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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

Assessment of liver disease in patients with chronic hepatitis C and unhealthy alcohol use

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Abstract

Hepatitis C virus (HCV) infection and unhealthy alcohol use are major drivers of the burden of liver disease worldwide and commonly co-occur. Assessment of underlying liver damage is a cornerstone of the clinical care of patients with chronic HCV infection and/or unhealthy alcohol use because many of them are diagnosed at advanced stages of disease. Early diagnosis of liver disease before decompensated liver cirrhosis becomes established is essential for treatment with direct acting antivirals and/or abstinence from alcohol consumption, which are the main therapeutic approaches for clinical management. In this review, we discuss current knowledge around the use of non-invasive methods to assess liver disease, such as abdominal ultrasound, controlled attenuation parameter, transient elastography, magnetic resonance imaging, and indices based on serum markers of liver injury.

Key Words: Hepatitis C virus; Alcohol; Liver fibrosis; Non-invasive methods; Ultrasound; Transient elastography

Core Tip: In this review, we discuss current knowledge around the use of non-invasive methods to assess underlying liver disease in patients with hepatitis C virus infection and/or unhealthy alcohol use. A timely diagnosis of liver disease is of the outmost

importance to avoid progression to decompensated liver disease and liver cancer. Antiviral treatment and abstinence from alcohol use are cornerstones of clinical care for these patients.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection and unhealthy alcohol intake are common co-occurring conditions, in part because people with HCV often consume more alcohol than the general population[1]. Conversely, alcohol use is associated with a higher prevalence of HCV infection exposure and greater HCV infection persistence; patients with alcohol use have a lower likelihood of spontaneously clearing acute HCV infection[2]. For these reasons, the prevalence of HCV infection among patients with alcohol use is higher than in the general population[3], which is usually around 1% in Western countries[4]. We have found a prevalence > 20% in our cohort of patients with alcohol use disorder (AUD) and admitted for hospital detoxification[5], which is much higher than many values reported in a meta-analysis published in 2013[3]. This contrast underscores the relevance of a history of prior injection drug use and other risk factors for the acquisition of HCV in an urban population of patients with AUD[6].

In addition to higher infection exposure and persistence, alcohol use may affect HCV viral replication in certain subsets of patients[7] and is associated with progressive liver fibrosis and more extensive liver injury than in patients without alcohol use [8]. HCV is also associated with increased mortality and other poor health outcomes in different subsets of patients with alcohol-use problems[9,10].

Currently, alcohol use is a major contributor to decompensated cirrhosis in patients with HCV infection[11]. Moreover, with the current availability of efficacious treatments for viral hepatitis, alcohol-related liver disease is becoming a major driver of liver disease burden worldwide[12].

HCV infection needs to be detected as early as possible among patients with unhealthy alcohol intake, and accurate assessment of alcohol intake is necessary in patients with HCV infection[12]. Assessment of underlying liver disease is crucial, given that many patients are diagnosed only after their liver disease has reached an advanced stage[13].

ASSESSMENT OF ALCOHOL USE IN PATIENTS WITH LIVER DISEASE

The American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines for the treatment of alcohol-related liver disease recommend using the alcohol use disorders identification test (AUDIT) to identify patients with AUD[14,15]. AUDIT includes 10 questions and explores consumption, dependence and alcohol-related problems according to the number of positive answers[16]. For patients with an AUDIT > 7, Diagnostic and Statistical Manual of Mental Disorders 5th edition is an appropriate tool used for the assessment of clinical, personal and social alcohol-related problems[17]. The severity of AUD, that encompasses both alcohol dependence and alcohol abuse, is based on the number of criteria that the patient meets (mild AUD: 2-3 criteria, moderate AUD: 4-5 criteria and severe AUD > 6). AUD represents the more extreme form of unhealthy alcohol use, a term that will be used throughout the manuscript[17].

In terms of amount, unhealthy alcohol use means drinking more than the recommended amount of alcohol by the National Institute of Alcohol abuse and Alcoholism [2 United States standard drinks (12oz of beer or 5oz of wine) *per* day or 14 drinks *per* week for men and 1 drink *per* day or 7 United States standard drinks *per* week for women or men aged > 65], what includes the spectrum from risky alcohol use to AUD[18].

It is important to note that for those who already have HCV infection there is no safe threshold of alcohol consumption and abstinence from alcohol should be the main treatment goal[12].

PATHOLOGIC FEATURES OF HCV-RELATED LIVER DISEASE AND ALCOHOL-RELATED LIVER DISEASE

The natural history of HCV-related liver disease is characterized by progressive liver fibrosis that eventually leads to liver cirrhosis and hepatocellular carcinoma[19]. Many cofactors are associated with a faster progression of liver fibrosis in patients with HCV infection, including age, duration of HCV infection, male sex, obesity, the presence of hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) co-infection, alcohol use, and immune suppression[20].

Alcohol-related liver disease includes several histological abnormalities ranging from simple steatosis to cirrhosis and liver cancer[21,22]. These various histological abnormalities can be present at the same time in a liver biopsy[21,22]. Alcoholic hepatitis is a complication associated with acute liver failure, an increased risk of infection, and high mortality that can be seen at any point in the natural history of alcohol-related liver disease[12].

Liver fibrosis is the best predictor of progression to decompensated cirrhosis in both chronic HCV infection and alcohol-related liver damage[23]. Liver biopsy is the preferred method to evaluate liver fibrosis, but it is costly, invasive[24] and rarely performed in patients with current alcohol or other substance use disorders[25]. In the present review, we will not discuss the particularities of liver biopsy[26] and focus instead on currently available non-invasive methods to assess the extent of liver damage in patients with HCV and/or unhealthy alcohol use.

THE NEED FOR ASSESSMENT OF LIVER DAMAGE

A timely diagnosis of liver disease in asymptomatic patients with HCV infection and/or AUD contributes to a better prognosis and facilitates treatment[27,28]. As noted, in patients with AUD, liver involvement is the main culprit of alcohol-related disease burden, and liver disease is usually detected in the advanced stages[28]. Almost 75% of patients with alcohol-related liver disease present with a non-elective hospital admission because of decompensated cirrhosis[29], so efforts should prioritize early identification of patients at risk for end-stage liver disease.

Despite the availability of efficacious treatments for viral hepatitis, the liver disease burden is expected to increase because of the growing prevalence of overweight and obesity and other unhealthy lifestyles in developed countries, which is predicted to drive an increase in the prevalence of non-alcoholic liver disease. In addition, many patients with metabolic syndrome also drink alcohol, and many patients with AUD have overweight or obesity and/or a sedentary lifestyle[30].

NON-INVASIVE METHODS FOR ASSESSMENT OF LIVER DAMAGE

Liver ultrasound

Liver ultrasound is both inexpensive and easily available, but it is rarely performed in patients with AUD and no apparent liver disease. The latest American Association for the Study of Liver Diseases guidelines for the management of chronic HCV infection are focused on the test-and-treat paradigm but recommend abdominal ultrasound for hepatocellular carcinoma surveillance only if the patient has already developed cirrhosis[31]. Although the latest European guidelines recommend liver ultrasound to early detect non-alcoholic steatohepatitis[32], there are no guidelines for the early detection of liver abnormalities among patients with high alcohol intake. Screening approaches for patients at risk for alcohol-related liver disease thus are a matter of debate[33,34]. It is also important to note that, in general, liver cancer surveillance among individuals with alcohol-related liver disease is far from optimal, and hepatocellular carcinoma is usually diagnosed at an advanced stage[22].

On abdominal ultrasound, liver steatosis has a hyperechogenic appearance because of the increased parenchymal reflectivity of intracellular fat accumulation[35]. Fat

content affects the sensitivity of abdominal ultrasound for detecting liver steatosis, and sensitivity severely decreases at fat contents lower than 10%–20%[28].

The precision of abdominal ultrasound in differentiating between steatosis and fibrosis is higher when liver fibrosis is more advanced because of an increase in coarse echoes without posterior beam attenuation[35-37]. Steatosis is usually classified as "mild," "moderate," or "severe"[37,38].

Despite operator dependency for the assessment of steatosis, there is agreement that liver ultrasound is inexpensive and reliable for the detection of moderate or severe liver steatosis[39,40]. The accuracy of abdominal ultrasound is lower for mild steatosis, however, it can be increased with a computer-aided method[40]. Ultrasound findings contribute to the detection of alcohol-related liver disease features in addition to liver steatosis, including (among others): Liver size, edge bluntness, parenchyma coarseness, surface nodularity, inferior vena cava abnormalities, the presence of portal hypertension, and spleen size[41].

The authors of a Cochrane review published in 2016 commented on the need for studies of large sample size to assess the efficacy of abdominal ultrasound in patients with alcohol-related liver disease[42], in part because their review could only include two studies[42]. Of these two studies, the first was performed in France in 1985 and included 126 patients with alcoholism[43]. In addition to abdominal ultrasound performed in the entire cohort, 100 patients also underwent liver biopsy. In that group of 100 patients, cirrhosis of the liver was confirmed in 72, and abdominal ultrasound had a sensitivity of 81% and a specificity of 79% to detect cirrhosis[43].

The second study was published in 2013 and performed in Korea and included 230 patients (81% male) who underwent liver biopsy, elastography and abdominal ultrasound[44]. The mean age of participants was 50.4 years. Ultrasound suggested heterogeneous liver in 199 patients (86.5%) and liver cirrhosis in 170 (74%). Cirrhosis of the liver was found in 111 participants, for a sensitivity of 94% and specificity of 49% for ultrasound detection of cirrhosis of the liver[44]. Because of the small number of patients included and the differences in the selection criteria in each of these two studies, the authors of the review could not reach any conclusion about the use of abdominal ultrasound for detecting underlying advanced liver disease among patients with unhealthy alcohol use[42].

In 2018, we published a study describing ultrasound findings among 301 consecutive AUD patients without clinically relevant liver disease who were admitted for hospital treatment of the disorder at Hospital Universitari Germans Trias i Pujol [34].

We obtained clinical and laboratory parameters at admission. An ultrasound was performed so as to identify the presence of liver steatosis, hepatomegaly, heterogeneous liver, and portal hypertension.

For this work, we studied unadjusted associations of ultrasound abnormalities with three prevalent conditions: Alcohol-related liver injury (ALI), advanced liver fibrosis (ALF) and HCV infection. ALI was defined as the presence of at least two of the following: Aspartate aminotransferase (AST) levels ≥ 74 < 300 U/L, AST/alanine aminotransferase (ALT) ratio > 2, and total bilirubin> 1.2 mg/dL. ALF was measured with fibrosis-4 (FIB-4)[45] and was defined as a FIB-4 score ≥ 3.25. We performed logistic regressions to detect if ALI, ALF and/or HCV were associated with having two or more abnormalities in the liver ultrasound.

In summary, 80% of the patients were male, had a median age of 46 years, drank a median of 180 grams of alcohol *per* day upon admission and 21.2% had HCV infection. Median serum AST was 42 U/L, median serum ALT was 35 U/L, the prevalence of ALI and ALF was 16% and 24%, respectively. A total of 57.2% patients had steatosis, 49.5% had hepatomegaly, 17% had heterogeneous liver, while 16% had portal hypertension. Of interest, 77% of patients had one abnormality, and 45% had ≥ 2.

In the multivariate models, both ALI and ALF were significantly associated with the presence of ≥ 2 abnormalities, with odds ratios (ORs) of 5.2 for ALI and 4.7 for ALF. HCV infection did not predict the presence of more than two abnormalities[34].

Most patients included in the study who had only one ultrasound abnormality had mild to moderate steatosis or hepatomegaly, which are both potentially reversible with alcohol cessation. In light of those findings, we believe that abdominal ultrasound could be implemented in the everyday clinical care of patients seeking treatment for AUD, as it could help in clinical decision-making and treatment selection.

Liver abnormalities were quite common in the study, even in patients without HCV, ALI, or ALF, and only 31% of patients without any of those conditions had a completely normal ultrasound. Accordingly, we think that sharing information about ultrasound abnormalities may promote alcohol cessation in patients with AUD who are unaware of their underlying liver disease[34]. Other researchers have previously

reported that sharing findings suggestive of poor health outcomes with patients leads to a decrease in unhealthy alcohol use[46].

Liver cancer has an incidence of 2.9% *per* year in individuals who have cirrhosis of the liver[22]. Hepatocellular carcinoma entails a dire prognosis if not detected early [47], which is why patients with alcohol-related end stage liver disease should undergo an abdominal ultrasound every 6 months[22]. However, periodic surveillance is challenging because many patients miss appointments[22], and less than 30% of liver cancers are detected by surveillance in Europe and the United States[22,48]. In our series, liver cancer was found in two participants[34].

Besides the early identification of steatosis or cirrhosis of the liver, abdominal ultrasound could be used for detecting other forms of liver damage. In fact, alcohol use is common among individuals with other forms of liver disease, and there is no safe level of alcohol consumption in these situations[8,30]. As previously mentioned, alcohol use is a cofactor in liver disease progression in individuals with HCV, HBV, non-alcoholic fatty liver disease, and hemochromatosis, among others. A threshold of a consumption of more than 30 grams of alcohol *per* day for men and 20 g for women is arbitrarily used to support the diagnosis of alcohol-related liver disease[12]. Nevertheless, as overweight and obesity are highly prevalent in the developed world, alcohol-related and non-alcoholic steatosis can co-occur[49]. In our case series of AUD patients, the median body mass index was 24.7, indicating that a sizable proportion of participants were overweight or obese[34].

In addition, liver ultrasound can also detect other forms of liver disease that are less prevalent, like parenchymatous or vascular diseases (non-cirrhotic portal hypertension, hepatic vein congestion, and Budd Chiari).

Transient elastography

Transient elastography has been used for more than a decade to accurately assess liver fibrosis, measuring liver stiffness in patients with chronic HCV infection or HBV infection, with or without HIV co-infection, and in non-alcoholic liver disease[50-52]. In transient elastography, a piston vibrator that is placed in the intercostal space generates a shear wave, and velocity is measured below the skin surface. It measures liver stiffness in kilopascals (kPa), and elastography readings usually range from 2.5 to 75 kPa[53].

The method has also been used to a lesser extent for analyzing liver injury in patients with AUD. A study that included 199 consecutive patients at risk for alcohol-related liver disease found that transient elastography provided an assessment of fibrosis (either significant fibrosis, Ishak score ≥ 3) and cirrhosis (Ishak score ≥ 5) that was comparable to liver biopsy with high accuracy (area under the curve ≥ 0.92)[33]. Some authors have pointed out that steatohepatitis may lead to overestimation of liver fibrosis[54]. The risk of overestimation especially applies in patients who are abstinent, as liver stiffness decreases with cessation of alcohol use, especially with baseline values higher than 7 kPa[55].

In 2016, a systematic review and meta-analysis found that transient elastography could reliably exclude ALF or cirrhosis of the liver. The authors suggested that the same cut-offs described for viral hepatitis-related liver disease should be applied with caution to other forms of liver damage, particularly alcohol-related liver disease[56]. Mueller and colleagues have suggested adapting elastography cut-offs in patients who present with elevated AST or bilirubin[54]. The studies in that meta-analysis, which included only patients with alcohol-related liver disease, had a wide range of participant numbers and an ALF prevalence ranging from 53% to 80%[57-61].

Results of an individual-level meta-analysis published in 2018 that included 1026 patients suggested that cut-offs for transient elastography should be higher[58]. In that study, higher concentrations of AST and bilirubin were significantly associated with higher liver stiffness values ($P < 0.01$)[58]. In addition, the presence of non-severe alcoholic hepatitis was associated with liver stiffness ($P < 0.0001$). Also, higher AST ($P < 0.01$) and higher bilirubin ($P = 0.01$) levels and increased prothrombin activity ($P = 0.01$) were significantly associated with non-severe alcoholic hepatitis. That meta-analysis described specific liver stiffness cut-offs based on concentrations of AST and bilirubin[58].

French researchers used transient elastography to assess ALF in a cohort study of patients with HCV/HIV co-infection. They found that ALF was more prevalent among patients with an alcohol-related diagnosis (OR 3.06; 95%CI: 1.42–6.60) compared to those with non-hazardous alcohol intake[62].

A recently published study describes the use of transient elastography for the measurement of liver and spleen stiffness (a surrogate marker of portal hypertension), as well as spleen length in a retrospective cohort of 499 patients with HCV or alcohol-

related liver disease[63]. Participants with HCV had higher mean spleen stiffness and spleen length but lower liver stiffness when compared to participants with alcohol-related liver disease. The authors concluded that the use of those measurements, as well as the spleen stiffness/liver stiffness and spleen length/spleen stiffness ratios, could be helpful to measure burden of disease and risk for disease-specific complications[63].

Other researchers have confirmed that elastography is a good predictor of clinical events[64]. Transient elastography has also been proven to be cost-effective in primary care[65], and other authors have used it to detect chronic alcohol-related liver disease after alcohol cessation[66] or to detect improvements in liver fibrosis after successful HCV antiviral therapy[67].

Transient elastography thus represents a promising tool for assessing underlying liver damage in patients with unhealthy alcohol use and/or HCV infection[28]. It is important to note that transient elastography results may be affected by the thickness of subcutaneous fat, width of intercostal spaces, by the presence of ascites, by the patients' breathing or by an uneven distribution of liver fibrosis. In addition, the presence of hepatic congestion or steatosis may also distort transient elastography results[28,56].

Table 1 includes a summary of the most relevant studies that have used transient elastography in patients with alcohol-related liver disease.

Controlled attenuation parameter

The controlled attenuation parameter (CAP) is a non-invasive tool for detecting steatosis. It measures ultrasound attenuation during transmission through fatty liver tissue[68]. CAP software can be incorporated into transient elastography devices, thus facilitating the non-invasive measurement of steatosis and fibrosis[28].

Cut-offs for moderate and severe liver steatosis were defined in a recently published patient-level meta-analysis that included 2735 participants with liver biopsy and CAP. Their diagnostic accuracy ranged from 0.65 to 0.90[69]. The etiology of liver disease was HBV in 37% of patients, HCV in 36% and or non-alcoholic fatty liver disease in 20%, and participants with unhealthy alcohol use were under-represented[69]. As all patients included had liver diseases that are strongly associated with liver fibrosis, these cut-offs require further validation in other and healthier populations[70].

A study by Thiele and colleagues included 562 patients with alcohol-related liver steatosis and found that CAP above 290 dB/m ruled in any steatosis with a 88% specificity and a 92% positive predictive value, whereas CAP below 220 dB/m ruled out steatosis with a 90% sensitivity but with a 62% negative predictive value[71]. The authors concluded that it was useful for the diagnosis of severe alcohol-related steatosis and could also rule in any liver steatosis. In patients admitted for alcohol detoxification who did not have obesity, CAP rapidly declined[71]. This finding underscores the synergic effect of obesity and alcohol use in patients seen in clinical practice[72].

A study by Unalp-Arida and colleagues measured liver stiffness and CAP in 4870 participants in the National Health and Nutrition Examination Survey cohort, and found that liver stiffness in the highest quartile was associated, among others, with HCV infection, increased age and body mass index and CAP[73].

Virtual touch quantification

Virtual touch quantification is a point shear wave elastography technique, using acoustic radiation force impulse technology also offers good diagnostic accuracy for liver fibrosis assessment[74]. It has been used in patients with chronic liver disease of different origins, mainly due to viral hepatitis[75,76].

Magnetic resonance imaging

Magnetic resonance imaging and proton magnetic resonance spectroscopy are promising methods for quantifying hepatic fat content[35]. Magnetic resonance measurement of liver steatosis does not appear to be affected by the type of liver disease or the presence of liver inflammation or iron overload, features that may distort results obtained with other non-invasive methods. Despite these potential advantages, magnetic resonance imaging is costly and time-consuming[28]. Moreover, information is scarce about its applicability in alcohol-related liver disease.

Laboratory-driven indices

There are several non-invasive indices that are derived from laboratory parameters aimed for the estimation of liver fibrosis. Some of those parameters are used in

Table 1 Studies that have used transient elastography in patients with alcohol-related liver disease				
Ref.	Number of patients	Advanced liver fibrosis (≥ 3)	Sensitivity[1]	Specificity[1]
Nguyen-Khac *et al*[58], 2018	103	51%	87%	80%
Nahon *et al*[59], 2008	147	75%	87%	89%
Kim *et al*[107], 2009	45	80%	97%	78%
Mueller *et al*[57], 2010	101	45%	91%	75%
Janssens *et al*[60], 2010	49	65%	72%	76%
Fernandez *et al*[61], 2015	135	53%	91%	68%

[1]Sensitivity and specificity are calculated using liver biopsy as the gold standard.

everyday clinical practice, including AST, ALT, and platelets. As far back as 1991, Poynard and colleagues described the poly-gamma-l-glutamic acid index, which included prothrombin time, gamma-glutamyl transferase (GGT), and apolipoprotein A1[77]. In a group of 333 individuals with high alcohol consumption, the index correctly classified a heavy drinker as harboring liver cirrhosis most of the time (89%) at a value ≥ 9[77]. The accuracy increased with the addition of alpha-2 macroglobulin (known as the PGAA index)[78].

Other tests, such as the enhanced liver fibrosis (ELF) test, FibroTest (FT), and HepaSCORE, are commercially available and combine different serum markers that are not used in everyday clinical practice. ELF includes type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1[79]. FT, also known as FibroSure in the United States, combines age and sex, alpha-2 macroglobulin, haptoglobulin, apolipoprotein A1, GGT, total bilirubin, and ALT[80]. HepaSCORE includes bilirubin, GGT, hyaluronic acid, alpha-2 macroglobulin, age, and sex[81]. The patented indices seem to perform better than non-patented versions against the gold standard of liver biopsy[82], but because of their cost, they are less frequently used in health systems with budget constraints.

Among the indices that include routinely measured parameters, the most commonly used are FIB-4[45] and the AST/platelet ratio index (APRI)[83]. Both indices have been validated against liver biopsy in patients with HCV and in patients with HCV and HIV co-infection[84-86]. Both FIB-4 and APRI are better suited for the detection of the absence of liver fibrosis or the presence of ALF[45,83]. Experience with their use in patients with unhealthy alcohol use is far more limited[87], and some authors have expressed concerns around the potential overestimation of liver fibrosis in patients with alcohol-related liver disease[87,88].

Lieber and colleagues, publishing in 2006, reported assessment results for 1308 patients from two United States veterans' administration cooperative studies of alcoholic liver disease for the accuracy of APRI in non-invasive detection of liver fibrosis[87]. APRI had low sensitivity (13.2%) and specificity (77.6%) for the non-invasive estimation of significant fibrosis in individuals with alcohol-related liver disease, including those who also had HCV.

In different series of patients with HCV with or without co-infection, results have been mixed regarding if non-invasive indices are able to detect the association between alcohol use and liver fibrosis, probably because of how alcohol consumption was assessed and because of unmeasured confounding in the different cohorts studied. A cross-sectional study in a cohort of patients with HIV/AIDS in Baltimore found that heavy alcohol use was associated with ALF measured with the APRI score[89]. However, when patients were stratified according to the presence of HCV infection, the association between APRI score and unhealthy alcohol use was only found among those with no HCV infection[89].

In a cohort that only included women, Blackard and colleagues did not find an association between alcohol use and FIB-4 values as a continuous variable among patients with HCV/HIV co-infection, whereas immune suppression was associated with higher FIB-4 values[90]. In a more recent study in the same cohort, Kelly and colleagues found that light or moderate alcohol consumption (1-7 drinks *per* week), which was reported in 35.7% of the 686 patients included, was not associated with fibrosis progression measured by several FIB-4 determinations over time[91]. Conversely, drinking 8–14 drinks *per* week was associated with minimal acceleration of fibrosis progression, while drinking more than 14 drinks *per* week was clearly

associated with increased fibrosis progression[91].

In a study performed in our cohort of patients with AUD who were admitted for hospital treatment in 2012, FIB-4 used as a continuous variable was significantly higher among those with HCV/HIV co-infection compared to those with HCV infection only[92]. When we stratified results by the presence of HIV infection, we found that alcohol use affected FIB-4 values only in those with HCV infection, whereas immune depression exerted a more negative role than alcohol consumption in those with co-infection[92].

In the HIV-LIVE cohort in Boston, involving a cohort of patients with HIV infection and alcohol problems, lifetime alcohol consumption measured with the Lifetime Drinking History questionnaire was not associated with FIB-4 values < 1.45 consistent with the absence of fibrosis. The adjusted (A)ORs were 1.12 (95%CI: 0.25–2.52) for a lifetime consumption of 150–600 kg of alcohol *vs* < 150 kg (reference category) and 1.11 [(95%CI: 0.52–2.36) for > 600 kg *vs* < 150 kg; global *P* = 0.95][93]. Similar results were found for the presence of ALF (FIB-4 > 3.25) and with the use of APRI instead of FIB-4. Results did not differ among patients with HCV co-infection[93].

An analysis from the veterans aging cohort study (VACS) included a large number of patients (701 with HIV/HCV coinfection, 1410 with HIV infection, with 296 HCV infection, and 1158 with neither HIV nor HCV infection) and a different measure of alcohol consumption (AUDIT-C questionnaire and/or presence of alcohol-related diagnoses). The authors reported greater risks for ALF (measured with FIB-4) among patients with co-infection who had nonhazardous drinking (OR = 14.2; 95%CI: 5.91–34.0) or hazardous/binge drinking (OR = 18.9; 95%CI: 7.98–44.8), or who exhibited alcohol-related diagnoses (OR = 25.2; 95%CI: 10.6–59.7) in comparison to uninfected Veterans who were nonhazardous drinkers[94].

In a more recent study by our group that included 1313 patients with AUD who were admitted for hospital detoxification, 30.6% had ALF, estimated with a FIB-4 value > 3.25. Patients with HCV infection, who represented 18% of the total study population, were two times more likely than those without HCV infection to present with ALF (OR = 2.1; 95%CI: 1.5–3.1, *P* < 0.01)[25].

Despite these different results in terms of accuracy or the ability to detect associations between the presence either of AUD or HCV and ALF, non-invasive indices are performed in patients with alcohol or other substance use disorders that will not undergo a biopsy[93,95]. In addition, non-invasive indices can predict mid-term mortality in epidemiological studies[95,96], which is why FIB-4 has been included in the VACS cohort index[97]. This index, initially intended to predict mortality, also predicts the occurrence of other health outcomes[98], such as incident heart failure in patients living with HIV[99].

The Forns index, which was described in 2002, has been less frequently used in patients with unhealthy alcohol use[100]. Originally developed for detection of the absence of liver fibrosis in a cohort of patients with HCV, it includes platelets, cholesterol, and GGT levels, as well as age[100]. In a study by Naveau and colleagues published in 2009, the accuracy of the Forns index for detecting biopsy-proven ALF was lower than that of other non-patented biomarkers (APRI and FIB-4)[82]. Furthermore, other researchers have expressed concerns regarding the use of the Forns index in alcohol-related liver disease, given that GGT levels differ between patients with HCV or alcohol-related liver disease[101]. Despite those concerns, in our group, we have used the Forns index to estimate liver fibrosis in drug users with HCV infection with or without HIV infection[96] and in patients with AUD[25]. The Forns index accurately predicted mid-term mortality and detected ALF in a fashion that was comparable to APRI and FIB-4[25].

Table 2 includes a summary of the more relevant papers describing assessment of alcohol use with non-patented indices to estimate liver fibrosis in patients with HCV infection.

Combination of non-invasive methods

Because non-invasive indices are better suited for the detection of either the absence of liver fibrosis or the presence of ALF, several approaches of the sequential use of different methods have been proposed. A study published in 2017 by Spanish researchers showed that use of the ELF test with or without a confirmation elastography was cost-effective compared with a single liver biopsy for the detection of liver fibrosis in patients with HCV and alcohol-related liver disease[102].

Another new approach is the use of both FIB-4 and transient elastography to detect ALF in patients with FIB-4 values within the intermediate range (1.45–3.25)[103]. This approach has been used in a Russian cohort of individuals with high alcohol intake, HIV infection, and a high prevalence of chronic HCV infection[103].

Table 2 Studies that used non-patented indices to estimate liver fibrosis in patients with hepatitis C virus infection and unhealthy alcohol use

Ref.	Setting	Non-invasive method	Method for detecting alcohol consumption	Finding
Lieber *et al*[87], 2006	Veterans' affairs studies (2) of alcoholic liver disease	APRI[1]	Average alcohol intake	Low sensitivity and specificity of APRI in comparison to liver biopsy, especially in patients with HCV
Chaudhry *et al*[89], 2009	HIV Hopkins clinical cohort	APRI[1]	Past 6 mo of hazardous drinking	No effect of alcohol on APRI values in HCV/HIV co-infection
Blackard *et al*[90], 2011	WIHS cohort	FIB-4[2]	Recent drinking	No association between alcohol intake and FIB-4 values in HCV/HIV co-infection
Muga *et al*[92], 2012	Patients with AUD admitted for detoxification	FIB-4[2]	Past 6 mo of unhealthy drinking	No association between FIB-4 and alcohol use in HCV/HIV co-infection
Fuster *et al*[93], 2013	HIV-LIVE cohort	FIB-4[2] and APRI[1]	LDH	No association between LDH and liver fibrosis measured with FIB-4 or APRI
Lim *et al*[94], 2014	VACS cohort	FIB-4[2]	AUDIT-C[3]	Advanced liver fibrosis correlated with alcohol use
Kelly *et al*[91], 2017	WIHS cohort	FIB-4[2]	Average number of drinks *per* week, past 6 mo	Light/moderate drinking was not associated with accelerated fibrosis progression
Sanvisens *et al*[25], 2018	Patients with AUD admitted for detoxification	FIB-4[2]; APRI[1]; Forns	Past 6 mo, daily alcohol intake	Patients with HCV were two times as likely to present with advanced liver fibrosis

[1]Aspartate aminotransferase (AST)/platelet ratio index: AST to platelet ratio index = {[Patient AST/AST upper limit of normal (IU/L)]/platelet count (10^9 /L)} × 100.

[2]FIB-4 = Age × AST (IU/L)/platelet count (10^9/L) × alanine aminotransferase (IU/L)$^{1/2}$.

[3]AUDIT-C: Alcohol use disorders identification test. HCV: Hepatitis C virus; AST: Aspartate aminotransferase; APRI: AST/platelet ratio index; FIB-4: Fibrosis-4; AUD: Alcohol use disorder; HIV: Human immunodeficiency virus; LDH: Lifetime drinking History; WIHS: Women's interagency HIV study; VACS: Veterans aging cohort study.

Future directions for the non-invasive assessment of liver damage

The measurement of small non-coding microRNAs (miRNAs) is a promising field [104]. In fact, miR-155 and miR-122 have been proposed as potential markers of different forms of liver diseases, including those related to HCV and alcohol[105].

Other markers that could be used in the future are extracellular vesicles, the small membrane vesicles released by cells that transport mRNA, miRNA, proteins, and lipids, and circulating nucleic acids, including cell-free DNA and cell-free non-coding RNA[106].

CONCLUSION

Underlying liver disease can be accurately estimated with the use of several non-invasive methods that spare the necessity of performing a liver biopsy. The widespread use of these methods can help to accurately identify patients at risk for the development of end-stage liver disease. In addition to treatment with direct-acting antivirals for those with HCV infection, abstinence from alcohol consumption should be strongly recommended, given the overlap between alcohol-related and metabolic liver diseases.

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