. Such phenomenon is influenced by several factors; in particular, hepatic stellate cells are the major source of extracellular matrix. During liver injury, these cells are activated by cytokines (e.g. tumor necrosis factor alpha [TNF-α], tumor growth factor beta [TGF-β], platelet derived growth factor [PDGF]) to a proliferative, fibrogenic and contractile type of myofibroblasts ultimately leading to fibrogenesis. Concomitantly, other cytokines, such as interleukin-10, promote extracellular matrix degradation. Furthermore, once activated, hepatic stellate cells may secrete cytokines involved in different processes such as fibrogenesis (TGF-β1, connective tissue growth factor), chemotaxis (monocyte chemotaxis protein-1), proliferation (PDGF, endothelin-1) and matrix degradation (metalloproteinase) [24].

The pathogenesis of liver fibrosis induced by HCV-infection is only partially understood (Fig. **1**). HCV may induce oxidative stress and recruitment of inflammatory cells, with activation of hepatic stellate cells and collagen deposition; moreover, some HCV proteins may directly stimulate the fibrogenic and inflammatory pathways of hepatic stellate cells [25]. HCV non-structural genes (NS3 and NS5B) induce an increased expression of TGF-β1 and of other pro-fibrogenetic factors in infected hepatocytes, possibly explaining the occurrence of progressive liver fibrosis with minimal inflammation [26].

The histological pattern of fibrosis progression varies according to the etiology of liver disease. In chronic hepatitis C, liver fibrosis is initially limited to the portal tracts; afterwards, septa expand into the liver parenchyma, forming bridges between two portal tracts or portal tracts and central veins; this process may ultimately evolve into complete cirrhosis. The rate of occurrence and the degree of progression of liver fibrosis in such a context remain largely speculative. Such a progression may take years or decades to develop, and staging of hepatic fibrosis is therefore of paramount clinical importance for the prognostic evaluation of the individual patient. In patients with chronic viral hepatitis, a precise definition of the stage of hepatic fibrosis is one of the most important parameters to evaluate the risk of disease progression and the need for starting an immediate antiviral therapy [27]. In fact, the degree of liver fibrosis determines the evolution of liver disease, the indication for therapy and, ultimately, the probability of response. The rate of fibrosis progression has been estimated from serial liver biopsy studies. In one of the largest study, Poynard *et al*. found that fibrosis progression was fairly linear over time but was asymmetrically distributed, suggesting that patients do not all progress at the same rate [28]. Numerous studies evaluated potential predictors of fibrosis progression in the context of HCV-infection. In the study of Poynard *et al*. above mentioned [28], male gender, chronic alcohol use and older age at infection were significantly associated with a more rapid progression of disease. Other factors such as the duration of HCV infection, long-term immune-suppression and hepatitis B co-infection have also been found associated with progression [29]. Longitudinal data showed that the presence of both fibrosis and necro-inflammation on initial biopsy were predictive of future fibrosis progression [30,31]. Moreover, more recent data evaluated other possible factors such as steatosis, insulin resistance, genetic polymorphism in inflammatory, oxidative stress and viral factors as HCV quasispecies evolution and direct toxic effect of HCV proteins; nevertheless, how these factors may promote the hepatic fibrosis in some but not in all the patients remains poorly understood.

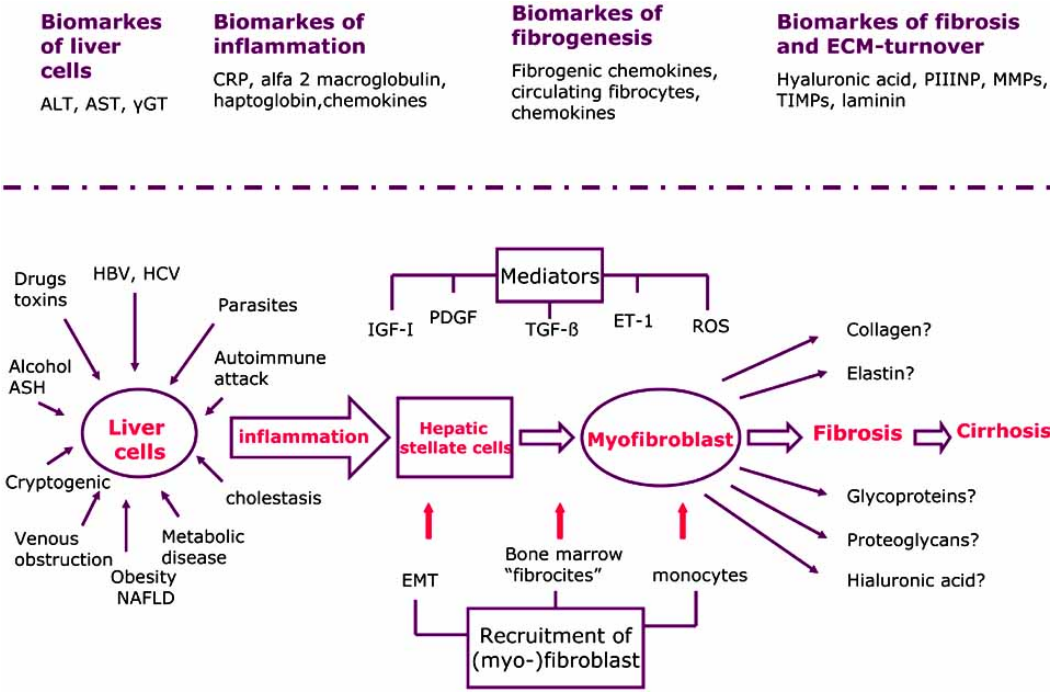

Fig. (1). Pathogenesis of liver fibrosis and cirrhosis based on the activation of hepatic stellate cells and differentiation of matrix-synthesizing myofibroblasts. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma glutamil transpeptidase; CRP, c-reactive protein; PIIINP, procollagen III; MMPs, metalloproteinases; TIMPs tissue inhibitor metalloproteinases. (Modified by Gressner *et al*. [86]).

ROLE OF LIVER BIOPSY IN THE DIAGNOSIS OF LIVER FIBROSIS

In HIV/HCV co-infected individuals, liver biopsy remains the gold standard for evaluating presence, type and stage of liver fibrosis. Liver biopsy may allow a better evaluation not only of hepatic fibrosis, but also of hepatic inflammation, necrosis, steatosis and hepatic iron load. However, liver biopsy has a number of limitations because it is invasive, expensive and its interpretation exhibits considerable intra- and inter-observer variability. Some reports suggested that cirrhosis might be missed on a single blind percutaneous liver biopsy in 10-30% of cases [32-34], whereas when three different liver samples were analysed, the percentage of correct diagnosis reached up to 80-100% [35].

It has been demonstrated that an adequate liver biopsy sample should contain more than 5 portal tracts and be at least 15 mm in length [36-38]. Colloredo *et al*. proposed that an adequate bioptic specimen should be at least 20 mm in length with at least 11 complete portal tracts, whereas other authors recommended larger samples, up to 25 mm in length [39,40] The need for obtaining a liver sample of adequate size is in contrast with the patient's need of a procedure causing limited pain and low hemorrhagic risks. As expected, these risks are higher in subjects with a more advanced liver fibrosis [41,42]. Therefore, liver biopsy may be often refused by patients [43]. Another shortcoming of liver biopsy is its cost as it always requires hospitalization for 6-18 hours. A cost-benefit analysis showed that in the US the cost of a liver biopsy is 1032 USD and it may reach 2745 USD when complications occur [44].

THE IDEAL NON-INVASIVE MARKERS OF LIVER FIBROSIS

In the last few years, many studies have been performed to identify possible non-invasive markers associated with liver fibrogenesis, activity, and stage of fibrosis in patients with chronic, potentially progressive, hepatic disease. These markers should provide measurement of fibrogenesis activity and accurate estimation of the stage of liver fibrosis, should not be influenced by co-morbidities, and finally should be sensitive and reproducible. Many studies evaluated direct markers of fibrogenesis, defined as biochemical parameters measurable in the peripheral blood that represent a direct expression of either the deposition or the removal of extracellular matrix in the liver. These direct markers of liver fibrosis include the collagens family (procollagen III, type IV collagen and type IV collagen 7s domain), the collagenases and their inhibitors (metalloproteinases and their tissue inhibitors), the glycoproteins (hyaluronic acid, laminin, human cartilage glycoprotein 39 [YKL-40]), and the cytokines associated with the fibrogenetic process (TGF-β1, TNF-β) (Table **1**). These markers might be extremely useful in the clinical practice, as they could be used not only to evaluate liver fibrosis, but also to assess the progression of liver fibrogenesis with a high prognostic value, and also to estimate and monitor the efficacy and the clinical response to anti-fibrotic drugs [31]. However, at the moment, the direct markers of liver fibrosis have been mainly tested for their performance in the assessment of the current stage of liver fibrosis. An easier and less expensive approach is based on the combination of haematological or biochemical parame-

Table 1. Direct Non Invasive Markers of Liver Fibrosis

Marker	Diagnostic Assay	Liver Disease	Characteristic	Pathophysiology
Hyaluronic acid [50,54]	ELISA	HCV, AFLD, NAFLD, HBV	Component of ECM in every tissue	Synthesized by HSCs and degraded by sinusoidal endothelial cells
YKL-40 [51]	RIA,ELISA	AFLD, HCV	Co-expressed with type IV collagen in basement membranes	Involved in remodelling and degradation
Laminin [52]	RIA, EIA	HCV, NAFLD	Co-expressed with type IV collagen in basement membranes	Increased deposition in viral diseases
Type IV collagen [49,52,53]	ELISA, RIA	HCV, NAFLD	Main collagen component of the basement membrane	Increased with severity of liver fibrosis
Procollagen III [49]	RIA	HCV, AFLD	Propeptide	Released during matrix deposition and remodelling
MMP-2 [55]	ELISA	HCV	Collagenase	Correlates with fibrosis
TIMP-1 [59,60]	ELISA	HCV	Metalloproteinase	Inhibitor of collagenase
Three marker panel [60]		HCV	Combination of hyaluronic acid, TIMP-1, α2 macroglobulin	Better accuracy than isolated markers

Abbreviations: AFLD= alcoholic fatty liver disease, NAFLD= non alcoholic fatty liver disease, ECM= extracellular matrix, HSCs= hepatic stellate cells, YKL-40= human cartilage glycoprotein -39, MMP-2= metalloproteinase 2, TIMP-1= tissue inhibitor metalloproteinase 1.

ters that reflect the stage of liver disease. Such approach, often based on routinely performed blood tests, has led to the identification of markers able to define the stage of liver fibrosis with an accuracy comparable to that of direct markers (Table **2**).

The aim of most non-invasive markers of liver fibrosis currently reported in the literature was to discriminate between "insignificant" (F0-F1 by METAVIR) and clinical "significant" fibrosis (≥ 2 by METAVIR) or to identify or exclude liver cirrhosis in patients with well compensated chronic liver disease. The presence of significant fibrosis in the liver is usually considered as the hallmark of a progressive liver disease and represents a clear indication for a rapid initiation of antiviral therapy in patients with chronic HCV infection, as suggested by International Guidelines [45,46]. In fact, patients with insignificant fibrosis do not progress or progress slowly towards cirrhosis [30,47]; on the other hand, the presence of cirrhosis, even if compensated, requires specific management and monitoring of its clinical complications.

THE DIRECT AND INDIRECT MARKERS OF LIVER FIBROGENESIS

The diagnostic performance of most direct and indirect markers of liver fibrosis has been evaluated in all the common forms of chronic liver disease, including HCV and HBV infections and alcoholic and non alcoholic steato-hepatitis.

Table **1** summarizes the direct markers of liver fibrogenesis, that include hyaluronic acid, glycoproteins (laminin, YKL-40), collagenases and their inhibitors and cytokines.

Hyaluronic acid has been mainly investigated in the context of HCV-infection. In different cohort studies, it showed a good accuracy in discriminating low and mild fibrosis, with area under the curve (AUC) values ranged from 0.82 to 0.92. In a study including 326 patients the AUC was 0.86 with a specificity of 95% for significant fibrosis, while the AUC was 0.92 and the specificity was 89.4% for cirrhosis using a cut-off level for hyaluronic acid of 110 μg/L [48]. However, different results were found in another cohort study including more than 400 cases that reported an AUC of 0.73 for significant fibrosis; this study used a cut off level for hyaluronic acid of 50 μg/L to exclude cirrhosis, observing negative predictive value and sensitivity of 100% [49].

Among the glycoproteins, laminin has been evaluated especially for significant liver fibrosis, showing an overall accuracy of 81% [50]. YKL-40 is a recently described glycoprotein that belongs to the chitinase family. It is mainly expressed by human cartilage and human liver. YKL-40 is a relatively new marker of hepatic fibrosis and it has been only preliminarily evaluated in chronic liver diseases, showing an AUC of 0.81, with 78% sensitivity and 81% specificity, but the accuracy in predicting liver cirrhosis was lower [51].

Among the collagens, type IV collagen has been extensively investigated as non-invasive markers of liver fibrosis. Type IV collagen is composed of a major triple helix, an amino-terminal triple-helix (7s domain) and a carboxy-terminal globular domain. Type IV collagen has been studied in HCV-infection, with a good diagnostic performance for advanced liver fibrosis [52,53]. The diagnostic performances of type IV collagen and hyaluronic acid have been compared in HCV-infected subjects and a significant superiority of the

Table 2. Indirect Non Invasive Markers of Liver Fibrosis

Biomarker	Parameters	Liver Disease	Rationale
AAR [63]	AST to ALT ratio	HCV, NAFLD	AST and ALT levels increase with progressive fibrosis
APRI [64-68]	AST to platelet ratio	HCV, HIV/HCV	Statistical association with liver fibrosis
Forns-index [70-72]	Combination of age, platelet, γGT, cholesterol	HCV, HIV/HCV	Statistical association with liver fibrosis
GUCI [73]	Combination of AST, INR, platelet	HCV	Statistical association with liver fibrosis
FIB-4 [74,75]	Platelet, AST, ALT, age	HIV/HCV	Statistical association with liver fibrosis
Fibrotest [76-78]	Combination of α2macroglobulin, ApoA1, bilirubin, γGT, haptoglobin	HCV, HIV/HCV, HBV, AFLD	Statistical association with liver fibrosis
Glycocirrho test 79	Profiles of serum protein N-glycans	Chronic liver diseases (mostly HCV)	Glycoproteins are produced mainly by hepatocytes
FPI [80]	Combination of HOMA-IR, age, cholesterol, AST, alcohol intake	HCV	Statistical association with liver fibrosis
Hepascore [81]	Bilirubin, γGT, hyaluronic acid, α2M, age, gender	HCV	Statistical association with liver fibrosis
Fibrometer test [82]	Platelet, prothrombin index, AST, α2macroglobulin, age, gender	Mixed	Statistical association with liver fibrosis

Abbreviations: AFLD = alcoholic fatty liver disease, NAFLD = non alcoholic fatty liver disease, AAR= aspartate to alanine aminotrasferase ratio, ApoA1= apolipoprotein A1, APRI= AST to platelet ratio index, GUCI= Goteborg University Cirrhosis Index, INR= international normalised ratio, FPI= fibrosis probability index, HOMA-IR= homeostasis model assessment of insulin resistance, γGT= gamma glutamil transpeptidase.

latter marker was observed [51,54]. Procollagen III performed less well than type IV collagen and hyaluronic acid in HCV-infected subjects [48,51]. Collagenases and their inhibitors include metalloproteinase 2 (MMP-2) and tissue inhibitor metalloproteinase 1 (TIMP-1) are not commonly used as direct marker of liver fibrosis due to technical difficulties in standardization [55]. Another index called MP3 combining procollagen III and MMP-1 showed a good specifity in detecting liver fibrosis [56,57].

The measurement of serum cytokines such as TGF-β and TNF- β potentially involved in liver fibrogenesis have been evaluated in few studies, demonstrating that they are less able to predict liver fibrosis than extracellular matrix tests [38,58].

Algorithms combining hyaluronic acid, procollagen III and tissue inhibitor metalloproteinase (TIMP-1) or hyaluronic acid, TIMP-1 and α2-microglobulin have been evaluated in cohort studies including patients with chronic liver disease, without significant improvement in accuracy, sensitivity and specificity compared to single extracellular matrix components [59,60].

The role of hyaluronic acid, procollagen III and YKL-40 in HIV/HCV co-infected and HCV mono-infected subjects has been evaluated in few studies. These studies did not show significant differences in the two groups in relation to the diagnosis of liver fibrosis [61]. Recently, another study evaluated the predictive value of hyaluronic acid, procollagen III, YKL-40, MMP-1, MMP-2 and TIMP-1 in HIV/HCV co-infected subjects. In this study hyaluronic acid and TIMP-1 showed to be quite sensitive and specific to predict the degree of liver fibrosis [62].

One of the main limitations to the clinical use of direct markers of liver fibrosis is that they are not routinely available in all settings. As a consequence, simpler and less expensive markers are needed to be used more extensively in the clinical practice.

The simpler indirect marker of liver fibrosis are transaminases, especially when associated as the aspartate to alanine aminotrasferase ratio (AAR) to detect liver cirrhosis [63]. Despite the substantial advantages, this marker has been associated with a extremely high variability in most of the studies performed [58]. Therefore, it cannot be used to distinguish intermediate stages of fibrosis. The APRI score combined aspartate aminotransefrase (AST) and platelets count [64] was evaluated in several studies including HCV-infected subjects and showed a good diagnostic performance and reproducibility, particularly for excluding advanced fibrosis or cirrhosis (AUC range from 0.77 t 0.94) [65-68]. More recently, Lok *et al*. evaluated another index that included AST, platelet counts, alanine aminotransferase (ALT) and international normalised ratio (INR), with an improvement of the diagnostic accuracy, in particular for liver cirrhosis [69].

The Forns index, that combined age, cholesterol levels, gamma glutamil transpeptidase (γGT) and platelet counts, was proposed to better differentiate between no/minimal (F0-F1) and significant (≥ F2) fibrosis in HCV-infected subjects, but it does not provide any information on liver cirrhosis [70]. Additionally, such index seems less accurate in subjects with HCV genotype 3, that is usually associated with low cholesterol levels [71]. APRI score and Forns index have been evaluated in 357 HIV/HCV co-infected subjects. In this specific population, both these markers showed a lower diagnostic accuracy than in HCV mono-infected subjects [72]; the most important limitation of these scores is that they leave almost half of the patients unclassified.

Another index that combined AST, platelet counts and INR showed good accuracy for the diagnosis of liver cirrhosis in HCV-infected subjects, but without giving a significant improvement when compared with the individual tests [73]. The FIB-4 is a score recently validated in HIV/HCV co-infected subjects that combines AST, ALT, age and platelets [74]. Such an index showed a good accuracy especially for advanced stages of liver fibrosis [75].

The most often investigated combination set of non-invasive markers of liver fibrosis is the Fibrotest that combines five blood tests including γGT, bilirubin, haptoglobin, apolipoprotein A1 and α2-microglobulin, adjusted for gender and age [76]. The main advantage of Fibrotest is the possibility of classifying all the stages of liver fibrosis. It has been mainly tested in chronic HCV-infection and it showed an AUC of 0.85 for significant fibrosis. In the only study performed in HIV/HCV patients, Fibrotest performed well especially for cirrhosis (AUC 0.87) that could be excluded with a 100% negative predictive value [77]. Available data suggest that Fibrotest performs well in subjects with grade of fibrosis F0-F1 or F4, while it performs less well in the intermediate stage (F2) [78].

The SHASTA index, that included hyaluronic acid, albumin and AST, demonstrated to accurately stage mild or advanced fibrosis in a cohort of 137 HIV/HCV co-infected patients. In particular, more advanced fibrosis stages were significantly correlated with hyaluronic acid levels > 86 ng/mL [79].

A recent comparative study of indirect markers of liver fibrosis conducted on 190 patients with chronic HCV-infection evaluated the performance of APRI score, Forns index and Fibrotest. Fibrotest showed the best accuracy, with an AUC of 0.81 for significant fibrosis and of 0.71 for liver cirrhosis. This study evaluated these markers also in subjects with persistently normal transaminases. In this limited population, APRI score demonstrated the best accuracy [68]. In the same report, an algorithm to use sequentially these markers was proposed, with a significant improvement of diagnostic accuracy of liver fibrosis, and ultimately, reducing the need for liver biopsy.

A non-invasive marker based on the profile of serum glycoproteins (Glycocirrhotest), when associated with Fibrotest, showed a 100% specificity and a 75% sensitivity for the identification of liver cirrhosis [80]. Recently, an index including insulin resistance and alcohol consumption has been also investigated, but its performance showed to be inferior compared to simpler markers (AUC 0.77) and has not been validated [81].

Some scores combine both direct and indirect markers of liver fibrosis. Hepascore includes bilirubin, γGT, hyaluronic acid, α-2 macroglobulin, age and sex and showed a good

accuracy for the diagnosis of advanced fibrosis and cirrhosis [82]. Fibrometer combines hyaluronic acid, prothrombin time, platelet counts, AST, urea, age and α-2 macroglobulin and the formula was adjusted for the cause of liver disease [83]. In a prospective comparison of six non-invasive markers of liver fibrosis in HCV-positive subjects, Fibrometer showed the best diagnostic performance, but its superiority over other scores was statistically significant only when compared with Forns score [84]. In this study, some combinations as MP3 plus APRI, Fibrotest plus APRI and MP3 plus Fibrotest gave better results than single scores, probably because they do not share the same biological parameters.

IMPLICATIONS FOR THE USE OF NON-INVASIVE MARKERS IN THE CLINICAL PRACTICE

Although several non-invasive markers of liver fibrosis have been developed in the last few years, their use in the clinical practice is still limited. In fact, inter laboratory variability, lack of reproducibility and the risk of misdiagnosis (up to 20%), do not allow to recommend these methods in substitution of liver biopsy [46,85]. One of the main limitations for the use of non-invasive markers is the difficult diagnosis of intermediate stages of liver fibrosis [58]. Most of the models at the moment available use two different cut-offs, a lower and a high, to exclude and to predict advanced liver fibrosis, respectively. As a consequence, some patients in the intermediate stage might remain still unclassified. On the other hand, what the clinician needs is a diagnostic tool that is accurate and not invasive. This tool should be more acceptable by the patients than liver biopsy, and should not underestimate the stage of fibrosis and the presence of cirrhosis. As a consequence, non-invasive markers should be firstly used to classify those patients in whom their performances are accurate, limiting liver biopsy to the subset in whom a precise non-invasive staging is not possible. Nevertheless, it is easily predicted that in the near future non-invasive markers may become more accurate and will be validated and standardized in different patient categories, so that their use in the clinical practice will be much more frequent.

However, the correct clinical management of advanced liver fibrosis and/or cirrhosis should be based on other different approaches such as nutritional advice (e.g. avoid alcohol abuse), identification of portal hypertension and screening for hepatocellular carcinoma through abdomen ultrasound.

CONCLUSIONS

Many biomarkers of liver fibrosis have been recently proposed in HCV mono-infected or in HIV/HCV co-infected subjects in order to potentially substitute liver biopsy. From the data provided in literature, the direct markers of liver fibrosis may have a better performance in excluding liver cirrhosis, particularly in the HCV mono-infected population. The indirect markers of liver fibrosis may have a role in excluding HCV-related cirrhosis, also in the context of HIV-infection; however, further studies on larger cohort of patients are needed. Combination panels of non-invasive biomarkers may improve the accuracy of single tests, but further studies are required. Algorithms sequentially combining non-invasive biomarkers may increase the diagnostic accuracy in identifying liver fibrosis or cirrhosis, with a reduction of the need of performing liver biopsy. For all these reasons, in the near future, non-invasive markers of liver fibrosis may become an important tool for the management of liver diseases in the current clinical practice.

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