UNIVERSITAT DE BARCELONA

Investigation on new aspects of diagnosis and natural history of severe forms of alcohol-associated liver disease

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Investigation on new aspects of diagnosis and natural history of severe forms of alcohol-associated liver disease

Doctoral thesis dissertation presented by Jordi Gratacós Ginès to apply for the degree of doctor at the University of Barcelona.

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ABBREVIATIONS AND ACRONYMS

ABIC	Age-Bilirubin-INR-Creatinine
ACLF	Acute-on-chronic liver failure
AFD	Alcoholic foamy degeneration
AH	Alcohol-associated hepatitis
ALD	Alcohol-associated liver disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUD	Alcohol use disorder
AUDIT	Alcohol use disorder identification test
DNA	Deoxyribonucleic acid
DSM-V	Diagnostic and statistical manual of mental disorders, fifth edition
EMA	European Medicines Agency
FDA	Food and Drug Administration
GAHS	Glasgow alcoholic hepatitis score
HSD17B13	Hydroxysteroid 17-beta dehydrogenase 13
MARC1	Mitochondrial amidoxime reducing component 1
MAUD	Medications for alcohol use disorder
MBOAT7	Membrane bound O-acyltransferase domain containing 7
mDF	Maddrey's discriminant function
MELD	Model for End-stage Liver Disease
MetALD	Metabolic and alcohol related/associated liver disease
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NLR	Neutrophil-to-lymphocyte ratio
PNPLA3	Patatin-like phospholipase domain-containing protein 3
REHALC	Registro Español de Hepatopatía por Alcohol
SAE	Serious adverse event
TM6SF2	Transmembrane 6 superfamily 2

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format. The thesis consists of 8 objectives (1 general and 7 specific) and 3 articles. Articles:

1. Jordi Gratacós-Ginès, Emma Avitabile, Carla Montironi, Alex Guillamon-Thiery, Helena Hernández-Évole, María-José Moreta, Delia Blaya, Silvia Ariño, Ana-Belén Rubio, Martina Pérez-Guasch, Marta Cervera, Marta Carol, Núria Fabrellas, Anna Soria, Adrià Juanola, Isabel Graupera, Pau Sancho-Bru, Alba Díaz, Mar Coll, Ramon Bataller, Pere Ginès, Elisa Pose. Alcoholic Foamy Degeneration, an Entity Resembling Alcohol-Associated Hepatitis: Diagnosis, Prognosis, and Molecular Profiling. Clin Gastroenterol Hepatol. 2023 Dec 6:S1542-3565(23)00970. Impact Factor (JCR22): 12.6; Q1 Gastroenterology & Hepatology.

2. Jordi Gratacós-Ginès, Pilar Ruz-Zafra, Miriam Celada-Sendino, Aina Martí-Carretero, Clàudia Pujol, Rosa Martín-Mateos, Víctor Echavarría, Luis-Enrique Frisancho, Sonia García, Mónica Barreales, Javier Tejedor-Tejada, Sergio Vázquez-Rodríguez, Nuria Cañete, Carlos Fernández-Carrillo, María Valenzuela, David Martí-Aguado, Diana Horta, Marta Quiñones, Vanesa Bernal-Monterde, Silvia Acosta, Tomás Artaza, José Pinazo, Carmen Villar-Lucas, Ana Clemente-Sánchez, Ester Badia-Aranda, Álvaro Giráldez-Gallego, Manuel Rodríguez, Pau Sancho-Bru, Joaquín Cabezas, Meritxell Ventura-Cots, Conrado Fernández-Rodríguez, Victoria Aguilera, Santiago Tomé, Ramon Bataller, Juan Caballería, Elisa Pose. Recurrent alcohol-associated hepatitis is common and is associated with increased mortality. Hepatology. 2024. In press. Impact Factor (JCR22): 14.0; Q1 Gastroenterology & Hepatology.

3. Jordi Gratacós-Ginès, Pol Bruguera, Martina Pérez-Guasch, Ana López-Lazcano, Roger Borràs, Helena Hernández-Évole, Maria-Teresa Pons-Cabrera, Anna Lligoña, Ramon Bataller, Pere Ginès, Hugo López-Pelayo, Elisa Pose. Medications for alcohol use disorder promote abstinence in alcohol-associated cirrhosis: Results from a systematic review and meta-analysis. Hepatology. 2024 Feb 1;79(2):368-379. Impact Factor (JCR22): 14.0; Q1 Gastroenterology & Hepatology.

THESIS SUMMARY (in Catalan)
RESUM DE LA TESI

Títol: Recerca en nous aspectes relacionats amb el diagnòstic i la història natural de formes de presentació greus de la malaltia hepàtica per alcohol

Introducció: la malaltia hepàtica per alcohol (MHA) és la causa principal de cirrosi al món i la primera causa de mort per malaltia hepàtica a Europa. L'hepatitis associada a l'alcohol (HA) és una forma de presentació greu de la MHA; el *gold-standard* pel diagnòstic és l'anàlisi histològica del fetge en un context clínic adequat, però actualment el diagnòstic sol ser basat en criteris clínics i analítics en la majoria de casos. Malgrat això, hi ha altres malalties hepàtiques, com ara la degeneració espumosa del fetge per alcohol (DEFA), que es poden presentar de manera similar i no s'acostumen a tenir en compte en el diagnòstic diferencial de l'HA. Pel que fa al pronòstic a llarg termini després d'un episodi d'HA, se sap que l'abstinència a l'alcohol hi té un paper fonamental. Tot i que els pacients que han patit una HA tenen tendència a reprendre el consum d'alcohol durant el seguiment, es desconeix la incidència i característiques dels episodis recurrents d'HA. A més, pel que fa a medicacions que promoguin l'abstinència a l'alcohol, se'n sap poc de la seva eficàcia i seguretat en pacients amb MHA.

Hipòtesis: la primera hipòtesi és que el diagnòstic diferencial de l'HA amb la DEFA és important de cara a establir el pronòstic i el tractament. La segona, que el consum d'alcohol en fases avançades de la MHA s'associa a importants complicacions clíniques com ara la recurrència de l'HA.

Objectius: de manera general, augmentar el coneixement respecte al diagnòstic i la història natural de les formes de presentació greus de la MHA. Específicament, determinar la prevalença de DEFA en casos de sospita clínica d'HA, buscar noves eines no invasives pel diagnòstic diferencial i determinar el pronòstic i signatura genètica a nivell hepàtic dels pacients amb DEFA. Així mateix, descriure la incidència, característiques i impacte pronòstic de les

recurrències d'HA; i determinar l'eficàcia i seguretat de medicacions pel TUA en pacients amb MHA avançada.

Mètodes: realització de 3 estudis científics. El primer, una anàlisi d'una cohort prospectiva de 230 pacients amb sospita clínica d'HA sotmesos a biòpsia hepàtica per a confirmació del diagnòstic i amb seguiment prospectiu a l'Hospital Clínic de Barcelona entre 2010 i 2020. El segon, un estudi retrospectiu a partir del registre espanyol de MHA, incloent 1285 pacients ingressats a 28 centres espanyols amb diagnòstic clínic o histològic d'HA entre 2014 i 2021. El tercer, una revisió sistemàtica amb meta-anàlisi sobre l'eficàcia de medicacions pel TUA en pacients amb cirrosi.

Resultats principals: respecte el primer estudi, en el 20% dels pacients amb sospita clínica d'HA es van observar troballes histològiques compatibles amb altres malalties, la més freqüent de les quals va ser la DEFA (8% del total de la cohort). Els nivells de triglicèrids, significativament més elevats en pacients amb DEFA, foren el biomarcador no invasiu amb la millor precisió diagnòstica (àrea sota la corba de 0,886 [0,807-0,964, interval de confiança del 95%]) per diferenciar la DEFA de l'HA. La supervivència a llarg termini dels pacients amb DEFA fou del 100% malgrat no tractar-se amb corticoides i el seu perfil d'expressió gènica, diferenciat del de pacients amb HA, va mostrar una sobre-expressió dels gens implicats en el metabolisme lipídic i la funció mitocondrial. En relació al segon estudi, observàrem que la incidència d'HA recurrent fou del 11% en un període de 8 anys. El major risc de desenvolupar una recurrència el tingueren els pacients més joves (per sota 50 anys), amb major consum d'alcohol (per sobre les 10 unitats al dia) i amb història prèvia de descompensacions per MHA. Els pacients que desenvoluparen HA recurrent tingueren pitjor supervivència al final del seguiment (61%, vs. 79% en pacients sense recurrència); de fet, el fet de presentar una HA recurrent es va associar de manera independent a la mortalitat (*hazard ratio* 1,55 [1,11-2,18]). Finalment, pel que fa al tercer estudi, es va posar de manifest l'escassetat d'estudis publicats en relació al tractament farmacològic del TUA en pacients amb cirrosi per alcohol. Malgrat l'alta heterogeneïtat dels estudis, la meta-anàlisi demostrà l'eficàcia de les medicacions pel TUA en l'assoliment de l'abstinència a l'alcohol en pacients amb cirrosi, amb una disminució del risc de consum actiu del 32% respecte a

placebo o altres comparadors. Dels 638 pacients inclosos en els braços de tractament actiu, només 5 desenvoluparen esdeveniments adversos greus possiblement o probablement relacionats amb les medicacions d'estudi.

Conclusions: la DEFA és una entitat diferenciada de l'HA, que es pot identificar a partir dels nivells de triglicèrids i que confereix un bon pronòstic a llarg termini. L'HA recurrent és freqüent, sobretot en pacients joves amb descompensacions prèvies, i s'associa a una alta mortalitat. El tractament farmacològic del TUA és eficaç i segur en pacients amb MHA avançada.

1. INTRODUCTION

1.1. ALCOHOL-ASSOCIATED LIVER DISEASE (ALD).

1.1.1. EPIDEMIOLOGY

Chronic liver diseases are a prominent cause of morbimortality at a global level, accounting for 4% of all deaths world-wide[1]. Alcohol-associated liver disease (ALD) is one of the most prevalent causes of liver disease. In fact, it is the leading cause of cirrhosis, accounting for almost 60% of cirrhosis diagnoses in Europe and North America[2–4].

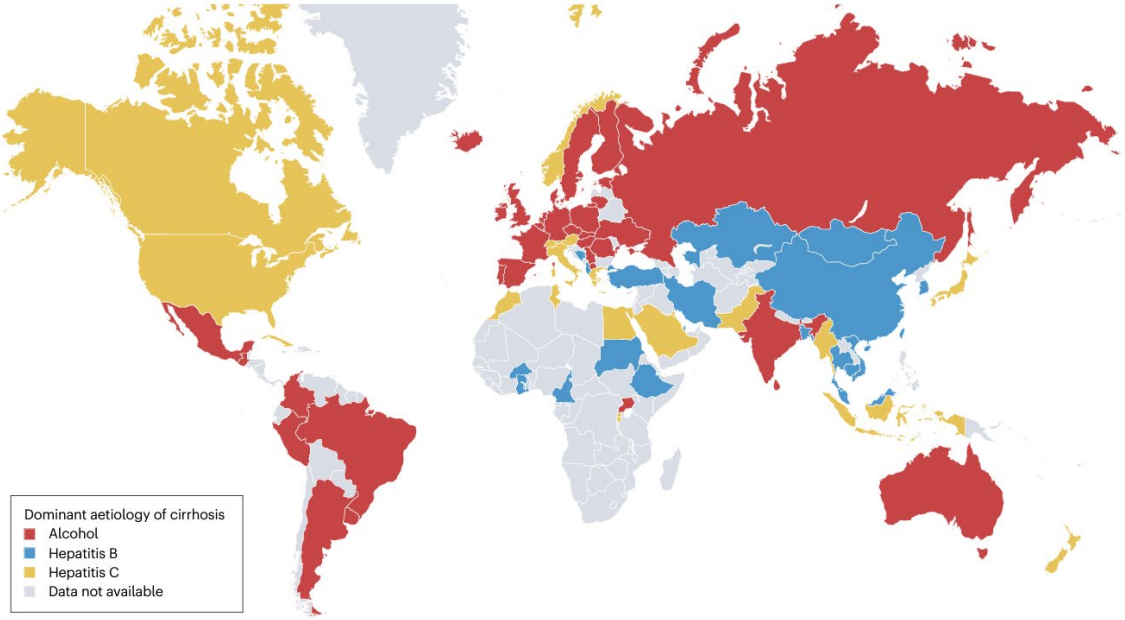


Figure 1. Dominant reported etiology of cirrhosis from 1993 to 2021.
Data were obtained from Alberts CJ, et al.[5] *Image reproduced from Huang DQ, et al.*[6]

Moreover, ALD is the second-leading cause of liver-related deaths world-wide and by far the leading cause in Europe[7]. Of note, ALD-related mortality has been increasing since the start of the COVID-19 pandemic in 2020[8,9], possibly owing to a shift in drinking patterns and a decreased accessibility to health care.

1.1.2. NATURAL HISTORY OF ALD

The term ALD includes several clinical phenotypes and different pathological liver alterations, ranging from asymptomatic disease in patients with steatosis to life-threatening complications in patients with advanced fibrosis and steatohepatitis.

The pathogenesis of ALD begins with the deposit of fatty droplets in the hepatocytes' cytoplasm as a result of alcohol metabolization; this phenomenon, called steatosis, occurs in most patients with prolonged heavy alcohol use[10]. In approximately one out of every four patients, the fat deposition in the liver generates a local intrahepatic inflammatory response, leading to the development of steatohepatitis. Sustained liver inflammation in the liver is known to be the main trigger of liver fibrosis, that consists in a progressive collagen deposition and extracellular matrix remodeling. Liver fibrosis deposition is the main driver of progression of liver disease due to alcohol[11]. In advanced stages of the disease, when fibrosis becomes prominent, collagen bridges develop between portal tracts and central veins and ultimately form nodules within the liver. This latter stage, known as cirrhosis, develops in 8-20% of patients with fibrosis during the natural history of the disease[12–14]. In the last phase of ALD, the liver architecture becomes markedly damaged causing an increase in intrahepatic vascular resistances and a subsequent increase in portal pressure[15].

Regarding the clinical presentation of alcohol-associated liver disease, two different stages may be distinguished: a first stage of asymptomatic or scarcely symptomatic disease, in which the patients may not have any clinical manifestation of liver disease, and the clinical stage of the disease, that is characterized by the development of complications of liver cirrhosis and portal hypertension and that includes a number of liver-related complications, such as ascites, hepatic encephalopathy, variceal bleeding, acute kidney injury and infections. The symptomatic stage of the disease, termed decompensated cirrhosis, arises in 20-40% of patients with cirrhosis[16]. Moreover, liver cirrhosis significantly increases the probability of developing hepatocellular carcinoma, which occurs in 3-10% of patients[16].

Alcohol-associated hepatitis (AH) is a specific variant of ALD clinically differentiated from decompensated cirrhosis that is characterized on pathological evaluation by steatosis, changes on the architecture of the hepatocytes and

infiltration of the liver by inflammatory cells[17,18]. Although the prevalence of AH is not fully known, it is believed to be around 10-35% of patients with fibrosis and active drinking[19,20]. AH will be discussed in further detail in the following section.

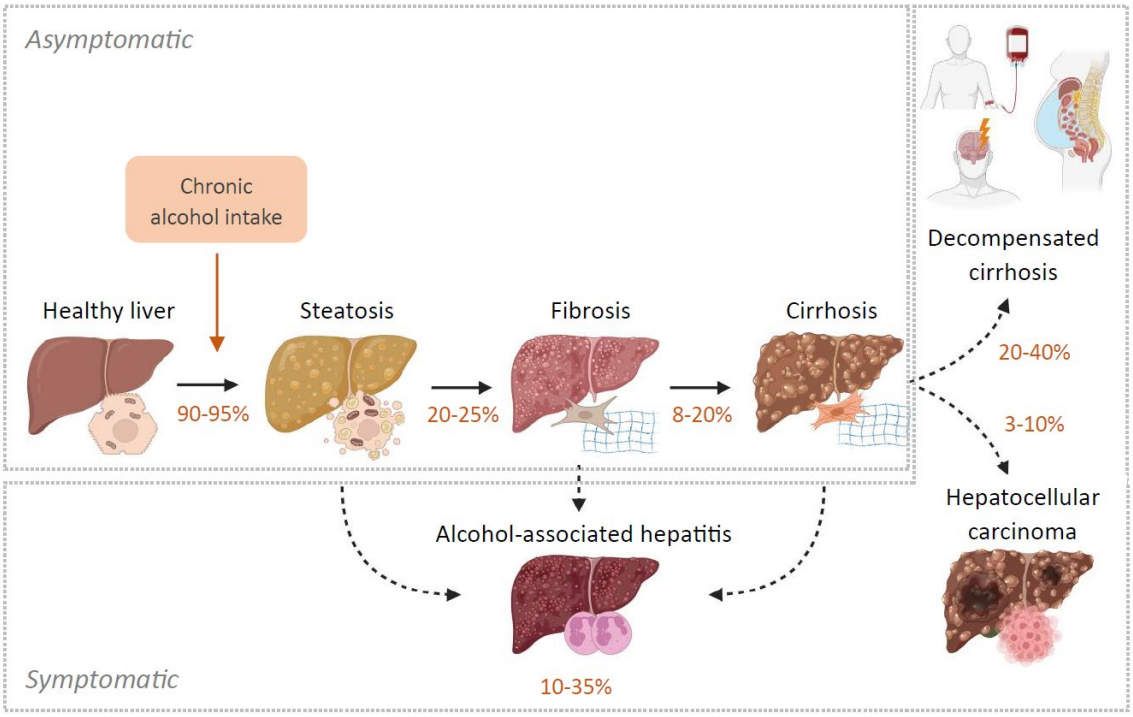


Figure 2. Natural disease course of alcohol-associated liver disease.
Original figure

Naturally, development and progression of ALD is dependent on alcohol intake[21,22]. However, most individuals who drink heavily will never develop an advanced liver disease, suggesting that other factors may contribute to disease progression. In the last few years there has been significant progress in understanding the pathogenesis and natural history of ALD. Genome wide association studies have discovered genetic risk factors of ALD, such as variations in the genes encoding patatin-like phospholipase domain-containing protein 3 (PNPLA3)[23–25], transmembrane 6 superfamily 2 (TM6SF2)[25–27] and membrane bound O-acyltransferase domain containing 7 (MBOAT7)[26]. Furthermore, population-based studies have identified specific patterns of alcohol consumption[28], female sex[29] and metabolic risk factors as important accelerators of disease progression[30–33]. Concerning metabolic risk factors, much has been studied in recent years; several studies, some of which derive from large

databases like the Genomic Alcohol Cohort Consortium or the United Kingdom Biobank, have found body mass index, diabetes and metabolic syndrome to be associated with the development of advanced liver disease both in ALD patients[19] and in the general population[25,33,34]. Moreover, the presence of metabolic risk factors has also been linked to increased overall and liver-related mortality in patients with ALD[31]. In fact, the high prevalence of coexistence of alcohol and metabolic risk factors as factors of liver disease led to the proposal of the new nomenclature of MetALD to refer to these patients with both etiological factors[35].

Other known risk factors for ALD progression are Hispanic ethnicity[36], tobacco smoking[37], and other underlying liver diseases[38–41]. Some protective factors for ALD have also been postulated, mainly genetic variants in hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) and mitochondrial amidoxime reducing component 1 (MARC1) genes[24,42–44], and coffee consumption[34,45,46].

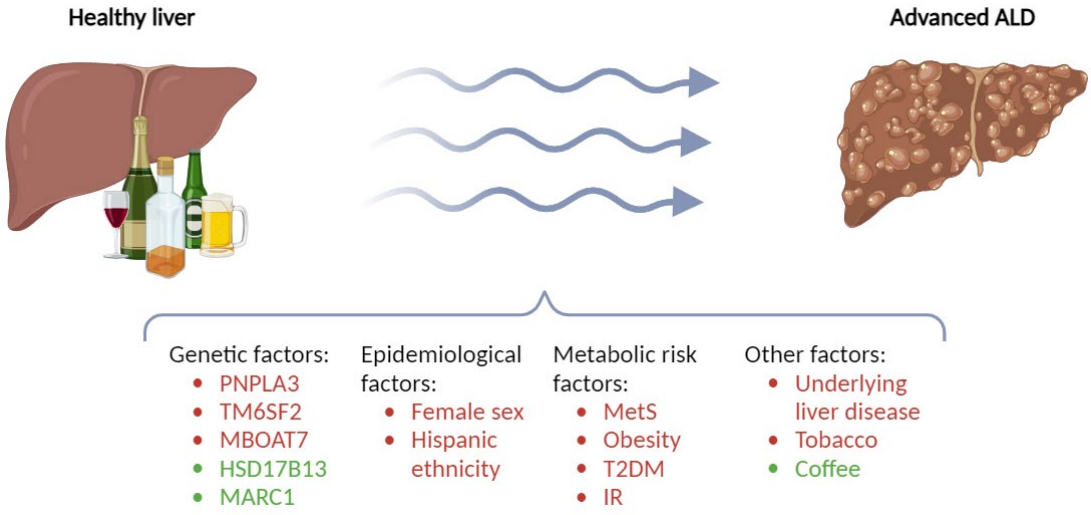


Figure 3. Modifying factors of ALD progression. Factors in green are protective; factors in red are risk factors.

Abbreviations: ALD, alcohol-associated liver disease; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; IR, insulin resistance; MARC1, mitochondrial amidoxime reducing component 1; MBOAT7, membrane bound O-acyltransferase domain containing 7; MetS, metabolic syndrome; TM6SF, transmembrane 6 superfamily 2; T2DM, type 2 diabetes mellitus; PNPLA3, patatin-like phospholipase domain-containing protein 3.

Original figure

Despite all the above-mentioned advances in the understanding of the disease natural history, ALD is still to this day commonly diagnosed in late stages of decompensated cirrhosis or during a hospitalization for AH[47]. This explains to a large extent why readmission and mortality rates remain so high in ALD.

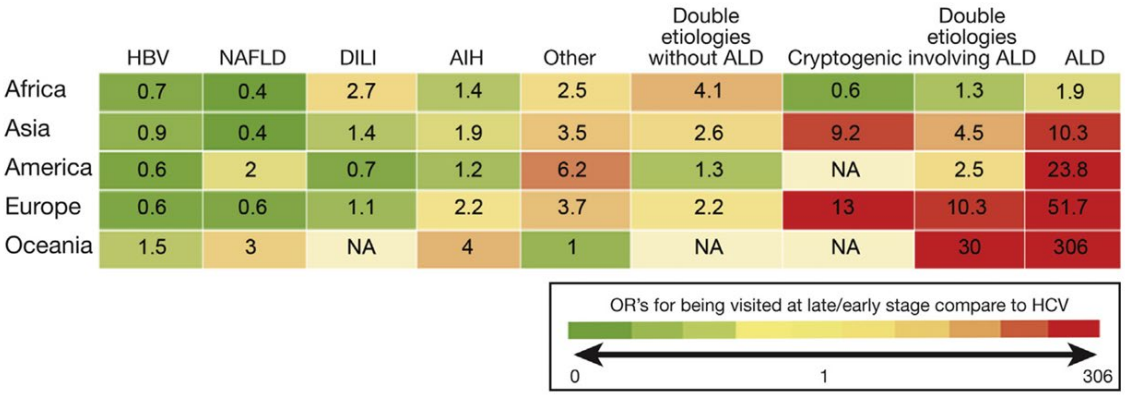


Figure 4. Heatmap expressing the likelihood of having a medical visit at advanced vs early stages compared with HCV by continent, being green the lowest likelihood and red the highest.

Abbreviations: AIH, autoimmune hepatitis; ALD, alcohol-associated liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

Reproduced from Shah ND, et al.[47]

1.2. ALCOHOL-ASSOCIATED HEPATITIS (AH)

1.2.1. BASIC CONCEPTS

AH is a clinical syndrome characterized by a recent onset of jaundice and malaise in patients with sustained heavy alcohol consumption and underlying ALD. Patients with AH often present with decompensated ALD and laboratory tests typically reveal high bilirubin levels and coagulopathy[20]. In severe cases of AH, bacterial infections and/or systemic inflammatory response trigger acute-on-chronic liver failure (ACLF), a syndrome characterized by multiorgan failure and associated to very high short-term mortality[48,49]. As previously stated, AH prevalence is not well-known but it was classically presumed to be around 10-

35% of patients with ALD and active drinking[19,20]. Recent data from North America point to an increasing incidence of AH, especially among young adults and women[36,50], and more pronounced since the start of the COVID-19 pandemic[51,52].

1.2.2. DIAGNOSIS

The diagnosis of AH is usually based on a combination of clinical and laboratory findings. The pathological substrate in the liver biopsy consists in a combination of steatosis, hepatocyte injury and inflammatory infiltration of the liver, which are the definitory criteria of steatohepatitis[17]. The pathological assessment is considered the gold-standard for the diagnosis of AH[16,53] in a compatible clinical setting.

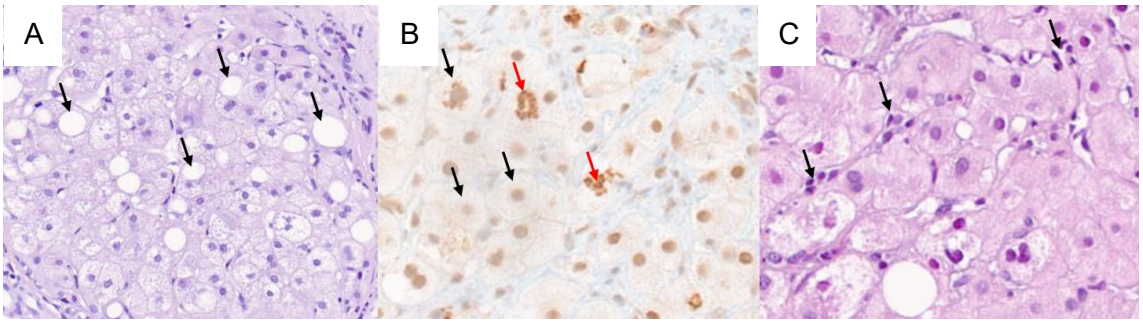
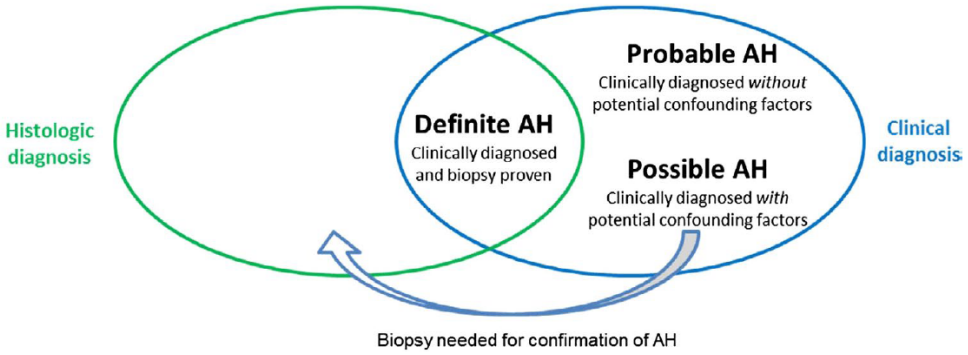


Figure 5. Liver pathology images showing the definitory criteria of AH. (A) Steatosis (black arrows), H&E staining; (B) Hepatocellular injury: hepatocyte ballooning (black arrows) and Mallory-denk bodies (red arrows), ubiquitin staining; (C) Inflammatory infiltrates (black arrows), H&E staining.
Abbreviations: AH, alcohol-associated hepatitis; H&E, hematoxylin and eosin.
Original image

In 2016, in an attempt to decrease the heterogeneity in the diagnosis of AH, a panel of experts from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) defined the diagnostic criteria of the disease: 1) onset of jaundice within the previous 8 weeks; 2) ongoing alcohol consumption of more than 40 grams of alcohol per day (female) or more than 60 grams per day (male) for a minimum of 6 months, with less than 60 days of abstinence before the onset of jaundice; 3)

serum total bilirubin level above 3 milligrams per deciliter; 4) aspartate aminotransferase (AST) level above 50 international units per liter, ratio of AST to alanine aminotransferase (ALT) over 1.5, and both AST and ALT values lower than 400 international units per liter; and 5) ruling out of potential confounding factors[54]. They also set the recommendation of performing a liver biopsy only in patients with diagnostic uncertainty. Based on these criteria, the NIAAA Consortium experts established a classification for patients with suspected AH according to the probability of having AH: 1) *definite AH,* when biopsy-proven; 2) *probable AH,* when meeting all criteria, not requiring biopsy confirmation; and 3) *possible AH,* when not meeting all criteria thus needing biopsy for confirmation of AH[54].



Clinical diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L
- Serum total bilirubin >3.0 mg/dL

Potential confounding factors

- Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
- Possible drug-induced liver disease (suspect drug within 30 days of onset of jaundice)
- Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
- Presence of atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80.

Figure 6. Consensus definitions for alcohol-associated hepatitis from the NIAAA Consortia.

Abbreviations: AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; NIAAA, National Institute on Alcohol Abuse and Alcoholism; SMA, smooth muscle antibody.

Reproduced from Crabb DW, et al.[16]

International clinical practice guidelines have adopted the recommendations of the NIAAA Consortium for the diagnosis of AH[16,53,55]. More recently published clinical guidelines on ALD from the American College of Gastroenterology have even suggested these criteria could be used instead of the liver biopsy assessment to decide patient eligibility for clinical trials[55], considering the contraindications of this population for transparietal liver biopsy and the low availability of a transjugular approach in the majority of the centers treating these patients. However, despite the support from international guidelines, it is well-known that the concordance of clinically-diagnosed AH and pathological signs of AH is not optimal. On one hand, in a considerably high proportion of patients, ranging from 10 to 45%, liver biopsy does not confirm the suspicion of AH[56–59], but rather supports an alternative diagnosis requiring a different treatment strategy[60,61]; on the other hand, in a study recently published by our group, 37% of patients not meeting the NIAAA Consortium criteria had actually signs of AH on pathological examination and had similar mortality compared to patients who met the criteria[59].

Several conditions are to be considered in the differential diagnosis of AH. Regarding non-alcohol-related conditions, biliary obstruction and viral hepatitis are fairly easy to rule out by performing abdominal ultrasound and serologies, respectively. Other etiologies of liver disease presenting as acute hepatitis, such as ischemic hepatitis, drug-induced liver injury, autoimmune hepatitis or Wilson's disease, may be harder to exclude and thus require a liver biopsy[20]. Furthermore, some alcohol-related entities may also mimic AH and are often overlooked in clinical practice, including foamy liver degeneration[62], alcoholic fatty liver with jaundice[63], advanced fibrosis or cirrhosis without significant steatosis or inflammatory infiltrates, and predominant pericellular fibrosis[64]. Importantly, all the above-mentioned conditions have significantly different prognosis compared to AH and do not benefit from corticosteroid treatment, so differential diagnosis is warranted.

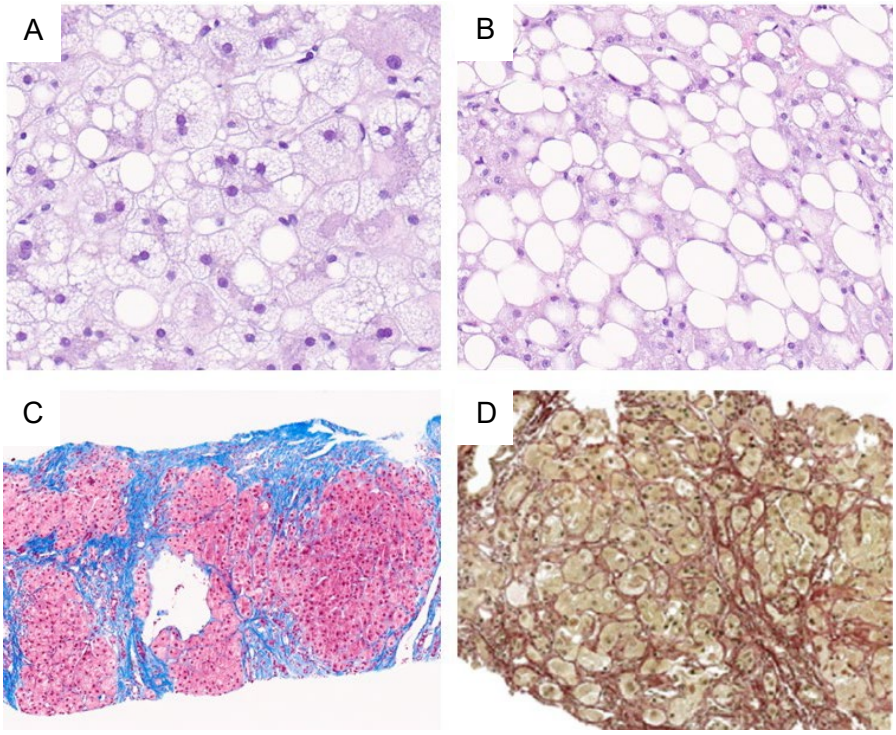


Figure 7. Liver pathology images of patients with alcohol-related liver conditions to be considered in the differential diagnosis of AH. (A) Alcoholic foamy degeneration (microvesicular steatosis), H&E staining; (B) Alcoholic fatty liver with jaundice (macrovesicular steatosis), H&E staining; (C) Cirrhosis without steatohepatitis, Masson's trichrome staining; (D) Predominant pericellular fibrosis, Sirius red staining.

Abbreviation: AH, alcohol-associated hepatitis.

Images A, B and C are original. Image D is reproduced from Lackner C, Stauber RE, et al.[64]

As a result of the diagnostic pitfalls of clinical criteria and the costs and invasiveness of the liver biopsy, several studies have investigated new non-invasive diagnostic biomarkers of AH. Serum keratin-18 fragments and circulating extracellular vesicles of sphingolipid cargo have been shown to be useful both for diagnostic and prognostic purposes in this setting[57,65–67].

To sum up, the diagnosis of AH is currently performed on the basis of combined clinical and laboratory data in most cases. Although very few studies have evaluated the correlation between the NIAAA consortium criteria and histological signs of steatohepatitis, recent evidence suggests this correlation is far from

optimal. Consequently, there is an unmet need to increase knowledge regarding the differential diagnosis of AH and to develop new non-invasive diagnostic biomarkers that perform better than currently used NIAAA criteria.

1.2.3. PROGNOSIS

Short-term

Survival during the first 3 months following an episode of AH is largely dependent on liver factors[68], regardless of alcohol consumption. Naturally, patients who continue drinking despite being diagnosed with AH have worse short-term prognosis; however, this is usually not the case as patients with AH tend to get admitted into the hospital for management and alcohol intake is then discontinued. The main drivers of short-term mortality in AH are: 1) liver disease severity at first presentation[69–71]; 2) development of infections and acute-on-chronic liver failure (ACLF)[49,72–74]; and 3) absence of treatment response[75,76].

Liver disease severity

Several prognostic scoring systems based on baseline factors have been developed to predict mortality in patients with AH. The most commonly used scores in clinical practice are the modified Maddrey's discriminant function (mDF)[69,77], the Age-Bilirubin-INR-Creatinine (ABIC)[78] and the Model for End-Stage Liver Disease (MELD)[71]. Two additional widely used scoring systems are the neutrophil-to-lymphocyte ratio (NLR)[79], which also uses baseline results, and the Glasgow Alcoholic Hepatitis (GAHS)[70], which combines baseline data with day 6-9 results. A modified GAHS, that incorporates NRL into the model, was also developed recently[79]. Although all these scores perform fairly well, recent data from a world-wide cohort suggest that MELD score is superior to all other scores to predict short-term mortality in AH[80].

MELD score was initially developed to predict survival in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunts[81] and was later used to improve patient allocation in the liver transplant waiting list[82]. It was subsequently validated as prognostic score in different cohorts of patients with varying etiologies and severity of liver disease[83], including patients with AH[71,84,85]. The MELD-sodium score, which is an updated version of the MELD score that includes serum sodium in the prediction model[86], does not significantly improve the survival prediction in patients with AH[80,85]. Similarly, the MELD 3.0, which is the most modern version of the MELD score and includes albumin level and female sex in the model[87], does not seem to improve the survival prediction either[88,89], although data from prospective studies are lacking.

Regarding other prognostic scores, mDF, which includes bilirubin level and prothrombin time, has been classically the most widely used, indicating severe disease when scoring >32[69,77]. However, it has the limitations of heavily relying on prothrombin time, which is poorly standardized across different laboratories, and not including a variable related to kidney function. The GAHS and the ABIC scores, which in addition to bilirubin and prothrombin time include age and renal function assessment (blood urea and serum creatinine, respectively), were subsequently developed to predict mortality longer term[70,78]. The NLR, which has been shown to predict mortality in a variety of digestive diseases, has a modest prognostic performance in AH but is associated to the development of acute kidney injury and infections in this population[79].

Scores	Variables included	Severity stratification
mDF	1. Bilirubin 2. Prothrombin time	- Severe if ≥32 - Mild to moderate if <32
MELD	1. Bilirubin 2. INR 3. Serum creatinine	- Severe if ≥21 - Mild to moderate if <21
ABIC	1. Bilirubin 2. INR 3. Serum creatinine 4. Age	- High risk of death if ≥9 - Moderate risk if 6.71-9 - Low risk if <6.71
GAHS	1. Bilirubin 2. Prothrombin time 3. Blood urea 4. Age 5. White blood cell count	- High risk of death if ≥9 - Moderate to low risk if <9
NLR	1. Neutrophil count 2. Lymphocyte count	- High risk of death if >8 - Moderate risk and prediction of response to steroids if 5-8 - Low risk if <5

Table 1. Characteristics of the main prognostic scoring systems in AH.
Abbreviations: ABIC; age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; GAHS, Glasgow alcoholic hepatitis score; INR, international normalized ratio; MELD, model for end-stage liver disease; mDF, Maddrey's discriminant function; NLR, neutrophil-to-lymphocyte ratio.
Original table

Disease severity strongly affects prognosis, as patients with more severe disease as per high values in any of the above-mentioned prognostic scoring systems have much higher short-term mortality than patients with low values. Consequently, stratifying AH based on severity is necessary for treatment decision-making[90]. The most commonly used thresholds for stratification are a mDF score of 32, or a MELD score of 21[71]. Patients with scores equal to or above these cutoffs are classified as having a severe AH; conversely, patients with scores below these cutoffs are categorized in the moderate AH group[16,53,55]. Patients with severe AH have mortality rates of 15-20% at 28 days and up to 30%

at 90 days[91–93]; these patients are usually treated with corticosteroids in the absence of contraindications[91] and are currently considered for inclusion in clinical trials[54]. On the other hand, patients with moderate AH have higher survival rates, are not candidates to corticosteroids and have currently no approved treatment with the exception of best supportive care and alcohol cessation[94]. Nonetheless, once regarded as having good prognosis, nowadays we know these patients have considerably high mortality as well, both short and long-term, ranging from 3 to 12% at 90 days and from 10 to 20% at 1 year[95–99]. Future studies to further investigate the natural history, prognosis and potential treatments for moderate AH are needed.

Infections and acute-on-chronic liver failure

Bacterial infections are common in patients with AH, especially in cases of severe AH, and may occur in almost 50% of patients[74,91,92]. They may be present at admission or develop during hospitalization[74,100]. The most common sites of infection are the lungs, the ascitic fluid, the bloodstream and the urinary tract[74,91,92] .

The occurrence of infections is associated with increased short-term mortality[100,101], particularly in patients who do not receive appropriate first-line antibiotic treatment[73]. Whether corticosteroid therapy increases the risk of infection in AH is still a matter of debate. On one hand, in a sensitivity analysis of patients included in a clinical trial of prednisolone vs pentoxifylline, patients treated with prednisolone developed infections more frequently specifically after treatment, and had more serious infections[100]. On the other hand, a meta-analysis of randomized trials published in 2016 did not find an increased rate of bacterial infections in patients treated with steroids[102]. Furthermore, data from a prospective study in severe AH indicate that the main contributor to the development of bacterial infections is precisely the absence of response to corticosteroid treatment[74], suggesting that early improvement in liver function may be a key factor in preventing infections and that the benefit of steroids in the adequate subset of candidate patients outweighs its risks. Nonetheless, it must

be noted that there is some evidence indicating that fungal infections are more prevalent in patients treated with steroids[102], including invasive aspergillosis, which has been shown to be an ominous complication in this population[103].

Due to the importance of bacterial infections in the prognosis of patients with AH, a clinical trial using prophylactic amoxicillin-clavulanate was performed to reduce the incidence of infections and subsequently improve survival[92]. Unfortunately, in spite of a reduction in infection rates, no survival benefit was observed. Similarly, in an intervention cohort of patients with AH treated with rifaximin, infection rate was lower compared to a historical cohort but survival was similar[104]. A recently published, open-label, randomized trial from India using fecal microbiota transplantation reported a reduction in infection rates and improved survival at 1 year compared to prednisolone[105]. Nevertheless, mechanistic effects of fecal microbiota transplantation might go beyond the prevention of infections and need to be further evaluated in the upcoming years.

One possible complication occurring in patients with severe AH which is often triggered by infection is ACLF[73]. Various diagnostic criteria of ACLF and staging systems have been proposed by several international scientific associations depending on the epidemiology and characteristics of liver diseases in specific areas of the world[72,106–108]. Despite apparent differences, there is an overall consensus on ACLF being characterized by a marked deterioration in hepatic function accompanied by extrahepatic organ failure in a patient with underlying chronic liver disease[109]. Patients who develop ACLF have notably decreased survival, which is further decreased with every added organ failure. In the landmark CANONIC study, ACLF either prevalent or incident was observed in 31% of patients with cirrhosis admitted into the hospital for an acute decompensation of their liver disease; 28-day mortality among patients with ACLF was 34%[72]. Of note, different prevalences and mortality rates have been reported depending on the definition of ACLF used.

Organ failure	Definition	28-day mortality
Liver	- Bilirubin ≥12 mg/dL	6%
Kidney	- sCr ≥2 mg/dL or RRT	16%
Brain	- HE grades III and IV	8%
Coagulation	- INR ≥2.5	5%
Circulation	- Use of vasoactive drugs	7%
Lungs	- PaO_2/FiO_2 ≤200 - SpO_2/FiO_2 ≤214	7%
Stages	**Definition**	**28-day mortality**
No ACLF	- Absence of organ failure - Single organ failure + sCr <1.5 mg/dL + no HE	5%
ALCF grade 1	- Single kidney failure - Single brain failure + sCr 1.5-1.9 mg/dL - Single organ failure (liver, coagulation, circulatory or lung) + sCr 1.5-1.9 mg/dL and/or HE grade 1-2	20%
ALCF grade 2	- 2 organ failures	30%
ALCF grade 3	- 3 organ failures or more	80%

Table 2. Organ failures and staging in ACLF, and associated 28-day mortality, according to the definitions from the European Association for the Study of the Liver. Mortality rates in the top half of the table are considering single organ failures. Abbreviations: ACLF, acute-on-chronic liver failure; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; PaO2, partial pressure of arterial oxygen; RRT, renal replacement therapy; sCr, serum creatinine; SpO2, pulse oximetric saturation.

Original table, data from Moreau R, et al.[72] *and Moreau R, et al.*[110]

When specifically focusing on ACLF in patients with AH, data is relatively scarce and limited by the fact that few liver biopsies are performed in patients with ACLF, which in turn tend to have notably altered liver tests consistent with the diagnostic criteria of AH from the NIAAA Consortium. In the PREDICT study, where the diagnosis of AH was based on clinical criteria, the most common precipitants of ACLF were AH and bacterial infection, either alone or in combination with other events[73]. In the CANONIC study, AH was defined based on liver biopsy examination; unfortunately, very few biopsies were performed and thus the real prevalence of AH in this study is unknow[72]. However, the fact that heavy alcohol use was a leading precipitant of ACLF possibly reflects a rather high prevalence of AH in this cohort.

Possibly, the most important study addressing the epidemiology and prognosis of ACLF in patients with AH was published in 2018 by Sersté and colleagues[48], who studied consecutive patients with biopsy-proven severe AH admitted to the Liver Unit of Erasme Hospital, in Brussels. Authors reported a 48% prevalence of ACLF at admission and a 18% incidence of ACLF during hospitalization. Mortality at 28 days was 54% for prevalent ACLF and 23% for incident ACLF. Furthermore, in a recently published study evaluating the short-term prognosis of patients admitted to the intensive care unit due to ACLF, patients with severe AH-related ACLF had higher mortality and severe AH was independently associated with an increased risk of death even after adjusting for age, MELD score and presence of infection[49].

In summary, infections and ACLF are common in patients with AH and markedly impact short-term prognosis.

Response to treatment

Treatment of AH is based on a combination of general measures and specific therapy for alcohol-induced liver injury. General measures may relate to nutritional support[111,112], treatment of concomitant clinical decompensations of liver cirrhosis, such as endoscopic band ligation for esophageal variceal bleeding or terlipressin for hepatorenal syndrome, or prevention and treatment of comorbid

conditions, such as thiamine for Wernicke's encephalopathy or antibiotics for bacterial infections. Specific treatment of liver injury in the setting of AH has been extensively studied with rather disappointing results overall. Despite several trials have been conducted aiming at different pathophysiological mechanisms, only glucocorticoids have consistently been shown to improve short-term survival in AH[69,91,113].

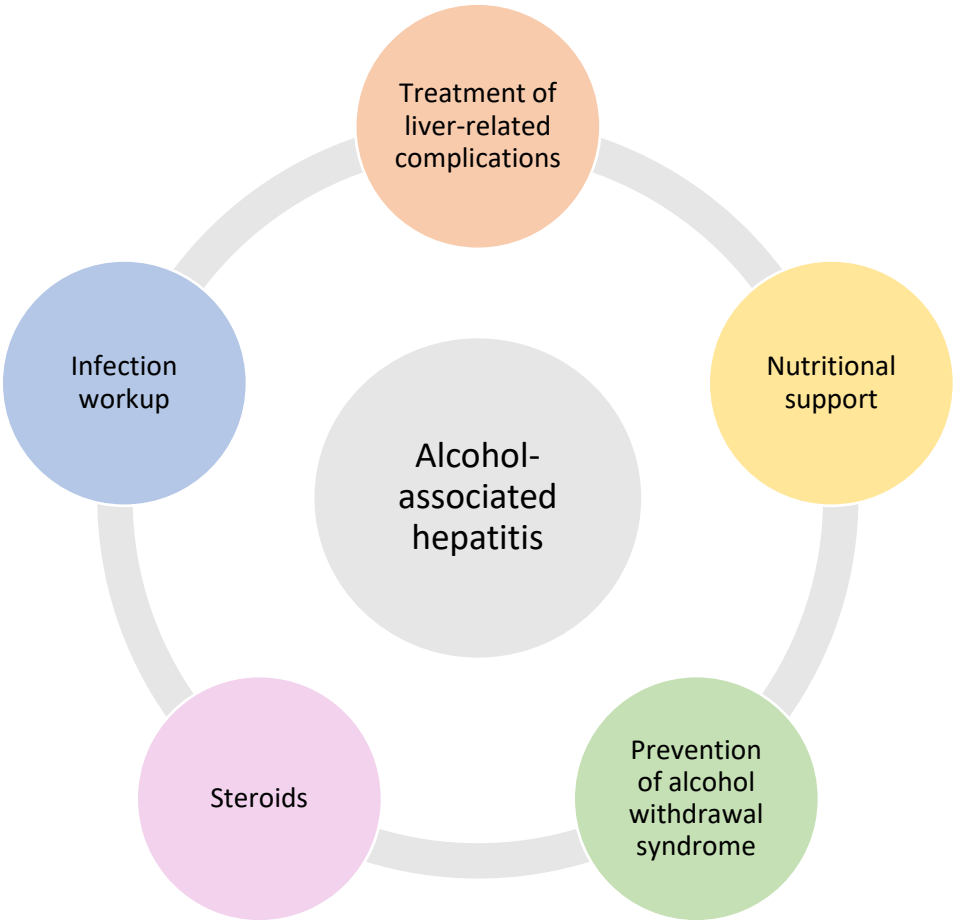


Figure 8. Management of alcohol-associated hepatitis.
Original figure

Several studies have assessed the prognostic implications of early response to treatment with corticosteroids in AH. Early improvements in liver function, either assessed by serum bilirubin level changes alone or by MELD score, were shown to predict short-term mortality in AH[75,84]. Thereafter, a dynamic prognostic model,

the Lille model, which combines baseline pretreatment data with serum bilirubin levels after 7 days of steroid treatment was developed to assess survival at 6 months[76]. Based on a cutoff of 0.45 in this model, patients are categorized into two groups: corticosteroid responders (Lille score below 0.45) and corticosteroid non-responders (Lille score of 0.45 or greater). Responders had a 6-month survival of around 85%, compared to 25% in non-responders[76]. A later published meta-analysis of individual patient data from 5 randomized controlled trials further subclassified response in complete response, partial response and null response, on the basis of the percentile distribution of the Lille score. In this subclassification, the survival benefit was observed both in partial and complete responders (Lille score <0.56)[113].

However, the best strategy for predicting mortality in patients with severe AH is possibly a combination of baseline prognostic scores, for instance MELD, and dynamic scores based on treatment response, such as the Lille model. This approach was presented by Louvet and colleagues in an article published in Gastroenterology in 2015[114].

Of note, highly selected patients with AH not responding to corticosteroids may be candidates for an expedited pathway to early liver transplantation[115,116]. Early liver transplantation is the most effective treatment for severe AH, as it modifies the natural history of the disease; consequently, it is the treatment option with the greatest impact on survival.

Long-term

Prognostic factors of long-term survival are different from those of short-term survival. Studies assessing long-term risk factors of death in AH have showed inconsistent results regarding the association between important short-term predictors of mortality, such as the MELD score, and survival at one year or later. However, these studies have been consistent in indicating that the most important factor influencing long-term prognosis after surviving an episode of AH is sustained alcohol abstinence[96,117,118].

Impact of alcohol abstinence

Patients who survive an episode of AH and achieve prolonged alcohol abstinence have increased survival compared to patients who resume alcohol consumption. In a retrospective analysis of patients included in several prospective studies with biopsy-proven AH, complete abstinence was independently associated with increased survival at the date of last follow-up[118]. However, abstinence in this study was assessed retrospectively by patient or family member interview or by reviewing the patients' medical records, which could introduce bias. In a contemporary study performed in France including patients with biopsy-proven severe AH in which data on alcohol consumption was collected prospectively, authors reported that alcohol consumption below 30 grams of alcohol per day during follow-up was independently associated with survival in patients who were alive after 6 months, which is in line with the previously-discussed article. Additionally, authors observed a dose-dependent effect of alcohol on the probability of death at the end of follow-up[117]. In an interesting study performed a few years later only including patients with mild to moderate AH, 5-year survival rates of abstinent and non-abstinent individuals were significantly different, being 74% and 41% respectively[96]. The fact that studies both in severe AH and mild to moderate AH observed an association between alcohol abstinence and long-term survival further supports the idea that long-term prognosis in AH is predominantly determined by other factors different from disease severity at presentation.

In spite of the importance of alcohol abstinence in the prognosis of patients with AH, the percentage of patients achieving alcohol abstinence after being discharged from the hospital for an episode of AH is markedly low. In the studies discussed in this section, complete abstinence after 5 years was 30%[96] and 39%[118]. In the prospective French study, the definition of abstinence was based on the absence of alcohol relapse (minimum 30 grams of alcohol per day) and thus abstinence rates at 5 years were higher, around 65%[117]. In another study performed in the United States in which alcohol consumption status was assessed at 30 days, complete abstinence was reported in around 50% of

patients[119], indicating that a significant percentage of relapses occur early after being discharged from the hospital.

AH recurrence

As returning to alcohol consumption after an episode of AH is common, the idea that some patients might develop recurrent episodes of AH during follow-up seems reasonable. Surprisingly, very few studies have investigated this hypothesis. In a retrospective study using a large inpatient database from the United States, the reported rate of readmission at 30 days due to recurrent AH was 16%[120]. However, this study had two important drawbacks: 1) patients with AH were selected based on International Classification of Diseases-9th revision codes and there was no verification on whether these patients met the NIAAA criteria for probable or definite AH; and most importantly 2) 30 days does not seem to be enough time to assess recurrence of AH considering that patients necessarily have to go through a recovery phase and a subsequent new alcohol-induced liver injury. Similarly, in another study performed in the United State in which readmission causes were also assessed at 30 days, incidence of recurrent AH was 19% in the test cohort (retrospective cohort) but only 2% in the validation cohort (prospective cohort)[119]. The inconsistent results between the two cohorts might again reflect the limitation of using diagnostic codes and assessing recurrence in such short follow-up.

To date, the only study specifically aimed at evaluating recurrent AH was published by Potts and colleagues in 2013[121]. In this study, medical records were retrospectively reviewed to identify patients with severe AH based on clinical and laboratory criteria comparable to the current NIAAA criteria. Ten out of 56 patients (18%) developed recurrent AH during follow-up. Mean interval between first and second episodes of severe AH was 19 months. Furthermore, recurrent AH episodes were more severe compared to first episodes in terms of MELD score and 4 out of 7 patients (57%) with data on clinical status died during follow-up.

While the hypothesis of recurrent AH being notably prevalent seems plausible on the basis of high alcohol recidivism after first AH, larger studies with multicentric design are needed to adequately assess frequency, risk factors and survival.

1.3. ALCOHOL USE DISORDER

1.3.1. BASIC CONCEPTS. ASSOCIATION WITH LIVER DISEASES.

Alcohol use disorder (AUD) is a chronic and usually relapsing condition[122] characterized by persistent alcohol consumption despite negative consequences. The term AUD was introduced in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) from the American Psychiatric Association[123] with the objective to unify the concepts of abuse and dependence, and to reduce stigmatization by avoiding words such as “alcoholism” or “alcoholic”[124]. According to the DSM-V, AUD is defined as a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 out of 11 criteria, occurring within a 12-month period. Depending on the number of criteria met, AUD can be classified in 3 groups of severity: mild (2-3 criteria), moderate (4-5 criteria) or severe (6 or more criteria). Mild to moderate AUD relates to abuse, while severe AUD includes alcohol dependence.

1. Alcohol is often consumed in larger amounts or over a longer period that was intended.
2. Desire or unsuccessful efforts to cut down or control alcohol use.
3. A substantial amount of time is spent in activities needed to obtain alcohol, use alcohol, or recover from the effects of alcohol.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfil responsibilities at work, school or home.
6. Continued alcohol use despite related social or interpersonal problems.
7. Stopping or reducing social, occupational or recreational activities due to alcohol use.
8. Recurrent alcohol use in physically hazardous situations.
9. Continued alcohol use despite knowledge of a physical or psychological problem likely to be caused or exacerbated by alcohol.
10. Tolerance, defined by either a need for markedly increased amounts of alcohol to achieve intoxication or desired effect or a markedly reduced effect with continued use of the same amount of alcohol.
11. Withdrawal, manifesting as either the alcohol withdrawal syndrome or alcohol, or a closely related drug, is taken to relieve or avoid withdrawal symptoms.

Table 3. Criteria for alcohol use disorder from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). Alcohol us disorder is diagnosed when 2 criteria are met.
Adapted from MacKillop J, et al.[125]

AUD is among the most prevalent mental disorders, affecting about 5% of adults globally[126]. It is more common in male individuals, although the sex gap has been narrowing in recent years, and in upper-middle to high-income countries[126], where prevalence could be as high as 10%. AUD is associated with a high burden of disease, with more than 3 million attributed deaths per year worldwide[127].

Furthermore, it is the leading risk factor for both death and disability-adjusted life-years in population below 50 years of age[127].

Among all diseases related to alcohol consumption, digestive diseases are the leading causes of alcohol-attributable deaths. Moreover, the contribution of alcohol to deaths from liver diseases is the highest among any known condition, around 50%[126], reflecting the strong existing link between AUD and liver disorders.

Naturally, screening for AUD in the general population is of paramount importance if we want to reduce the global burden of diseases worldwide, particularly of ALD. Strong evidence supports the efficacy of screening and brief intervention for AUD in primary care[128–130]; unfortunately, it has important barriers for its implementation in a real-life setting[131]. Another strategy that may be more clinically actionable and cost-effective to implement is to perform AUD screening in groups at increased risk, such as patients with psychiatric disorders or other drug addictions[132]. Many tools have been developed and validated for screening of AUD; unfortunately, none of them has been specifically tested in patients with advanced liver disease, in whom reliability could be lower, especially if hepatic encephalopathy is present[133]. The time-line follow back is the gold-standard, but it is time-consuming. Consequently, another questionnaire, the Alcohol Use Disorder Inventory Test (AUDIT) has become the most widely used[134]. It comprises 10 short questions and only takes about 5 minutes to perform, so it may be applicable in hepatology clinics, especially considering the high prevalence of AUD in patients with liver disease and the markedly negative impact that alcohol abuse has on the prognosis of this population. In fact, the systematic use of AUDIT-C (a shorter version of AUDIT, of only 3 questions) has been shown to increase the detection of AUD in liver transplant recipients by 40% with respect to hepatologists assessment alone[135]. The simple act of performing an AUDIT and providing feedback to the patient is useful to reduce alcohol consumption in the community[136] and might also have beneficial effects for patients with liver diseases.

In regards to treatment of AUD, the two main goals are the prevention and treatment of alcohol withdrawal syndrome in the short term, and the induction and

maintenance of alcohol abstinence in the long term. For the purpose of this doctoral thesis, hereafter AUD treatment will be used to refer to treatment for induction and maintenance of abstinence.

An optimal treatment for AUD in patients with ALD should be on-site, integrated, flexible and long-term. Moreover, despite the growing evidence on the efficacy of harm-reduction strategies in the general population[137], the goal in patients with ALD should be complete alcohol abstinence[138]. The two treatment mainstays are psychosocial interventions and pharmacological therapy, which are most effective when combined[139].

1.3.2. PSYCHOSOCIAL INTERVENTIONS

Psychosocial interventions focus on promoting motivation to stop drinking. Several strategies are available: brief intervention and counseling, psychotherapy (motivational enhancement therapy and cognitive behavioral therapy), peer-support groups and contingency management. These strategies have proven to be very effective in reducing harmful drinking in primary healthcare[129] and have even been shown to reduce the risk of developing ALD[140]. Nevertheless, information on effectiveness in special key groups, such as comorbid drinkers, is limited[129].

Several studies have investigated the use of psychosocial interventions in patients with liver diseases. Most of these studies included patients with AUD and viral hepatitis infection with or without advanced fibrosis[141–144]. In this setting, psychotherapy alone either with motivational enhancement or cognitive behavioral therapy has been shown to be effective in induction but not in maintenance of alcohol abstinence[145]. These strategies might be less effective in patients with ALD, who by definition have a more severe AUD. Surprisingly, very few studies have addressed this question in this subpopulation. Moreover, results are inconsistent. In a classical clinical trial including hospitalized patients with alcohol-related digestive conditions (most of them with cirrhosis), a 2-hour in-hospital motivational intervention did not improve alcohol abstinence at 3 months compared to medical care alone[146]. In contrast, in another trial in liver transplant

candidates, authors reported a reduction in drinks per drinking day in patients receiving motivational enhancement therapy[147].

Besides the effectiveness of psychosocial interventions, treatment adherence is another important aspect worth considering. Adherence to these approaches is highly variable and influenced by poor physical condition[133], which is common in patients with ALD. Consequently, the integration of psychosocial interventions with the routine medical care of these patients in the same clinic has shown to be feasible and to increase treatment adherence[148].

More complex integrated care models developed in recent years delivering both psychosocial interventions and pharmacological therapies to patients with ALD by means of a multidisciplinary team have been associated with increased abstinence rates[149,150] and even survival in some settings[151].

1.3.3. PHARMACOLOGICAL INTERVENTIONS

Several anticraving medications for AUD (MAUD) have demonstrated to be effective either alone or in combination with psychosocial interventions. Approved medications by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of AUD are disulfiram, naltrexone and acamprosate. Nalmefene is also approved by the EMA. Additionally, sodium oxybate is only approved for AUD in Italy and Austria, and baclofen in France.

Disulfiram was the first treatment to be approved for AUD and is still widely used by addiction specialists. It is an inhibitor of acetaldehyde dehydrogenase and thus causes distressing symptoms when consumed together with alcohol, acting as a dissuasive medication. Disulfiram should be avoided in patients with ALD, especially those with advanced fibrosis, as it may cause acute liver failure and death[152,153]. Naltrexone is an opioid receptor antagonist that acts by reducing dopamine release and decreasing reward sensation. Despite being issued a warning by the FDA due to its potential to induce hepatocellular injury, a recent observational study has suggested it is safe and effective in patients with ALD[154]. Furthermore, an unpublished randomized clinical trial in patients with cirrhosis

presented in the International Liver Congress 2023 reported increased alcohol abstinence and a reduction in alcohol lapse at 3 months in patients treated with naltrexone compared to placebo without significant differences in the percentage of side effects[155]. Nalmefene is another opioid receptor antagonist that has been shown to reduce heavy drinking; therefore, it is indicated for harm-reduction strategies[156]. Information regarding its use in patients with ALD is lacking. Acamprosate is a N-methyl-D-aspartate glutamate receptor antagonist that reduces withdrawal-induced hyper-glutamatergic states which are thought to trigger relapse. Data on efficacy and safety in patients with ALD is limited to retrospective cohorts[157]. Sodium oxybate is a gamma-aminobutyric acid agonist that reduces craving in patients with AUD[158]. However, there are some concerns regarding potential abuse of the drug, especially in patients with psychiatric comorbidity[159]. Efficacy and safety in patients with ALD are unknown. Finally, baclofen is a selective gamma-aminobutyric acid B receptor agonist approved for spasticity conditions. It has an inhibitory effect on the dopamine network reducing alcohol-reinforced behaviors. Several cohort studies and randomized clinical trials support its efficacy and safety in patients with alcohol-associated cirrhosis[160].

Many other medications have been tested in AUD showing signs of beneficial effects but have not been granted approval so far for this indication. Some examples are topiramate, ondansetron and gabapentin.

Lastly, fecal microbiota transplantation has shown promising preliminary results for the treatment of AUD both in animal models and humans[161,162].

Drug	Action mechanism	Evidence	Safety in ALD
Disulfiram	Inhibitor of ADH	Moderate	Caution in early stages, CI in advanced stages
Naltrexone	Opioid receptor antagonist	Moderate	Black box warning but probably safe
Nalmefene	Opioid receptor antagonist	Moderate	Probably safe
Acamprosate	NMDA glutamate receptor antagonist + GABA mimetic	Moderate	Safe, but caution if renal dysfunction
Sodium oxybate	GABA agonist	Low	Probably safe
Baclofen	$GABA_B$ receptor agonist	Low	Probably safe
Topiramate	$GABA_A$ receptor agonist, among others	Moderate	Probably safe
Ondansetron	Serotonin 5-HT_3 receptor antagonist	Low	Probably safe
Gabapentin	Inhibition of calcium currents via high-voltage-activated channels	Low	Probably safe

Table 4. Main characteristics of currently available medications for alcohol use disorders.

Abbreviations: ADH, acetaldehyde dehydrogenase; ALD, alcohol-associated liver disease; CI, contraindication; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; 5-HT_3, 5-hydroxytryptamine 3.

Original table

In spite of the absence of high-quality evidence, particularly clinical trials, regarding the effects of MAUD in patients with ALD, recent cohort studies have found an association between MAUD and long-term survival in patients with cirrhosis[163–165]. Moreover, the use of these drugs in patients with compensated alcohol-associated cirrhosis is cost-saving, meaning that they provide more

benefits than no intervention, with less costs[166]. Consequently, their use should be key in inducing and maintaining alcohol abstinence in patients with ALD, in whom psychosocial interventions alone have not consistently shown to be effective and are hindered by difficulties in treatment adherence. Nevertheless, most patients with ALD are currently not considered for MAUD. In fact, recent data indicate that MAUD prescription rates in ALD are below 15%[163], and are even lower in cirrhosis[164,167]. These rates are shocking considering the specific features of this population and the negative impact that alcohol consumption has in the survival of patients at any stage of ALD[168]. Reasons for the low prescription rate of pharmacological treatment are multiple, with identifiable barriers coming from social conditions, healthcare providers or even patients themselves. First, from the providers' perspective and as previously stated, evidence of efficacy deriving from clinical trials in patients with ALD is limited, as most studies published to date have excluded patients with cirrhosis or AH. This lack of evidence also contributes to increasing the safety concerns, which are already high on the theoretical basis of potential toxicity due to impaired liver metabolism[169]. Second, hepatology providers have also reported low comfort and deficient addiction training[170], which may particularly influence prescription rates in centers lacking an integrated addiction unit. Third, patients with ALD have frequent misconceptions with regards to the natural history of AUD and the effects of MAUD, including lack of understanding about the chronicity of AUD and beliefs that treatment for them is futile[171]. Lastly, other challenges relate to socioeconomic characteristics, mainly financial difficulties or insurance policies, and transportation barriers[171].

In conclusion, although much evidence is available regarding pharmacological interventions in patients with AUD, important gaps of knowledge remain particularly in individuals suffering from advanced liver diseases. Hence, high-quality evidence in this field is urgently needed to change the natural history of ALD.

2. HYPOTHESIS

Advances in the management of alcohol-associated liver disease have been hampered by important gaps in the understanding of key aspects of the diagnosis, natural history and prognostic determinants of this condition. Therefore, the hypotheses of this doctoral thesis are the following:

1. An accurate differential diagnosis of alcohol-associated hepatitis with other entities such as alcoholic foamy degeneration is relevant for prognosis and treatment.

2. Active alcohol consumption in advanced stages of alcohol-associated liver disease is associated with poor outcomes such as recurrence of alcohol-associated hepatitis.

3. OBJECTIVES

General objective: to increase the knowledge in regards to the diagnosis and natural history of severe forms of alcohol-associated liver disease, with a special focus on alcohol-associated hepatitis differential diagnosis and recurrence, and on the management of alcohol use disorder.

Specific objectives:

1. To assess the prevalence of alcoholic foamy degeneration in the differential diagnosis of alcohol-associated hepatitis.

2. To analyze the performance of the current diagnostic criteria of alcohol-associated hepatitis for the differential diagnosis with alcoholic foamy degeneration, and to investigate new noninvasive diagnostic tools.

3. To unveil the genetic signature and long-term prognosis of alcoholic foamy degeneration.

4. To assess the incidence of recurrent episodes of alcohol-associated hepatitis.

5. To identify risk factors for recurrence of alcohol-associated hepatitis.

6. To characterize the severity and impact on prognosis of recurrent episodes of alcohol-associated hepatitis.

7. To investigate the efficacy and safety of medications for alcohol use disorder in advanced stages of alcohol-associated liver disease.

4. MATERIAL, METHODS, AND RESULTS

ARTICLE 1

ALCOHOLIC FOAMY DEGENERATION, AN ENTITY RESEMBLING ALCOHOL-ASSOCIATED HEPATITIS: DIAGNOSIS, PROGNOSIS, AND MOLECULAR PROFILING

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Alcoholic Foamy Degeneration, an Entity Resembling Alcohol-Associated Hepatitis: Diagnosis, Prognosis, and Molecular Profiling

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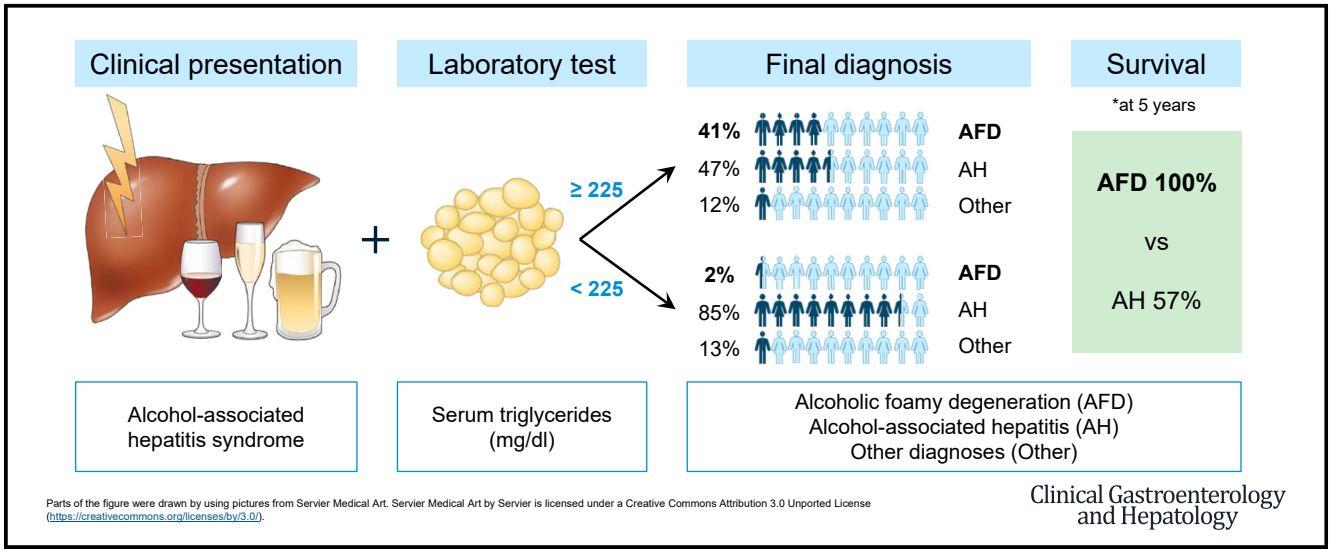

BACKGROUND & AIMS: **Alcoholic foamy degeneration (AFD) is a condition with similar clinical presentation to alcohol-associated hepatitis (AH), but with a specific histologic pattern. Information regarding the prevalence and prognosis of AFD is scarce and there are no tools for a noninvasive diagnosis.**

METHODS: **A cohort of patients admitted to the Hospital Clinic of Barcelona for clinical suspicion of AH who underwent liver biopsy was included. Patients were classified as AFD, AH, or other findings, according to histology. Clinical features, histology, and genetic expression of liver biopsy specimens were analyzed. The accuracy of National Institute on Alcohol Abuse and Alcoholism criteria and laboratory parameters for differential diagnosis were investigated.**

RESULTS: **Of 230 patients with a suspicion of AH, 18 (8%) met histologic criteria for AFD, 184 (80%) had definite AH, and 28 (12%) had other findings. In patients with AFD, massive steatosis was more frequent and the fibrosis stage was lower. AFD was characterized by down-regulation of liver fibrosis and**

Abbreviations used in this paper: AFD, alcoholic foamy degeneration; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; IL, interleukin; MELD, model for end-stage liver disease; NIAAA, National Institute on Alcohol Abuse and Alcoholism.

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inflammation genes and up-regulation of lipid metabolism and mitochondrial function genes. Patients with AFD had markedly better long-term survival (100% vs 57% in AFD vs AH; $P = .002$) despite not receiving corticosteroid treatment, even in a model for end-stage liver disease–matched sensitivity analysis. Serum triglyceride levels had an area under the receiver operating characteristic of 0.886 (95% CI, 0.807–0.964) for the diagnosis of AFD, whereas the National Institute on Alcohol Abuse and Alcoholism criteria performed poorly. A 1-step algorithm using triglyceride levels of 225 mg/dL (sensitivity, 0.77; specificity, 0.90; and Youden index, 0.67) is proposed for differential diagnosis.

CONCLUSIONS: **AFD in the setting of suspicion of AH is not uncommon. A differential diagnosis is important because prognosis and treatment differ largely. Triglyceride levels successfully identify most patients with AFD and may be helpful in decision making.**

Keywords: Triglycerides; Biopsy; Histology; Survival.

Alcohol-associated hepatitis (AH) is a syndrome characterized by recent onset of jaundice that may be accompanied by liver decompensation in patients with ongoing alcohol abuse and frequently underlying liver disease.[1–4] Although the prevalence of AH is not well known, its incidence and impact on global health are probably increasing, especially in young adults.[5,6]

In clinical practice, the diagnosis of AH is most often made with clinical and laboratory criteria, following the recommendations of a panel of experts from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[7] Nevertheless, these criteria have shown moderate performance for noninvasive diagnosis of AH, with a non-negligible percentage of false-positive diagnoses.[8] Among entities resembling AH, alcoholic foamy degeneration (AFD) is a poorly known and underrecognized condition.

AFD is defined by a histologic pattern of microvesicular fatty degeneration with foamy appearance of hepatocytes in the absence of, or with minimal signs of, steatohepatitis.[9] The real prevalence of this entity in the context of suspicion of AH is not known. The few studies assessing the prognosis of AFD have reported contradictory results[10,11]; however, in a large series on the natural history of AFD this condition seems to have better short-term prognosis compared to AH, with rapid improvement of liver function in the absence of corticosteroid treatment.[10]

A differential diagnosis between AH and AFD seems clinically relevant because it may guide decisions on specific treatment with corticosteroids or even consideration for early liver transplant. However, identification of AFD remains challenging in cases of clinical suspicion of AH because a liver biopsy is rarely performed in this setting.[12]

In this context, the aims of this study were to assess the real prevalence and prognosis of AFD and provide new noninvasive tools for identification of this entity in clinical practice.

Patients and Methods

Study Design and Population

This study included consecutive patients with clinical suspicion of AH admitted to the Hospital Clinic of Barcelona from January 1, 2010, to December 31, 2020, and with clinical follow-up evaluation in our unit. Clinical suspicion of AH was defined based on the diagnostic coding in the patients' medical records. Codes in our center are assigned by data managers based on the clinical diagnosis made by the team responsible for the patient during hospitalization. All reports are reviewed internally to ensure a correct coding. Codes for AH during the study period were as follows: alcoholic hepatitis, with ascites; and alcoholic hepatitis, without ascites.

Exclusion criteria were as follows: absence of liver biopsy during hospitalization, insufficient sample size for histologic diagnosis (biopsy length <10 mm or <5 portal tracts), and lack of informed consent to be included in the study.

Liver Histology and Classification of Patients

The transjugular approach with measurement of hepatic venous pressure gradient was preferred in most cases to percutaneous biopsy. The main reasons to use a transjugular approach were impairment of coagulation tests and the presence of ascites. Liver biopsy specimens were formalin-fixed, paraffin-embedded, and stained by standard methods, including hematoxylin and eosin and Masson's trichrome staining in all cases.

AFD was diagnosed on liver pathology when a pattern of microvesicular steatosis was present, with an absence of, or minimal signs of, steatohepatitis.[9] Microvesicular steatosis was defined as the infiltration of the hepatocyte's cytoplasm by numerous small fat droplets of uniform size, causing an enlargement of the cell, without nuclear displacement (Figure 1). Patterns of steatosis not meeting these criteria were not considered as microvesicular steatosis and, thus, were not classified as AFD.[13] A histologic diagnosis of AH was defined by the presence of any type of steatosis, associated with hepatocyte degenerative changes (hepatocellular ballooning and/or Mallory–Denk bodies) and lobular inflammatory infiltration[14] (Figure 1). When signs of AFD and AH were present in the same specimen, it was classified as one or the other depending on the predominant pattern, defined

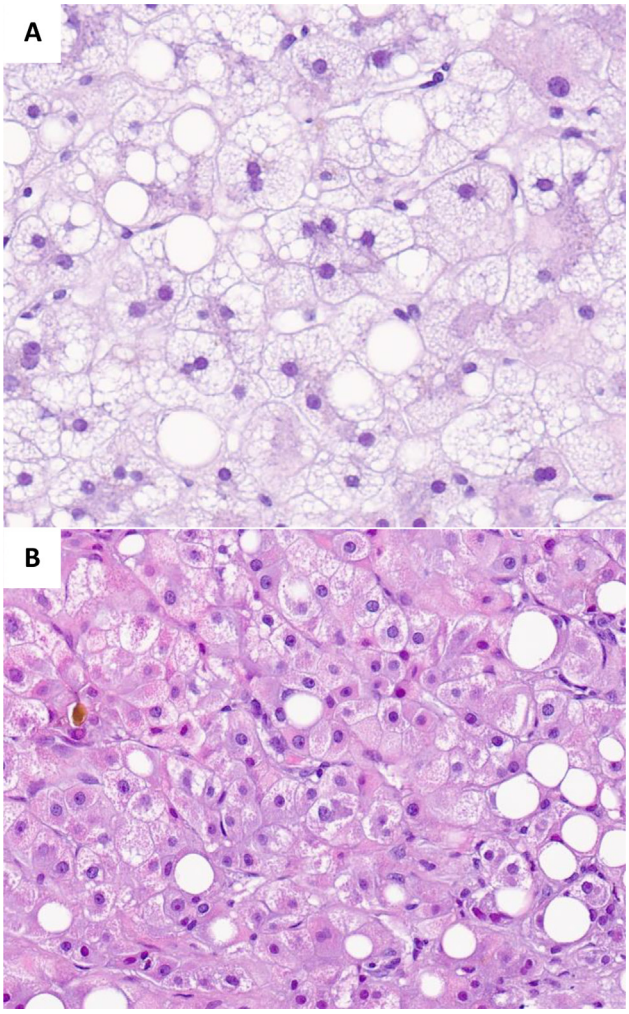

Figure 1. (*A*) Liver pathology examination in patients with alcoholic foamy degeneration (AFD). AFD is characterized by a pattern of microvesicular steatosis, which is defined by an infiltration of the hepatocytes' cytoplasm by small lipid droplets, uniform in size, that do not displace the cell nucleus. The infiltrated hepatocytes are enlarged and have a foamy appearance. (*B*) Liver pathology examination in patients with alcohol-associated hepatitis (AH). AH is characterized by steatohepatitis, defined by any degree of steatosis (any type of steatosis, although macrovesicular steatosis is by far the most common pattern), hepatocyte degenerative changes (hepatocellular ballooning and/or Mallory–Denk bodies), and lobular inflammatory infiltration, predominantly neutrophilic.[13]

as the one occupying more than 50% of the sample's area. Patients whose liver biopsy assessment did not meet the criteria for the diagnosis of AFD or AH were classified as *other findings* and excluded from the main analysis. Liver biopsy specimens from all patients were reviewed by 2 expert pathologists (A.D. and C.M.) who were blinded to the patients' characteristics and outcomes. The agreement between both pathologists was 97% (196 of 202 cases). In the few cases of disagreement, final consensus was reached after a joint revision of the slide using a multihead microscope.

What You Need to Know

Background

Patients with a clinical syndrome of alcohol-associated hepatitis (AH) in fact may have other clinical entities, such as alcoholic foamy degeneration (AFD), which do not benefit from corticosteroids.

Findings

AFD is a differentiated entity from AH and has an excellent long-term prognosis. Levels of triglycerides help to identify patients with AFD.

Implications for patient care

The results of this study may be important for clinicians to avoid unnecessary treatments and for patients for a correct knowledge of their prognosis. They also may interest researchers when considering patients with AH for clinical trials.

Patients were categorized into 2 groups based on the pathology diagnosis: AFD, which corresponded to the study group, and AH, which was established as the control group.

In regard to fibrosis, it was evaluated using both Meta-analysis of Histological Data in Viral Hepatitis[15] and Study of Alcohol-related LiVer disease in Europe[16] staging systems.

Data Collection

The inclusion date was set as the date that the liver biopsy was performed. Demographic, clinical, and biochemical data at the time of liver biopsy were collected carefully, including previous alcohol consumption quantified in standard units/day,[17] comorbidities (ie, cardiovascular diseases and metabolic risk factors), and previous or current episodes of decompensation of cirrhosis. Prognostic scores including model for end-stage liver disease (MELD), Maddrey's discriminant function, and Child–Pugh scores were also calculated. Fulfillment of the clinical criteria for probable AH of both the NIAAA[7] and the modified NIAAA criteria with the addition of C-reactive protein levels[8] was analyzed (Supplementary Table 1). Furthermore, other variables were reviewed and registered, such as the treatment that the patients received, episodes of hepatic decompensation after discharge, and time of alcohol abstinence. Per protocol, all patients were evaluated by an addiction specialist during hospitalization and were referred to the addiction unit after discharge. Alcohol use was assessed by patient self-reporting and by urine ethyl glucuronide, when available. Finally, we assessed survival based on the patients' clinical status on the date of the last follow-up evaluation.

RNA Extraction and Sequencing Analysis

Paraffin-embedded liver biopsy specimens from patients with AFD with sufficient tissue sample available were used for genetic expression analysis. A randomly selected group of 20 patients with AH was used for comparison. Further details on RNA extraction and sequencing analysis are shown in the Supplementary Methods.

Statistical Analysis

Quantitative variables with a normal distribution were expressed as means and SD and those with a non-normal distribution were expressed as median and interquartile range. Categoric variables were expressed as absolute count and percentages. Differences between groups were studied with the chi square test, *t* test, or Mann–Whitney test. Factors associated with the presence of AFD on liver histology were studied with a univariate and multivariate logistic regression analysis. Variables included in the multivariate analysis were those with a *P* value in the univariate analysis <.05 and those that were clinically relevant (ie, sex). Due to the relatively low number of AFD cases, a single multivariate analysis including all relevant variables would not be statistically acceptable; therefore, we performed

Table 1. Baseline Characteristics of Patients Included in the Study Classified According to the Diagnosis of AFD or AH

	Patients with AFD (n = 18)	Patients with AH (n = 184)	*P* value
Age, *y*	47 (38–57)	52 (45–59)	.074
Sex, female	6 (33)	54 (29)	.724
Obesity	3 (17)	46 (25)	.620
Diabetes mellitus	3 (17)	43 (23)	.419
Alcohol use, *SU/d*	10 (6–16)	10 (7–20)	.294
Duration of alcohol use, *y*	20 (14–22)	30 (23–38)	**<.001**
Decompensation at inclusion	5 (28)	138 (75)	**<.001**
Ascites	4 (22)	120 (65)	**<.001**
Overt hepatic encephalopathy	1 (6)	61 (33)	.053
Variceal bleeding	0 (0)	13 (7)	.244
Spontaneous bacterial peritonitis	0 (0)	10 (5)	.310
HVPG, *mm Hg*	10.5 (5.0–19.0)	18 (14.4–22.0)	**.012**
C-reactive protein level, *mg/dL*	1.3 (0.0–3.0)	3.2 (1.42–5.17)	**.019**
Serum creatinine level, *mg/dL*	0.9 (0.7–1.1)	0.8 (0.6–1.2)	.603
Total cholesterol level, *mg/dL*	264 (181–440)	124 (98–171)	**<.001**
Triglyceride level, *mg/dL*	273 (197–661)	124 (93–170)	**<.001**
AST level, *IU/L*	203 (136–382)	122 (85–165)	**<.001**
ALT level, *IU/L*	107 (72–151)	48 (32–77)	**<.001**
GGT level, *IU/L*	960 (568–1804)	251 (124–613)	**<.001**
AP level, *IU/L*	344 (156–541)	216 (143–343)	**.020**
Total bilirubin level, *mg/dL*	7.9 (2.2–14.1)	10.8 (3.8–21.2)	.201
Albumin level, *g/L*	29 (24–34)	26 (24–31)	.169
Leukocytes, $\times 10^9$/L	5.7 (3.6–7.3)	8.5 (6.1–13.2)	**.002**
Platelets, $\times 10^9$/L	160 (101–232)	112 (75–186)	.056
INR	1.1 (1.1–1.4)	1.7 (1.4–2.1)	**<.001**
MELD score	17 (10–20)	22 (17–27)	**.002**
Maddrey's discriminant function	18 (12–34)	54 (34–76)	**<.001**
Child–Pugh score	8 (7–10)	11 (9–12)	**.001**

NOTE. Values are median (±interquartile range) or absolute count (percentage). Bolded values are those with *P* value <.05.
AFD, alcoholic foamy degeneration; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, model for end-stage liver disease; SU, standard units.

numerous models of logistic regression including up to 4 variables. Considering the variables associated independently with the presence of AFD in the multivariate analysis, a receiver operating characteristic curve analysis was performed for each variable and the Youden index was calculated to identify the cut-off value with the best performance for a noninvasive diagnosis of AFD. Survival curves were calculated with the Kaplan–Meier method and compared with the log-rank test in the overall cohort and in a randomly MELD-matched cohort at a 2:1 ratio (2 cases of AH per 1 case of AFD). The significance level for all statistical tests was set at .05 two-tailed. All statistical analysis were performed using SPSS version 25.0.0.1.

Ethical Aspects

All research was conducted in accordance with both the Declaration of Helsinki and Istanbul. The protocol was approved by the institutional review board of the hospital and all patients provided written informed consent to participate in the study.

Results

Prevalence and Clinical Characteristics

A total of 317 patients with clinical suspicion of AH were hospitalized in the Liver Unit of the Hospital Clinic of Barcelona during the study period and 230 patients were included in the study (Supplementary Figure 1). Eighteen patients met the histologic criteria of AFD, with a prevalence of 8% in the study cohort.

Baseline characteristics of patients with AFD and AH are shown in Table 1. Patients with AFD presented a less severe impairment of liver function tests as shown by lower MELD values, Maddrey's discriminant function, and Child–Pugh scores, and a lower prevalence of decompensation of liver disease. Higher levels of aminotransferases, γ-glutamyl transferase (GGT), cholesterol, and triglycerides, and lower values of the international normalized ratio were found in patients with AFD. Of note, total bilirubin levels were not significantly different when comparing both entities. In regard to treatment, 109 (59%) patients with AH received corticosteroids compared with only 3 (17%) patients with AFD ($P < .001$).

Evolution and Survival

All patients with AFD survived the index hospitalization. After a median of 7 days from admission, patients with AFD presented a characteristic clinical pattern of rapid reduction in aminotransferase levels (median aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels decreased from 203 IU/L to 77 IU/L and from 107 IU/L to 44 IU/L, respectively) and serum bilirubin levels (median levels decreased from 7.9 mg/dL to 3.1 mg/dL), as well as MELD score (median MELD score decreased from 17 to 11). Moreover, a trend toward normalization of lipid profile was evident, with median triglyceride levels decreasing from 273 mg/dL to 153 mg/dL, and median cholesterol levels decreasing from 264 mg/dL to 187 mg/dL (Supplementary Figure 2).

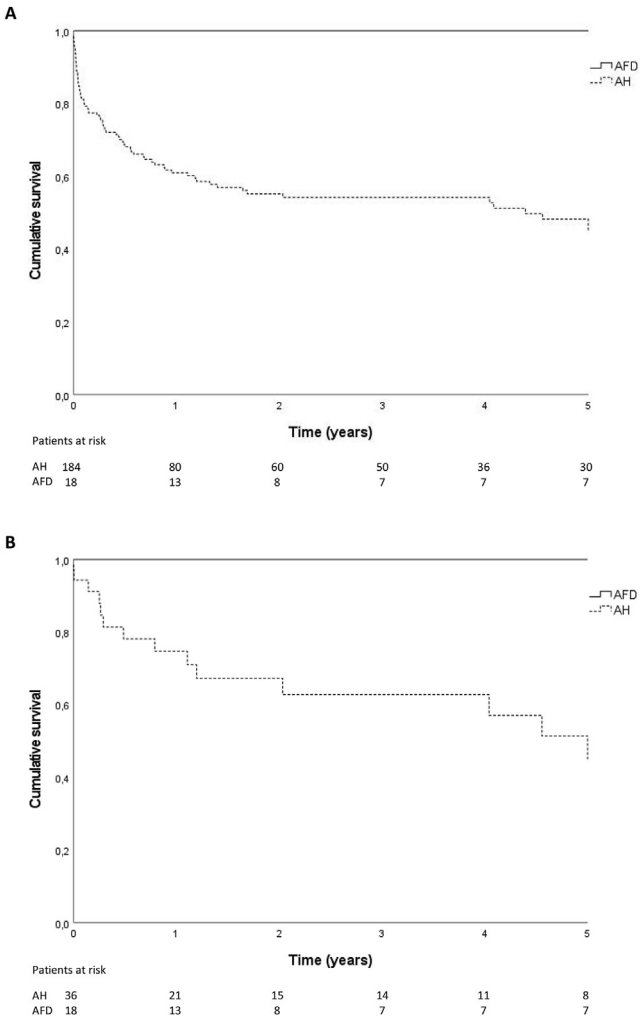

Figure 2. Kaplan–Meier curves showing the long-term survival of patients with alcoholic foamy degeneration (AFD) and alcohol-associated hepatitis (AH) in (*A*) the total cohort ($P = .002$, log-rank test), and (*B*) the MELD-matched cohort ($P = .005$, log-rank test).

In the long term, after 5 years of follow-up evaluation, patients with AFD had a survival rate of 100% (median follow-up period, 618 days [range, 375–2753]). Only 1 patient had recurrent hospitalizations for decompensation of liver disease in the context of persistent alcohol consumption. The excellent prognosis of patients with AFD contrasted with the poor survival of patients with AH: 57% survival in AH (median follow-up period, 347 days [range, 64–1234]) (Figure 2*A*). In the MELD-matched cohort, the 5-year survival rate in patients with AH remained significantly lower compared with that of patients with AFD (100% in AFD vs 60% in AH; $P = .005$) (Figure 2*B*).

Table 2. Histologic Findings on Liver Biopsy Examination of Patients With AFD and AH

	Patients with AFD (n = 18)	Patients with AH (n = 184)	*P* value
METAVIR fibrosis stage (F)			**<.001**
F0	5 (28)	1 (1)	
F1	2 (11)	13 (7)	
F2	4 (22)	13 (7)	
F3	5 (28)	26 (14)	
F4	2 (11)	129 (71)	
SALVE fibrosis stage (SFS)			**<.001**
SFS 0	1 (6)	0 (0)	
SFS 1	3 (17)	3 (2)	
SFS 2	7 (39)	24 (13)	
SFS 3	5 (28)	26 (14)	
SFS 4	2 (11)	129 (71)	
Perisinusoidal fibrosis	13 (72)	139 (76)	.755
Massive steatosis (>2/3 of the sample)	16 (89)	54 (29)	**<.001**
Microvesicular steatosis (any degree)	18 (100)	46 (25)	**<.001**
Portal inflammatory infiltrate	2 (11)	93 (50)	**.001**
Lobular inflammatory infiltrate	6 (33)	130 (76)	**<.001**
Neutrophilic infiltration	2 (11)	124 (67)	**<.001**
Steatohepatitis	2 (11)	184 (100)	**<.001**
Ductular reaction	4 (22)	75 (41)	.124
Canalicular cholestasis	9 (50)	102 (55)	.658
Ductular cholestasis	4 (22)	45 (25)	.833
Hepatocyte ballooning	3 (17)	161 (88)	**<.001**
Mallory–Denk bodies	2 (11)	169 (92)	**<.001**
Apoptotic bodies	1 (6)	6 (3)	.611
Megamitochondria	4 (22)	31 (17)	.565

NOTE. Values are absolute count (percentage). Bolded values are those with *P* value <.05.
AFD, alcoholic foamy degeneration; AH, alcohol-associated hepatitis; F, Meta-analysis of Histological Data in Viral Hepatitis fibrosis stage; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis; SALVE, Study of Alcohol-related LiVer disease in Europe; SFS, Study of Alcohol-related LiVer disease in Europe fibrosis stage.

Alcohol consumption was also assessed during follow-up evaluation. A similar proportion of patients underwent clinical follow-up evaluation in our center's Addiction Unit after their index hospitalization (62% in AFD vs 68% in AH; $P = .768$). The percentage of patients who remained abstinent from alcohol at the last follow-up visit was similar between both groups (42% in AFD vs 49% in AH; $P = .634$).

Histologic Features

Histologic features from liver biopsy specimens of patients with AFD were compared with those of patients with AH (Table 2). Patients with AFD had massive steatosis (>2/3 of the sample) in a higher proportion when compared with patients with AH (89% vs 30%; $P < .05$). Advanced fibrosis defined by a Meta-analysis of Histological Data in Viral Hepatitis stage >F2 or a Study of Alcohol-related LiVer disease in Europe fibrosis stage >2 was significantly less common in patients with AFD (39% vs 85%; $P < .001$), whereas perisinusoidal fibrosis had a similar prevalence in the 2 groups (72% in AFD vs 76% in AH; $P = .755$). Of note, 48 patients had findings compatible with both AFD and AH. However, only 2 patients had a predominant pattern of microvesicular steatosis; therefore, only these 2 patients were classified as AFD.

Transcriptomic Analysis

A transcriptomic analysis of 17 of 18 liver biopsy specimens from patients in the AFD cohort was performed and compared with that of 20 randomly selected liver biopsy specimens from patients in the AH cohort. Baseline characteristics of both groups were similar (data not shown). RNA sequencing analysis showed that patients with AFD and AH have different gene expression patterns (Supplementary Figure 3). On the principal component analysis, patients with AFD clustered apart

from patients with AH, although a moderate overlap was seen between both groups (Supplementary Figure 4). Furthermore, the functional analysis of the deregulated genes using Ingenuity Pathway Analysis (Qiagen) showed that when compared with patients with AH, patients with AFD had different expression of genes and functional pathways that have been related to the pathogenesis of AH (Supplementary Figure 5). Pathways associated with liver fibrosis, hepatic stellate cell activation, wound healing, and mesenchymal cell activation were down-regulated in AFD. We also found down-regulation of genes involved in inflammatory pathways related to the role of macrophages, fibroblasts, and endothelial cells in rheumatoid arthritis; interleukin (IL)1, IL6, IL8, IL17, and IL22 signaling pathways; or C-X-C chemokine receptor type 4 signaling pathway, among others. By contrast, a significant up-regulation was seen in AFD in functional pathways associated with mitochondrial function and lipid metabolism, cholesterol, and triglyceride biosynthesis, such as pyridoxal-5-phosphate or adipogenesis pathways.

Differential Diagnosis With Alcohol-Associated Hepatitis

On univariate regression analysis, variables associated with the presence of AFD were younger age; shorter duration of alcohol use; absence of ascites; lower hepatic venous pressure gradient; higher levels of AST, ALT, GGT, alkaline phosphatase, cholesterol, and triglycerides; and lower leukocyte count, international normalized ratio, and MELD score. Interestingly, NIAAA criteria were not associated with the presence of AH in the univariate analysis (Table 3). Several models of multivariate analysis were performed including variables related to alcohol use, liver enzyme levels, liver function scores, and lipid profile. Notably, when included together in a multivariate model, duration of alcohol use, AST level, and triglyceride level, but not MELD score, were independently associated with the presence of AFD (Table 3).

Because NIAAA criteria are currently the most widely used clinical criteria for the diagnosis of AH, we investigated the performance of these criteria for the differential diagnosis of AH and AFD. NIAAA criteria showed moderate sensitivity (70%) with low specificity (44%) and a diagnostic accuracy of 65% for the differential diagnosis between AH and AFD. Overall performance of the modified NIAAA C-reactive protein criteria was better, but not optimal (sensitivity, 73%; specificity, 45%; and diagnostic accuracy, 68%) (Supplementary Table 2).

Because the precision of these criteria was suboptimal, we investigated other noninvasive tools for the differential diagnosis. Four analytical parameters, ALT, AST, cholesterol, and triglyceride levels, were associated with high diagnostic accuracy. Of those, serum triglyceride levels had the best diagnostic performance for the diagnosis of AFD, with an area under the receiver operating characteristic curve of 0.886 (95% CI, 0.807–0.964), and 225 mg/dL was the value with the best diagnostic performance (sensitivity, 0.77; specificity, 0.90; and Youden index, 0.67) (Supplementary Figures 6 and 7). Using this threshold, we generated a 1-step, easy-to-use algorithm that identifies a subpopulation of patients with clinical suspicion of AH in whom the diagnosis of AFD is notably prevalent (Figure 3).

Table 3. Univariate and Multivariate Analysis of Factors Associated With AFD

Variable	OR	*P*	95% CI
Univariate analysis			
Age, *y*	0.951	.047	0.905–0.999
Sex, male	1.204	.724	0.430–3.372
Alcohol use, *SU/d*	0.951	.146	0.890–1.018
Duration of alcohol use, *y*	0.904	.001	0.853–0.957
Ascites at inclusion	0.152	.001	0.048–0.482
HVPG, *mm Hg*	0.897	.015	0.822–0.979
C-reactive protein level, *mg/dL*	0.723	.066	0.511–1.022
Total cholesterol level, *mg/dL*	1.016	<.001	1.010–1.023
Triglyceride level, *mg/dL*	1.005	.002	1.002–1.008
AST level, *IU/L*	1.002	.030	1.000–1.004
ALT level, *IU/L*	1.003	.009	1.001–1.006
GGT level, *IU/L*	1.001	<.001	1.000–1.001
AP level, *IU/L*	1.003	.009	1.001–1.004
Total bilirubin level, *mg/dL*	0.963	.186	0.911–1.018
Leukocytes, $\times 10^6$/L	0.803	.012	0.676–0.953
INR	0.031	<.001	0.005–0.201
MELD score	0.903	.004	0.842–0.967
NIAAA criteria for probable AH	0.533	.209	0.200–1.423
Multivariate analysis			
Duration of alcohol use, *y*	**0.893**	**.001**	**0.833–0.987**
Triglyceride level, *mg/dL*	**1.003**	**.005**	**1.001–1.005**
AST level, *IU/L*	**1.004**	**.020**	**1.000–1.007**
MELD score	0.938	.286	0.834–1.055

NOTE. Different models of multivariate analysis were created including a maximum of 4 variables. Models were generated by combining 1 variable from each of the following: duration of alcohol use, liver function (MELD or INR), liver enzymes (AST, ALT, AP, or GGT), and lipid profile (cholesterol or triglycerides). The model shown includes the variables that were associated most consistently to AFD in all models generated. Bolded values are those with *P* value <.05.
AFD, alcoholic foamy degeneration; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, model for end-stage liver disease; NIAAA, National Institute of Alcohol Abuse and Alcoholism; OR, odds ratio; SU, standard unit.

Discussion

In this study, we report the actual prevalence of AFD, a poorly known entity frequently misdiagnosed as AH, with differentiated histologic features and genetic signature, and a drastically different prognosis. In addition, we provide a simplified, clinically actionable algorithm based on triglyceride levels for the differential diagnosis between AFD and AH.

We used multiple approaches to provide evidence that AFD is a differentiated entity from AH. From a clinical perspective, we found that some clinical features

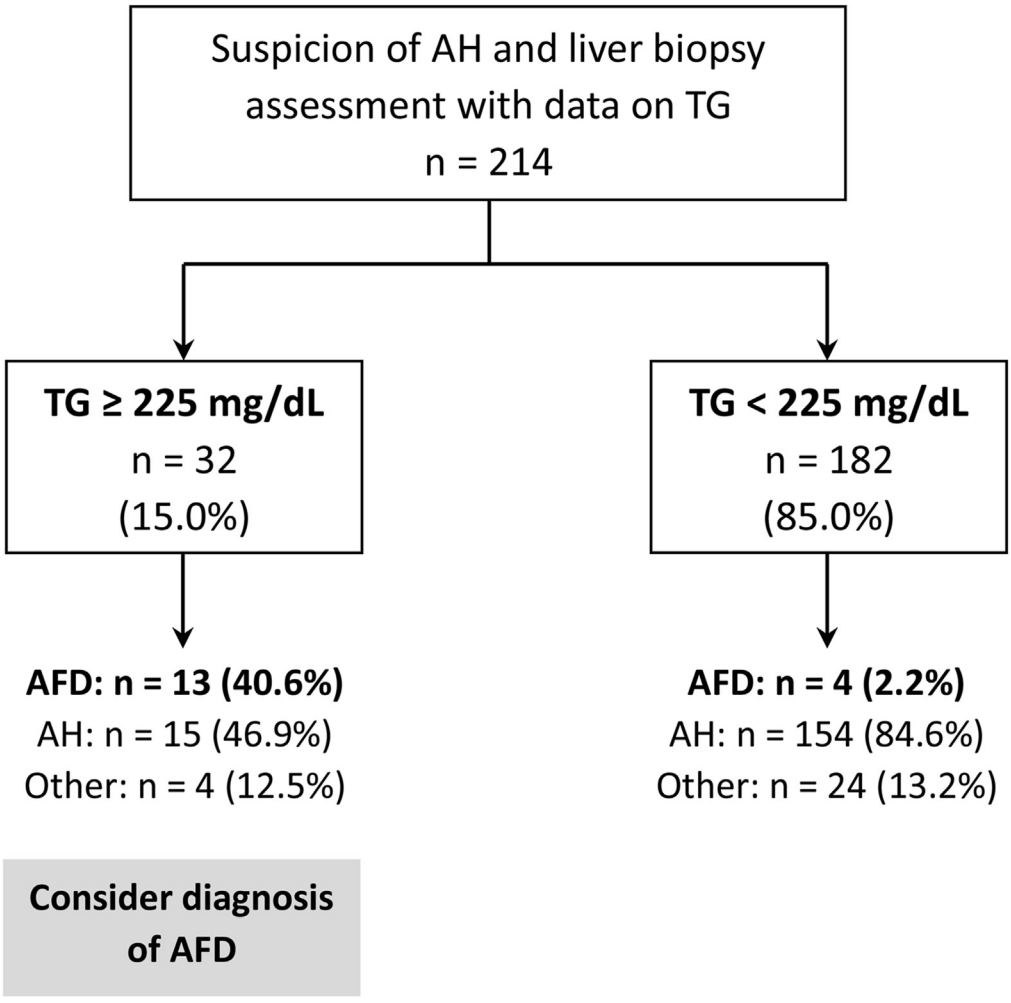

Figure 3. Simplified algorithm for identification of patients with alcoholic foamy degeneration (AFD) according to serum triglyceride levels. AH, alcohol-associated hepatitis; TG, triglyceride.

of patients with AFD differ from those of patients with AH. Notably, these patients present less frequently with clinical decompensation of liver disease. Moreover, impairment of liver function is less severe when compared with that of patients with AH, as shown by a lower MELD score. In contrast, levels of aminotransferases and GGT are markedly higher in patients with AFD.

Regarding the pathogenesis of AFD, lipid metabolism seems to play a key role in this condition. Massive fat infiltration is the most characteristic histologic feature in the liver pathology analysis of these patients. This finding is accompanied by a marked increase in circulatory triglyceride and cholesterol levels. In parallel with this, lipid metabolism–related genes were overexpressed in the transcriptomic analysis of liver biopsy specimens of patients with AFD when compared with AH.

One of the most relevant findings of this study is the excellent prognosis of patients with AFD, which is drastically different from that of patients with AH.[18,19] Published data on long term prognosis of patients with AFD is lacking and the few studies that have assessed short and midterm prognosis have yielded contradictory results.[10,11] Our study clearly shows an excellent prognosis of this population, both short and long term, with neither deaths nor liver transplants occurring during follow-up evaluation. Furthermore, significant differences in survival were also shown when matching patients with AFD to patients with AH based on MELD score at admission. Of note, AFD patients improved spontaneously despite not receiving corticosteroids. This finding, together with the absence of hepatic and systemic inflammation, should discourage the use of steroids in AFD.

To date, an AFD diagnosis has relied only on liver biopsy assessment. However, current clinical practice guidelines recommend using the NIAAA noninvasive criteria for the diagnosis of probable AH, restricting the liver biopsy to a limited number of cases of diagnostic uncertainty or coexistence of confounding factors.[3,4] We provide a 1-step algorithm based on serum triglyceride levels, which have shown the best accuracy for identifying patients with AFD (area under the receiver operating characteristic, 0.886; 95% CI, 0.807–0.964). Given the wide availability and low cost of serum triglyceride measurements, the provided algorithm may be useful to guide decision making in clinical practice.

This study had some limitations that should be mentioned. First, it is possible that patients with confounding factors for the diagnosis of AH were more prone to have a liver biopsy proposed and this may have affected the cohort composition. However, this is unlikely

because a liver biopsy is performed in the majority of patients with suspicion of AH in routine clinical practice in our unit, considering the possibility of erroneous diagnoses using only clinical criteria.[8] Second, misclassification owing to sampling error or misinterpretation of histologic features is possible, especially in patients with mixed features of AH and AFD. The fact that 2 independent pathologists evaluated each sample nuances this potential limitation. Finally, despite being a large series of patients with AFD, the number of patients included was relatively low; ideally, the diagnostic capacity of serum triglyceride levels for the identification of AFD should be explored further in future studies.

In conclusion, AFD is a previously neglected entity differentiated from AH, with excellent prognosis and no need for steroid treatment. Serum triglyceride levels are a valuable tool for the identification of this condition.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.11.031.

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Pere Ginès (Funding acquisition: Equal; Supervision: Equal; Writing – review & editing: Equal)

Elisa Pose Méndez (Conceptualization: Lead; Funding acquisition: Equal; Investigation: Equal; Methodology: Equal; Project administration: Lead; Writing – original draft: Supporting; Writing – review & editing: Equal)

Conflicts of interest

These authors disclose the following: Isabel Graupera has received a grant from Pfizer (77145101). Ramón Bataller is on the speakers bureau of AbbVie and Gilead. Pere Ginès has received funding from Gilead and Grífols, speaking fees from Pfizer and consulted or attended advisory boards for Gilead, RallyBio, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Behring, Roche Diagnostics International and Boehringer Ingelheim. The remaining author discloses no conflicts.

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Supplementary Methods

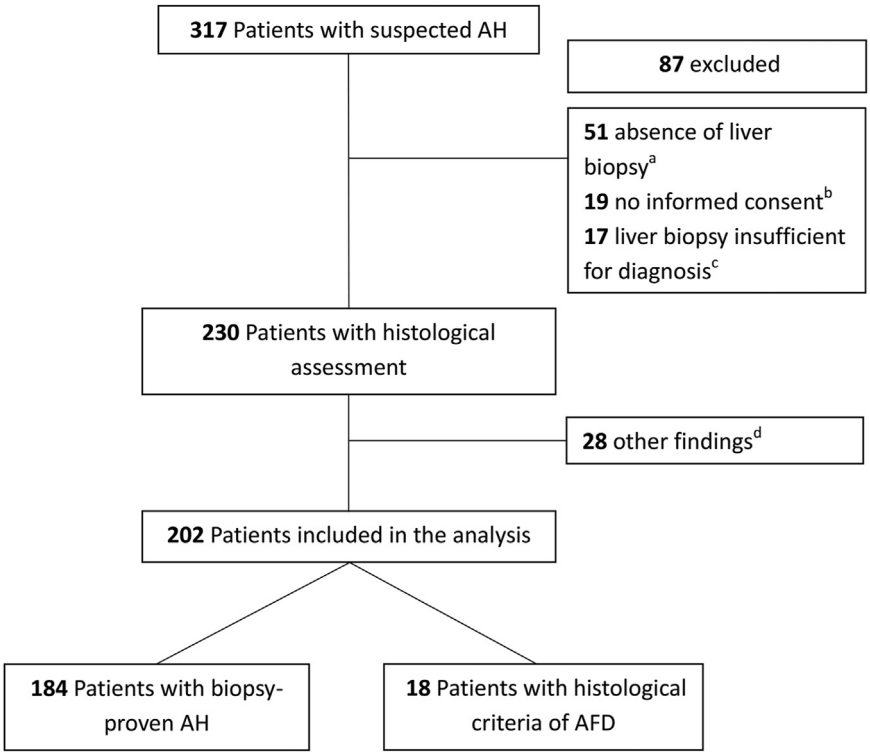
RNA Extraction and Sequencing Analysis

RNA extraction was performed using the RNeasy formalin-fixed, paraffin-embedded kit (Qiagen) following the manufacturer's protocol. RNA concentration was assessed using Nanodrop and Agilent RNA 6000 Nano and Pico Chips (cat# 5067-1511 and 5067-1513; Agilent Technologies).

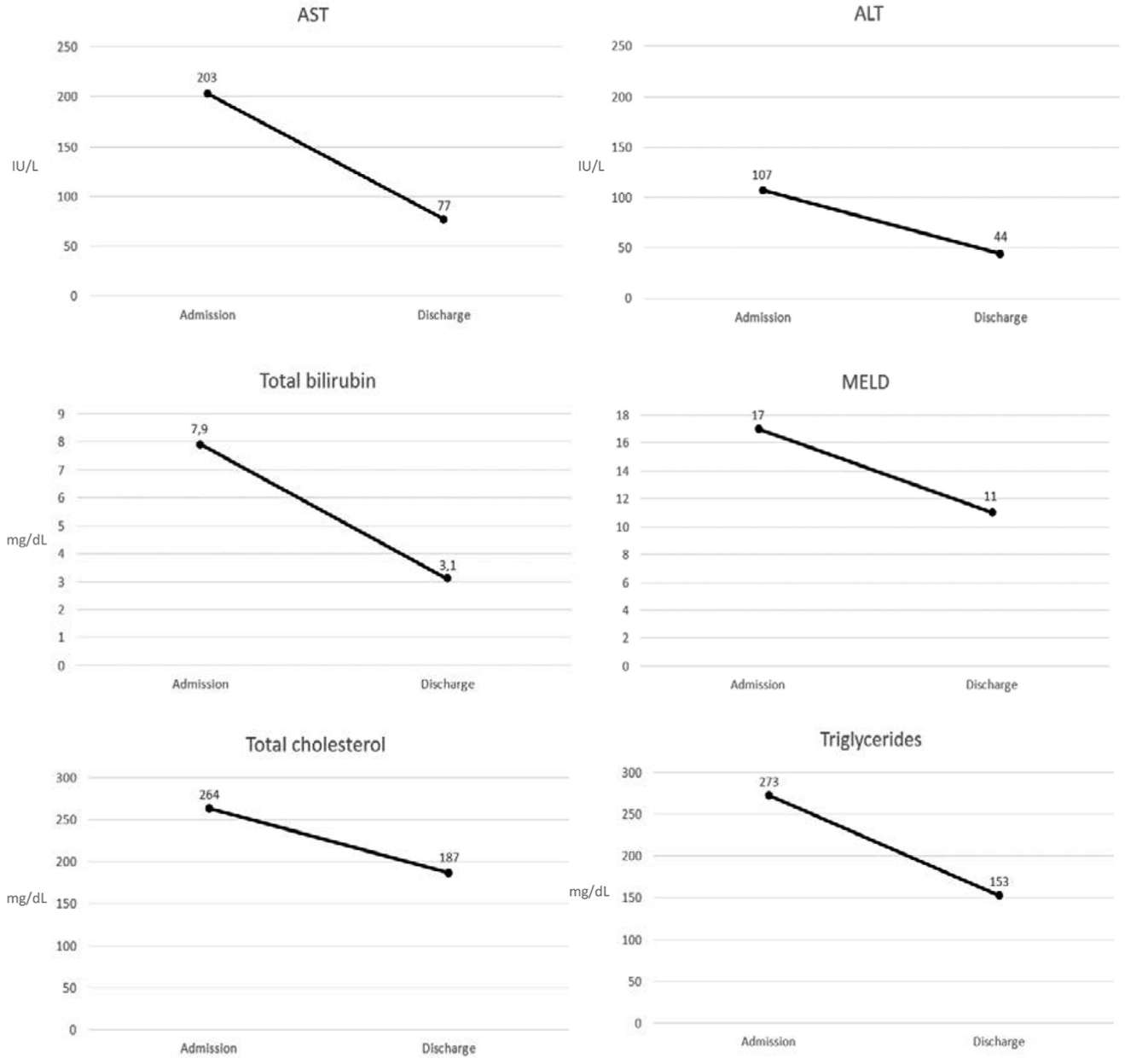
Sequencing libraries were prepared using the SMARTer Stranded Total RNA-seq Kit v2 – Pico Input Mammalian kit (cat# 634411; Takara Bio USA), following the kit user manual (revision 050619). In summary, starting from 50 ng formalin-fixed, paraffin-embedded RNA samples, and without fragmentation before first-strand complementary DNA synthesis, the first-strand complementary DNA synthesis was performed using SMARTScribe reverse transcriptase, for 90 minutes at 42°C, 10 minutes at 70°C, and paused at 4°C. Afterwards, Illumina Adapters and Indexes were added, performing a preamplification polymerase chain reaction (60 seconds at 94°C, 5 cycles of 15 seconds at 98°C, 15 seconds at 55°C, 30 seconds at 68°C, and paused at 4°C). Then, ribosomal complementary DNA was depleted with ZapR v2 and R-Probes v2 (Takara Bio). Finally, enrichment of libraries was achieved by polymerase chain reaction (60 seconds at 94°C; 13–17 cycles of 15 seconds at 98°C, 15 seconds at 55°C, 30 seconds at 68°C, and paused at 4°C). Final libraries were visualized on an Agilent 2100 Bioanalyzer using the Agilent High Sensitivity DNA kit (cat# 5067-4626; Agilent Technologies), quantified using the Qubit dsDNA HS DNA Kit (cat# Q32854; Thermo Fisher Scientific), and sequenced in a NovaSeq 6000 (Illumina, Inc) with 100-nucleotide paired-end reads.

Unique mapped reads (Novoalign software v3.02.08) were summarized as counts representing the gene expression levels for more than 20,800 different genes present in the AmpliSeq Human Gene Expression panel. Low expressed genes were not considered from the differential expression phase if the sum of counts was less than 100. Linear modeling and differential expression were calculated by means of limma Rpackage (Smyth GK, 2015). Fold changes, moderated P values, and their adjusted P values for multiple testing were calculated using the Benjamini–Hochberg procedure to estimate the false-discovery rate. RNA concentration and quality were determined with a Pico Bioanalyzer.

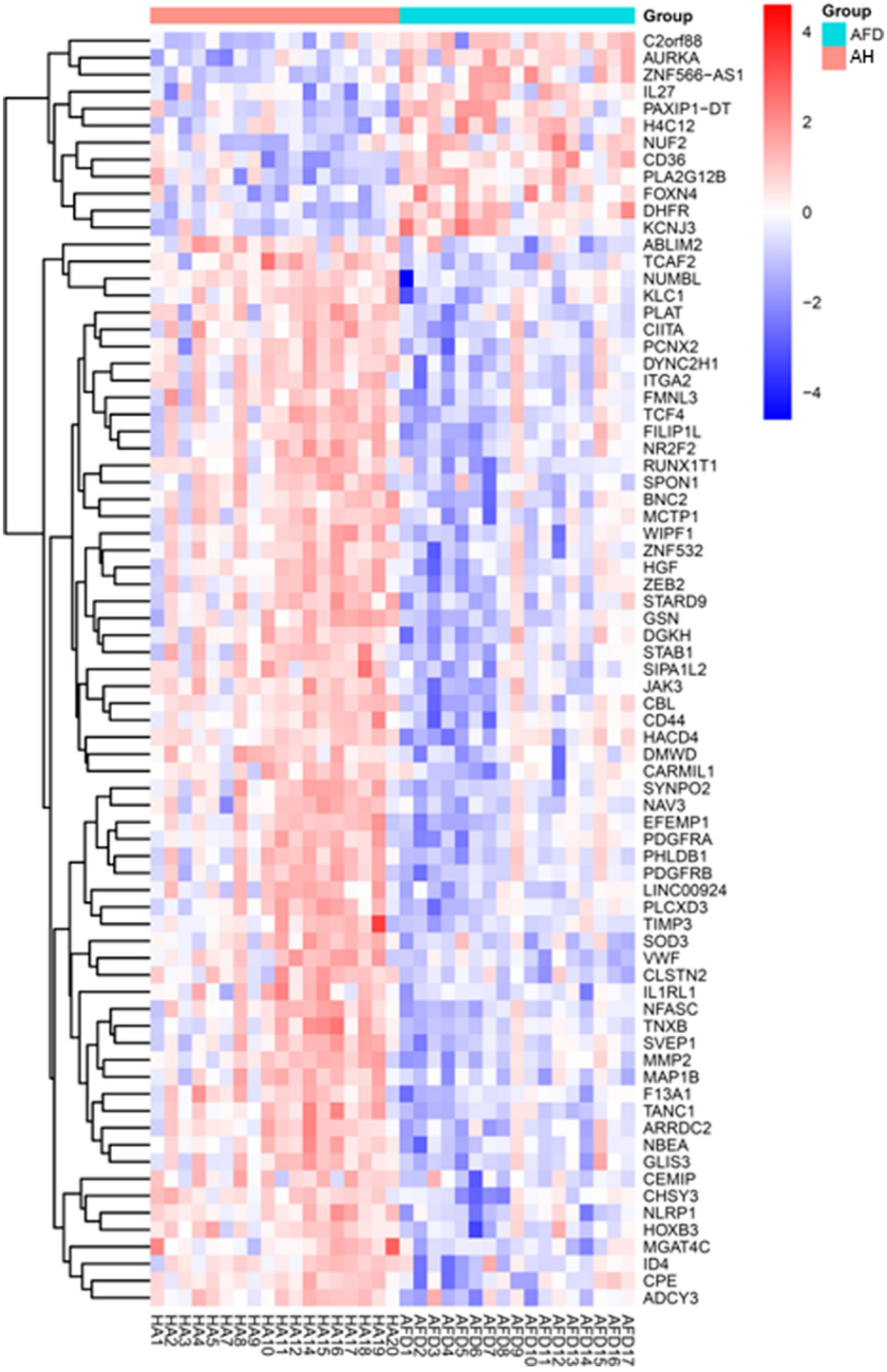
Unsupervised principal component analysis was performed by princomp function using R statistical software (v3.4.3).



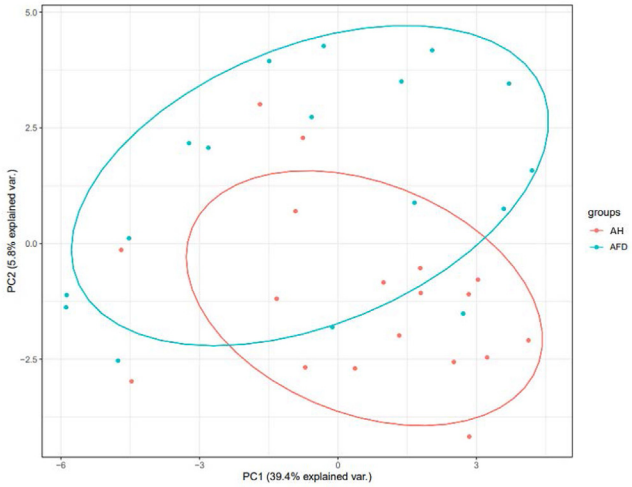
Supplementary Figure 1. Study flowchart. [a]Patients diagnosed with alcohol-associated hepatitis (AH) based on the National Institute on Alcohol Abuse and Alcoholism clinical criteria. [b]Patients signed the informed consent for liver biopsy but did not sign the informed consent to be included in the study. [c]Biopsy specimens less than 10 mm in length or with fewer than 5 portal tracts were considered invalid. [d]Patients with histologic features different from AH and AFD: advanced fibrosis with minimal or no steatosis (n = 17), predominant macrovesicular steatosis (n = 10), and isolated perisinusoidal fibrosis (n = 1). AFD, alcoholic foamy degeneration.



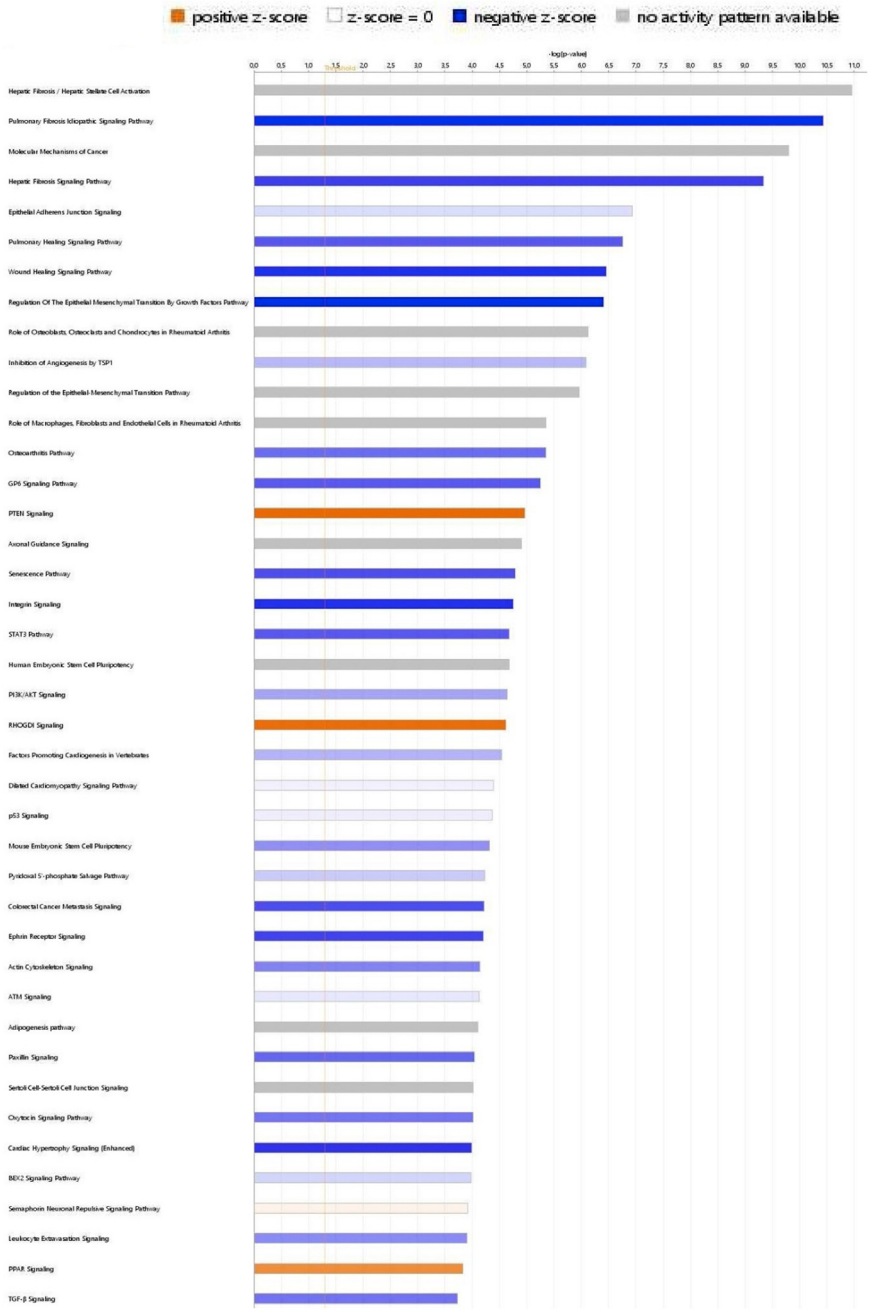
Supplementary Figure 2. Changes in laboratory tests in patients with alcoholic foamy degeneration. The median time between tests was 7 days. ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease.



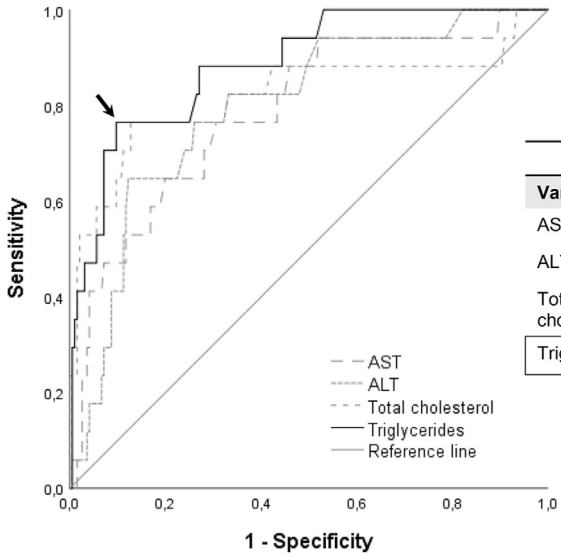
Supplementary Figure 3. Heatmap of the most up-regulated (red) and down-regulated (blue) genes in liver biopsy specimens of patients with alcoholic foamy degeneration (AFD) (*right*) and alcohol-associated hepatitis (AH) (*left*).



Supplementary Figure 4. Principal components analysis plot of the transcriptomics of patients with alcoholic foamy degeneration (AFD) and alcohol-associated hepatitis (AH). PC1, principal component 1; PC2, principal component 2.

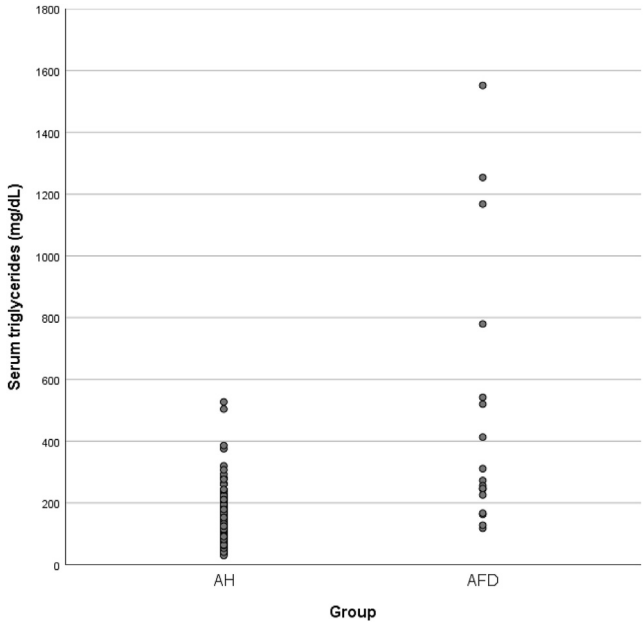


Supplementary Figure 5. Functional enrichment analysis of canonical pathways in patients with alcoholic foamy degeneration (AFD) compared with patients with alcohol-associated hepatitis (AH), using Ingenuity Pathway Analysis. Pathways in blue are down-regulated; pathways in orange are up-regulated.



Area under the ROC curve		
Variables	**Area**	**CI 95%**
AST	0.786	0.669-0.903
ALT	0.796	0.691-0.902
Total cholesterol	0.821	0.680-0.961
Triglycerides	0.886	0.807-0.964

Supplementary Figure 6. Area under the receiver operating characteristic curve representing the performance of different variables for the diagnosis of alcoholic foamy degeneration. The best cut-off value for serum triglycerides (*arrow*) was 225 mg/dL (sensitivity, 0.77; specificity, 0.90; Youden index, 0.67). ALT, alanine aminotransferase; AST, aspartate aminotransferase; ROC, receiver operating characteristic.



Supplementary Figure 7. Individual values of serum triglycerides in patients with alcohol-associated hepatitis (AH) and alcoholic foamy degeneration (AFD).

Supplementary Table 1. NIAAA and NIAAAm-CRP Clinical Criteria for the Diagnosis of Probable Alcohol-Associated Hepatitis

NIAAA clinical criteria
1. Onset of jaundice within prior 8 weeks.
2. Ongoing consumption of >40 g (female) or >60 g (males) alcohol/d for ≥6 months, with <60 days of abstinence before the onset of jaundice
3. Aspartate aminotransferase level >50 IU/L, aspartate aminotransferase/alanine aminotransferase ratio >1.5, and both values <400 IU/L
4. Total serum bilirubin level >3.0 mg/dL
5. Absence of potential confounding factors[a]
NIAAAm-CRP clinical criteria
1. Onset of jaundice within prior 8 weeks
2. Ongoing consumption of >40 g (female) or 60 g (males) alcohol/day for ≥6 months, with <120 days of abstinence before the onset of jaundice
3. Aspartate aminotransferase level ≥50 IU/L, aspartate aminotransferase > alanine aminotransferase
4. Total serum bilirubin level ≥2.5 mg/dL
5. C-reactive protein ≥1 mg/dL

NIAAA, National Institute of Alcohol Abuse and Alcoholism; NIAAAm-CRP, modified National Institute of Alcohol Abuse and Alcoholism–C-reactive protein.
[a]Confounding factors included the following: possible ischemic hepatitis (ie, severe upper gastrointestinal bleeding, hypotension, or cocaine use within 7 days), possible drug-induced liver injury, uncertain alcohol use assessment, and atypical laboratory tests such as antinuclear antibody >1:160 or smooth-muscle antibodies >1:80.

Supplementary Table 2. Performance of NIAAA Criteria and NIAAAm-CRP Criteria for the Differential Diagnosis of Patients With AFD and AH

	AH	AFD	Total		AH	AFD	Total
NIAAA+	129 (70)	10 (56)	139 (69)	NIAAAm-CRP+	123 (73)	6 (55)	129 (72)
NIAAA-	55 (30)	8 (44)	63 (31)	NIAAAm-CRP-	45 (27)	5 (45)	50 (28)
Total	184	18	202	Total	168	11	179

	Value, %	95% CI		Value, %	95% CI
Sensitivity	70	63–77	Sensitivity	73	66–80
Specificity	44	22–69	Specificity	45	17–77
PPV[a]	83	77–89	PPV[a]	84	76–90
NPV[a]	27	17–39	NPV[a]	30	17–46
Diagnostic accuracy[a]	65	58–72	Diagnostic accuracy[a]	68	60–74

NOTE. Neither NIAAA (odds ratio, 1.88; 95% CI, 0.70–5.01) nor NIAAAm-CRP (odds ratio, 2.28; 95% CI, 0.66–7.83) criteria were able to differentiate alcoholic foamy degeneration from alcohol-associated hepatitis. Values shown are the absolute count (percentage) for the top half of the table and the percentage for the bottom half of the table.
AFD, alcoholic foamy degeneration; AH, alcohol-associated hepatitis; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIAAAm-CRP, modified National Institute on Alcohol Abuse and Alcoholism–C-reactive protein; NPV, negative predictive value; PPV, positive predictive value.
[a]Values shown are considering the prevalence of alcohol-associated hepatitis in this cohort (80%).

ARTICLE 2

RECURRENT ALCOHOL-ASSOCIATED HEPATITIS IS COMMON AND IS ASSOCIATED WITH INCREASED MORTALITY

Jordi Gratacós-Ginès, Pilar Ruz-Zafra, Miriam Celada-Sendino, Aina Martí-Carretero, Clàudia Pujol, Rosa Martín-Mateos… Elisa Pose; REHALC registry investigators

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RECURRENT ALCOHOL-ASSOCIATED HEPATITIS IS COMMON AND IS ASSOCIATED WITH INCREASED MORTALITY

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KEYWORDS: Alcohol-related, relapse, prognosis, survival, cirrhosis.

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CONFLICTS OF INTEREST: Ramon Bataller is on the speakers' bureau for AbbVie and Gilead. All other authors report no conflicts.

AUTHOR CONTRIBUTIONS:

JGG: Conceptualization, methodology, formal analysis, investigation, writing original draft, visualization. JC: Conceptualization, supervision. EP: Conceptualization, methodology, writing original draft, project administration. All the other authors contributed to patient and data recruitment, as well as manuscript review and editing.

LIST OF ABBREVIATIONS

ACLF: Acute-on-chronic liver failure

AH: Alcohol-associated hepatitis

AKI: Acute kidney injury

EASL-CLIF: European association for the study of the liver, chronic liver failure

EtG: Ethyl glucuronide

GGT: Gamma-glutamyl transferase

HR: Hazards ratio

ICD-10: International Classification of Diseases, 10th revision

INR: International normalized ratio

MAH: Moderate alcohol-associated hepatitis

MELD: Model for end-stage liver disease

OR: Odds ratio

RAH: Recurrent alcohol-associated hepatitis

SAH: Severe alcohol-associated hepatitis

ABSTRACT

Background: Alcohol relapse after surviving an episode of alcohol-associated hepatitis (AH) is common. However, the clinical features, risk factors and prognostic implications of recurrent AH (RAH) are not well described.

Methods: A registry-based study of patients admitted to 28 Spanish hospitals for an episode of AH between 2014 and 2021. Baseline demographics and laboratory variables were collected. Risk factors for RAH were investigated using Cox regression analysis. We analyzed the severity of the index episodes of AH and compared it to that of RAH. Long-term survival was assessed by Kaplan-Meier curves and log-rank test.

Results: A total of 1,118 patients were included in the analysis, 125 (11%) of whom developed RAH during follow-up (median: 17 [7-36] months). The incidence of RAH in patients resuming alcohol use was 22%. Median time to recurrence was 14 (8-29) months. Patients with RAH had more psychiatric comorbidities. Risk factors for developing RAH included age <50 years, alcohol use >10 units/day and history of liver decompensation. RAH was clinically more severe compared to first AH (higher MELD, more frequent ACLF and hepatic encephalopathy). Moreover, alcohol abstinence during follow-up was less common after RAH (18% vs 45%, p<0.001). Most importantly, long-term mortality was higher in patients who developed RAH (39% vs 21%, p=0.026) and presenting with RAH independently predicted high mortality (HR 1.55 [1.11-2.18]).

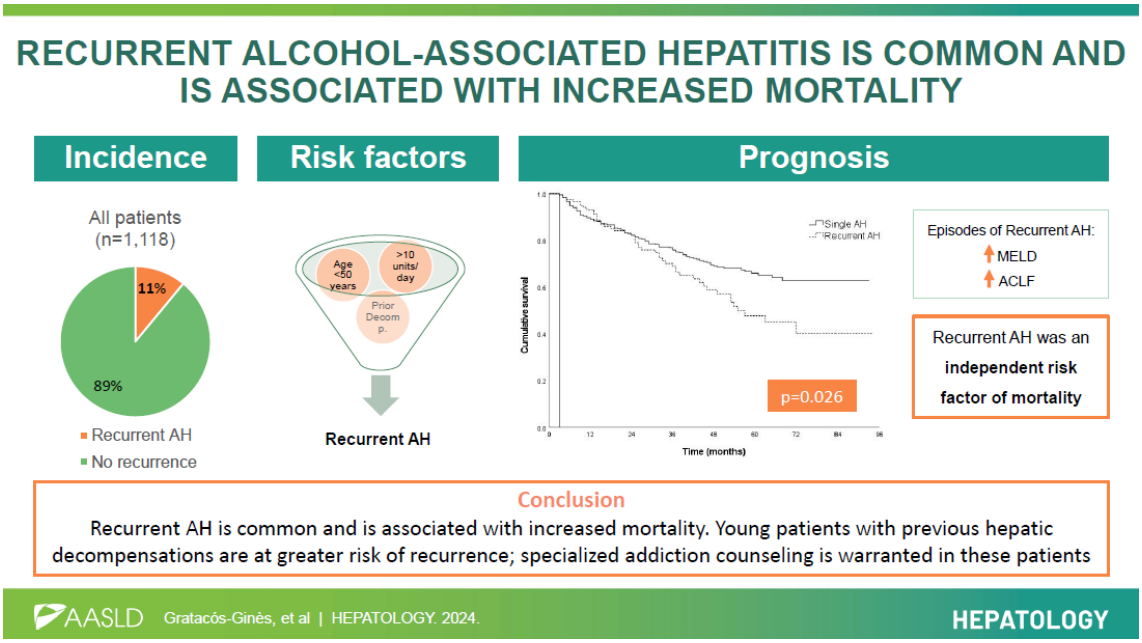
Conclusions: RAH is common and has a more aggressive clinical course, including increased mortality. Patients surviving an episode of AH should undergo intense alcohol use disorder therapy to prevent RAH.

Abstract word count: 248.

LAY SUMMARY

- Repeated episodes of alcohol-associated hepatitis are common.
- People younger than 50 years of age are more likely to present a repeated episode of alcohol-associated hepatitis.
- Importantly, patients with repeated episodes have higher risk of death.

GRAPHICAL ABSTRACT



INTRODUCTION

Alcohol-associated hepatitis (AH) is a clinical entity that may develop in patients with underlying alcohol-associated liver disease at any stage and active alcohol use. It is characterized by recent onset of jaundice and malaise, and it is frequently associated with acute decompensation of liver disease. In severe cases, a systemic inflammatory response develops, which may lead to bacterial infections, acute-on-chronic liver failure (ACLF) and death(1).

Alcohol-associated hepatitis places a significant burden on global health. Although the epidemiology of AH has not been well-studied, recent reports suggest an increase in the incidence of the disease, mainly in young adults(2). Moreover, mortality rates are high across the severity spectrum of the disease, ranging from 10-20% at 1 year in moderate AH (MAH)(3–5), to more than 30% at 28 days in severe AH (SAH) and non-response to corticosteroids(6–9). Finally, health expenditures associated to AH are high due to frequent development of complications requiring a high amount of resources and need for re-admissions in survivors(10–12).

The cornerstone in the management of patients after an episode of AH is the achievement of long-term alcohol abstinence, which has been consistently shown to be the main predictive factor of long-term survival(13–15). Published data regarding cumulative incidence rates of alcohol relapse after one episode of AH are conflicting. In Europe, these rates range from 35% to 65% at 5 years (14–16), while in the United States they seem higher, with reported rates as high as 37% at 30 days(12). Patients who resume alcohol consumption during follow-up are at high risk of developing further complications of liver disease(14,17,18). One of these complications could be a new episode of AH, a phenomenon which has been termed as recurrent AH (RAH)(19). Despite there being a notable proportion of patients resuming alcohol consumption after the diagnosis of AH, the clinical features of RAH have not been adequately described. To the best of our knowledge, only one small retrospective case series describing patients with RAH has been published to date(19).

The aims of this study were to assess the incidence of RAH, to characterize the episodes as well as to identify those patients who are most likely to develop RAH after surviving an AH episode, and to determine the impact of RAH on survival.

PATIENTS AND METHODS

Study design and population

We performed a retrospective registry-based study of patients admitted to 28 Spanish hospitals for an episode of AH between January 1st 2014 and December 31st 2021. Patients with International Classification of Diseases, 10th revision (ICD-10) codes for AH (K70.10: Alcoholic hepatitis without ascites; and K70.11: Alcoholic hepatitis with ascites) as primary or secondary diagnoses were considered for inclusion. Patients who had history of AH prior to 2014 were not included in the study. AH was defined as according to the National Institute on Alcohol Abuse and Alcoholism criteria as "probable" or "definite" when a liver biopsy was performed to establish the diagnosis (Supplementary Table 1). First AH was defined as an episode of "probable" or "definite" AH in a patient with no previous history of AH. Recurrent AH was defined as any episode of "probable" or "definite" AH occurring at least 3 months after a previous episode, in a patient with history of AH during the study period. Admissions within 3 months of a previous AH episode were considered to be related to the index AH.

Exclusion criteria were: i) hepatocellular carcinoma exceeding the Milan criteria; ii) previous liver transplant; or iii) severe extrahepatic disease, including extrahepatic neoplasia, with a life expectancy of <6 months.

For the purpose of the study, we performed two types of main analyses:

1) Patients alive after first AH, comparing those who presented RAH during follow-up vs. those who did not. Patients were considered to have survived an index AH if they were alive at the time of discharge from the hospital.

2) Episodes of AH, comparing all first AH vs. all RAH, as well as paired episodes: first AH vs. RAH developing in the same patients. In this analysis we assessed all episodes, including those resulting in death during the first admission.

We also performed sensitivity analyses in a) SAH vs. MAH; and b) RAH presenting before vs. after the start of the COVID-19 pandemic in Spain (March 2020).

Both MELD score and Maddrey's discriminant function score were used to classify AH episodes based on severity: SAH if MELD >20 or Maddrey's ≥32; MAH if MELD ≤20 or Maddrey's <32.

Data collection

A careful review of the patients' medical records was performed by all participant centers. Data on demographics, substance use, comorbidities, previous history of liver disease, clinical presentation and laboratory tests at admission was collected. Acute kidney injury (AKI) was defined following the EASL Guidelines on Decompensated Cirrhosis(20). Acute-on-Chronic Liver Failure (ACLF) was defined according to the EASL-CLIF definition(21); due to the lack of detailed information on oxygen support in the patients' medical records, we adapted the definition of respiratory failure to the need of endotracheal intubation in the absence of West Haven's grade 3 and 4 hepatic encephalopathy as in previous studies(22). Furthermore, we gathered data on new decompensations of liver disease occurring during hospitalization.

Clinical information on follow-up was also collected, including mortality, cause of death and alcohol consumption. Assessment of alcohol consumption was based on data from the addiction unit and results of biomarkers to identify alcohol consumption (ethyl glucuronide, EtG) where available. In the remaining cases, information on alcohol consumption was obtained by patient self-reporting and/or by a family-member interview in the liver unit. Patients lost to follow-up and those with temporary alcohol relapses during follow-up were considered non abstinent on an assumption of worst-case scenario in regard to missing data.

Data collected for each episode of AH was recorded in independent confidential electronic case report forms. We created an electronic database in the Research Electronic Data Capture platform, which was managed by the main researcher of the study (JGG) and by an external professional appointed by the board of the *Asociación Española para el Estudio del Hígado* (AEEH).

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared by Chi square or Fischer's tests. Quantitative variables were expressed as median and interquartile range (25^{th} – 75^{th} percentile) and were analyzed using T-test (normal distribution), Mann-Whitney test (non-normal distribution) or Wilcoxon. Factors associated to recurrence of AH and death were studied with Cox regression analysis and expressed as hazards ratio (HR). For the multivariate analyses, we included variables

with a *p* value <0.05 in the univariate analyses and those that were deemed clinically relevant (i.e., sex). The Youden Index was applied to continuous variables to identify the value with the best performance. Survival curves were calculated with the Kaplan-Meier model and compared with log-rank test. For the survival analysis, patients who underwent a liver transplant were censored at the time of transplant. Transplant-free survival was also assessed. A competing risk analysis was not performed owing to the low incidence of liver transplantation (<5% of the study population). Given that the definition of RAH used implied a 3-month survival after the first AH episode, patients who died or were lost to follow-up within 3 months from the first admission were excluded from patient survival analysis, but were included in all other patient analyses as well as episode analyses. The significance level for all statistical tests was set at 0.05 two-tailed. All statistical analyses were performed using SPSS version 25.0.0.1.

Ethical aspects

All research was conducted in accordance with both the Declaration of Helsinki and Istanbul. The study protocol was approved by the Ethics Committee of Hospital Clinic of Barcelona in March 2021 and received a waiver of informed consent. It was also approved by the Ethics Committees of all the participating centers in the months following.

RESULTS

Baseline characteristics and incidence of RAH

In the study period, 1,285 patients were admitted with the clinical diagnosis of AH. One hundred sixty-seven patients were excluded from the analysis. The main cause for exclusion from patient analysis was death during first admission (n=154), to include only patients at risk of RAH. Of the remaining 1,118 patients, 125 (11%) presented RAH during follow-up (Fig. 1). Thirty-eight (3%) patients experienced multiple recurrences; the greatest number of recurrent episodes diagnosed in a single patient was 3. Median follow-up was 17 [7-36] months and median time to recurrence was 14 (8-29) months. Baseline characteristics are shown in Table 1. At first presentation, patients who later developed RAH were younger, had a higher proportion of psychiatric comorbidity as well

as previous history of hepatic decompensations. Ascites was the most frequent previous liver decompensation (34%), followed by overt hepatic encephalopathy (13%).

Out of 1,118 patients included, 439 (39%) had a specialized follow-up in an addiction unit (EtG available in 151 [34%]), 560 (50%) did not and in 119 (11%) data on addiction follow-up were missing. As expected, alcohol consumption rates after discharge were different between patients who developed RAH and patients who did not (100% vs 51% patients resumed alcohol consumption after the index episode, respectively, $p<0.001$). When considering only patients who resumed alcohol consumption during the 17-month follow-up (n=569, 51%), the incidence of RAH was 22% (Fig. 2). In this subgroup of patients, baseline characteristics were similar to those of the total study cohort (Supplementary Table 2).

Out of the 1,118 patients with AH, 690 (62%) presented with SAH and of these, 72 (10%) presented recurrent SAH during follow-up. Demographics and previous history of these patients were highly comparable to those of the total cohort (Supplementary Table 3).

Alcohol consumption rates after discharge among patients with SAH were equivalent to those of the total cohort (100% in recurrent SAH during follow-up vs 51% in patients without recurrence, $p<0.001$).

Risk factors for RAH

We analyzed the factors associated to AH recurrence in the study cohort. The univariate Cox regression analysis identified age <50 years, history of psychiatric comorbidity and hepatic decompensations, alcohol use >10 units/day and other drug use (not including tobacco). In the multivariate Cox regression analysis, age <50 years (HR 1.99 [1.36-2.91]), alcohol use >10 units/day (HR 1.58 [1.09-2.30]) and prior hepatic decompensations (HR 2.58 [1.76-3.77]) remained as independent risk factors of AH recurrence (Table 2). An additional multivariate Cox regression analysis was performed adding the follow-up variable of alcohol consumption. In this model, besides resuming alcohol consumption, age <50 years and a history of liver decompensations were still shown to be independent risk factors of recurrence (Supplementary Table 4).

In the subgroup of patients with SAH, factors independently associated to recurrence were age <50 years (HR 2.06 [1.27-3.36]) and prior hepatic decompensation (HR 2.19 [1.35-3.55]).

Characteristics and severity of first AH vs. RAH episodes

We next compared the characteristics of all first vs. all recurrent AH episodes, including episodes occurring in patients who died within 3 months of the first admission. During the study period, we recorded 1,446 admissions due to AH. Of those, 171 (11.8%) were classified as RAH and 1,275 (88.2%) as first AH. Median follow-up was 11 [3-24] months after RAH and 15 [6-32] months after first AH. The main characteristics of the episodes are shown in Table 3. Notably, episodes of RAH were more severe as shown by significant differences in multiple relevant prognostic variables: higher Maddrey's discriminant function, MELD and Child-Pugh scores, lower platelet count and higher INR. We also found a higher proportion of ACLF at admission, with no significant differences in the percentages of individual organ failures (Supplementary Table 5). In addition, the development of overt hepatic encephalopathy during hospitalization was also more frequent when being admitted for RAH.

The analysis of paired episodes of first AH and first RAH revealed very similar findings (Supplementary Table 6); admissions due to RAH had a higher Maddrey's discriminant function, plus higher MELD and Child-Pugh scores. Moreover, a greater impairment in liver function was shown with every further recurrence (Supplementary Table 7). A non-statistically significant trend towards higher proportion of ACLF at admission in RAH was also observed when analyzing paired episodes. On this analysis, recurrent admissions had a higher percentage of renal failure, as well as trends towards greater proportion of organ failure in the remaining systems (Supplementary Table 8).

Interestingly, the probability of maintaining alcohol abstinence throughout the follow-up period was notably lower after an episode of RAH than after a first AH (18% vs. 45%, $p<0.001$; OR for RAH: 0.29 [0.18-0.45]). Of note, neither the disease severity at first presentation (SAH or MAH) nor the steroid response based on Lille score at day 7 <0.45 were associated with alcohol abstinence, although there was a trend towards higher abstinence rates after SAH when compared to MAH (OR for abstinence in SAH: 1.25 [0.97-1.61]).

When performing a sensitivity analysis in SAH episodes, we found 974 (67%); of those, 847 (86%) were first AH and 132 (14%) were RAH. Liver tests and liver function scores were similar between first and RAH episodes. Of note, development of hepatic encephalopathy during hospitalization was significantly more common in RAH (31% vs

44%, *p*=0.003). As regards to treatment, episodes of RAH were less frequently treated with steroids (68% vs 55%, *p*=0.002), although response rates were comparable (49% vs 58%, *p*=0.134). The main characteristics of these episodes are shown in Supplementary Table 9.

We performed a sub-analysis of RAH from the prepandemic vs. pandemic periods. Interestingly, we found no differences in liver function tests and prevalence of decompensation and ACLF (Supplementary Table 10). Survival of RAH was not significantly different when comparing patients diagnosed in the prepandemic vs pandemic periods (78% vs 65% at 1 year, *p*=0.084). Furthermore, the time of presentation was not associated to higher alcohol abstinence (OR for prepandemic period: 1.61 [0.61-4.28]).

Survival of the study cohort and effect of RAH on prognosis

At the time of the last follow-up visit, 47 (39%) patients who developed RAH had died, compared to 150 (21%) patients who did not develop RAH (*p*=0.026) (Fig. 3). Causes of death in both groups are listed in Supplementary Table 11. Fifty-five (5%) patients underwent liver transplantation during follow-up, 50 in the group of patients without RAH and 5 in the group of RAH. A trend towards lower transplant-free survival in patients with RAH was also observed (58% in RAH vs. 75% in patients without RAH, *p*=0.176). One hundred fifty-six (14%) patients were lost to follow-up and thus not included in the survival analyses.

As the episodes of RAH were more severe in terms of liver function impairment and presence of ACLF, we also aimed at assessing the impact of these episodes on survival by comparing the survival rates at different time points after presenting a first AH and a RAH. Notably, survival was lower after RAH compared to first AH at every point in time, although statistical significance was only reached after 12 months of follow-up (Table 4A).

Survival rates at different time points in the subgroup of SAH and MAH are shown in Table 4B and 4C, respectively. In SAH, survival was lower after RAH compared to first AH throughout the follow-up, but statistical significance was only observed beyond 24

months in this subpopulation. In MAH, survival rates were lower after RAH only beyond 12 months and, similarly, statistical significance was reached at 24 and 36 months.

To further identify the impact of RAH on survival, we analyzed the baseline factors that were associated with mortality in this cohort. Interestingly, presenting RAH was one of them (HR 1.53 [1.05-2.23]). Other independent factors associated with mortality were older age, ACLF at admission, higher leukocyte count, lower platelet count and higher values of MELD and Child-Pugh scores (Table 5).

DISCUSSION

In this study, we have described the clinical features of RAH in a large and multicentric cohort of patients. To our knowledge, this is the first large study assessing this clinical condition. We have determined the risk factors that identify the subgroup of patients at higher risk for RAH and demonstrated that recurrent episodes are intrinsically more severe and have a notable impact on prognosis.

In our study cohort, in addition to alcohol relapse, which is a *sine qua non* condition for the development of RAH, age <50 years and previous decompensations of liver disease were also risk factors for RAH. The fact that younger age was found to be an independent risk factor for recurrence might reflect a more severe alcohol use disorder with different drinking patterns(23) in these patients or even an intrinsic tendency of some individuals to progress to more severe forms of liver disease. Moreover, considering that recent studies have pointed to a higher incidence of AH in younger patients(2), greater attention should be paid in the coming years to the possibility of increased admissions due to RAH. The association between prior decompensations and AH recurrence suggests that patients with more advanced disease are at higher risk of recurrence. Furthermore, studies in post-liver transplant patients have also found an association between this variable and increased mortality and harmful use of alcohol(24), which supports our findings. However, a survival benefit of early liver transplantation was observed in patients with previous decompensations, suggesting that patients with RAH may also be candidates for early liver transplantation. Nevertheless, taking into account the high rates of alcohol relapse in our study, this indication should be taken with caution and only considered in highly selected patients.

Patients presenting with RAH constitute a population with an alarming severity of alcohol use disorder, as patients resumed alcohol consumption even after experiencing a previous AH episode, a clinical event that is associated with high morbidity and mortality. Alcohol abstinence rates in our study remained extremely low even after RAH, as more than 80% of the patients resumed alcohol consumption during follow-up. These results support the need for targeted and specialized treatment for alcohol use disorder in patients at risk of RAH and in patients presenting with RAH. The optimal treatment should be based on the combination of addiction counseling and pharmacological therapy, which has shown to be safe and to improve alcohol abstinence rates in patients with advanced liver disease in a recent systematic review and meta-analysis(25). However, few patients with AH were included in this study and, therefore, further research is needed to confirm these findings in this specific population.

In this study we also described the characteristics of the RAH episodes. We found that these episodes are clinically more severe, as shown by a higher proportion of ACLF, worse liver function and lower platelets levels, as an indirect marker of more severe portal hypertension. Moreover, patients admitted for RAH were more prone to developing hepatic encephalopathy during hospitalization. All these features, together with the fact that these patients already have a higher proportion of previous liver-related complications, suggest that RAH is possibly taking place in more advanced stages of liver disease. A relevant message for hepatologists treating patients with AH would be that patients presenting a recurrent episode of AH have *per se* a greater probability of developing complications of liver disease and dying from liver-related causes. Furthermore, a second hospitalization for AH reflects an uncontrolled alcohol addiction, which limits significantly the access to early liver transplantation thus hindering yet further the survival of these patients. Consequently, close monitoring to rule out complications, infections and organ failures is needed to decrease mortality rates in these patients.

This study has some limitations that should be acknowledged. First, patients were selected based on ICD-10 codes; although this is an accepted and widely-used strategy in registry-based studies(26,27), the possibility of certain selection bias due to miscoding of patients cannot be excluded. The fact that patient information was collected retrospectively using medical records may also add bias. However, this limitation was

partially overcome by the multicentric design including mostly tertiary care centers and by performing a close monitoring of the database, guaranteeing the granularity of the data. Moreover, Spanish health care system shares electronic medical records with all public health institutions, so the possibility of missing relevant clinical information is very low. Additionally, lost to follow-up rate in our study was low compared to previous cohort studies in patients with AH (28), which is a major strength of our study. Finally, an additional limitation may be the arbitrary requirement of a minimum 3-month span between episodes of AH to consider the second admission as a recurrence. Nevertheless, studies on natural history of AH have described this period as the time frame in which the changes in liver function may be attributable to AH (29,30). Furthermore, the paired analysis indicated worsening of liver function in recurrent admissions, supporting the idea that second admissions were indeed new episodes of AH.

In conclusion, RAH is common in patients with a prior AH, it is intrinsically more severe compared to first AH and is associated with increased mortality. Close monitoring and specialized addiction therapy in follow-up should be considered for all patients with AH, with special attention being given to younger patients who have a history of prior hepatic decompensations, especially if they are being admitted for a recurrent episode of AH.

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Note: author names in **bold** designate shared co-first authorship.

SUMMARY OF TABLES AND FIGURES

	Patients without RAH during follow-up (n = 993)	Patients with RAH during follow-up (n = 125)	*p* value
Age (years)	52 (45-58)	47 (41-55)	**<0.001**
Sex (female)	271 (27)	36 (29)	0.742
Marital status (married/partner)[a]	270 (42)	36 (41)	0.979
Residence in rural area[a]	293 (45)	36 (36)	0.101
Working status (active worker)[a]	186 (31)	23 (28)	0.364
Education (college/university)[b]	119 (25)	14 (22)	0.538
Obesity (BMI >30)[c]	169 (21)	22 (21)	0.878
Type 2 diabetes	109 (11)	13 (11)	0.845
Psychiatric comorbidity	206 (21)	36 (29)	**0.043**
Alcohol use (units/day)	10 (6-13)	10 (7-15)	0.174
Duration of alcohol use (years)	20 (12-30)	23 (15-31)	0.299
Binge drinking[a]	361 (60)	58 (60)	0.904
Tobacco use[d]	559 (59)	75 (64)	0.658
Other drug use[d]	119 (13)	22 (19)	0.096
Clinical stage of liver disease before admission			**0.004**
No history of liver disease	460 (46)	41 (32)	
Fibrosis without cirrhosis	75 (8)	11 (9)	
Compensated cirrhosis	235 (24)	28 (22)	
Decompensated cirrhosis	165 (17)	37 (30)	
Other[e]	58 (6)	8 (6)	
Previous hepatic decompensation	225 (23)	48 (39)	**<0.001**
Ascites	200 (20)	42 (34)	**<0.001**
Spontaneous bacterial peritonitis	14 (1)	7 (6)	**0.001**
Overt hepatic encephalopathy	47 (5)	16 (13)	**<0.001**
Bleeding due to PHT	52 (5)	13 (10)	**0.018**

Table 1. Baseline demographics and previous history of patients included in the study, divided in two groups depending on the status of recurrence at the end of follow-up.

[a]Missing datum in 30-40%.
[b]Missing datum in 50-60%.
[c]Missing datum in <20%.
[d]Missing datum in <5%.
[e]Viral hepatitis without fibrosis (n=12), metabolic dysfunction-associated steatotic liver disease (n=43), not specified (n=11).
Values are absolute count (percentage).
Abbreviations: BMI, body mass index; PHT, portal hypertension; RAH; recurrent alcohol-associated hepatitis.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	***p* value**	**95% CI**	**HR**	***p* value**	**95% CI**
Age < 50 (years)	**1.969**	**<0.001**	**1.374-2.821**	**1.988**	**<0.001**	**1.356-2.914**
Sex (female)	0.881	0.523	0.598-1.298	0.889	0.581	0.584-1.351
Psychiatric comorbidity	**1.481**	**0.047**	**1.005-2.183**	1.427	0.085	0.952-2.139
Alcohol use >10 units/day	**1.591**	**0.010**	**1.117-2.266**	**1.583**	**0.016**	**1.091-2.297**
Duration of alcohol use (years)	1.007	0.471	0.988-1.025			
Tobacco use	1.220	0.300	0.838-1.775			
Other drug use	**1.633**	**0.039**	**1.026-2.600**	1.053	0.839	0.641-1.730
Previous hepatic decompensation	**2.309**	**<0.001**	**1.605-3.321**	**2.575**	**<0.001**	**1.758-3.771**

Table 2. Univariate and multivariate analysis of baseline risk factors for AH recurrence.

Abbreviations: CI, confidence interval; HR, hazards ratio.

	First AH (n = 1,275)	Recurrent AH (n = 171)	*p* value
Hepatic decompensation at admission	771 (60)	105 (61)	0.852
Ascites	702 (55)	89 (52)	0.407
Spontaneous bacterial peritonitis	48 (4)	2 (1)	0.079
Overt hepatic encephalopathy	233 (18)	41 (24)	0.073
Bleeding due to PHT	72 (6)	10 (6)	0.914
Bacterial infection at admission	224 (18)	34 (20)	0.464
Acute kidney injury at admission	202 (16)	27 (16)	0.977
Acute-on-chronic liver failure at admission	163 (13)	33 (19)	**0.025**
SAH	847 (66)	132 (77)	**0.004**
Laboratory tests			
C-reactive protein (mg/dL)	4.2 (1.7-10.5)	5.0 (1.9-13.3)	0.413
Serum creatinine (mg/dL)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.625
AST(IU/L)	143 (100-219)	154 (110-225)	0.260
ALT (IU/L)	54 (36-82)	55 (37-80)	0.879
GGT (IU/L)	425 (169-1052)	279 (146-700)	**0.007**
AP (IU/L)	172 (124-254)	179 (123-236)	0.502
Total bilirubin (mg/dL)	8.8 (5.5-15.2)	10.3 (6.2-16.0)	0.059
Albumin (g/L)	27 (24-31)	26 (23-30)	0.053
Leukocytes (x10^9/L)	7.9 (5.8-11.4)	7.1 (5.2-10.0)	**0.007**
Platelets (x10^9/L)	99 (66-154)	79 (44-109)	**<0.001**
INR	1.6 (1.4-2.0)	1.8 (1.4-2.1)	**0.004**
Liver function scores			
Maddrey's discriminant function	40 (25-60)	43 (31-64)	**0.037**
MELD	21 (17-25)	22 (19-26)	**0.005**
ABIC	7.7 (6.8-8.7)	7.8 (6.9-8.6)	0.861
Child-Pugh score	10 (9-11)	10 (9-12)	**0.037**
Complications during hospitalization			
Spontaneous bacterial peritonitis	57 (4)	9 (5)	0.667
Overt hepatic encephalopathy	292 (23)	61 (36)	**<0.001**
Bleeding due to PHT	76 (6)	14 (8)	0.262
Bacterial infection	361 (28)	53 (31)	0.478

Table 3. Main characteristics of first AH and RAH episodes.

[a]Include N-acetylcysteine, enteral nutrition and pentoxifylline.
Values are median (± interquartile range) or absolute count (percentage).
Abbreviations: ABIC, age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IU, international units; MELD, model for end-stage liver disease; PHT, portal hypertension; SAH: severe alcohol-associated hepatitis.

A)	First AH (n = 1,218)[a]	Recurrent AH (n = 162)[a]	*p* value[c]
Alive at 1 month	1,093 (90)	140 (86)	0.198
Alive at 3 months	1,013 (83)	132 (82)	0.591
Alive at 6 months	973 (80)	120 (74)	0.077
Alive at 12 months	897 (75)	104 (64)	**0.008**
Alive at 24 months	823 (70)	87 (54)	**<0.001**
Alive at 36 months	775 (67)	84 (52)	**<0.001**
B)	**First SAH (n = 812)[a]**	**Recurrent SAH (n = 125)[a]**	***p* value[c]**
Alive at 1 month	692 (85)	103 (82)	0.413
Alive at 3 months	619 (76)	95 (76)	0.995
Alive at 6 months	586 (72)	84 (67)	0.252
Alive at 12 months	528 (66)	73 (58)	0.105
Alive at 24 months	473 (60)	60 (48)	**0.010**
Alive at 36 months	441 (57)	58 (46)	**0.025**
C)	**First MAH (n = 401)[b]**	**Recurrent MAH (n = 37)[b]**	***p* value[c]**
Alive at 1 month	396 (99)	37 (100)	1.000
Alive at 3 months	390 (97)	37 (100)	0.610
Alive at 6 months	383 (96)	36 (97)	1.000
Alive at 12 months	365 (92)	32 (87)	0.217
Alive at 24 months	346 (89)	28 (76)	**0.031**
Alive at 36 months	330 (88)	27 (73)	**0.021**

Table 4. Survival rates at different time points after an episode of first AH vs. RAH in A) the total cohort; B) the subgroup of SAH episodes; and C) the subgroup of MAH. First AH episodes were censored at time of recurrence.

[a]Information on outcome missing in <5%.
[b]Information on outcome missing in 5-10%.
[c]Chi-square test.
Abbreviations: AH, alcohol-associated hepatitis; LT, liver transplantation.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	***p* value**	**95% CI**	**HR**	***p* value**	**95% CI**
Age (years)	**1.035**	**<0.001**	**1.025-1.046**	**1.034**	**<0.001**	**1.018-1.049**
Sex (female)	0.834	0.098	0.673-1.034	0.825	0.198	0.616-1.105
Alcohol use >10 units/day	1.103	0.323	0.908-1.340			
Obesity	**1.504**	**<0.001**	**1.181-1.914**	1.207	0.207	0.901-1.618
Type 2 diabetes	**1.472**	**0.004**	**1.131-1.917**	1.305	0.155	0.904-1.884
Recurrent AH	**1.414**	**0.012**	**1.077-1.855**	**1.529**	**0.028**	**1.048-2.230**
Previous hepatic decompensation	**1.729**	**<0.001**	**1.425-2.098**	1.049	0.749	0.781-1.409
Decompensation at admission	**2.111**	**<0.001**	**1.697-2.627**	0.965	0.849	0.668-1.394
Bacterial infection at admission	**1.392**	**0.004**	**1.109-1.748**	1.048	0.773	0.762-1.442
ACLF at admission	**2.766**	**<0.001**	**2.213-3.458**	**1.438**	**0.031**	**1.033-2.002**
C-reactive protein at admission	0.996	0.397	0.988-1.005			
AST (IU/L)	0.999	0.128	0.998-1.000			
ALT (IU/L)	**0.996**	**0.002**	**0.994-0.999**	1.000	0.698	0.997-1.002
GGT ([IU/L]x10)	**0.992**	**<0.001**	**0.990-0.994**	0.998	0.186	0.995-1.001
AP (IU/L)	**0.998**	**<0.001**	**0.997-0.998**	0.999	0.284	0.998-1.001
Albumin (g/L)	**0.942**	**<0.001**	**0.924-0.960**	0.987	0.369	0.959-1.016
Leukocytes (x10^9/L)	**1.019**	**0.044**	**1.001-1.037**	**1.034**	**0.024**	**1.004-1.065**
Platelets (x10^9/L)	**0.996**	**<0.001**	**0.995-0.998**	**0.997**	**0.005**	**0.995-0.999**
MELD score	**1.074**	**<0.001**	**1.064-1.083**	**1.042**	**<0.001**	**1.021-1.064**
Child-Pugh score	**1.467**	**<0.001**	**1.371-1.571**	**1.187**	**0.014**	**1.036-1.360**

Table 5. Univariate and multivariate analysis of baseline risk factors of mortality. Presenting with an episode of RAH was an independent risk factor of death.

Abbreviations: ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; CI, confidence interval; HR, hazard ratio; IU, international units; MELD, model for end-stage liver disease.

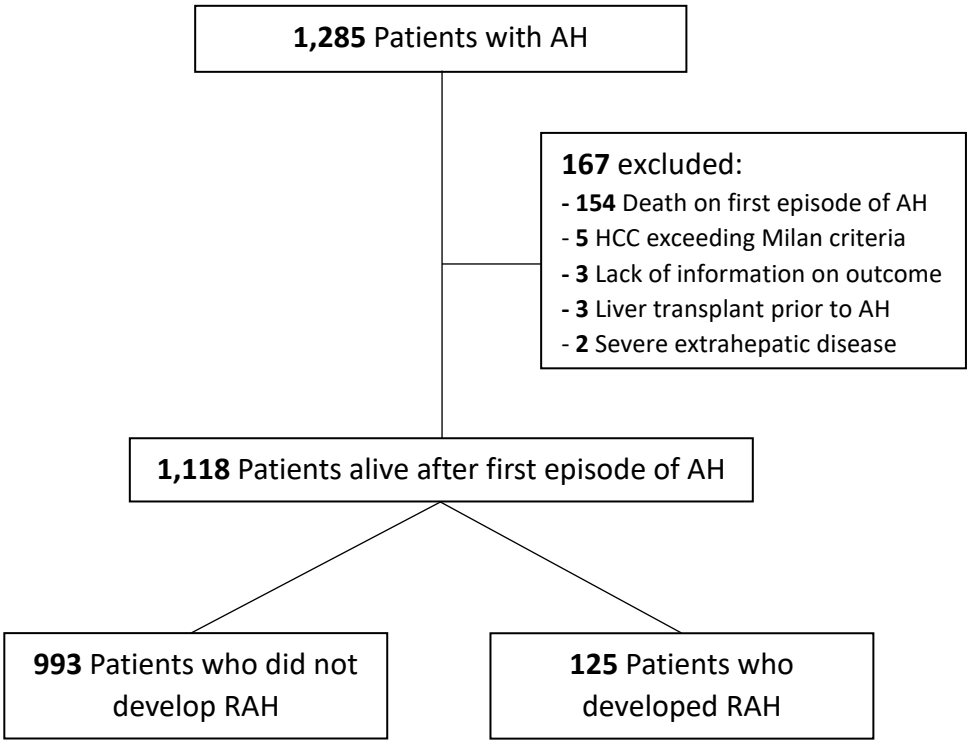

Figure 1. Study flowchart.

Abbreviations: AH, alcohol-associated hepatitis; HCC, hepatocellular carcinoma; RAH, recurrent alcohol-associated hepatitis.

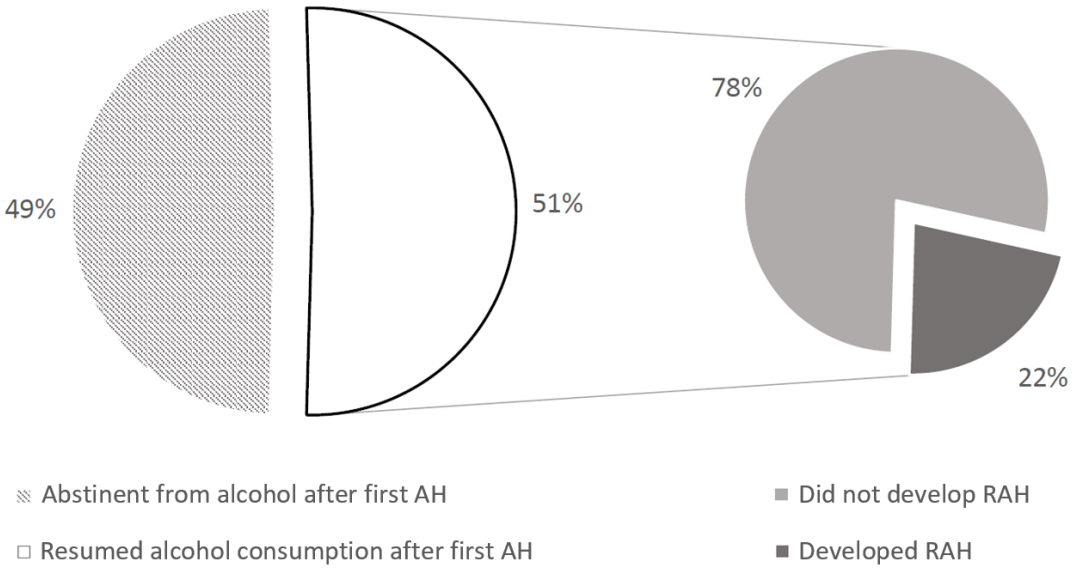

Figure 2. Incidence of RAH in patients who resumed alcohol consumption after surviving a first AH.

Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

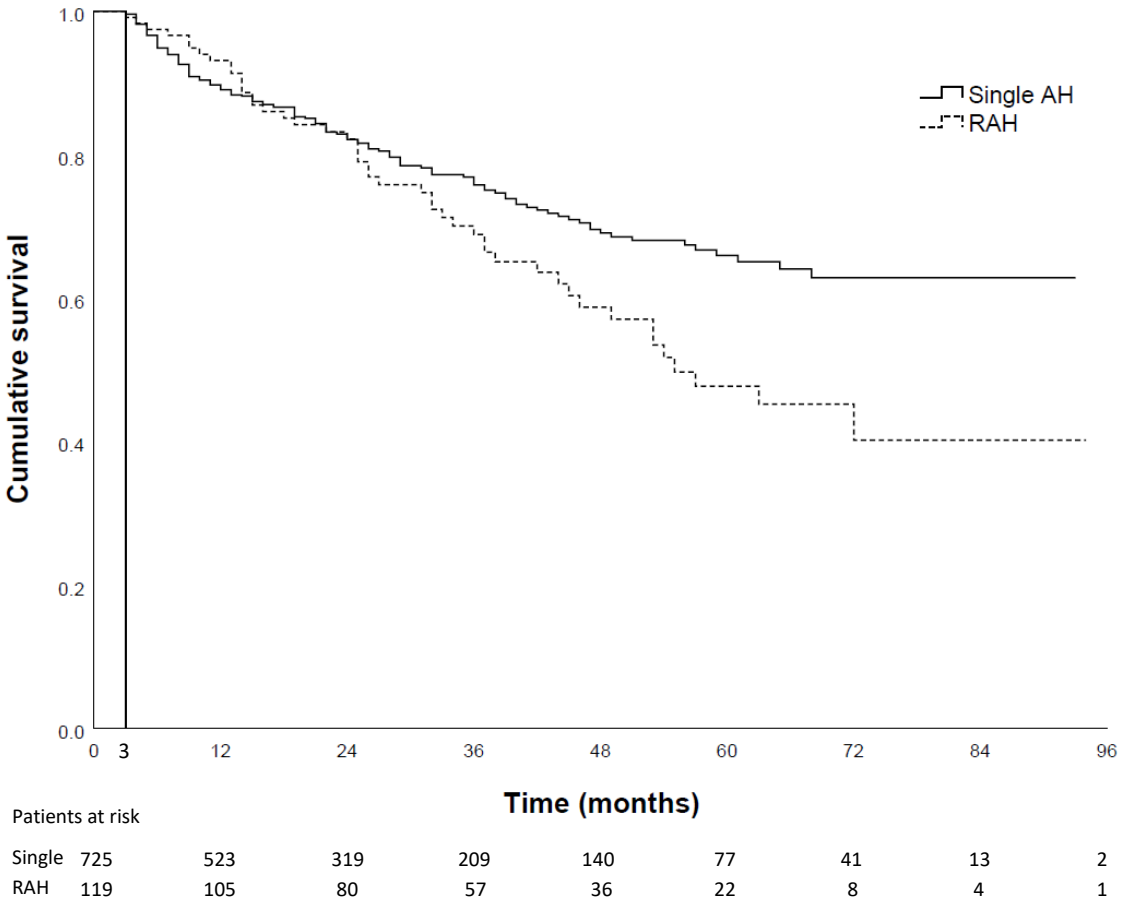

Figure 3. Kaplan-Meier curves showing the survival of patients who did not develop RAH during follow-up (single AH) and patients who did develop RAH (RAH). p = 0.026 (log-rank test).

Abbreviations: RAH, recurrent alcohol-associated hepatitis.

NIAAA clinical criteria:

1. Onset of jaundice within prior 8 weeks.
2. Ongoing consumption of >40 (female) or 60 (males) g alcohol/day for 6 months or more, with less than 60 days of abstinence before the onset of jaundice.
3. Aspartate aminotransferase >50 IU/L, aspartate aminotransferase/alanine aminotransferase ratio >1.5, and both values <400 IU/L.
4. Total serum bilirubin >3.0 mg/dL.
5. Absence of potential confounding factors*.

*Confounding factors included: possible ischemic hepatitis (i.e., severe upper gastrointestinal bleeding, hypotension, or cocaine use within 7 days); possible DILI; uncertain alcohol use assessment; and atypical laboratory tests such as antinuclear antibody >1:160 or SMA >1:80.

Supplementary Table 1. NIAAA clinical criteria for diagnosis of "probable alcohol-associated hepatitis".

Abbreviations: DILI, drug-induced liver injury; NIAAA, National Institute of Alcohol Abuse and Alcoholism; SMA, smooth-muscle antibodies.

	Patients without RAH during follow-up (n = 444)	Patients with RAH during follow-up (n = 125)	*p* value
Age (years)	50 (45-57)	47 (41-55)	**0.002**
Sex (female)	117 (27)	36 (29)	0.604
Marital status (married/partner)[a]	102 (35)	36 (41)	0.516
Residence in rural community[a]	122 (41)	36 (36)	0.345
Working status (active worker)[a]	79 (29)	23 (28)	0.881
Education (college/university)[b]	47 (23)	14 (22)	0.846
Obesity (BMI >30)[c]	75 (21)	22 (21)	0.972
Type 2 diabetes	52 (12)	13 (11)	0.675
Psychiatric comorbidity	102 (23)	36 (29)	0.199
Alcohol use (units/day)	10 (7-13)	10 (7-15)	0.474
Duration of alcohol use (years)	20 (10-30)	23 (15-31)	0.065
Binge drinking[a]	178 (64)	58 (61)	0.548
Tobacco use[d]	271 (64)	75 (64)	0.895
Other drug use[d]	67 (17)	22 (19)	0.621
Clinical stage of liver disease before admission			0.341
No history of liver disease	182 (41)	41 (32)	
Fibrosis without cirrhosis	34 (8)	11 (9)	
Compensated cirrhosis	106 (24)	28 (22)	
Decompensated cirrhosis	96 (22)	37 (30)	
Other[e]	26 (6)	8 (6)	
Previous hepatic decompensation	120 (27)	48 (39)	**0.011**
Ascites	109 (25)	42 (34)	**0.033**
Spontaneous bacterial peritonitis	7 (2)	7 (6)	**0.009**
Overt hepatic encephalopathy	29 (7)	16 (13)	**0.018**
Bleeding due to PHT	33 (7)	13 (10)	0.261

Supplementary Table 2. Baseline demographics and previous history of patients who resumed alcohol consumption after hospital discharge, divided in two groups depending on the status of recurrence at end of follow-up.

[a]Missing datum in 30-40%.
[b]Missing datum in 50-60%.
[c]Missing datum in <20%.
[d]Missing datum in <5%.
Values are absolute count (percentage).
Abbreviations: BMI, body mass index; PHT, portal hypertension; RAH; recurrent alcohol-associated hepatitis.

	Patients without recurrent SAH during follow-up (n = 618)	Patients with recurrent SAH during follow-up (n = 72)	*p* value
Age (years)	51 (45-57)	47 (44-52)	**<0.001**
Sex (female)	178 (29)	21 (29)	0.995
Marital status (married/partner)[a]	180 (44)	24 (47)	0.782
Residence in rural area[a]	182 (45)	24 (40)	0.605
Working status (active worker)[a]	103 (27)	11 (23)	0.780
Education (college/university)[b]	71 (24)	10 (26)	0.719
Obesity (BMI >30)[c]	125 (25)	11 (18)	0.238
Type 2 diabetes	66 (11)	6 (8)	0.524
Psychiatric comorbidity	117 (19)	18 (25)	0.222
Alcohol use (units/day)	10 (7-14)	10 (8-14)	0.244
Duration of alcohol use (years)	20 (13-30)	20 (15-30)	0.632
Binge drinking[a]	219 (60)	32 (55)	0.532
Tobacco use[d]	310 (53)	39 (57)	0.452
Other drug use[c]	70 (13)	11 (17)	0.377
Clinical stage of liver disease before admission			0.087
No history of liver disease	251 (41)	19 (26)	
Fibrosis without cirrhosis	37 (6)	6 (8)	
Compensated cirrhosis	166 (27)	19 (26)	
Decompensated cirrhosis	125 (20)	23 (32)	
Other[e]	37 (6)	5 (7)	
Previous hepatic decompensation	171 (28)	28 (40)	**0.034**
Ascites	156 (25)	24 (33)	0.095
Spontaneous bacterial peritonitis	9 (1)	4 (6)	**0.034**
Overt hepatic encephalopathy	36 (6)	10 (14)	**0.006**
Bleeding due to PHT	36 (6)	6 (8)	0.355

Supplementary Table 3. Baseline demographics and previous history of patients with SAH included in the study, divided in two groups depending on the status of recurrence at the end of follow-up.

[a]Missing datum in 30-40%.
[b]Missing datum in 50-60%.
[c]Missing datum in <20%.
[d]Missing datum in <5%.
[e]Viral hepatitis without fibrosis (n=8), metabolic dysfunction-associated steatotic liver disease (n=29), not specified (n=5)
Values are absolute count (percentage).
Abbreviations: BMI, body mass index; PHT, portal hypertension; SAH; severe alcohol-associated hepatitis.

	Multivariate analysis		
Variable	**HR**	***p* value**	**95% CI**
Age < 50 (years)	**1.562**	**0.025**	**1.059-2.305**
Sex (female)	0.844	0.431	0.554-1.287
Psychiatric comorbidity	1.249	0.281	0.834-1.870
Alcohol use >10 units/day	1.324	0.139	0.913-1.919
Other drug use	0.922	0.745	0.566-1.502
Previous hepatic decompensation	**1.955**	**<0.001**	**1.323-2.889**
Alcohol consumption during follow-up	**87.813**	**<0.001**	**12.238-630.118**

Supplementary Table 4. Multivariate analysis of factors associated to recurrence of AH, including alcohol consumption during follow-up.

Abbreviations: CI, confidence interval; HR, hazards ratio; PHT, portal hypertension.

	First AH (n = 1275)	Recurrent AH (n = 171)	*p* value
Liver failure	458 (36)	69 (40)	0.258
Kidney failure	87 (7)	13 (8)	0.706
Cerebral failure	59 (5)	9 (5)	0.712
Coagulation failure	105 (8)	14 (8)	0.982
Circulatory failure	101 (8)	8 (5)	0.131
Respiratory failure	52 (4)	9 (5)	0.469

Supplementary Table 5. Individual organ failures in first AH and RAH.

Values are absolute count (percentage).
Abbreviations: AH, alcohol-associated hepatitis.

	First AH (n = 125)	First RAH (n = 125)	*p* value
Hepatic decompensation at admission	60 (48)	75 (60)	0.066
Ascites	53 (42)	64 (51)	0.201
Spontaneous bacterial peritonitis	2 (2)	2 (2)	1.000
Overt hepatic encephalopathy	17 (14)	31 (25)	**0.024**
Bleeding due to PHT	8 (6)	9 (7)	0.815
Bacterial infection at admission	16 (13)	22 (18)	0.303
Acute kidney injury at admission	13 (10)	18 (14)	0.325
Acute-on-chronic liver failure at admission	12 (10)	22 (18)	0.073
SAH	72 (57)	94 (75)	**0.004**
Laboratory tests			
C-reactive protein (mg/dL)	4.7 (2.6-15.9)	4.7 (1.9-12.4)	0.386
Serum creatinine (mg/dL)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.569
AST(IU/L)	161 (109-237)	157 (112-224)	0.880
ALT (IU/L)	53 (37-83)	53 (37-81)	0.915
GGT (IU/L)	642 (283-1,315)	292 (141-827)	**<0.001**
AP (IU/L)	187 (126-283)	181 (118-236)	0.208
Total bilirubin (mg/dL)	7.6 (5.1-15.0)	9.9 (5.7-16.2)	0.054
Albumin (g/L)	28 (24-32)	26 (23-30)	0.114
Leukocytes (x10^9/L)	7.7 (5.4-10.9)	6.9 (5.2-10.0)	0.350
Platelets (x10^9/L)	94 (62-147)	85 (51-118)	**0.012**
INR	1.5 (1.3-1.8)	1.7 (1.4-2.1)	**0.003**
Liver function scores			
Maddrey's discriminant function	36 (23-51)	43 (30-65)	**0.003**
MELD	19 (17-23)	22 (19-26)	**0.001**
ABIC	7.1 (6.2-8.1)	7.7 (6.6-8.6)	**0.005**
Child-Pugh score	10 (9-11)	10 (9-12)	**0.002**

Supplementary Table 6. Characteristics of paired episodes of first AH and first RAH; that is, including only patients experiencing recurrence.

Values are median (± interquartile range) or absolute count (percentage).
Abbreviations: ABIC, age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IU, international units; MELD, model for end-stage liver disease; PHT, portal hypertension; RAH, recurrent alcohol-associated hepatitis; SAH: severe alcohol-associated hepatitis.

	First RAH (n = 38)	Second RAH (n = 38)	*p* value
Hepatic decompensation at admission	23 (61)	26 (68)	0.472
Ascites	21 (55)	23 (61)	0.642
Spontaneous bacterial peritonitis	0 (0)	0 (0)	NA
Overt hepatic encephalopathy	8 (21)	8 (21)	1.000
Bleeding due to PHT	2 (5)	1 (3)	0.556
Bacterial infection at admission	6 (16)	10 (26)	0.260
Acute kidney injury at admission	2 (5)	8 (21)	**0.042**
Acute-on-chronic liver failure at admission	6 (16)	9 (24)	0.387
SAH	24 (63)	32 (84)	**0.037**
Laboratory tests			
C-reactive protein (mg/dL)	4.9 (1.4-13.3)	5.3 (1.3-16.0)	0.974
Serum creatinine (mg/dL)	0.7 (0.6-0.8)	0.8 (0.6-1.0)	0.242
AST(IU/L)	142 (115-205)	139 (105-240)	0.857
ALT (IU/L)	51 (39-83)	57 (34-78)	0.731
GGT (IU/L)	396 (197-870)	261 (156-668)	0.108
AP (IU/L)	183 (114-284)	182 (134-239)	0.852
Total bilirubin (mg/dL)	8.2 (5.9-16.1)	11.0 (7.3-15.9)	0.299
Albumin (g/L)	28 (24-30)	26 (23-30)	0.462
Leukocytes (x10^9/L)	6.8 (5.8-10.2)	7.4 (5.4-10.0)	0.773
Platelets (x10^9/L)	73 (44-93)	72 (40-104)	0.892
INR	1.6 (1.4-2.0)	2.0 (1.6-2.2)	**0.016**
Liver function scores			
Maddrey's discriminant function	36 (28-56)	52 (32-66)	0.081
MELD	21 (18-24)	24 (21-26)	**0.024**
ABIC	7.6 (6.8-8.8)	8.2 (7.4-8.8)	0.179
Child-Pugh score	10 (9-12)	11 (10-12)	0.443

Supplementary Table 7. Characteristics of paired episodes of first RAH and second RAH, including only patients experiencing two recurrent episodes.

Values are median (± interquartile range) or absolute count (percentage).
Abbreviations: ABIC, age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IU, international units; MELD, model for end-stage liver disease; NA, not applicable; PHT, portal hypertension; RAH, recurrent alcohol-associated hepatitis; SAH: severe alcohol-associated hepatitis.

	First AH (n = 125)	First RAH (n = 125)	*p* value
Liver failure	40 (32)	50 (40)	0.157
Kidney failure	3 (2)	11 (9)	**0.026**
Cerebral failure	2 (2)	7 (6)	0.090
Coagulation failure	6 (5)	10 (8)	0.286
Circulatory failure	2 (2)	6 (5)	0.154
Respiratory failure	1 (1)	5 (4)	0.098

Supplementary Table 8. Individual organ failures in paired episodes of first AH and first RAH; that is, including only patients experiencing recurrence.

Values are absolute count (percentage).
Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

	First SAH (n = 847)	**Recurrent SAH (n = 132)**	***p* value**
Hepatic decompensation at admission	614 (72)	90 (68)	0.240
Ascites	566 (67)	77 (58)	**0.036**
Spontaneous bacterial peritonitis	43 (5)	2 (2)	0.074
Overt hepatic encephalopathy	203 (24)	35 (27)	0.575
Bleeding due to PHT	57 (7)	9 (7)	0.977
Bacterial infection at admission	163 (19)	27 (20)	0.777
Acute kidney injury at admission	173 (20)	25 (19)	0.662
Acute-on-chronic liver failure at admission	157 (19)	33 (25)	0.112
Laboratory tests			
C-reactive protein (mg/dL)	5.4 (2.6-13.5)	4.6 (1.5-13.5)	0.750
Serum creatinine (mg/dL)	0.7 (0.5-1.0)	0.7 (0.6-1.0)	0.471
AST (IU/L)	138 (100-199)	139 (111-201)	0.159
ALT (IU/L)	49 (35-73)	52 (37-74)	0.510
GGT (IU/L)	285 (132-615)	240 (114-575)	0.226
AP (IU/L)	162 (119-222)	170 (118-209)	0.756
Total bilirubin (mg/dL)	11.9 (7.4-18.8)	11.2 (7.7-18.0)	0.774
Albumin (g/L)	26 (23-29)	26 (23-29)	0.534
Leukocytes (x10^9/L)	7.9 (5.5-11.4)	7.0 (5.0-10.6)	**0.010**
Platelets (x10^9/L)	94 (61-146)	73 (39-96)	**<0.001**
INR	1.9 (1.6-2.2)	1.8 (1.7-2.1)	0.327
Liver function scores			
Maddrey’s discriminant function	51 (39-72)	55 (38-71)	0.953
MELD	23 (21-27)	23 (21-26)	0.569
ABIC	8.0 (7.2-8.9)	8.0 (7.4-8.9)	0.239
Child-Pugh score	11 (10-12)	11 (10-12)	0.729
Complications during hospitalization			
Spontaneous bacterial peritonitis	52 (6)	8 (6)	0.923
Overt hepatic encephalopathy	259 (31)	58 (44)	**0.003**
Bleeding due to PHT	68 (8)	14 (11)	0.334
Bacterial infection	283 (33)	45 (34)	0.928
Treatment			
Corticosteroids	574 (68)	72 (55)	**0.002**
Lille score	0.65 (0.20-0.92)	0.74 (0.20-0.92)	0.289
Response to steroids (Lille score <0.45)	281 (49)	42 (58)	0.134
Reasons for steroid ineligibility			
Confirmed or suspected infection	79 (29)	19 (32)	
Gastrointestinal bleeding	7 (3)	3 (5)	

Spontaneous improvement	22 (8)	9 (15)	
Death within 24h of admission	4 (1)	1 (2)	
Refusal of treatment	3 (1)	1 (2)	
Others	6 (2)	2 (3)	
Not specified	152 (56)	25 (41)	
Other specific treatments[a]	49 (6)	2 (2)	**0.035**

Supplementary Table 9. Main characteristics of first SAH and recurrent SAH episodes.

[a]Include N-acetylcysteine, enteral nutrition and pentoxifylline.
Values are median (± interquartile range) or absolute count (percentage).
Abbreviations: ABIC, age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IU, international units; MELD, model for end-stage liver disease; PHT, portal hypertension; SAH, severe alcohol-associated hepatitis.

	Prepandemic RAH (n = 107)	Postpandemic RAH (n = 64)	*p* value
Hepatic decompensation at admission	68 (64)	37 (58)	0.456
Ascites	58 (54)	31 (48)	0.465
Spontaneous bacterial peritonitis	1 (1)	1 (2)	1.000
Overt hepatic encephalopathy	29 (27)	12 (19)	0.236
Bleeding due to PHT	4 (4)	6 (9)	0.180
Bacterial infection at admission	22 (21)	12 (19)	0.774
Acute kidney injury at admission	16 (15)	11 (17)	0.718
Acute-on-chronic liver failure at admission	22 (21)	11 (17)	0.589
SAH	81 (76)	51 (80)	0.548
Laboratory tests			
C-reactive protein (mg/dL)	4.2 (1.6-10.4)	5.4 (2.2-16.8)	0.204
Serum creatinine (mg/dL)	0.7 (0.6-1.0)	0.7 (0.6-1.0)	0.455
AST(IU/L)	140 (100-213)	182 (103-238)	0.271
ALT (IU/L)	53 (35-89)	60 (42-81)	0.251
GGT (IU/L)	408 (164-992)	278 (124-607)	0.906
AP (IU/L)	167 (124-244)	178 (131-216)	0.810
Total bilirubin (mg/dL)	8.7 (5.5-14.1)	11.1 (7.0-16.8)	0.519
Albumin (g/L)	27 (24-31)	26 (23-30)	0.751
Leukocytes (x10^9/L)	7.7 (5.5-11.0)	7.2 (5.4-10.6)	0.680
Platelets (x10^9/L)	94 (61-143)	77 (49-114)	0.738
INR	1.6 (1.4-2.0)	1.7 (1.4-2.1)	0.926
Liver function scores			
Maddrey's discriminant function	39 (24-56)	43 (30-63)	0.921
MELD	20 (18-24)	22 (20-25)	0.448
ABIC	7.8 (6.6-8.5)	7.8 (7.1-8.9)	0.186
Child-Pugh score	10 (9-11)	10 (9-11)	0.137
Complications during hospitalization			
Spontaneous bacterial peritonitis	8 (7)	1 (2)	0.156
Overt hepatic encephalopathy	41 (38)	20 (31)	0.388
Bleeding due to PHT	8 (7)	6 (9)	0.674
Bacterial infection	35 (33)	18 (28)	0.530
Treatment			
Corticosteroids	48 (45)	27 (42)	0.733
Other specific treatments[a]	16 (15)	7 (11)	0.456

Supplementary Table 10. Main characteristics of RAH episodes presenting before and after the start of the COVID-19 pandemic.

[a]Include N-acetylcysteine, enteral nutrition and pentoxifylline.
Values are median (± interquartile range) or absolute count (percentage).
Abbreviations: AH, alcohol-associated hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; IU, international units; MELD, model for end-stage liver disease; PHT, portal hypertension; RAH, recurrent alcohol-associated hepatitis; SAH: severe alcohol-associated hepatitis.

	Patients without RAH who died (n = 150)	Patients with RAH who died (n = 47)	*p* value
Liver-related	78 (52)	34 (72)	**0.014**
Bleeding due to PHT	13 (9)	7 (15)	0.217
SBP or sepsis	11 (7)	1 (2)	0.193
Hepatocellular carcinoma	5 (3)	0 (0)	0.442
Kidney injury	1 (1)	2 (4)	0.080
ACLF	38 (25)	17 (36)	0.148
Others	10 (7)	7 (15)	0.080
Non-Liver-related	55 (37)	8 (17)	**0.012**
Cardiovascular	6 (4)	4 (9)	0.219
Extrahepatic cancer	12 (8)	0 (0)	0.098
Accident	4 (3)	1 (2)	0.391
Infections	16 (11)	2 (4)	0.183
Other	17 (11)	1 (2)	0.056
Uknown	17 (11)	5 (11)	0.895

Supplementary Table 11. Causes of death in patients who did and did not develop RAH during follow-up.

Values are absolute count (percentage).
Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

ARTICLE 3

MEDICATIONS FOR ALCOHOL USE DISORDER PROMOTE ABSTINENCE IN ALCOHOL-ASSOCIATED CIRRHOSIS: RESULTS FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

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ORIGINAL ARTICLE

Medications for alcohol use disorder promote abstinence in alcohol-associated cirrhosis: Results from a systematic review and meta-analysis

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Abstract

Background and Aims: The role of medications for alcohol use disorder (MAUD) in patients with cirrhosis is not well established. Evidence on the efficacy and safety of these drugs in these patients is scarce.

Approach and Results: We performed a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol guidelines on the efficacy of MAUD in patients with cirrhosis. A search was conducted in PubMed, Embase, and Scopus, including all studies until May 2022. The population was defined as patients with AUD and cirrhosis. The primary outcome was alcohol abstinence. Safety was a secondary outcome. We performed a random-effect analysis and expressed the results as relative risk of alcohol consumption. Heterogeneity was measured by I^2. Out of 4095 unique references, 8 studies on 4 different AUD treatments [baclofen (n = 6), metadoxine (n = 1), acamprosate (n = 1), and fecal microbiota transplant (n = 1)] in a total of 794 patients were included. Four were cohort studies, and 4 were RCTs. Only RCTs were included in the meta-analysis. MAUD was associated with a reduced rate of alcohol consumption [relative risk = 0.68 (CI: 0.48–0.97), P = 0.03], increasing alcohol abstinence by 32% compared to placebo or standard treatment, despite high heterogeneity (I^2 = 67%). Regarding safety, out of 165 serious adverse events in patients treated with MAUD, only 5 (3%) were possibly or probably related to study medications.

Conclusion: MAUD in patients with cirrhosis is effective in promoting alcohol

Abbreviations: AA, alcohol abstinence; ACP, acamprosate; AE, adverse event; AH, alcohol-associated hepatitis; AKI-HRS, acute kidney injury-hepatorenal syndrome; ALD, alcohol-associated liver disease; BAC, baclofen; DFL, days to first lapse; DR, days to relapse; MAUD, medications for alcohol use disorder; MD, mean difference; MTD, metadoxine; PDN, prednisone; PHES, psychometric HE score; PTX, pentoxifylline; SRMA, systematic review and meta-analysis; TAC, total alcohol consumption.

Hugo López-Pelayo and Elisa Pose shared co-first authorship.

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abstinence and has a good safety profile. Larger studies on the effects of MAUD are needed, especially in patients with advanced liver disease.

BACKGROUND

Alcohol consumption is the most common cause of advanced liver disease in Europe and the United States, accounting for the majority of deaths, liver transplants, and costs caused by liver diseases.[1–4] Patients with alcohol-associated liver disease (ALD) frequently have an underlying condition characterized by persistent alcohol consumption and inability to stop alcohol intake despite having adverse health and social consequences, which has been referred to as the key element for the diagnosis of AUD.[5] Nine out of 10 people who regularly drink over 60 grams of alcohol/day develop steatosis, and between 20%–40% of them have a certain degree of fibrosis. Consequently, the coexistence of ALD and AUD is commonly seen in clinical practice. In fact, liver disease is the second cause of death in adults with AUD.[6,7]

Alcohol abstinence represents the main therapeutic goal in patients with ALD since it is the most relevant prognostic factor in these patients, improving survival and clinical outcomes even at advanced stages of liver disease.[8,9] Based on clinical practice guidelines, treatment of AUD in patients with ALD relies on the combination of psychosocial interventions and pharmacological therapy.[10,11] Although psychosocial interventions are the cornerstone for the treatment of AUD, medications for AUD (MAUD) have an important role in the management of this condition as an adjuvant treatment, especially in cases of moderate to severe AUD.[12,13] The potential beneficial effect of these drugs may be particularly impactful in advanced stages of liver disease such as cirrhosis, in which alcohol consumption has been shown to have a markedly deleterious effect and is associated with very poor outcomes.[14] This fact is of utmost importance considering that currently, most cases of incident ALD are diagnosed in advanced stages of the disease, such as compensated or decompensated cirrhosis or even alcohol-associated hepatitis (AH).[3,15]

Currently, 3 medications are approved by both the European Medicine Agency and the Food and Drugs Administration for the treatment of AUD in Europe and the United States: naltrexone, acamprosate, and disulfiram; in addition, nalmefene is also approved for this use in Europe.[16] Sodium oxybate is only available in Austria and Italy,[17] and although baclofen is widely available, it is only approved for the treatment of AUD in France.[18] Topiramate and gabapentin have shown beneficial effects in several clinical trials,[19–21] and although not yet approved by the European Medicine Agency and the Food and Drugs Administration for the treatment of AUD, their use is recommended in some clinical practice guidelines for the management of patients with AUD.[12,22]

It is important to note that most studies investigating the efficacy of MAUD exclude patients with advanced stages of liver disease, particularly cirrhosis and AH.[23,24] This may be partially due to concerns regarding the safety profile of these drugs in subjects with impaired liver metabolism, considering that toxicity of pharmacological therapy may be theoretically higher in these patients.[25] Additionally, hepatology providers report low comfort and addiction education in the management of AUD (77% report deficient addiction training).[26] These factors are probably responsible for the dramatically low rates of MAUD prescription in this population, ranging from 10% to 14% in reports.[27,28]

This study aims at performing a systematic review and meta-analysis (SRMA) on the efficacy and safety of MAUD in patients with alcohol-associated liver cirrhosis.

METHODS

The study protocol was registered with the International Prospective Register of Systematic Reviews (CRD42021268112) on August 19, 2021. The SRMA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol.[29]

Search strategy

The search strategy was conducted on PubMed, Embase, and Scopus databases. A search was performed using medical subject headings and text words, applied in PubMed, and then adapted to Embase and Scopus. The initial search included studies published until August 2021; an update search was performed in May 2022. Only articles in English, Spanish, French, German, Portuguese, Italian, and Russian were included. There was no restriction based on publication year. Abstracts presented to scientific meetings were not included due to lack of detailed information. Reference lists from other reviews were examined to identify further eligible studies. In brief, the search strategy was formatted to combine a phrase for cirrhosis, 1 for alcohol use disorder treatments, and 1 for pharmacological treatments (Supplemental materials, http://links.lww.com/HEP/H948).

Eligibility criteria

Study design

Manuscripts with the following study design were included in the search: RCTs, case-control studies (both prospective and retrospective), and case series with more than 10 patients.

Population

Eligible studies for the systematic review were those including subjects over 18 years old with AUD[5] and diagnosis of liver cirrhosis, defined by clinical, laboratory, and radiological tests and/or histopathological criteria. Studies that included a mixed population of subjects with and without liver cirrhosis were also considered eligible. A sensitivity analysis in patients with liver cirrhosis could not be done due to the absence of information on subgroup analysis in these studies. Studies including only patients with HCC or patients with previous liver transplants were excluded. Only RCTs were included in the meta-analysis. In studies with more than 1 treatment arm, each of the arms was considered individually. Studies designed to analyze the effect of pharmacological interventions on alcohol withdrawal syndrome, with no available information on the effect of these interventions on AUD, were excluded.

Interventions/comparators

The search included any pharmacological therapy that has been tested for the treatment of AUD in patients with ALD. An initial search was performed to assess all the tested treatments in this population. The following treatments were subsequently included in the main search: disulfiram, naltrexone, naloxone, nalmefene, acamprosate, sodium oxybate, topiramate, ondansetron, baclofen, gabapentin, varenicicline, metadoxine, N-acetylcysteine, and fecal microbiota transplantation. All pharmacological regimes for AUD were included in the search, regardless of the clinical setting of the indication (outpatient or inpatient, provided that there was a follow-up after hospital discharge). Nonpharmacological treatments were not included. All comparators were accepted, including placebo, psychosocial intervention alone, or no treatment.

Outcomes

The primary outcome was alcohol abstinence (AA), defined as the proportion of patients that remained abstinent from alcohol at the end of follow-up. Secondary outcomes included: (a) the duration of alcohol abstinence, including days to relapse (DR), defined as 4 or more drinks per day or overall consumption of 14 or more drinks per week over a period of at least 4 weeks, and days to first lapse (DFL), defined as any episode of alcohol consumption not classified as relapse,[30] (b) total alcohol consumption (TAC), defined as median units of alcohol consumption per day, (c) changes in liver tests, (d) development of liver-related complications, including ascites, HE, acute kidney injury-hepatorenal syndrome, variceal bleeding, and infections, (e) short and long-term survival, (f) serious adverse events (SAEs), including those which lead to hospitalization or death, (g) patient retention in the trial, and (h) adherence to treatment.

Study selection and data extraction

Study selection was performed using the platform Rayyan (R). The process was divided into 2 phases: an initial screening in which only titles and abstracts were reviewed to assess eligibility, and a subsequent full-text examination to confirm the fulfillment of inclusion criteria and rule out any of the exclusion criteria.

After the removal of duplicates, 4 reviewers divided into 2 pairs (Jordi Gratacós-Ginès–Martina Pérez-Guasch and Pol Bruguera–Ana López-Lazcano) reviewed the references obtained by the search. Half of the references were randomly assigned to each pair of reviewers. Studies were included if both reviewers selected the article as eligible and excluded if both classified the study as not eligible. In case of disagreement, a third reviewer (Elisa Pose or Hugo López-Pelayo) evaluated the eligibility of the study.

Extraction of the data from the eligible studies was performed by the reviewers. When encountering different publications from the same study, only the most comprehensive information was extracted and put together to avoid study overrepresentation. The information extracted included: (a) general information (eg, year, lead author, and study title), (b) study information (eg, recruitment, screening process, and inclusion/exclusion criteria), and (c) participants' characteristics, interventions, comparator, and outcome measures.

Quality assessment

The risk of bias was assessed using the Cochrane risk of Bias tool 2 for RCTs[31] and the Newcastle-Ottawa Scale for observational studies.[32]

Statistical analysis

Quantitative variables are presented as means and SD, while categorical variables are expressed as percentages. Meta and Metafor libraries and software R version 4.2.1

were used to perform the meta-analysis. The primary outcome, defined as AA, was expressed as the RR of alcohol consumption with 95% CIs. Data from studies with more than 1 treatment arm were combined into 1 single arm. Weighted pooled RRs were calculated using both random-effect and common-effect models; the interpretation of results and discussion was based on the results of the random-effect model. Heterogeneity was estimated using I^2; values < 25% were considered to represent low heterogeneity, 25%–50% moderate heterogeneity, 50%–75% high heterogeneity, and > 75% very high heterogeneity.[33] Subgroup analyses were not performed. Regarding the RCTs on baclofen, an analysis of individual data from 1 of the studies[30] was carried out to calculate some missing variables and improve the granularity of the meta-analysis. However, a complete meta-analysis of individual data was not performed because the authors of some of the manuscripts included in this systematic review could not be reached.

RESULT

Characteristics of the studies

In all, 4354 studies were identified through database searching. After the removal of duplicates (n = 259), 4095 studies were considered. Of those, 4037 were excluded in the first screening phase. Fifty-eight studies fulfilled inclusion criteria; of those, 48 were finally excluded after full-text review. The reasons for exclusion were suboptimal study design (n = 36), lack of information on the outcomes of interest (n = 7), absence of patients with cirrhosis or absence of information on the stage of liver disease (n = 5), and language other than those predefined in the study protocol (n = 2). Finally, 8 studies were included (Figure 1), representing a study population of 794 patients for the systematic review. Of those, 562 (71%) had a diagnosis of liver cirrhosis: 309 (55%) patients had decompensated cirrhosis, while 171 (30%) had compensated cirrhosis; in 82 (15%) patients, data on the compensation status of liver cirrhosis were not available. Furthermore, 175 (31%) patients with cirrhosis had also a clinical diagnosis of AH.

Concerning the interventions, 6 studies investigated the effect of baclofen,[30,34–38] 1 analyzed metadoxine,[39] 1 acamprosate,[38] and 1 fecal microbiota transplant.[40] Regarding study design, 4 studies were RCTs,[30,34,39,40] 2 were prospective cohort studies without a control group,[36,37] and 2 were retrospective cohort studies.[35,38]

Duration of follow-up ranged from 12 weeks to 12 months, with a median follow-up of 6 months. Individual characteristics of each study, including type of study, study design, AUD-related outcomes, patient retention and adherence, liver function and liver-related outcomes, and safety profile, are summarized in Table 1.

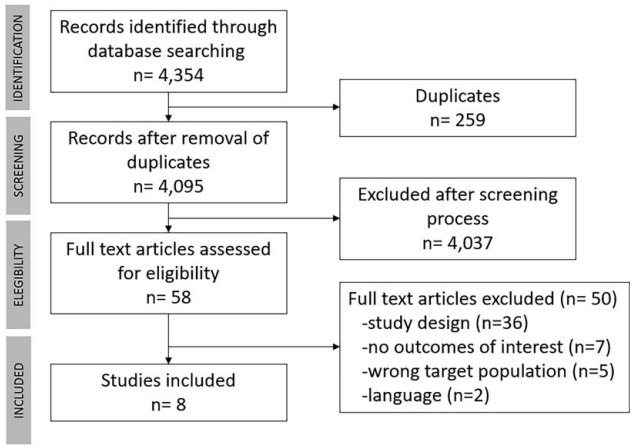

FIGURE 1 Flowchart of study selection.

Efficacy of pharmacological therapies on alcohol use disorder

Alcohol abstinence

All studies (n = 8) reported the effect of MAUD on AA. Four of those included a control group in the study design; of those, 2 found significant differences in favor of the study treatment, 1 with metadoxine,[39] and 1 with baclofen.[30] (Table 1). The other 2 studies did not find statistically significant differences between the treatment group and the control group.[34,40]

Four studies met the criteria for inclusion in the meta-analysis,[30,34,39,40] including 343 patients: 190 in the treatment arms and 153 in the control arms. AA occurred in 136 patients (39.7%), 97 (51.1%) in the treatment arms, and 39 (25.5%) in the control arms. In the random-effect model analysis, the use of any AUD pharmacological treatment showed a significant reduced risk of active alcohol consumption compared to the control therapy [relative risk = 0.68 (CI: 0.48–0.97), P = 0.03], (Figure 2A) representing an overall increase of 32% on AA. Heterogeneity of the studies was high (I^2 = 67%).

The risk analysis for specific treatments was only possible for baclofen. The estimate favored reduced risk of alcohol consumption in patients taking baclofen, but results were not statistically significant when using a random-effect model analysis [RR = 0.62 (CI: 0.29–1.34), P = 0.22], with very high heterogeneity (I^2 = 88%) (Figure 2B).

Duration of AA

Duration of AA was evaluated in 2 RCTs on baclofen.[30,34] Information on DFL and DR was available in both RCTs: 1 of them reported the information in the manuscript,[34] and in the other trial, it was calculated for the purpose of this study using individual data.[30] The RCT by Morley et al[34] found a significant increase in DFL and DR in patients treated with baclofen compared to placebo, with an effect size of 0.56

TABLE 1 Characteristics of the studies included in the systematic review.

Study	Type of study	Study design	AUD-related outcomes	Patient retention and adherence	Liver function and liver-related outcomes	Safety profile	Comments
Addolorato G, Lancet, 2007[30]	RCT, double-blinded	84 patients with AUD and cirrhosis (12% compensated and 88% decompensated) were randomized to BAC 30 mg/24 h or placebo for 12 wks. Follow-up: 12 wks.	-AA: 30/42 (71%) in BAC vs. 12/42 (29%) in placebo ($p = 0.000$). OR = 6.3 (95% CI 2.4–16.1).	-Dropouts: 14% in BAC vs. 31% in placebo (p = ns). -Adherence: BAC 83% vs. placebo 80% (p = ns).	Improvement in liver enzymes (except AST) and liver synthetic function in BAC and placebo arms.	No reported SAEs.	-Child-Pugh B or C: 74 patients (88%).
Higuera-de la Tijera F, World J Gastroenterol, 2015[39]	RCT, open-label	135 patients with AUD and AH + decompensated cirrhosis randomized to: 1) PDN 40 mg + MTD 500 mg/8 h for 1 mo. 2) PDN 40 mg for 1 mo. 3) PTX 400 mg/8 h for 1 mo. 4) PTX 400 mg/8 h + MTD 500 mg/8 h for 1 mo. Follow-up: 6 mo.	AA: 35/47 (75%) in MTD groups combined vs. 19/32 (59%) in control groups combined ($p = 0.020$).	-Dropouts: 11% in PDN vs. 9% in PDN + MTD vs. 6% in PTX vs. 9% in PTX + MTD (p = ns). - Adherence: 91%.	Reduction in the development of HE and AKI-HRS at 3 mo, only in MTD + PDN compared to PDN alone.	-89 patients had an SAE that led to death, 34 (38%) of whom were receiving MTD. -All dropouts were due to AEs.	-Median Child-Pugh score: 12. -Survival: increase in MTD groups compared to control therapy groups (50% vs. 18% for PTX (p = 0.01) and 49% vs 20% for PDN (p = 0.003)).
Morley KC, Br J Psychiatry, 2018[34]	RCT, double-blinded	104 patients with AUD ± cirrhosis (42% cirrhosis: 23% compensated and 19% decompensated) randomized to BAC 30 mg/24 h or BAC 75 mg/24 h or placebo for 12 wks. Follow-up: 12 wks.	-AA: 14/64 (22%) in BAC groups vs 3/31 (10%) in placebo (p = 0.15). -DFL: increase in BAC groups (31 d in BAC30mg and 25 d in BAC75 mg) compared to placebo (11 d) ($p < 0.05$). D = 0.56[a]. -DR: increase in BAC groups (35 d in BAC30 mg and 32 d in BAC75 mg) compared to placebo (17 d) ($p < 0.05$). D = 0.52[a]. -TAC: similar reduction in the 3 groups (n = ns).	-Dropouts: 31% in BAC75 mg vs. 33% in BAC30 mg vs. 27% in placebo (p = ns). - Adherence: 83% in BAC30 mg vs. 79% in BAC75mg vs. 88% in placebo (p = ns).	Improvement in liver enzymes but no change in MELD score in BAC and placebo arms.	-4 reported SAEs: 1 related, 2 possibly related, 1 unrelated to study medication. -10 dropouts due to AEs: 7 (20%) in BAC75 mg, 2 (6%) in BAC30 mg, and 1 (3%) in placebo ($p < 0.05$).	-Child-Pugh B or C: 20 patients (35%). -Increase in % days abstinent in BAC compared to placebo arms.
Bajaj JS, Hepatology, 2021[40]	RCT, double-blinded	20 patients with AUD and compensated cirrhosis were randomized to 1 dose of FMT or placebo. Follow-up: 6 mo.	AA: 3/10 (30%) in FMT vs. 1/10 (10%) in placebo (p = 0.520).	-Dropouts: none. - Adherence: 100%.	-No difference between arms regarding liver enzymes, liver synthetic function, and MELD. -Reduction in minimal HE (PHES) in FMT vs. placebo.	-Number of reported SAEs: 4 in FMT vs. 14 in placebo. Unrelated to study medication. -Number of patients with SAEs: 2 (20%) in FMT vs 8 (80%) in placebo (p = 0.020).	Reduction in craving at 15 days.

Yamini D, Alcohol Alcohol, 2014[35]	Retrospective cohort study	40 patients with AUD and AH + cirrhosis (~50% compensated and 50% decompensated) were treated with BAC 30 mg/24 h for a median of 5 mo. Follow-up: 12 mo.	AA: 34/35 (97%).	-Dropouts: 8%. -Adherence: 88%.	Improvement in liver enzymes, liver synthetic function, and MELD.	2 reported SAEs: 1 related and 1 unrelated to study medication (led to death).	
Barrault C, Eur J Gastroenterol Hepatol, 2017[36]	Prospective cohort study	100 patients with AUD ± cirrhosis (65% cirrhosis: 22% compensated and 43% decompensated) were treated with BAC, with a median dose of 40 mg/24 h. Follow-up: 12 mo.	- AA: 44/86 (51%). -TAC: reduction from 8 to 0 units/day[b] ($p = 0.004$). In patients with cirrhosis, reduction from 13 (9–18) to 0 (0–5) units/day[b].	- Dropouts: 14%. -Adherence: 83%.	Improvement in liver enzymes and liver synthetic function only in patients with cirrhosis and alcohol consumption up to 4 U/day[b].	-2 reported SAEs: both unrelated to study medication (both led to death). -25% of non-severe AEs.	Child-Pugh B or C: 22 patients (22%).
Owens L, Alcohol, 2017[37]	Prospective cohort study	219 patients with AUD ± cirrhosis (37.5%) were treated with BAC 30 to 90 mg/24 h. Follow-up: 12 mo.	-AA: 81/152 (53%). -TAC: reduction from 25 to 2 U/day. D = 0.77[a].	-Dropouts: 32%. -Adherence: 52%.	Improvement in liver enzymes.	-18 SAEs unrelated to study medication led to death, 10 due to complications of cirrhosis. -1 reported SAE related to the study medication.	
Tyson LD, Eur J Gastroenterol Hepatol, 2022[38]	Retrospective cohort study	92 patients with AUD and cirrhosis (59% compensated and 41% decompensated) were treated with BAC 15 to 150 mg/24 h or ACP 1998 mg/24 h. Follow-up: not specified.	AA: 37/92 (40%). BAC vs. ACP: 17/44 (39%) in BAC vs. 20/48 (42%) in ACP (p = ns). -TAC: reduction from 9 to 2 U/day in BAC vs. reduction from 14 to 1 U/day in ACP (p = ns).	-Dropouts: 11%. BAC vs. ACP: 18% in BAC vs. 4% in ACP ($p = 0.031$). Adherence: 88%. BAC vs. ACP: 98% in BAC vs. 79% in ACP ($p = 0.006$).	-No change in MELD score. -New hepatic decompensations: 7/44 (16%) in BAC vs. 6/48 (13%) in ACP (p = ns).	100 reported SAEs: 71 in BAC vs. 29 in ACP. 2 SAEs led to death (1 in BAC and 1 in ACP, both unrelated to study medication).	-Child-Pugh B or C: 38 patients (41%). -Median time on BAC vs. ACP: 8.2 vs. 2.8 mo.

[a]Cohen's D statistical.
[b]Converted from grams/day considering that 1 unit = 10 grams of alcohol.
Abbreviations: AA, alcohol abstinence; ACP, acamprosate; AE, adverse event; AH, alcohol-associated hepatitis; AKI-HRS, acute kidney injury-hepatorenal syndrome; BAC, baclofen; DFL, days to first lapse; DR, days to relapse; MTD, metadoxine; PDN, prednisone; PHES, psychometric HE score; PTX, pentoxifylline; TAC, total alcohol consumption.

and 0.52 for DFL and DR assessed by Cohen's D, respectively. This RCT included 2 arms of treatment with 30 and 75 mg per day, but when performing a sensitivity analysis with the different doses of baclofen, no significant differences were found. In the study by Addolorato et al[30] no significant differences were found in the calculated DFL and DR between baclofen and placebo. In the random-effect model analysis, including both trials, treatment with baclofen did not increase DFL nor DR, (Figure 3) although heterogeneity of the results was very high for both DFL and DR (I^2 = 97% and 84%, respectively).

Total alcohol consumption

Changes in TAC were assessed in 4 studies: 3 were observational studies[36–38] without a control group, and 1 was an RCT[34] (Table 1). The 3 cohort studies showed positive signals of the pharmacological treatment when comparing the end of treatment with baseline TAC. However, the only RCT that assessed TAC did not find significant differences when comparing baclofen with placebo[34] (Table 1).

Effects of pharmacological therapies on liver tests and liver-related outcomes

All studies except 1[39] reported the effect of the pharmacological therapy on liver tests, either assessed by liver enzymes[30,34–37,40] (aspartate aminotransferase , alanine aminotransferase, alkaline phosphatase, and/or gamma-glutamyl transpeptidase) or by synthetic liver tests, such as bilirubin, albumin, or international normalized ratio.[30,35–38,40] Model for End-Stage Liver Disease score was assessed in 4 studies.[34,35,38,40] None of the studies reported deleterious effects of any pharmacological treatment on liver tests. Furthermore, in 5 studies assessing the effect of baclofen,[30,34–37] a significant improvement in liver chemistry tests was observed (Table 1).

Only 3 studies reported liver-related outcomes (Table 1). Bajaj et al found improvement in minimal HE assessed by the psychometric HE score in patients with cirrhosis treated with fecal microbiota transplant compared with placebo[40]; Higuera-de la Tijera et al found a significant reduction in the development of HE and acute kidney injury-hepatorenal syndrome at 3 months in patients with AH in the arm treated with metadoxine in combination with prednisone compared to the arm treated with prednisone alone. This latter study was the only 1 that assessed survival, which was higher in patients in the metadoxine groups compared to those in the control groups.[39] Finally, in the study by Tyson et al, new hepatic decompensations occurred in 6 patients taking acamprosate and in 7 patients taking baclofen (P = ns), but there was no control group, so no assumptions regarding the effect of therapy can be made in this particular study.[38]

Safety profile

Adverse events were reported heterogeneously in the studies. Altogether, 165 SAEs were reported in 638 patients in the treatment arms, 57 of which led to death. No deaths were classified as related to study medication. Of the remaining 108 SAEs, 3 were judged to be related to study medication, 2 were possibly related, and all of them occurred in patients treated with baclofen (Table 1). The reported SAEs related or possibly related to study medication were acute confusion (n = 2), hospital admission due to suicidal ideation (n = 2), and treatment overdose (n = 1). Other nonserious adverse events described in treatment groups, mostly in baclofen groups, were sedation or drowsiness and shortness of breath.

When analyzing the studies that included control groups in their study design, the 4 RCTs included expressed the incidence of SAEs in treatment verus placebo/control groups. Regarding baclofen, Addolorato et al did not report any SAE in their study,[30] and Morley et al found no differences between the baclofen groups and the placebo group.[34] The RCT assessing the use of metadoxine[39] reported 89 total deaths at 6 months, 34 in the metadoxine group, and 55 in the nonmetadoxine groups, although no statistical comparisons were made between metadoxine arms combined and control arms. No other SAEs were reported in this trial. The study by Bajaj et al was the only trial that found a significantly higher incidence of SAEs in the placebo group (2 patients vs. 8 patients developed SAEs in fecal microbiota transplant vs. placebo, respectively, P = 0.02).[40]

Quality assessment

The methodological quality assessment for RCTs with the Risk of Bias tool 2 scale showed a low risk of bias in the 2 RCTs on baclofen and in the sole RCT on fecal microbiota transplant. It indicated some concerns in the RCT on metadoxine (Table 2A).

Regarding observational studies, quality assessment with the Newcastle-Ottawa Scale showed a median quality score of 4.8, ranging from 4 to 6 points, out of a maximum of 9 points (Table 2B). It is important to note that quality regarding comparability was low because none of the studies had a control group.

Others

Participant retention and adherence to treatment

Participant retention rate ranged from 68% to 92% in the cohort studies included.[35–38] The 3 RCTs in the outpatient setting had retention rates of 69%, 77%, and

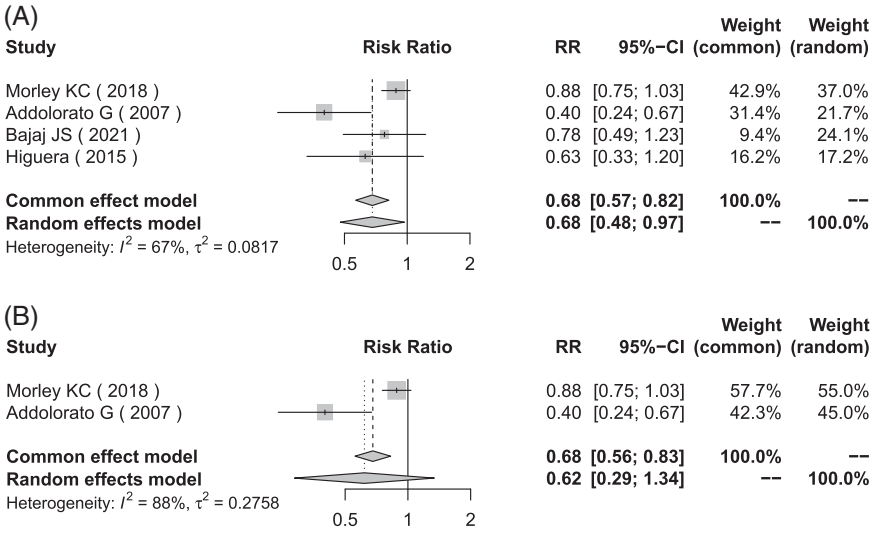

FIGURE 2 (A) Random- and common-effect model analysis of the relative risk of alcohol consumption in patients treated with any medication for alcohol use disorder compared to placebo or control therapy. (B) Random-effect and common-effect model analysis of the relative risk of alcohol consumption in patients treated with baclofen compared to placebo or control therapy.

100%,[30,34,40] respectively, while the only RCT in hospitalized patients reported a retention rate of 91%.[39]

Adherence to treatment was assessed differently in the studies included. In the cohort studies, adherence rates were either calculated through patient reports or prescription pick-up registries, ranging from 52% to 88%.[35–38] Concerning RCTs, adherence was reported heterogeneously. Morley et al reported an 83% adherence rate, considering correct adherence when patients took at least 80% of the prescribed dose, with no differences between the treatment arms.[34] Addolorato et al expressed adherence as the mean percentage of the dose taken, being 80% in the placebo and 83% in the baclofen group; differences between the 2 groups were not statistically significant.[30] Finally, adherence was 100% in the trial on fecal microbiota transplant by Bajaj et al and 91% in the RCT on metadoxine by Higuera-de la Tijera et al.[39,40]

DISCUSSION

To date, this is the first SRMA of scientific evidence on the efficacy and safety of MAUD in patients with cirrhosis. Despite the limited information due to the low number of studies, it is noteworthy to emphasize that MAUD showed positive signals on AA with an adequate safety profile in most studies. In fact, according to our meta-analysis and despite high heterogeneity, pharmacological therapy for AUD in patients with cirrhosis showed efficacy in achieving AA [RR = 0.68 (CI: 0.48–0.97)], with a 32% higher probability compared to placebo/control.

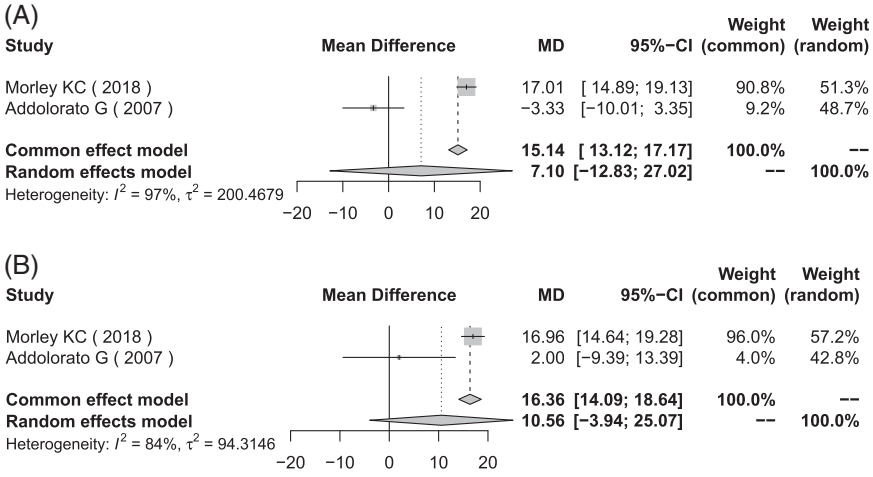

FIGURE 3 (A) Random-effect and common-effect model analysis of the mean difference in days to first lapse between treatment with baclofen and placebo. (B) Random-effect and common-effect model analysis of the mean difference in days to relapse between treatment with baclofen and placebo. Abbreviation: MD, mean difference.

TABLE 2 Summary of risk of bias assessments of included studies. (A) Assessment of RCTs using Cochrane Risk of Bias tool 2. (B) Assessment of observational studies using the Newcastle-Ottawa Scale.

(A)

Study ID	Intervention	Comparator	Outcome	Weight	Selection bias	Performance bias	Attrition bias	Detection bias	Selective reporting bias	Overall bias
Addolorato G, Lancet, 2007[30]	BAC	Placebo	AA DFL	1	✓	✓	✓	✓	✓	✓
Higuera-de la Tijera F, World J Gastroenterol, 2015[39]	MTD	PDN and PTX	AA Mortality	1	✓	©	©	©	✓	©
Morley KC, Br J Psychiatry, 2018[34]	BAC	Placebo	AA DFL DR	1	✓	✓	✓	✓	✓	✓
Bajaj JS, Hepatology, 2021[40]	FMT	Placebo	AA AE Craving	1	✓	✓	✓	✓	✓	✓

Judgement: ✓ Low risk © Some concerns ✗ High risk

(B)

Study ID	Medication	Year	Selection (0 – 4 stars)	Comparability (0 – 2 stars)	Exposure/Outcome (0 – 3 stars)	Overall (0 – 9 stars)
Yamini et al.[35]	BAC	2014	★★		★★	4★
Owens et al.[37]	BAC	2017	★★★		★★★	6★
Barrault et al.[36]	BAC	2017	★		★★★	4★
Tyson et al.[38]	BAC / ACP	2022	★★★	★	★	5★

Abbreviations: AA, alcohol abstinence; ACP, acamprosate; AE, adverse events; BAC, baclofen; DFL, days to first lapse; DR, days to relapse; MTD, metadoxine; PDN, prednisone; PTX, pentoxifylline.

A recent retrospective study assessing the effect of MAUD on clinical outcomes in patients with cirrhosis suggested a beneficial effect of these medications on survival and incidence of complications of cirrhosis.[27] However, the prescription of MAUD is not standard clinical practice for these patients,[27,28,41] and this is particularly true for patients with decompensated cirrhosis, in whom the rates of use of MAUD reported in a recent study were as low as 6%.[27] In this SRMA, we collected 309 (39%) patients with decompensated cirrhosis treated with pharmacological therapy for AUD. Although the characteristics of the studies included did not allow a sensitivity analysis in decompensated cirrhosis, beneficial effects of therapy with no safety concerns were shown in the analysis of the whole group of patients with liver cirrhosis. These results should encourage the use of MAUD to promote AA in patients with cirrhosis, including those with decompensated liver disease.

The results of this meta-analysis yielded some interesting findings. First, it showed that AUD pharmacological therapy increases the probability of AA in patients with cirrhosis compared to placebo/control by 32%. Also, it is the first meta-analysis performed in patients with ALD, which is the most common organic disease associated with AUD. Second, the fact that an individual meta-analysis for specific medications was only possible to perform with 1 drug is very much representative of the lack of good clinical evidence and the need for more trials in this field. As for the individual analysis with baclofen, the estimate favored reduced risk of alcohol consumption in patients taking baclofen, although it did not reach statistical significance.

This study provides evidence on the efficacy of MAUD to achieve AA, which should be the main goal in the management of patients with ALD, as it has consistently been shown to be the main driver of prognosis in these patients.[8,42,43] Nevertheless, a reduction in alcohol consumption without achieving total AA, also known as "harm reduction," has also been associated with better clinical outcomes in the general population and in patients with ALD.[44,45] For this reason, TAC and duration of AA were also investigated in our study. Unfortunately, the low number of studies reporting these secondary outcomes limited our analysis.

Regarding safety, a fairly low number of SAEs were reported considering that this was a population of patients with cirrhosis. It should be noted that most patients were not in advanced stages of liver disease, as, in the majority of studies in which this is reported, the percentage of patients with Child-Pugh C was low.[34,36,38] In fact, 2 of the 3 studies including a higher number of patients with Child-Pugh B and C also reported the highest number of SAEs[38,39] although it must be highlighted that none of them were classified as related to study medication. Surprisingly, despite including 88% of patients with Child-Pugh B or C, Addolorato et al did not report any SAE in their trial on baclofen.[30] Furthermore, it is also important to note that no deleterious effects of pharmacological treatment on liver tests were reported with any of the drugs, nor an increase in the rate of hepatic decompensation. In addition, liver tests improved in most studies,[30,34–37] which is probably a consequence of high abstinence rates and a reduction in alcohol consumption. The positive data on safety derived from this analysis might have important clinical implications, as drugs evaluated in this study could be prescribed as alternatives to widely used medications for AUD treatment such as disulfiram, which has been previously associated with severe adverse events in patients with cirrhosis, and thus, its use in this population is not recommended.[11,46] Despite the good safety profile shown by the medications included in this SRMA, a note of caution should be taken in patients with decompensated disease and severe impairment of liver function. In this regard, further studies are needed focusing on safety in this highly vulnerable population.

This study has some limitations that should be mentioned. First, the studies included have heterogeneous populations, including patients with and without cirrhosis and different settings (inpatient and outpatient). Although an individual data analysis was planned to overcome this limitation, it was not possible because some of the authors did not provide the original databases of the studies. Moreover, the studies included were designed with multiple outcomes, and in some of them, the primary end point was not AA. Because our study aimed at evaluating the current state of the evidence in the literature, we opted for broad inclusion criteria. Even with this inclusive approach, which explains the abovementioned limitations, only 8 studies were finally included in the systematic review and only 4 in the meta-analysis. This highlights the scarce amount of evidence regarding such an important topic. Finally, because the search for specific MAUD was predefined in the study protocol, it is possible that some other drugs with limited use in clinical practice may not have been included in the search. Nevertheless, we believe that the inclusion of other drugs with marginal use for this indication would not have substantially impacted our results. The main strengths of our review are the thorough search and data extraction strategy and the comprehensive analysis, including data on safety, liver tests, and liver-related outcomes.

In conclusion, despite the shortness of information, the pharmacological therapy for AUD in patients with alcohol-associated cirrhosis has been shown to promote AA in this study, with a good safety profile. Until more RCTs with hard end points and longer follow-ups in patients with advanced liver disease are performed, the results of this study should encourage the wider use of MAUD in patients with cirrhosis.

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AUTHOR CONTRIBUTIONS

Jordi Gratacós-Ginès: Conceptualization, methodology, formal analysis, investigation, writing original draft, and visualization. Pol Bruguera, Martina Pérez-Guasch, and Ana López-Lazcano: Investigation. Roger Borràs: Formal analysis and data curation. Ramón Bataller and Pere Ginès: Supervision. Hugo López-Pelayo: Conceptualization, methodology, and investigation. Elisa Pose: Conceptualization, methodology, investigation, writing original draft, project administration, and funding acquisition. All authors contributed to the writing review and editing.

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Presentation: Preliminary data of this study were presented at the XXXII Congrés de la Societat Catalana de Digestologia (January 2023, Tarragona, Spain), the 48 Congreso anual de la Asociación Española para el Estudio del Hígado (March 2023, Madrid, Spain), and the International Liver Congress, EASL Congress (June 2023, Vienna, Austria).

CONFLICTS OF INTEREST

Pol Bruguera is on the speakers' bureau and received grants from Lundbeck. He received grants from Camurus and Pfizer. Maria T. Pons-Cabrera is employed by Lundbeck, Pfizer, and Esteve. Ramón Bataller is on the speakers' bureau for AbbVie. Pere Ginès consults and received grants from Ferring, Gilead, and Grifols. He consults for CSL Behring, Intercept, Martin Pharmaceuticals, Promethera, RallyBio, and Sequana. He received grants from Mallinckrodt. Hugo López-Pelayo received grants from Lundbeck. The remaining authors have no conflicts to report.

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SUPPLEMENTARY MATERIALS

List 1. Search strategy in *PubMed* and results from the updated search in May 2022.

Results: 2.799 studies

Search strategy:

(("Therapeutics"[Mesh] OR “therapeutics” OR “treatment”) OR ("Drug Therapy"[Mesh] OR “drugtherapy”) OR (“disulfiram”[MeSH] OR “disulfiram” OR “antabus” OR “antabuse”) OR ("Naltrexone"[Mesh] OR ”naltrexone” OR ”antaxone”)OR ("Naloxone"[Mesh] OR “naloxon”) OR (“nalmefene” OR “selincro”) OR ("Acamprosate"[Mesh] OR “acamprosate” OR “campral” OR “aotal”) OR ("Sodium Oxybate"[Mesh] OR “sodium oxybate” OR “somsanit”) OR ("Topiramate"[Mesh] OR “topiramate” OR “topamax”) OR ("Ondansetron"[Mesh] OR “ondansetron” OR “zofran”) OR ("Baclofen"[Mesh] OR “baclofen” OR “baclophen” OR “lioresal” OR “GHB” or “gamma Hydroxybutyric acid” or “gamma aminobutyric acid”) OR ("Gabapentin"[Mesh] OR “gabapentin” OR “neurontin” OR “convalis”) OR ("Varenicline"[Mesh] OR “varenicicline” OR “champix” OR “chantix”)OR (“metadoxine” OR “metadoxyl”) OR ("Acetylcysteine"[Mesh] OR “n-acetylcysteine”)) **AND** (("Alcoholism"[Mesh] OR “alcoholism” OR “alcohol dependence” OR “alcohol addiction” OR “alcohol abuse” OR “ethanol abuse” OR “alcohol use disorder”) OR ("Alcohol Abstinence"[Mesh]OR “alcohol abstinence” OR “ethanol abstinence”) OR ("Harm Reduction"[Mesh] OR “harm-reduction”)) **AND** ("cirrho*" OR "Liver cirrhosis"[Mesh] OR “cirrhosis” OR “liver disease” OR "Liver Diseases, Alcoholic"[Mesh])

List 2. Search strategy in *Embase* and results from the updated search in May 2022.

Results: 1.517 studies

Search strategy:

Therapeutics OR therapeutics OR treatment OR Drug Therapy OR drugtherapy OR disulfiram OR disulfiram OR antabus OR antabuse OR Naltrexone OR naltrexone OR antaxone OR Naloxone OR naloxon OR nalmefene OR selincro OR Acamprosate OR acamprosate OR campral OR aotal OR Sodium Oxybate OR sodium oxybate OR

somsanit OR Topiramate OR topiramate OR topamax OR Ondansetron OR ondansetron OR zofran OR Baclofen OR baclofen OR baclophen OR lioresal OR GHB OR gamma Hydroxybutyric acid OR gamma aminobutyric acid OR Gabapentin OR gabapentin OR neurontin OR convalis OR Varenicline OR varenicicline OR champix OR chantix OR metadoxine OR metadoxyl OR n-acetylcysteine **AND** Alcoholism OR alcoholism OR alcoholdependence OR alcohol addiction OR alcohol abuse OR ethanol abuse OR Alcohol Abstinence OR alcohol abstinence OR ethanol abstinence OR harm reduction **AND** cirrho* OR Liver cirrhosis OR cirrhosis OR liver disease

List 3. Search strategy in *Scopus* and results from the updated search in May 2022.

Results: 38 studies

Search strategy:

(therapeutics OR therapeutics OR treatment OR drug AND therapy OR drugtherapy OR disulfiram OR disulfiram OR antabus OR antabuse OR naltrexone OR naltrexone OR antaxone OR naloxone OR naloxon OR nalmefene OR selincro OR acamprosate OR acamprosate OR campral OR aotal OR sodium AND oxybate OR sodium AND oxybate OR somsanit OR topiramate OR topiramate OR topamax OR ondansetron OR ondansetron OR zofran OR baclofen OR baclofen OR baclophen OR lioresal OR ghb OR gamma AND hydroxybutyric AND acid OR gamma AND aminobutyric AND acid OR gabapentin OR gabapentin OR neurontin OR convalis OR varenicline OR varenicicline OR champix OR chantix OR metadoxine OR metadoxyl OR n-acetylcysteine) **AND** (alcoholism OR alcoholism OR alcoholdependence OR alcohol AND addiction OR alcohol AND abuse OR ethanol AND abuse OR alcohol AND abstinence OR alcohol AND abstinence OR ethanol AND abstinence OR harm AND reduction) **AND** (cirrho* OR liver AND cirrhosis OR cirrhosis OR liver AND disease)

5. DISCUSSION

ALD is one of the most important liver diseases worldwide both in terms of prevalence and mortality[1]. In fact, it is the number one leading cause of cirrhosis and cirrhosis-associated mortality in Europe[2,7]. Furthermore, patients with ALD have frequent hospital readmissions and account for the highest economic burden among all causes of chronic liver disease[172]. One of the most severe presentations of ALD is AH, which can sometimes be a diagnostic challenge. AH often requires in-hospital management and is associated with increased short-term mortality[20]. Despite the importance of the disease, research on the field has been rather scarce compared to other causes of liver disease[173]. Consequently, many gaps of knowledge remain in different aspects of the disease.

Therefore, the overall objective of this doctoral thesis was to increase the knowledge in regards to the diagnosis and natural history of severe forms of ALD, with a special focus on AH differential diagnosis with alcoholic foamy degeneration (AFD), recurrent episodes of AH and management of alcohol use disorder in advanced stages of liver disease.

The first project of this doctoral thesis was designed to investigate the differential diagnosis of AH and AFD. The former condition may be diagnosed in clinical practice based on clinical and analytical data if the NIAAA criteria are met, or after liver biopsy evaluation in cases of uncertainty or presence of confounding factors[54]. On the other hand, AFD is diagnosed based on a clinical presentation similar to that of AH with a pathological examination characterized by predominant microvesicular steatosis in the absence or with minimal signs of steatohepatitis[62]. A cohort of patients with suspicion of AH was analyzed in order to determine: 1) the prevalence of AFD in this clinical setting; 2) the performance of the current NIAAA criteria to differentiate AH from AFD and the diagnostic capacity of other noninvasive tools; 3) the long-term prognosis of patients with AFD; and 4) the genetic signature of the liver in patients with AFD.

The first important finding of this project is that the prevalence of AFD in cases of suspicion of AH is around 8%. Our study is the first to determine the prevalence of this condition in this specific clinical setting; previous studies had focused on

cohorts of patients with ALD regardless of clinical presentation, in which AFD was significantly less common[174]. This finding suggests that, although AFD has a broad clinicopathological spectrum, including asymptomatic or paucisymptomatic patients[174], clinical presentation as AH is probably one of the most common. Another important observation is that in up to 20% (8% with AFD and 12% with other diagnoses) of patients who underwent a liver biopsy in our study the suspicion of AH was not confirmed upon histological examination. Furthermore, the performance of the current NIAAA criteria[54,59] to differentiate AH from AFD was modest, with an accuracy of 65%. The recently published NIAAA modified criteria with the addition of C-reactive protein[59] only improved slightly the accuracy of the classical criteria. These data are worth keeping in mind considering that some international clinical guidelines on the management of patients with ALD advocate for using the noninvasive NIAAA criteria not only for the clinical decision-making in patients with suspicion of AH, but also as inclusion criteria for clinical trials in AH[55].

Given that the accuracy of the NIAAA criteria was not optimal for the differential diagnosis of AH, other available and widely used noninvasive biomarkers were investigated in this project. Among all biomarkers analyzed, serum triglyceride levels had the best diagnostic performance, followed by total serum cholesterol. In accordance with previously published data[62,174,175], patients with AFD had markedly higher levels of both biomarkers, suggesting an important contribution of lipid metabolism in the pathogenesis of the disease. Based on a cut-off value of serum triglycerides of 225 milligrams per deciliter, we were able to create a one-step, clinically actionable algorithm which classified patients into two groups of very different diagnostic probabilities, thus showing the importance of testing for lipid metabolism parameters when evaluating a patient with a clinical suspicion of AH.

To further study the differences between AFD and AH, a thorough pathological examination of all biopsies was performed by two independent expert pathologists. Of note, patients with AFD had massive steatosis (more than 2/3 of the sample) on a consistent basis and inflammatory signs were rarely seen. Additionally, patients with AFD had less advanced liver fibrosis as compared to patients with AH, which is consistent with the findings of the series published by

Uchida and colleagues that was the first ever description of this entity[62]. To explore in detail the pathophysiological mechanisms underlying AFD, we performed transcriptomic analyses of liver biopsy specimens from patients with AFD and compared them to those of patients with AH. AFD specimens had a down-regulation in several pathways that have been associated with the pathogenesis of AH, such as liver fibrosis, hepatic stellate cell activation, wound healing and several interleukin-signaling pathways[20], among many others; in contrast, they showed an up-regulation in mitochondrial function and lipid metabolism pathways. Similar findings in transcriptomic analyses were reported in a recent study[175].

Lastly, the clinical evolution and long-term survival of patients with AFD and AH were consistent with the hypothesis of the two entities being separate conditions with different pathogenesis, as all patients with AFD were alive and transplant-free after a median follow-up of 20 months, while patients with AH had a 57% survival after a median follow-up of 12 months. Similar differences were observed when comparing survival of AFD with a cohort of patients with AH matched by MELD. Of note, most patients with AFD did not receive corticosteroids but spontaneously recovered regardless following alcohol abstinence. Therefore, considering that previous studies reported controversial results in terms of the prognosis of AFD[174,175], the results of our study seem to settle the debate by showing convincing evidence that patients with AFD have markedly better prognosis both short and long term.

One of the main strengths of our study is that the majority of patients that were admitted to the hospital with a suspicion of AH were performed a liver biopsy and thus included in the analysis. Therefore, although possible, a selection bias in the study cohort was significantly nuanced. Another important strength of our study is the long outpatient follow-up, which was up to 5 years in many cases. The two main limitations are: 1) the possibility of misclassification of patients due to sampling error, which is an inherent limitation of any study using transjugular or percutaneous liver biopsies and that could only be overcome by performing surgical biopsies, unethical in this setting; and 2) the small sample size of the AFD cohort and the absence of a validation set.

One important unanswered question in this research area is why some patients develop AFD and others develop AH. The decisive factors underlying different response mechanisms to the same external stressor remain unknown. Is this response genetically-driven? Is microvesicular steatosis the effect of a saturated metabolization pathway? And furthermore, can the same patient develop different alcohol-associated diseases in separate points in time?

In a classical study published in 1995, authors observed that patients with alcohol-associated microvesicular steatosis of the liver had frequently a certain mutation in the hepatic mitochondrial DNA[176]. Moreover, a few case reports in pediatric population have associated other mitochondrial DNA mutations with microvesicular fatty changes in the liver[177]. In addition, drugs causing mitochondrial disfunction may also induce microvesicular steatosis[178]. However, other genetic disorders encoding different proteins in different locations within the cell have also been associated with microvesicular steatosis. An example of this is lysosomal acid lipase deficiency[179]. Furthermore, a recent study published in the *New England Journal of Medicine* found that germline mutations in CIDEB, which encodes for a protein found in hepatic lipid droplets that enables the assembly of microvacuoles into macrovacuoles, were associated with a lesser degree of hepatic inflammation, fibrosis and reduced odds of developing liver disease[180]. All these genetic abnormalities, along with other unknown epigenetic and molecular changes, could be responsible for the different phenotypical presentations of ALD; therefore, future translational research on the field is needed to elucidate the metabolic pathways and mechanisms underlying this condition.

In summary, differential diagnosis of AH must include AFD. AFD is a distinct entity from AH with a specific genetic signature and may be distinguished by serum triglyceride levels. Patients with AFD have an excellent long-term prognosis that contrasts with the poor survival of patients with AH.

The second study included in this doctoral thesis was designed to improve the understanding on recurrent episodes of AH. In a real-world setting, patients who

survive a first episode of AH often resume alcohol consumption in the months following hospital discharge[119,181]. Consequently, recurrence of AH may be a common complication in this patient population. Nevertheless, published data on the actual incidence of recurrent AH and impact on prognosis is very scarce. Only one small study in recent years was designed to address this question[121]. In that study, authors reported an AH recurrence rate of 18% at the end of the follow-up period. Recurrent episodes were associated to poor liver function and high mortality. However, the small sample size (only 10 patients with recurrent AH) limited comparisons and precluded authors from generating robust conclusions. In light of the lack of data, a large multicentric retrospective study using a database from the Spanish registry of alcohol-associated liver disease (REHALC, from the Spanish *Registro Español de Hepatopatía por Alcohol*) was designed. The main objectives of this study were to assess the incidence of recurrent AH, to define its risk factors, and to characterize the severity of recurrent episodes and their impact on survival.

In this second study we found that 11% of patients who survived a first episode of AH developed recurrent AH during the study period. Among patients who resumed alcohol consumption, it was 22%. These frequencies are below those reported in prior studies that assessed readmissions at 1 month based on diagnostic codes[119,120]. However, considering that many patients with AH are readmitted for complications of liver disease in the first month after discharge regardless of active alcohol consumption, the possibility of having misclassified readmissions at 1 month as recurrences based solely on diagnostic codes in prior studies seems highly probable, especially if NIAAA criteria are not manually checked in every patient. In the study by Potts and col., mean time to recurrence was 19 months[121], which is much more plausible because patients need to recover from the first AH in order to develop a recurrent episode. In that study, frequency of recurrent AH was also higher than the one observed in our study; nonetheless, sample size was small and patient selection was based on retrospective chart review, which is prone to bias and could have missed patients with AH that did not present a recurrent episode, overestimating the actual incidence of recurrent AH. Consequently, we firmly believe the results of our study are much more reliable than those previously reported in the literature. In

fact, in a large contemporary study published just a few months ago in which authors used very similar selection criteria, 9% of patients developed recurrent AH[182], which is clearly in line with our findings.

Another important finding of our study is that patients with a higher risk of recurrence were younger (below 50 years of age), consumed more alcohol on a daily basis and had a history of prior clinical decompensations of liver disease in a higher percentage. The age factor and the amount of alcohol consumed could be reflecting a more severe AUD with different drinking patterns in young patients[183]. Additionally, the presence of prior decompensations has been associated to returning to consume alcohol after early liver transplantation for severe AH[184], which could again be a sign of a more severe AUD.

Moreover, we confirmed in a large multicentric cohort the observation made by Potts and col.[121] regarding a greater severity of recurrent episodes compared to first episodes. This observation was also shown in our study when performing paired analyses comparing first episodes vs. recurrent episodes occurring in the same patient. Surprisingly, although recurrent episodes were more severe, mortality in the first 6 months after discharge was not significantly different in first episodes and recurrent episodes. Conversely, we found significant differences in long-term survival. Naturally, for a recurrent episode to take place, patients have to necessarily recover from the first AH hit; therefore, a possible explanation for the similar short-term outcomes could be that patients who develop recurrent AH might have an intrinsic capacity to recover from alcohol-induced liver injury in the acute phase, but might be unable to fully recover in the mid to long-term after subsequent liver injuries. In the contemporary study by Patidar and col. in a large United States' cohort[182], long-term survival in a landmark survival analysis was also higher in patients without recurrence. Unfortunately, short-term survival was not evaluated in the study because landmark time was set at 1 year and thus all deaths happening during the first year were excluded from the survival analysis.

This study has several strengths and limitations. One major strength is the multicentric design with many hospitals from different locations in Spain participating in the study, allowing for an accurate and large sample with granularity of the data. Two additional important strengths of our study are the

long-term outpatient follow-up and the low rate of patients lost to follow-up as compared to previous registry-based studies[93], which significantly diminish the risk of missing important clinical events after discharge from the hospital. Furthermore, the characteristics of the Spanish population and the Spanish healthcare system also prevent information from being lost, as patients rarely move to other regions, tend to use the public healthcare services for important clinical events, and data are shared between all public institutions within the same region. In regards to limitations, most derive from the retrospective nature of the registry, making particular events difficult to capture, such as alcohol slips and relapses, or adherence to medications. Also, as previously discussed, the fact that admissions were identified based on diagnostic codes may be a source of bias; we tried to nuance this limitation by manually reviewing the charts of every patient included. Lastly, probably the most important limitation of our study is the arbitrary minimum of a 3-month period to consider subsequent episodes as recurrences. By definition, recurrence implies absence of disease for a certain time. However, information on how long it takes for the liver to recover from alcohol-associated injuries is quite limited. Our rationale for selecting a period of 3 months was based on a study on natural history of AH[185] and another study on AH transplant candidates[186]. In both studies, 3 months seem to be the time frame in which improvements in liver function were observed. Patients that had not improved after the first 3 months were highly likely to eventually need a liver transplant[186]. In conclusion, in the absence of a laboratory test confirming recovery after a first episode of AH, the most reasonable and evidence-supported time span between episodes seems to be 3 months.

To confirm these findings, future studies in the field will need prospective designs, include multiple centers ideally across different continents and have a long-term follow-up. Also, future trials in patients with ALD focusing on AUD outcomes, such as abstinence or drinks per drinking day, will probably have to be designed to assess the outcome at a longer term in order to capture alcohol recidivism and recurrent AH, which we have convincingly shown that affects long-term prognosis.

The third study of this doctoral thesis was designed to answer the last objective: to investigate the efficacy and safety of medications for alcohol use disorder in advanced stages of alcohol-associated liver disease. By doing so, we thought we might also be able to give insights on the natural history of the disease and on the recurrence of AH.

The rationale behind this third study was that, despite alcohol abstinence is the main prognostic factor of long-term survival in patients with ALD, recommendations with regards to pharmacological interventions to achieve abstinence in this population were not robust. Reasons for this are multiple, but probably combine safety concerns from the addiction specialists' perspective and lack of overall knowledge from the hepatologists side. Consequently, we aimed at condensing the existing evidence regarding MAUD in patients with advanced ALD, specifically cirrhosis, by performing a systematic review and meta-analysis. Of note, our study is the first attempt at analyzing such an important topic with a systematic approach.

Because we suspected that evidence was rather scarce, we chose to be inclusive and have broad inclusion criteria. Studies with mixed populations of patients with and without cirrhosis were considered eligible, as were studies in inpatient and outpatient settings and studies with and without comparator. Even case series were considered eligible provided they included more than 10 patients. In spite of that, one of the most important findings of the study is the incredibly limited amount of information regarding this topic, with only 8 studies being finally included in the systematic review and only 4 clinical trials in the meta-analysis. Notably, a contemporary meta-analysis with similar methods including only studies with baclofen has yielded comparable results[187].

The second important finding of the study is that MAUD are effective in the maintenance of abstinence in patients with cirrhosis, with an alcohol consumption risk reduction of 32%, with most studies evaluating the outcome at 12 weeks. This is a very relevant finding considering that evidence derived from observational studies was fairly strong but it had not been consistently shown in clinical trials[160,188]. However, given that MAUD aim at achieving alcohol abstinence, which might change over time, measuring the outcome at 12 weeks

may be arbitrary and is probably a short period to assess the effect on relevant clinical outcomes. Unfortunately, longer clinical trials are often not feasible. In consequence, the duration of the trials included in our meta-analysis limits the possibility of drawing robust conclusions in that respect. To date, data suggesting that MAUD influence the natural history of ALD by reducing the incidence of liver-related outcomes are supported by observational studies. In a retrospective cohort study of more than 50,000 patients with alcohol-associated cirrhosis, a discharge diagnosis of AUD was associated with a reduced risk of 30-day readmission[189]. Although authors lacked information on addiction referrals and AUD treatment to assess causality, they hypothesized that the reduction in the readmission rate could be a result of AUD management. In another retrospective cohort study including United States Veterans with cirrhosis and AUD, pharmacotherapy-based treatment for AUD was associated with reduced odds of incident decompensation[164]. Furthermore, another study in US population showed that MAUD not only decreased the probability of new decompensating events, but did so in a time of exposure-depending way, with a further decrease in the probability of decompensation with every added year under therapy[165]. With respect to specific drugs, this association was evident for naltrexone and gabapentin. Moreover, in the particular setting of AH, pharmacological treatment for AUD has been recently associated with a lower probability of developing recurrent AH episodes[182]. Lastly, in regards to survival, several retrospective cohort studies have found an association between the use MAUD and increased long-term survival[163–165], without significant differences between specific drugs. In summary, our meta-analysis adds much needed evidence deriving from randomized controlled trials on the efficacy of MAUD in the maintenance of abstinence in patients with cirrhosis. While awaiting confirmation from prospective studies, sustained abstinence with the use of MAUD seems to impact the natural history of ALD.

The third finding of our study meriting a comment is the safety profile of MAUD. One hundred and sixty-five severe adverse events (SAE) were reported in 638 patients when combining treatment arms, which is a relatively low number considering that the majority of patients had cirrhosis. Only 5 SAE were possibly or probably associated to study drugs. However, it should be noted that SAE

reporting was not homogeneous between studies and that the percentage of patients with decompensated cirrhosis was fairly low. In fact, the few studies including patients with decompensated cirrhosis were also those reporting the highest number of SAE[157,190]. Therefore, despite MAUD seem to be safe in patients with cirrhosis, more studies are needed to confirm these findings particularly in patients with decompensated cirrhosis.

The most important strength of our study is the rigorous search and data extraction process, which is essential in any systematic review and meta-analysis but particularly in one with such a shortage of studies. The main limitations are attributable to the characteristics of the studies included and reflect the current state of the evidence regarding this topic: heterogeneous populations, lack of consistency regarding outcome measures, etc. As a consequence, the meta-analysis heterogeneity was high and robust recommendations for changing clinical practice cannot be made at this point.

In summary, we have addressed our work hypotheses by 1) providing convincing evidence of the importance of an accurate differential diagnosis of AH; and 2) increasing the knowledge regarding the natural history of ALD with a comprehensive description of recurrent episodes of AH and a meta-analysis on the efficacy and safety of pharmacological interventions for AUD.

6. CONCLUSIONS

The final conclusions of this doctoral thesis are the following:

1. In a significant proportion of patients with suspicion of alcohol-associated hepatitis, clinical diagnosis is not confirmed after the pathological assessment of the liver biopsy. The current noninvasive criteria for the diagnosis of alcohol-associated hepatitis have a modest performance.

2. Alcoholic foamy degeneration is a common condition in the differential diagnosis of alcohol-associated hepatitis and may be distinguished by serum triglyceride levels.

3. Alcoholic foamy degeneration has a specific genetic signature and an excellent prognosis without the need for corticosteroid treatment.

4. Recurrent alcohol-associated hepatitis is common, particularly in young patients with prior liver decompensation.

5. Recurrent episodes of alcohol-associated hepatitis are more severe and have a negative impact on patient survival.

6. Medications for alcohol use disorder are safe and effective in the maintenance of alcohol abstinence and might be able to change the natural history of alcohol-associated liver disease.

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