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TOPIC HIGHLIGHT

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Diagnostic challenges in alcohol use disorder and alcoholic liver disease

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Abstract

Alcohol use disorders represent a heterogeneous spectrum of clinical manifestations that have been defined by the Diagnostic and Statistical Manual of Mental Disorders-5. Excessive alcohol intake can lead to damage of various organs, including the liver. Alcoholic liver disease includes different injuries ranging from steatosis to cirrhosis and implicates a diagnostic assessment of the liver disease and of its possible complications. There is growing interest in the possible different tools for assessing previous alcohol consumption and for establishing the severity of liver injury, especially by non-invasive methods.

Key words: Alcoholic liver disease; Alcohol use disorder; Diagnosis; Diagnostic and Statistical Manual of Mental Disorders-5; Screening tests; Markers of previous alcohol consumption; Non-invasive fibrosis assessment

Core tip: Alcohol use disorders have been defined by the Diagnostic and Statistical Manual of Mental Disorders-5. Excessive alcohol intake can lead to damage of various organs, including the liver, and can induce complex psychiatric and somatic comorbidities. Alcoholic liver disease includes different injuries ranging from steatosis to cirrhosis and implicates a diagnostic assessment of the liver disease and of its possible complications. The assessment of previous alcohol consumption and the non-invasive evaluation of liver fibrosis are areas of growing interest in this field.

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INTRODUCTION

The global lifetime prevalence of alcohol use disorders (AUDs) in the adult population has been estimated to be up to 16%, with the highest rates to be found in Eastern Europe[1]. AUD can underlie a constellation of alcohol-related comorbidities, including psychiatric, neurologic, cardiovascular, gastrointestinal and hematologic ones. In particular, alcoholic liver disease (ALD) constitutes the first cause of liver cirrhosis in the Western countries[2] and the second most common cause of liver transplantation[3]. Rehm *et al*[4] estimated that in 2010, liver cirrhosis was responsible for 493300 deaths and 14544000 disability adjusted life years (DALYs) worldwide. Furthermore, in this study, alcohol use was strongly associated with overall liver cirrhosis rates, with 47.9% of cirrhosis deaths and 46.9% of DALYs lost due to cirrhosis attributable to

Table 1 Diagnostic and Statistical Manual of Mental Disorders-5 criteria for alcohol use disorders

Criterion	Group	
1	Impaired control	The individual may take alcohol in larger amounts or over a longer period than was originally intended
2		The individual may express a persistent desire to cut down or regulate alcohol use and may report multiple unsuccessful efforts to decrease or discontinue use
3		The individual may spend a great deal of time obtaining alcohol, drinking alcohol, or recovering from its effects
4		Craving is manifested by an intense desire or urge for alcohol that may occur at any time but is more likely when in an environment where alcohol previously was obtained or used
5	Social impairment	Recurrent alcohol use may result in a failure to fulfil major role obligations at work, school, or home
6		The individual may continue alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol use
7		Important social, occupational, or recreational activities may be given up or reduced because of alcohol use. The individual may withdraw from family activities and hobbies in order to use alcohol
8	Risky use	This may take the form of recurrent alcohol use in situations in which it is physically hazardous
9		The individual may continue alcohol use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
10	Pharmacological criteria	Tolerance, as defined by a need for a markedly increased dose of alcohol to achieve the desired effect or by a markedly reduced effect when the usual dose is consumed
11		Withdrawal, that is a syndrome that occurs when blood or tissue concentrations of alcohol decline in an individual who had maintained prolonged heavy alcohol use

alcohol consumption. It is thus important to set a correct diagnosis of alcohol use disorder and of alcohol-related comorbidities, in a multidisciplinary setting, in order to establish a timely and appropriate treatment (for review see Addolorato *et al*[5]).

ALCOHOL USE DISORDER: THE ERA OF DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS-5

AUDs represent a heterogeneous spectrum of clinical manifestations. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV differentiates alcohol "abuse" from alcohol "dependence". The former was defined by problematic use without compulsive use, significant tolerance or withdrawal, and the latter was defined as a syndrome involving compulsive use, with or without tolerance and withdrawal[6].

The recent new edition of DSM, the DSM-5, has revised this classification, abolishing the distinction between abuse and dependence and defining AUD as a cluster of behavioural and physical symptoms with a continuum or spectrum of severity[7]. Moreover, different from DSM-IV, the DSM-5 has eliminated "recurrent legal problems" as a criterion and has instead introduced "craving or a strong desire or urge to use alcohol" as a new criterion. This is important, especially in view of the use of craving as a biological treatment target[8].

There are 11 criteria for the diagnosis of AUD that can be divided into the overall groups of "impaired control" (criteria 1-4), "social impairment" (criteria 5-7), "risky use" (criteria 8-9) and "pharmacological criteria" (criteria 10-11) (Table 1). A minimum of two positive criteria are necessary to establish a diagnosis of AUD. Two to 3 positive criteria indicate a mild disease, 4 to 5 positive criteria indicate a moderate disease and 6 or more positive criteria indicate a severe disease.

The severity scale allows for classification of severity and for recognition of change of severity over time and of increase or remission as a result of treatment. It is, therefore, useful both in the first diagnostic assessment and in the follow up of the disease. As to identification of remission, early remission has been defined as $\geqslant 3$ to < 12 mo without symptoms (except craving) and full remission requires no symptoms (except craving) for 12 mo.

Among the "Alcohol-Related Disorders" the DSM-5 recognizes, besides AUD, alcohol intoxication, alcohol withdrawal, other alcohol-induced disorders and unspecified alcohol-related disorder (*e.g.*, alcohol-induced psychotic disorder and alcohol-induced depressive disorder)[7]. In addition, patients with alcohol use disorders are often afflicted with other "co-morbid" psychiatric disorders. Both internalizing (*e.g.*, mood and anxiety disorders) and externalizing (*e.g.*, antisocial personality disorder, attention deficit and hyperactivity, and other types of addictive disorders) psychiatric disorders are highly frequent within AUD patients compared with general population samples[9,10]. A psychiatric evaluation including screening and assessment for other psychiatric disorders is therefore mandatory when making a comprehensive evaluation of AUD patients.

Alcohol withdrawal syndrome (AWS) is a potentially life-threatening condition that can occur 6-24 h after sudden discontinuation of alcohol consumption and that can last up to 24-48 h after alcohol discontinuation. The clinical manifestations include increase in blood pressure and pulse rate, tremors, sweating, hyperreflexia, irritability, anxiety, headache, nausea and vomiting. The more aggressive manifestations can be characterized by delirium tremens, seizures, coma, cardiac arrest and death[11]. In the case of alcohol withdrawal delirium, symptoms occur generally 48-96 h after last drink but they can appear also after a longer period, up to seven days. Symptoms usually last for 48-72 h but they can persist for several

Table 2 CAGE questionnaire

1	Have you ever felt you should cut down on your drinking?
2	Have people annoyed you by criticizing your drinking?
3	Have you ever felt bad or guilty about your drinking?
4	Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?

Each response is scored as 0 or 1, with a higher score indicative of alcohol-related problems and a total of 2 or more clinically significant.

days[12]. Severity scores such as the revised Clinical Institute Withdrawal Assessment[13] are potentially useful in the assessment of AWS and in the clinical follow-up. They are, however, still not validated in the management of AWS[14].

Screening tools

Many screening tools have been developed and have been widely used, such as the CAGE questionnaire and the Michigan Alcoholism Screening Test and the Alcohol Use Disorders Identification Test (AUDIT)[15]. The CAGE questionnaire (Table 2) is an easy-to-use tool with an overall pooled sensitivity and specificity of 0.71 and 0.90, respectively, that has been suggested for use in general population screening[16]. In clinical practice, however, the "gold standard" remains the World Health Organization developed AUDIT[14,17] (Table 3). The AUDIT is a 10-item screening instrument with a sensitivity ranging from 51% to 97% and a specificity ranging from 78% to 96%[18]. Different scoring levels are possible: the maximum score is 40 and the screening test is considered positive if participants have a score $\geqslant$ 8 items for men up to age 60, or $\geqslant$ 6 for women, adolescents and men over age 60[19]. Shorter versions of this test have been developed: the AUDIT C[20], which includes the first three items, and a single screening question (the third item of the AUDIT: "How often do you have six or more drinks in one occasion?"), which should be followed by the whole AUDIT in the case of a positive answer[21].

Clinical manifestations

The clinical manifestations suggestive of harmful alcohol drinking include parotid enlargement, muscle wasting, malnutrition, Dupuytren's sign and symmetric peripheral neuropathy. Signs of extrahepatic alcohol-induced damage indicating cardiac (cardiomyopathy), muscular (skeletal muscle wasting), pancreatic (chronic pancreatitis and pancreatic endocrine and exocrine dysfunction), neurological (alcoholic neurotoxicity) and nutritional (malnutrition) involvement can occur in excessive alcohol intake[22].

Serum tests and markers of previous alcohol consumption

Serum gamma-glutamyltransferase (GGT) is the most frequently used marker for excessive alcohol intake. It has a specificity and sensitivity for alcohol consumption above 50 g/d of 75% and 73%, respectively[23]. GGT can, however, also be elevated in advanced fibrosis of any aetiology, in obesity and non-alcoholic fatty liver disease, and in relation to gender (males tend to present higher GGT values than females)[24,25].

Mean corpuscular volume (MCV) increases with excessive alcohol intake after 4-8 wk; however, its sensitivity is too low to justify its use as a single indicator. Moreover, given the long life-span of red blood cells (120 d) it is not suitable to detect short-term variations in alcohol consumption[26].

Another commonly used serum marker of previous alcohol consumption is carbohydrate deficient transferrin (CDT). The percentage of transferrin molecules that lack one or two complete N-glycan chains or that show incomplete N-glycan chains increases for a daily alcohol intake greater than 50 g for more than two weeks; therefore, CDT is considered an indicator for long-term alcohol consumption. CDT levels decrease after two to four weeks of abstinence, or more, depending on the baseline values[27]. This test has been considered to be a specific marker of chronic alcohol consumption (with a specificity and sensitivity for alcohol consumption above 50 g/d of 92% and 69%, respectively[23]) and a suitable tool to monitor alcohol abstinence. Moreover, the sensitivity of CDT increases without loss of specificity by combination with GGT and MCV[28].

The possibility of false positive values, however, raises concerns[29]. False positive values have been reported in genetic D variants of transferrin, inborn error of glycoprotein metabolism or severe liver disease[28]. In end-stage liver disease, CDT is not interpretable, independently of the aetiology.

Another possibility for alcohol use detection and monitoring comes from analysis of the hair. Alcohol itself is a volatile substance and not durably incorporated in the hair. By contrast, some of its metabolites, such as fatty acid ethyl esters (FAEE) and ethyl glucuronide (EtG), are durably incorporated and can be found in hair.

FAEE are derived from free fatty acids, triglycerides, lipoproteins or phospholipids, in the presence of ethanol. The sum of the concentration of four of these esters (ethyl myristate, ethyl palmitate, ethyl oleate and ethyl stearate) have been used as a marker of alcohol intake and for quantification. FAEE are incorporated into hair from sebum; therefore information regarding previous drinking and abstinence are not available with this method[30]. A range from 0.05 to 30 ng/mg hair has been found in a heterogeneous population, including non-drinkers up to patients in withdrawal treatment. A cut-off value of 0.5 ng/mg has been proposed for chronic excessive alcohol consumption with 90% sensitivity and specificity[31].

EtG is a phase Ⅱ-metabolite of ethanol mainly formed in the liver and represents 0.05% of the ingested ethanol. EtG is a non-volatile, water soluble conjugate that results from the reaction between ethanol and glucuronic acid, catalysed by the enzyme uridine diphosphate glucuronosyl transferase that is located in the endoplasmic reticulum[32]. EtG is detectable in blood and urine for a

Table 3 Alcohol use disorders identification test

	Questions	0	1	2	3	4
1	How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2-3 times a week	4 or more times a week
2	How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	Weekly	10 or more
3	How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4	How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Daily or almost daily	Monthly	Weekly	Daily or almost daily
5	How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	Daily or almost daily	Monthly	Weekly	Daily or almost daily
6	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Daily or almost daily	Monthly	Weekly	Daily or almost daily
7	How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Daily or almost daily	Monthly	Weekly	Daily or almost daily
8	How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Daily or almost daily	Monthly	Weekly	Daily or almost daily
9	Have you or someone else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10	Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

longer time than ethanol (respectively, 18 h and 80 h) and it can accumulate in the hair[33]. In patients undergoing a withdrawal treatment, EtG values ranged from 8 to 261 pg/mg head hair[34], although false negative results can occur[35].

The possible use of pubic hair in substitution of head hair, when they are not available, is a matter of debate. Paired analysis on head and pubic hair showed discrepant EtG levels in the two samples, suggesting that it is not advisable to switch from head to pubic hair. Moreover, the cut-off values used for EtG testing on head hair cannot be transposed to pubic hair. A possible advantage of pubic hair testing for EtG could be a higher sensitivity to identify social drinkers, although this point needs further validation[36].

EtG appears to be an interesting tool in investigating the history of alcohol intake since the segmental concentration of EtG correlates with the variations of alcohol consumption and with time of withdrawal, assuming a hair growth of 1 cm per month and comparing the alcohol consumption history to the EtG concentration in the different hair segments. Moreover, a strong positive correlation has been found between the EtG hair concentration and the amount of alcohol intake[34]. A concentration greater than 7 pg/mg has been suggested as being indicative of regular alcohol intake. More than 30 pg/mg can be considered as indicative of excessive and regular alcohol consumption[37]. Diagnostic sensitivity can be improved if EtG and CDT values are matched[38]. Therefore, this test is potentially useful for forensic purposes and in the clinical setting, for example in the evaluation for liver transplantation and in abstinence monitoring[34,39].

ALCOHOLIC LIVER DISEASE

ALD comprises different injuries, including simple steatosis, steatohepatitis with different grades of fibrosis and cirrhosis with its complications, such as hepatocellular carcinoma. These stages constitute a spectrum of injuries that can be simultaneously present in a patient in different combinations. The diagnosis of ALD is defined if there is clinical evidence of liver disease and laboratory abnormalities in combination with significant alcohol intake.

Steatosis is generally asymptomatic; it can be accompanied by disturbed liver tests and is reversible with abstinence. Twenty percent of patients who have developed steatosis and do not cease alcohol intake will likely develop fibrosis and cirrhosis[22]. Steatosis can evolve with the development of inflammation and hepatocellular injury to alcoholic steatohepatitis (ASH). These patients are generally asymptomatic but they can present nausea, vomiting and abdominal pain. Acute alcoholic hepatitis represents a severe type of ASH, which is characterized by abdominal pain, fever, increased white blood cell count, impaired blood clotting and jaundice.

In the case of cirrhosis, the physical findings are generally non-specific and independent from the aetiology. Gynecomastia and extensive spider naevi are, however, often present if alcohol is the predominant aetiological factor of the liver disease. In patients with decompensated cirrhosis, jaundice, ascites, variceal bleeding and hepatic encephalopathy can occur[14,40]. In addition, signs of extrahepatic alcohol-induced damage can further suggest a diagnosis of ALD and should be considered to provide appropriate treatment. It should be noted that some patients with histological features of ALD can be also asymptomatic.

As mentioned before, acute alcoholic hepatitis can also occur in the context of ASH, and it can present with recent onset of jaundice and/or ascites in a patient with excessive alcohol intake. Fever, with or without infection,

weight loss and malnutrition can be associated. Alcoholic hepatitis can progress to liver decompensation with ascites, encephalopathy and gastrointestinal bleeding, and it is a major risk factor of bacterial infection and type 1 hepatorenal syndrome[41].

The diagnostic assessment of the different manifestations of ALD include blood tests, imaging techniques and, when indicated, liver biopsy. The more advanced stages of the disease need a complete assessment with a more strict follow-up to evaluate the possible complications of liver disease, including hepatocellular carcinoma, as specified below.

Serum markers and prognostic scores

Increased liver test values, such as that of GGT, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are indicators of liver diseases, but they are not specific. In severe alcoholic hepatitis, however, AST is typically elevated 2-6 times the upper normal limit but rarely exceeds 300 IU/L, while ALT levels are commonly lower. Moreover, the AST/ALT ratio is generally > 2, although this finding is neither specific nor sensitive, especially in the cirrhotic stage[42]. In advanced liver disease, prolonged prothrombin time (PT), increased bilirubin levels or thrombocytopenia can occur.

In the case of acute alcoholic hepatitis, prognostic scores are useful to assess the short-term survival. The Maddrey discriminant function (DF), which includes PT and bilirubin, is the most used one. A DF $\geqslant$ 32 indicates a 1-mo survival without treatment of 50%-65%[43]. Other scores such as the Model for End-Stage Liver Disease, which includes bilirubin, creatinin, and international normalized ratio (INR), the Glasgow Alcoholic Hepatitis Score, which includes age, white blood cell count, urea, bilirubin, the patient's PT and the PT control value, and the ABIC score, which includes age, bilirubin, INR and creatinin, have been proposed, but need further validation in the context of ALD[14].

Imaging techniques

Ultrasound, computed tomography and magnetic resonance imaging can be used in the assessment of ALD. Although they do not contribute to defining the aetiology of liver disease, they can show steatosis and advanced stages of chronic liver disease up to cirrhosis and its complications, such as portal hypertension and hepatocellular carcinoma. Moreover, imaging techniques can rule out other obstructive biliary pathology or infiltrative and neoplastic disease of the liver[44]. Alcoholic cirrhosis can be suggested by a higher volume index of the caudate lobe, a more frequent visualization of the right posterior hepatic notch and smaller regenerative nodules[45].

Liver biopsy

There is a lack of consensus about performing liver biopsy in patients with a suspicion of ALD, given the absence of definitive evidence of the accuracy of liver biopsy in the diagnosis of ALD, the concerns regarding the representativity of liver biopsy and the related safety issues[46]. The recent EASL guidelines state that liver biopsy should not be performed in all patients affected by ALD, but that it is indicated to confirm the diagnosis and to assess the severity of the disease in cases of aggressive forms of ALD requiring intervention and in the case of possible cofactors contributing to the onset of liver disease[14]. Moreover, liver biopsy is useful in determining the outcome of patients affected by ALD, given that a histological diagnosis of ASH or cirrhosis is associated with an increase in mortality of at least 50%, in comparison with simple alcoholic steatosis[47].

The elementary histological lesions in ALD are macrovesicular steatosis, hepatocyte damage (ballooning), lobular inflammatory infiltrate and fibrosis, which can progress to cirrhosis[48]. These lesions can simultaneously be present in the same patient in various combinations and delineate simple steatosis, ASH and chronic hepatitis with fibrosis to cirrhosis[49]. Mallory's hyaline, megamitochondria, perivenular and perisinusoidal fibrosis can accompany these different stages of the disease.

The most common and precocious histological feature in ALD is macrovesicular steatosis. It is a lesion that needs follow-up since it is associated with a more rapid progression to fibrosis, and since cirrhosis can eventually occur in steatotic livers, also in the absence of ASH or fibrosis at the initial evaluation[50]. The coexistence of steatosis, hepatocyte damage (ballooning) and lobular inflammatory infiltration of polymorphonuclear neutrophils defines ASH. Mallory's hyaline and megamitochondria can be associated and are suggestive of active drinking, while the severity of the inflammation and cholestatic changes correlate with a poor prognosis[51]. ASH has, among the ALD-associated histological features, the highest risk of fibrosis progression and leads to cirrhosis in 40% of cases[52]. Steatohepatitis with periportal ductular reaction and cholestasis is often seen in severe ASH and is fairly specific for an alcoholic cause[53]. In this case, however, the presence of sepsis must be ruled out. If sepsis is excluded, cholestasis is associated with a worse clinical outcome and is an independent predictor of 3-mo mortality[54].

Semi-quantitative scoring systems to classify fibrosis in liver biopsies are commonly used in evaluating ALD, although they have not yet been validated in this specific disease. The most used ones are the METAVIR[55] and the Kleiner[56] scoring systems, which have a score for the fibrosis staging ranging from 0 (no fibrosis) to 4 (cirrhosis) (Table 4). Perisinusoidal arachnoid fibrosis ("chicken wire"-like fibrosis) is a scarring pattern characteristic of steatohepatitis (both alcoholic and non-alcoholic). A perivenular distribution of fibrosis is typical of alcohol-related damage, as opposed to periportal fibrosis which can be found in chronic viral hepatitis[57].

Non-invasive assessment of liver fibrosis

The research of non-invasive methods to assess the severity of liver fibrosis arouses great interest. Some methods

Table 4 Fibrosis staging systems

Stage	Metavir	Kleiner
0	No fibrosis	No fibrosis
1	Stellate enlargement of portal tract, but without septa formation	Perisinusoidal or periportal 1A: Mild, zone 3, perisinusoidal 1B: Moderate, zone 3, perisinusoidal 1C: Portal/periportal
2	Enlargement of portal tract but with rare septa formation	Perisinusoidal and portal/periportal
3	Numerous septa without fibrosis	Bridging fibrosis
4	Cirrhosis	Cirrhosis

include blood tests that combine different biomarkers of fibrosis. Originally developed for HCV-related chronic liver disease, these tests have been studied in ALD to set disease-specific cut-offs. The aim of using non-invasive methods for liver fibrosis is to identify patients with fibrosis, in order to start appropriate treatment to prevent the development of cirrhosis and to identify patients with cirrhosis who need monitoring of complications, such as portal hypertension and hepatocellular carcinoma[40].

The most promising tests in this field are FibroTest® (that combines alpha-2-macroglobulin, haptoglobin, GGT, ApoA1 and bilirubin, corrected for age and sex), FibrometerA® (that combines PT, alpha-2-macroglobulin, hyaluronic acid and age), and Hepascore® (that combines bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age and sex). The diagnostic value of these different tools has been studied in ALD and was comparable, with an AUROC around 0.80 for advanced fibrosis and around 0.90 for cirrhosis. Moreover, the non-invasive fibrosis tests have shown a potential value in predicting liver mortality, given the correlation between survival and baseline non-invasive fibrosis scores[58].

Another non-invasive method to detect liver fibrosis is elastography, which uses ultrasonic imaging to observe tissue shear deformation in response to an applied force, to measure liver stiffness (LS). In this setting, the most used methods are transient elastography (TE), acoustic radiation force impulse (ARFI) and shear wave elastography (SWE)[59].

Transient elastography is the most commonly used method at present, and it has been validated especially in patients affected by hepatitis C. Some studies, however, have been performed to assess the reliability of this technique in ALD. In the case of ALD, the boundary between F0-F3 and F4 appears to be the most important, since it permits the identification of patients who need a strict follow-up for the possible onset of varices and hepatocellular carcinoma[40].

A recent study using TE has indicated 12.9 and 22.6 kPa as cut-off values, respectively, of extensive fibrosis (≥ F3) and cirrhosis[60]. LS values ≥ 32.5 kPa are predictive of significant esophageal varices in ALD, higher than the cut-off for viral hepatitis (24.8 kPa)[61]. However, many factors can influence LS measurement in ALD. The presence of ASH and increased transaminase levels (especially AST > 100 IU/L) can influence LS measurement, independent of fibrosis stage. Moreover, alcohol intake can modify LS measurements, as it is increased in active drinkers and in relapsers and decreases after abstinence[62]. Therefore, LS measurement should be interpreted with caution in the diagnosis of ALD, but at the same time could be useful to assess an AUD and for the control of abstinence[63]. Moreover, a pharmacokinetic study showed that cytochrome P-450 isoenzymes and drug transporters tend to be up-regulated in alcoholics without advanced fibrosis (< 8.0 kPa) compared to healthy controls but are lower in severely increased LS (> 8.0 kPa). This study suggests a possible role of LS in pharmacokinetic predictions and individualized pharmacotherapy[64].

In clinical practice, it has been proposed that in the presence of increased LS (> 6 kPa), a correct assessment of the fibrosis stage can be performed only if AST < 100 IU/L and the patient is abstinent. If these criteria are met, LS values higher than 12.5 kPa indicate F4 cirrhosis. If AST is within the normal limits (and the patient is abstinent), both F3 and F4 can be detected (LS value between 8.0 and 12.5 kPa for F3 and ≥ 12.5 kPa for F4)[65].

The use of the more recently developed tools to detect LS, ARFI and SWE, is under research in order to assess their feasibility and the disease-specific cut-offs in ALD. A recent study enrolling ALD patients with histologically proven alcohol-related liver disease has proposed a cut-off value of LS measured by SWE of 13.1 kPa to rule out cirrhosis, although this issue needs to be confirmed in larger studies[66]. At present, although great effort has gone into developing various non-invasive tools, the TE® remains the most used and accurate test in this field.

CONCLUSION

Excessive alcohol intake can lead to a heterogenous spectrum of clinical manifestations that are included in the definition of "Alcohol Use Disorders". The multiple aspects of this disease, *i.e.*, complex psychiatric and somatic comorbidities, give rise to the need for a correct screening and diagnosis of the alcohol use disorder and of its clinical implications. Among these, ALD plays an important role and needs a detailed assessment, in view of the possible onset of complications and to correctly manage the patient.

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