Chapter

Liver Ultrasound Abnormalities in Alcohol Use Disorder

Daniel Fuster, Xavier Garcia-Calvo, Paola Zuluaga, Inmaculada Rivas, Arantza Sanvisens, Jordi Tor and Robert Muga

Abstract

Alcohol-related liver disease is the most common alcohol-related medical illness, and it is the major driver of liver-related deaths worldwide. However, no screening guidelines currently exist for the early detection of liver disease in patients with risky drinking or those with alcohol use disorder. Moreover, most patients with alcohol-related liver fibrosis, which is the main prognostic factor of progression to end-stage liver disease, have normal blood tests. Abdominal ultrasound is a cheap and readily available diagnostic procedure that is rarely used in patients with alcohol use disorder without overt liver disease. In addition, abdominal ultrasound can detect other forms of liver disease, which are not uncommon in patients with unhealthy alcohol use, and can have a negative impact on the natural history of alcohol-related liver disease. In this chapter we will review the current knowledge about the use of liver ultrasound in patients with alcohol use disorder for the early detection of alcohol-related liver disease, as well as the potential use to detect other forms of liver disease. We will also briefly discuss other methods for the noninvasive detection of liver steatosis and/or liver fibrosis in patients with alcohol use disorder.

Keywords: abdominal ultrasound, alcohol-related liver disease, alcohol use disorder, liver steatosis; cirrhosis

1. Introduction

According to the last update of the Global Burden of Disease Study, alcohol consumption is the seventh leading risk factor for both death and the burden of disease and injury [1]. Besides tobacco, alcohol accounts for a higher burden of disease than any other drug, and alcohol-related liver disease is the most common alcohol-related chronic medical illness [2]. In recent years, there has been a worldwide increase in liver-related mortality due to end-stage liver disease [3], mostly because of the impact of alcohol consumption [4, 5]. With the recent advances in hepatitis B and C treatment, alcohol-related liver disease has become the main cause of liver-related mortality [6].

It is important to note that, compared with other forms of liver disease, alcohol-related liver disease has received little attention in the literature, as it is often stigmatized as a self-inflicted disease [7]. This is also true in clinical practice, as

alcohol use is often not properly screened or accounted for in medical charts, both in primary care and hospital settings [8], and treatment for alcohol use is offered to a minority of patients [2].

In this chapter, after a brief introduction about generalities of alcohol-related liver disease and about the assessment of alcohol use in patients with liver disease, we will discuss the current evidence for the use of abdominal ultrasounds in patients with alcohol use disorder (AUD). The current evidence includes a recently published Cochrane review and our own experience with the systematic performance of abdominal ultrasounds in otherwise healthy adults with AUD admitted for hospital detoxification.

In addition, we will also discuss other potential benefits of the use of abdominal ultrasound to detect other forms of liver disease, which are not uncommon in patients with unhealthy alcohol use. We will address the use of liver ultrasound for hepatocellular carcinoma surveillance in patients with alcohol-related liver cirrhosis. Finally, we will include a brief mention of other available methods to screen for alcohol-related liver steatosis and alcohol-related liver fibrosis.

2. General overview of alcohol-related liver disease

Liver disease in patients with AUD encompasses a spectrum of histological abnormalities that includes steatosis, steatohepatitis, fibrosis, cirrhosis of the liver, and hepatocellular carcinoma [9, 10]. Those abnormalities, rather than being different stages of the disease, can coexist in the same patient. Acute alcoholic hepatitis is a severe complication that can occur at any point in the course of alcohol-related liver disease and is associated with liver failure and with high short-term mortality [2].

Alcohol-related liver steatosis in the absence of alcoholic hepatitis is potentially reversible with the cessation of alcohol consumption, but continued alcohol use is associated with progressive liver damage and an increased risk of alcoholic hepatitis [11]. Therefore, abstinence is advisable for patients with AUD and any form of alcohol-related liver disease, as it tends to diminish portal hypertension even in the more advanced forms of the disease [2]. Active alcohol consumption is a formal contraindication for liver transplantation, which is of concern as alcohol-related liver disease is the leading cause of liver transplantation in Europe [12].

A timely diagnosis of liver disease in apparently asymptomatic patients with AUD contributes to a better prognosis and facilitates treatment [13, 14]. In patients with unhealthy alcohol use, liver damage is a major driver of disease burden, and it is often diagnosed in advanced stages, including decompensated liver cirrhosis [14]. In fact, nearly 75% of patients with liver disease present for the first time with a nonelective hospital admission due to end-stage liver disease [5].

The use of liver ultrasound is recommended by the current European guidelines to promote an early detection of nonalcoholic steatohepatitis [15]. However, no guidelines exist for the screening and early detection of liver damage in unhealthy drinkers, and screening approaches in this population are currently a matter of debate [16, 17].

Therefore, there is a need for screening and early detection of alcohol-related liver disease in patients who drink alcohol in excess, as it is well established that sharing abnormal findings suggestive of liver disease with patients can trigger behavioral change and decrease the use of alcohol [18].

Moreover, surveillance aimed to detect hepatocellular carcinoma in patients with alcohol-related liver disease is suboptimal, and liver cancer is often diagnosed at a later stage when potential curative treatments are futile [10].

3. Assessment of alcohol use in patients with suspected liver disease

The Alcohol Use Disorders Identification Test (AUDIT) is a validated tool for identifying AUD in patients [19]. AUD encompasses both alcohol dependence and alcohol abuse [20], and represents the more extreme form of unhealthy alcohol use [21]. The use of AUDIT is recommended by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines [22, 23]. Other options are AUDIT-C (a shorter version of the AUDIT) [24], and the single-question screening tool that has been validated for the screening in primary care of unhealthy alcohol use, that is, the spectrum of alcohol use that goes from risky alcohol use to AUD [25].

Patients who screen positive for unhealthy alcohol use merit further assessment to rule out health consequences of alcohol with an emphasis on alcohol-related liver disease [2]. Besides laboratory testing, we believe that the performance of an abdominal ultrasound can be useful in this setting [17].

In addition, referral of patients to physicians who are specialists in addiction medicine is an option to increase the chances of successfully remaining abstinent [2].

4. General overview of abdominal ultrasound for the study of liver diseases

Abdominal ultrasound is a cheap and widely available technique that is not usually performed to detect subjacent liver abnormalities in patients with AUD without overt liver disease.

4.1 Normal ultrasound findings of the liver

Abdominal ultrasound is an accurate method for estimating liver size, which should be determined at the midclavicular line and in normal conditions is less than 16 cm [26]. The liver parenchyma should be evaluated for focal and/or diffuse abnormalities. The normal liver appears as homogeneous with an echogenic texture. In normal conditions, liver echogenicity equals or slightly exceeds that of the renal cortex. This comparison heavily relies on the visual perception of the observer and on the presence (or absence) of disease processes in the renal cortex [27].

The right and left lobes, as well as the caudate lobe can be identified with the use of an ultrasound [28]. Other structures that should be identified are the main lobal fissure, which separates the left and right lobes and appears as an echogenic line that extends to the gallbladder fossa; the falciform ligament, which divides the left lobe into the medial and the lateral segments and appears as an echogenic area in the left lobe; and the ligamentum venosum, which separates the caudate from the left lobe and appears as an echogenic line anterior to the caudate lobe [28].

An abdominal ultrasound can also identify the major hepatic and perihepatic vessels, including the inferior vena cava (IVC), the hepatic veins, the main portal vein, and the right and left branches of the portal vein [28]. The main portal vein is characterized by thick and echogenic walls and enters the liver at the hilum. It divides into the right and left portal branches, and the left branch then divides into medial and lateral branches. The hepatic veins, which drain in the inferior vena cava, have thinner walls in comparison to the portal vein [28]. In addition, abdominal ultrasound is a reliable method for a first-line evaluation of portal vein abnormalities suggestive of portal hypertension [29]. It is also very useful to evaluate the biliary tree and to detect ascitic fluid, and it can also be used to guide the performance of a paracentesis [28].

Doppler evaluation should be used to document blood flow characteristics and blood flow direction, which is crucial in the diagnosis of portal hypertension [30]. In addition, Doppler evaluation can distinguish nodular lesions that are suggestive of hemangiomas, of hepatocellular carcinoma, or of liver metastases [31].

Figure 1 shows how a normal liver appears in an abdominal ultrasound.

4.2 Liver ultrasound in alcohol-related liver disease

In abdominal ultrasounds, liver steatosis appears as hyper-echogenicity due to the increased parenchymal reflectivity that intracellular fat accumulation produces [32]. The sensitivity of abdominal ultrasound to detect liver steatosis is impacted by the amount of fat content and severely decreases if fat content is lower than 10–20% [14].

The results about the ability of liver ultrasound to differentiate between liver steatosis and liver fibrosis have been mixed [33–35], and it is easier to differentiate when the degree of liver fibrosis is higher, as there is an increase in coarse echoes without posterior beam attenuation [32, 33, 36].

How to quantify liver steatosis with abdominal ultrasound is also a matter of debate. Liver steatosis is often classified as "mild," "moderate," or "severe" based on hyper-echogenicity, the discrepancy between echo amplitude in the liver and the kidney, impaired visualization of hepatic vessels, and loss of echoes from the walls of the portal system [36, 37].

Many authors consider steatosis to be *mild* if there is presence of hyper-echogenic liver tissue with fine and tightly packed echo targets and of normal beam penetration with normal visualization of the diaphragm and portal vein borders [38].

If there is decreased beam penetration with slightly decreased visualization of the diaphragm and the portal vein borders as well as moderate or diffuse increase of echo intensity, liver steatosis would then be considered to be *moderate* [38].

If there is a marked increase in echogenicity with no visualization of the portal vein border, an obscured diaphragm and posterior portion of the right lobe, and reduced visibility of the kidney, liver steatosis would be considered *severe* [38].

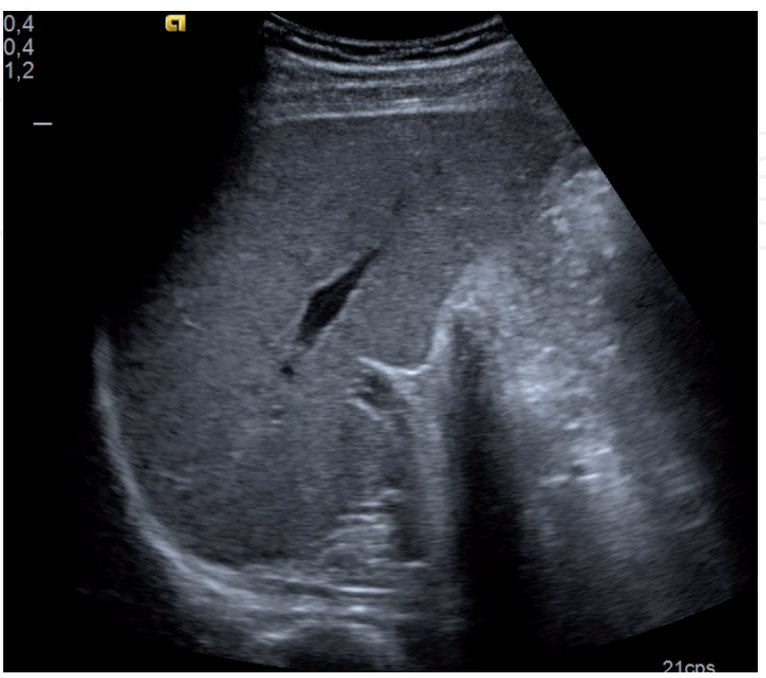

Figure 1.
Normal liver.

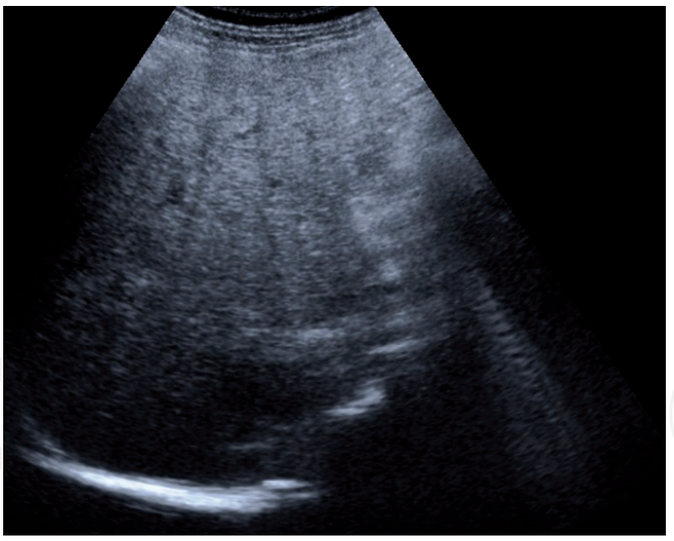

Figure 2.
Severe steatosis in an heterogeneous liver.

As mentioned in the introduction, different alcohol-related liver disease abnormalities can coexist in the same patient. **Figure 2** shows an abdominal ultrasound consistent with severe steatosis in a patient with AUD admitted for hospital treatment that also harbors a heterogeneous liver.

A potential weakness of liver ultrasound is operator dependency in assessing liver steatosis [27]. In a retrospective study that used static images of liver ultrasounds and included 168 patients from routine clinical practice and three independent radiologists, the mean inter-observer agreement rates for the presence of liver steatosis were 72%, while the mean intra-observer agreement 1 month later was 76% [27]. In that study, intra-observer agreement for the severity of liver steatosis ranged from 55 to 68% [27].

In general, there is agreement that abdominal ultrasound is a cheap and reliable method to identify moderate or severe liver steatosis [38], but its accuracy for mild forms of steatosis is lower and may increase with the use of a computer-aided method [38]. Besides liver steatosis, ultrasound findings that contribute to the detection of alcohol-related liver disease include (among others) liver size,

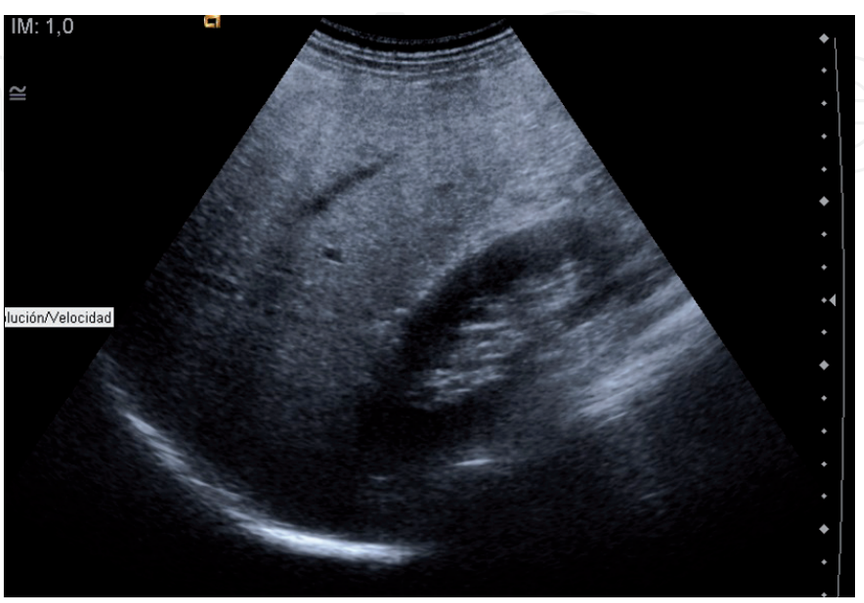

Figure 3.
Heterogeneous liver in a patient with AUD admitted for hospital detoxification.

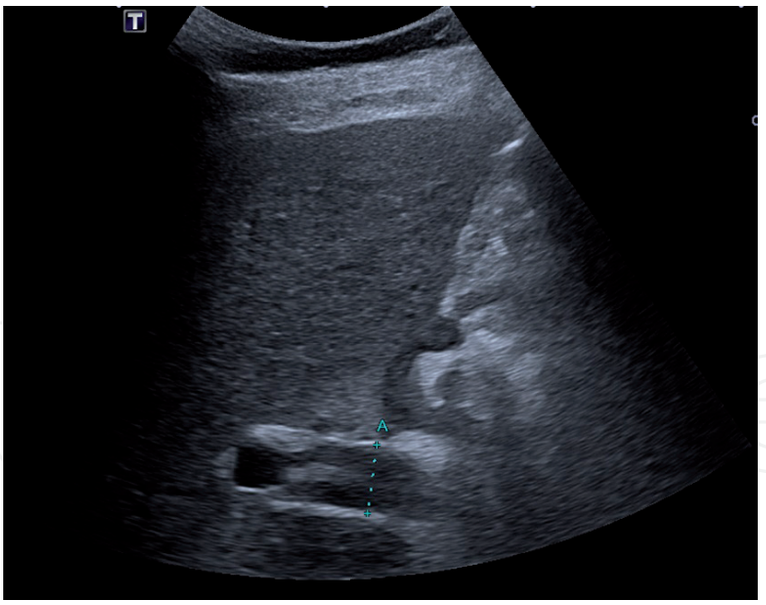

Figure 4.
Cirrhosis of the liver with an enlarged portal vein, consistent with portal hypertension.

bluntness of the edge, coarseness of parenchyma, nodularity of the surface, size of the lymph nodes around the hepatic artery, irregularity and narrowness of the inferior vena cava, portal vein velocity and caliber, and spleen size [28].

Figure 3 shows a heterogeneous liver in a 45-year-old patient with alcohol-related liver disease, and **Figure 4** shows an ultrasound of a 50-year-old patient with AUD and alcohol-related cirrhosis of the liver, as well as an enlarged portal vein, consistent with portal hypertension.

5. Use of liver ultrasound in patients with AUD: current evidence

Evidence about the use of liver ultrasounds to detect underlying liver disease in patients with AUD is scarce and includes a Cochrane systematic review and a recently published study by our group.

5.1 Cochrane systematic review

A Cochrane review published in 2016 stated that there was a need for studies of adequate sample size to study the efficacy of liver ultrasound in alcohol-related liver disease [39], as the review could only include two studies that aimed to assess alcohol-related liver cirrhosis with liver ultrasound [39].

The first study was published by French researchers in 1985 and included 126 alcoholic patients who underwent liver ultrasound [40]. Of those, a hundred patients also underwent liver biopsy. The mean age of participants was 55.6 years. In that study, the main ultrasound findings were as follows: 100 patients (78%) presented hepatomegaly, 59 (46%) presented heterogeneous liver, 44 (34%) presented portal hypertension, and 82 (64%) presented liver cirrhosis. In those who underwent liver biopsy, liver cirrhosis was confirmed in 72 participants, so ultrasound had a 81% sensitivity and 79% specificity for the detection of liver cirrhosis [40].

The second study was performed in Korea and published in 2013. It included 230 patients (81% male) who underwent abdominal ultrasound and liver elastography prior to liver biopsy [41]. The mean age of the study population was 50.4 years; 199 patients (86.5%) and 170 (74%) presented an ultrasound that was suggestive of

heterogeneous liver and liver cirrhosis, respectively. Liver cirrhosis was confirmed in 111 participants; therefore, ultrasound had a 94% sensitivity and 49% specificity for the detection of liver cirrhosis [41].

Due to differences in the selection criteria and the small number of patients included in both studies, the systematic review could reach no conclusion around the usefulness of liver ultrasound to detect underlying liver cirrhosis in patients with alcohol use [39].

5.2 Ultrasound findings of liver damage in a series of AUD patients consecutively admitted for hospital detoxification

We recently published a cross-sectional study of the use of abdominal ultrasound in 301 patients with AUD without overt liver disease that were admitted for hospital detoxification [17].

In that study, clinical and laboratory parameters were obtained at admission, and an abdominal ultrasound was performed on the third day of admission. Abdominal ultrasound was used to identify steatosis, hepatomegaly, heterogeneous liver, and portal hypertension. Portal hypertension was defined as having any of the following abnormalities: splenomegaly, enlarged portal vein, ascites, and/or abnormal portal vein flow.

For the purpose of the analysis, we defined analytical liver injury (ALI) as at least two of the following abnormalities: aspartate aminotransferase (AST) levels ≥74 < 300 U/L, AST/alanine aminotransferase (ALT) ratio >2, and total bilirubin>1.2 mg/dL. Advanced liver fibrosis (ALF) was measured with the FIB-4 (a noninvasive index for the detection of liver fibrosis) [42], and was defined as a FIB-4 score ≥ 3.25.

We wanted to study bivariate associations of ultrasound abnormalities with three commonly observed conditions, hepatitis C virus infection (HCV), ALI, and ALF. We also used logistic regression to see if any of those three conditions predicted the presence of two or more ultrasound abnormalities.

In brief, 80% of the participants were male, with a median age of 46 years (Interquartile range [IQR]: 39–51 years) and had an alcohol consumption of 180 g/day upon admission (IQR: 120–201 g). The prevalence of HCV was 21.2%; AST and ALT serum levels were 42 U/L (IQR: 23–78 U/L) and 35 U/L (IQR: 19–60 U/L), respectively; 16% of patients had ALI and 24% ALF. Ultrasound findings in the study population were as follows: 57.2% steatosis, 49.5% hepatomegaly, 17% heterogeneous liver, and 16% portal hypertension. Of note, 77% had at least one ultrasound abnormality, and 45% had ≥2.

In logistic regression analyses, ALI and ALF were associated with having ≥2 ultrasound abnormalities [Odds Ratio (OR) (95% Confidence Interval [CI]): 5.2 (2.1–12.8), $p < 0.01$ and 4.7 (2.2–9.7), $p < 0.01$, respectively], while HCV infection was not (we performed a multivariate regression model for each of the three potential predictors) [17].

Most patients with only one ultrasound abnormality had hepatomegaly or mild to moderate steatosis, both of which represent morphologic changes that are potentially reversible with alcohol cessation. Therefore, we believe that implementation of abdominal ultrasound in the regular care of patients seeking AUD treatment might be helpful for making clinical decisions and determining therapeutic interventions.

In fact, ultrasound abnormalities were very common in this series of patients, even in patients without HCV, ALI, and ALF, as only 31% of patients in that group had a totally normal abdominal ultrasound. In this regard, we believe that the use of ultrasound to detect early stages of liver disease may promote alcohol cessation, what might have a tremendous impact on the natural history of alcohol-related liver

cirrhosis, especially in patients that present earlier stages of the disease [17]. As previously described by other researchers, sharing findings that might impact negatively the prognosis with patients may also be associated with a decrease in unhealthy drinking [18]. Upon publication of this study, a literature search did not identify any large ultrasound study of AUD patients with compensated liver disease [17].

5.3 Hepatocellular carcinoma surveillance

As mentioned before, hepatocellular carcinoma is the last stage of alcohol-related liver disease, with an annual incidence of 2.9% in patients that already harbor liver cirrhosis [10]. It entails a very poor prognosis if not detected at the earliest possible stage [43]. This is the reason why all patients with alcohol-related cirrhosis should be included in hepatocellular carcinoma surveillance programs that typically consist of an abdominal ultrasound every 6 months [10].

However, periodical surveillance is not optimal in clinical practice, as surveillance is missed by one-third of patients and the interval between screening ultrasounds is often greater than 6 months [10]. In fact, less than 30% of hepatocellular carcinomas diagnosed in Europe and the USA are detected by surveillance [10, 44]. In addition, patients with alcohol-related liver cirrhosis are more likely to have deficient surveillance than those with HCV infection [43, 45].

In our series of 301 patients with AUD that underwent liver ultrasound, 15 (4.9%) had space occupying lesions; most of those lesions were hepatic hemangiomas, but hepatocellular carcinoma was diagnosed in 2 patients [17].

Figure 5 shows a liver nodule, suggestive of hepatocellular carcinoma over a cirrhotic liver in a 52-year-old woman with AUD and untreated chronic HCV.

5.4 Other potential uses of abdominal ultrasound in patients with AUD

Beyond the early detection of liver steatosis or liver cirrhosis, abdominal ultrasound might be useful for the detection of other forms of liver disease that may coexist with alcohol-related liver disease.

Alcohol use is common in patients with other forms of liver disease, and even alcohol use that would be considered moderate can be detrimental in these

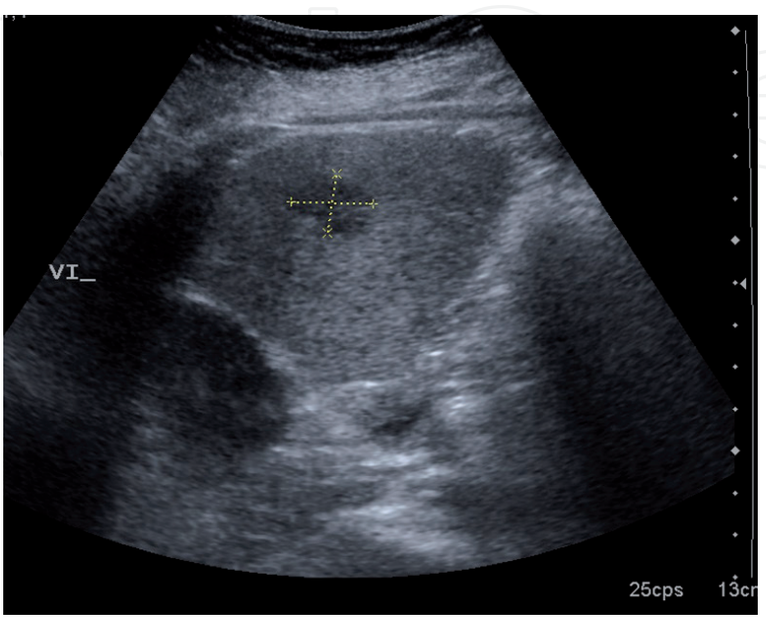

Figure 5.
A liver nodule, suggestive of hepatocellular carcinoma over a cirrhotic liver in a 52-year-old woman with AUD and untreated chronic hepatitis C virus infection.

situations [46, 47]. In fact, alcohol use is a cofactor for the progression of liver disease in patients with HCV, hepatitis B virus infection (HBV), nonalcoholic fatty liver disease, and hemochromatosis, among others. It is important to note that an arbitrary threshold of a daily alcohol intake of 30 grams for men and 20 grams for women is used to differentiate between alcohol-related liver damage and damage due to other etiologies [2]. However, with the current epidemic of overweight and obesity in Western societies, alcohol-related liver disease and nonalcoholic liver steatosis often coexist in the same patient [48]. In fact, in our cohort of patients with AUD that underwent abdominal ultrasound, the median body mass index was 24.7 kg/m^2, that is, a significant amount of patients were overweight [17].

In addition, the performance of abdominal ultrasound can detect less prevalent forms of liver disease, like vascular diseases (Budd-Chiari syndrome, hepatic vein congestion, and noncirrhotic portal hypertension) as well as other parenchymatous diseases.

6. Other noninvasive procedures used to detect liver steatosis in patients with AUD

Controlled attenuation parameter (CAP) is a noninvasive tool to detect liver steatosis that measures ultrasound attenuation when trespassing fatty liver tissue [49]. CAP software is incorporated into the transient elastography equipment, thus facilitating the bedside estimation of both liver steatosis and liver fibrosis [14].

In a recent individual patient data meta-analysis that included 2, 735 cases with both liver biopsy and CAP, cutoffs for moderate and severe liver steatosis were defined, with a diagnostic accuracy between 0.65 and 0.90 [50]. Patients included in that meta-analysis had mainly HBV (37%) and HCV (36%), or nonalcoholic fatty liver disease (20%), while patients with alcohol-related liver disease were underrepresented [50]. Given that all patients included in the meta-analysis harbored liver diseases that are strongly associated with liver fibrosis, there is a need for further validation of those cutoffs in a healthier population [51].

Another study by Thiele and colleagues published in 2018 that included 562 patients with alcohol-related liver steatosis found that CAP above 290 dB/m ruled in any steatosis with 88% specificity and 92% positive predictive value, while CAP below 220 dB/m ruled out steatosis with 90% sensitivity, but 62% negative predictive value [52]. Researchers concluded that CAP had a good diagnostic accuracy for diagnosing severe alcoholic liver steatosis and could be used to rule in any steatosis. The study also included a cohort of patients who were admitted for alcohol detoxification and found that CAP rapidly declined in nonobese patients [52]. This finding speaks to the double-hit model of alcohol use and obesity in a significant proportion of patients commonly seen in clinical practice [53].

7. Alternative noninvasive methods to detect liver fibrosis in patients with AUD

7.1 Transient elastography

Transient elastography has also been used for analyzing liver injury in patients with AUD. A study found elastography provided an assessment of fibrosis that was comparable to liver biopsy [16]. Other authors, however, have expressed concerns that alcohol-related steatohepatitis may distort results, leading to overestimation of

liver fibrosis in this population [54], especially in patients who maintain abstinence from alcohol, as liver stiffness seems to dramatically decrease with cessation of alcohol use [55].

A systematic review and meta-analysis published in 2016 that included 14 different studies suggested that transient elastography was a good method to exclude the presence of liver cirrhosis or advanced liver cirrhosis but advised that caution should be needed when using the same cutoffs described for viral hepatitis in other forms of liver disease [56].

A recently published individual patient data meta-analysis that included 1026 patients suggested that cutoffs for transient elastography should be higher, especially in patients with elevated AST and/or bilirubin, suggestive of active alcoholic hepatitis [57].

Therefore, transient elastography is a promising tool, but it is mainly used in European countries in specialty clinics or teaching institutions [14]. In other countries its use is limited because of budget constraints or because it is only approved for research purposes.

7.2 Noninvasive laboratory-driven indices

There are several noninvasive indices to estimate liver fibrosis that are derived from laboratory parameters routinely used in clinical practice, including AST, ALT, and platelet count.

Among those, the most widely used are the FIB-4 [42], and the AST/platelet ratio index (APRI) [58], which have been validated against the gold standard of liver biopsy in HCV-monoinfected patients as well as HCV- and HIV-coinfected patients [59–61]. These indices perform better for detecting either the absence of liver fibrosis or the presence of advanced liver fibrosis [42, 58]. However, clinical experience using these markers in patients with AUD is somewhat limited [62]. In fact, some researchers have expressed concerns because of potential overestimation of liver fibrosis when using these noninvasive indices in alcohol-related liver disease [62, 63].

In a series of patients with HIV and/or HCV infection, results around the ability of noninvasive indices to capture the impact of alcohol and liver fibrosis have been mixed, probably because of the different methods used to describe alcohol intake and other characteristics of the study population. A cross-sectional study in an urban cohort of HIV-infected individuals in Baltimore (USA) revealed that heavy alcohol use was associated with advanced liver fibrosis measured using the APRI score [64]. In that same study, when patients were stratified by HCV infection, high APRI score was associated with hazardous alcohol use only among patients without HCV infection [64]. In a cohort of HIV-infected women, Blackard and colleagues demonstrated that alcohol use was not associated with FIB-4 values among those with HCV-/HIV-coinfected women [65].

In a cohort of Boston HIV-infected patients with alcohol problems, lifetime alcohol consumption was not associated with the presence of advanced liver fibrosis (FIB-4 $\geq$ 3.25) [66, 67]. Another study performed in the Veterans Aging Cohort Study (VACS) reported greater risks of advanced liver fibrosis (measured with FIB-4) among HCV-/HIV-coinfected patients who exhibited any level of alcohol consumption or who had alcohol-related diagnoses [68].

Despite these somewhat discordant results, noninvasive markers of liver fibrosis have been widely used in populations with alcohol or other substance use disorders that are unlikely to undergo a liver biopsy [67, 69]. Besides, those noninvasive indices have been able to predict midterm mortality in epidemiological studies [69, 70]. A rather innovative approach is the combination of noninvasive indices and transient

elastography, so as to better characterize patients in the intermediate range of FIB-4 values (1.45–3.25) [71].

8. Conclusions

Abdominal ultrasound is a cheap and easily available noninvasive method that could be useful as a first-line screening to assess underlying liver disease in patients with excessive alcohol intake. For patients that need further assessment, transient elastography and CAP, if available, might be helpful in defining the extent and magnitude of alcohol-related liver disease.

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Conflict of interest

The authors report no conflict of interest.

Author details

Daniel Fuster[1*], Xavier Garcia-Calvo[1], Paola Zuluaga[1], Inmaculada Rivas[2], Arantza Sanvisens[1], Jordi Tor[1] and Robert Muga[1]

1 Internal Medicine Service, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain

2 Municipal Centre for Substance Abuse Treatment (Centro Delta), Badalona Serveis Assistencials, Badalona, Spain

*Address all correspondence to: dfuster.germanstrias@gencat.cat

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