Received: 29 December 2023 | Accepted: 18 April 2024

DOI: 10.1111/acer.15345

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

RESEARCH ARTICLE

Clinical features of individuals with laboratory values suggestive of advanced liver fibrosis when first treated for alcohol use disorder

Paola Zuluaga[1,2] | Daniel Fuster[1,2] | Rafael Blanes[3] | Anna Hernández-Rubio[1,2] | Laia Miquel[4,5] | Marta Torrens[2,6] | Gabriel Rubio[7,8] | Ferrán Bolao[5,9] | Suthat Liangpunsakul[10,11] | Enric Abellí-Deulofeu[1,2] | Fernando Rodriguez de Fonseca[12] | Robert Muga[1,2] | CohRTA

[1]Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, IGTP, Badalona, Spain

[2]Universitat Autònoma de Barcelona, Bellaterra, Spain

[3]Alcohol Unit, Hospital Universitari Son Espases, IdISPa, Palma de Mallorca, Spain

[4]Alcohol Unit, Department of Psychiatry, Hospital Clínic, IDIBAPS, Barcelona, Spain

[5]Universitat de Barcelona, Barcelona, Spain

[6]Department of Neuropsychiatry and Addictions, Hospital del Mar, IMIM, Barcelona, Spain

[7]Department of Psychiatry, Hospital Universitario 12 de Octubre, Madrid, Spain

[8]Universitat Complutense de Madrid, Madrid, Spain

[9]Department of Internal Medicine, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Spain

[10]Division of Gastroenterology and Hepatology, Department of Medicine and Biochemistry, Indiana University School of Medicine, Indianapolis, Indiana, USA

[11]Division of Gastroenterology and Hepatology, Department of Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[12]IBIMA Biomedical Research Institut-Malaga, Málaga, Spain

Correspondence
Paola Zuluaga, Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Universidad Autónoma de Barcelona, Ctra. Canyet, Badalona 08916, Spain.
Email: ypzuluaga.germanstrias@gencat.cat

Funding information
Centres de Recerca de Catalunya, Grant/Award Number: 2021-SGR-00945; Instituto de Salud Carlos III, Grant/Award Number: PI20/00883, JR20/00016, CD19/00019 and RD21/0009/0004; Plan Nacional sobre Drogas, Grant/Award Number: PNSD2020/024

Abstract

Background: Effective screening for alcohol-associated liver disease is relevant in the context of chronic, excessive alcohol consumption. Patients with alcohol-associated liver disease are often not diagnosed until their liver disease is decompensated. We analyzed the prevalence and associations of Fibrosis-4 index (FIB-4) values suggestive of advanced liver fibrosis in patients referred for their first treatment of alcohol use disorder (AUD).

Methods: We conducted a cross-sectional, multicenter study of noncirrhotic individuals referred for their first AUD treatment between March 2013 and April 2021. We obtained sociodemographic data, substance use characteristics, and blood samples at admission. We considered a FIB-4 value ≥2.67 suggestive of advanced liver fibrosis and used logistic regression analyses to identify features associated with this value.

Results: We included 604 patients (67% male), with a median age at admission of 48 years [IQR: 41–56 years]. The median duration of regular alcohol consumption was

Members of the CohRTA study are listed in the Appendix 1.

21 years [IQR: 18–30 years] and the median alcohol consumption was 105 standard drink units (SDU)/week [IQR: 63–160 SDU/week]. A FIB-4 value ≥ 2.67 was present in 19.3% of cases. These patients reported more frequent binge drinking (75.4% vs. 66%, $p = 0.05$) than those with FIB-4 values below 2.67. In multivariate analysis, a history of binge drinking (OR 1.9, 95% CI, 1.05–3.47), anemia (OR 2.95, 95% CI, 1.42–6.11), leukopenia (OR 7.46, 95% CI, 2.07–26.8), and total serum bilirubin >1 mg/dL (OR 6.46, 95% CI, 3.57–11.7) were independently associated with FIB-4 values ≥2.67.

Conclusions: One in five patients admitted to treatment for AUD without evidence of decompensated liver disease have FIB-4 values suggestive of advanced liver fibrosis. The presence of a binge drinking history, anemia, leukopenia, and elevated bilirubin levels is associated with high FIB-4 values.

KEYWORDS
advanced liver fibrosis, alcohol-associated liver disease, binge drinking, FIB-4 index, leukopenia

INTRODUCTION

Alcohol use disorder (AUD) stands as the most prevalent substance use disorder globally, particularly prominent in Western countries. Its prevalence is coupled with a significant burden of disease and mortality, as highlighted by the World Health Organization in 2018 (WHO, 2018). Despite the availability of screening tools and effective interventions, the proportion of individuals with AUD receiving treatment remains alarmingly low. In European countries and the USA, this figure does not exceed 20% (Kranzler & Soyka, 2018; Rehm et al., 2015), while in low- and middle-income countries, it falls below 10% (Rathod et al., 2018). Several factors contribute to this treatment gap, including social stigma surrounding AUD, inadequate recognition of the disorder—especially among younger individuals—and insufficient screening in primary care settings (Rossow et al., 2021). The stigma associated with AUD often leads to reluctance to seek help, while a lack of recognition and screening in primary care further compounds the issue.

Alcohol-associated liver disease (ALD) poses a significant global health concern and is the leading cause of liver-related mortality worldwide (Devarbhavi et al., 2023). Advanced liver fibrosis is a crucial predictor of mortality among patients with ALD, emphasizing the importance of early detection and intervention (Lackner et al., 2017). While only a subset of excessive alcohol users progress to advanced liver disease, several factors contribute to individual susceptibility, including genetic predisposition, female sex, obesity, smoking, and chronic viral infections (Schwantes-An et al., 2021; Seitz et al., 2018).

Despite the substantial impact of ALD, early detection remains challenging, with the majority of cases being identified at advanced stages (Shah et al., 2019). Liver fibrosis, a hallmark of ALD progression, can be detected even in individuals with normal levels of aspartate aminotransferase (AST), highlighting the limitations of relying solely on traditional biomarkers for early detection (Chang et al., 2021). Noninvasive screening methods, such as liver elastography and serum markers like the Enhanced Liver Fibrosis (ELF) test and FibroTest, offer promising alternatives to liver biopsy for detecting underlying fibrosis (Israelsen et al., 2024; Nguyen-Khac et al., 2018). These methods have shown favorable performance compared to biopsy and could facilitate early detection and risk stratification in clinical practice. However, challenges such as limited availability and cost currently hinder their widespread adoption in primary care settings.

Using the FIB-4 index as a screening tool in primary care addiction clinics for patients with excessive alcohol consumption appears to be a promising approach for identifying individuals at risk of advanced liver fibrosis. Several studies have demonstrated the effectiveness of FIB-4 in diagnosing liver fibrosis and predicting outcomes in patients with ALD. The FIB-4 index performs well compared to elastography, with a high area under the curve (AUC) of 0.9, indicating its efficacy in diagnosing liver fibrosis (Chrostek et al., 2019). In addition, several studies by Nguyen-Khac et al. (2018), Rasmussen et al. (2021), and Rhodes et al. (2021) highlight the utility of FIB-4 in identifying advanced ALD and predicting mortality and liver complications in patients with ALD. Given its accuracy and ease of use, FIB-4 could serve as a valuable screening tool in primary care addiction clinics, where patients are often referred for the initial treatment of AUD. In this study, we aimed to analyze the prevalence and associations of FIB-4 suggestive of advanced liver fibrosis in the context of primary care addiction clinics where patients are referred for the first treatment of AUD.

MATERIALS AND METHODS

Study participants

This was a cross-sectional, multicenter study, including patients with AUD without prior treatment for excessive alcohol consumption. Between March 2013 and April 2021, patients were recruited

from primary care Addiction Units linked to general hospitals in the Spanish National Health Service. No unit was available for the performance of transient elastography. Addiction physicians with training in Addiction Medicine or Addiction Psychiatry performed the clinical evaluation of each patient included in the study.

The participating centers were members of the CohRTA project, an open, prospective, and multi-centric cohort of patients with AUD who received treatment for the disorder. The study protocol was the same for each participating center and included inclusion criteria, structured questionnaires with socio-demographic data, characteristics of alcohol consumption, consumption of other substances, medical comorbidity scales, and laboratory data. A researcher chosen by the principal investigator of each center was responsible for collecting all the data and registering it in an online database that was specially designed for the CohRTA project (Coresoft Clínico, www.coresoft.es). More details of the protocol have been published elsewhere (Sanvisens et al., 2018).

All patients were 18 years or older and the diagnosis of AUD was assessed by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (American Psychiatric Association, 2013).

A total of 991 patients were recruited. However, we excluded patients with incomplete laboratory data ($n = 185$), hepatitis C virus infection ($n = 62$), human immunodeficiency virus infection ($n = 9$), and those who were diagnosed with underlying or decompensated liver cirrhosis ($n = 131$) after finishing the study protocol. A flowchart for the selection of the study population is shown in Figure 1.

Data collection

A questionnaire to evaluate the severity of AUD using DSM-5 criteria (mild, up to two criteria; moderate, up to four criteria; and severe, more than six criteria) was administered. Regular alcohol use was defined as daily or almost daily consumption. A standard drink unit (SDU) was used to quantify the weekly alcohol consumption. One SDU was defined as 100 mL of wine, 200 mL of beer, 50 mL of fortified wine or cava, or 25 mL of liquor or spirits (Gual et al., 1999). Binge drinking (BD) was defined as alcohol consumption greater than five SDUs in a period of less than 2 h. In the context of heavy drinkers, BD was defined as those patients with a preference for consuming most of the days, and BD pattern was established if the patient reported consumption six or more days a week in the last month. A family history of AUD in parents, cousins, or siblings and self-reported cocaine and cannabis use were also documented. We also captured the baseline laboratory parameters, such as complete blood count, coagulation parameter, comprehensive metabolic panel, hepatic panel, and erythrocyte sedimentation rate (ESR). The FIB-4 index ≥2.67 was used as an indicator for advanced liver fibrosis (Hagström et al., 2020; Rasmussen et al., 2021; Shah et al., 2009). The study was approved by the IRB of the coordinating center (Hospital Universitari Germans Trias i Pujol, Barcelona, Spain) (PI-13-031) and by the IRBs of each participating center, all of them in Spain: Hospital Universitari Son Espases, Palma de Mallorca; Hospital Clinic, Barcelona; Hospital del Mar, Barcelona; Hospital Universitario 12 de Octubre, Madrid and, Hospital Universitari de Bellvitge, Barcelona. The protocol and methods used in the study met the ethical standards and the principles of good clinical practice established in the Helsinki Declaration of 1975. All patients provided informed consent for data transfer and sample extraction.

Statistical analysis

We used basic descriptive statistics, including frequencies, percentages, medians, and interquartile ranges [IQRs] to characterize the study population.

The laboratory variables were categorized according to the normal values of each laboratory; leukopenia (leukocyte count

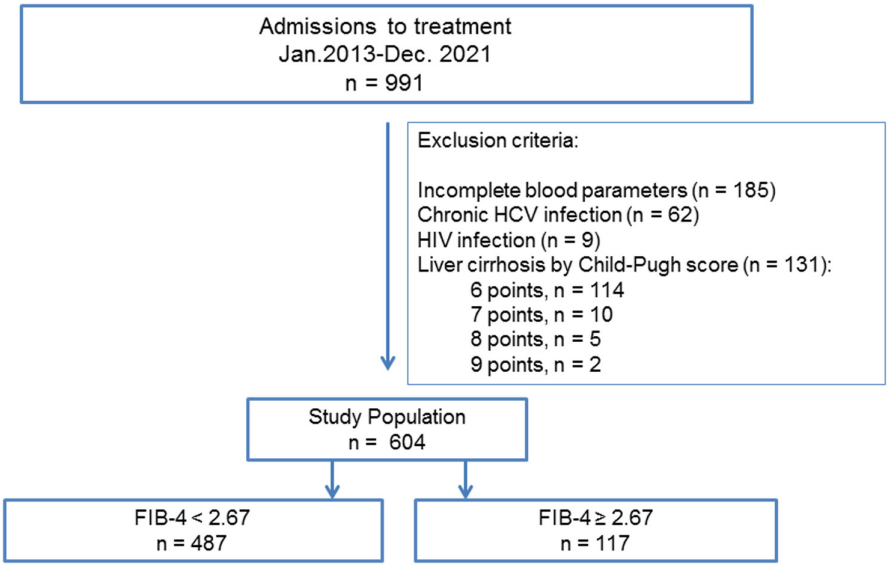

FIGURE 1 Flowchart for the selection of study participants.

<4000 × 10^9/L); erythro-sedimentation rate (ESR > 20 mm/h), bilirubin >1 mg/dL. Anemia was defined as a hemoglobin level below 13 mg/dL for men and below 12 mg/dL for women (World Health Organization, 2011).

We used the appropriate comparisons tests such as the chi-square test and Student's *T*-test for comparison between groups for categorical and continuous variables, respectively. The primary outcome of interest was the presence of advanced liver fibrosis, as determined by the FIB-4 index. We dichotomized our study population into two groups based on the FIB-4 index cut-off at 2.67. We conducted an univariate analysis for each variable and those with statistical significance were entered into the multivariate analysis. We designed the multivariable logistic regression model with the laboratory and sociodemographic variables that were associated with FIB-4 values suggestive of advanced liver fibrosis. We fitted the model with all variables in a single block and was further adjusted by sex. We did not include in the multivariable regression model any variable included in the FIB-4 formula (i.e. AST, ALT, age, and platelet count). In addition, we treated all variables as dichotomic. We reported the results as an odds ratio (OR) and a 95% confidence interval (CI). We considered *p*-values ≤0.05 statistically significant. We performed Statistical analyses using Stata software (version 11.1, College Station, Texas, USA).

RESULTS

Baseline characteristics of participants

We included 604 patients (67% men). The mean age of participants was 48 ± 11.2 years old. The average DSM-5 severity score was 8.3. The mean age at starting alcohol consumption was 16 years old and the mean age for regular alcohol consumption was 25 years old. On average, patients consumed 123 SDU per week (past month) and 64% reported a family history of AUD. The average FIB-4 index, hemoglobin, leukocytes, and platelets was 2, 14.4 g/dL, 7.5 × 10^9 cells/L, and 233.8 × 10^9 cells/L, respectively. The mean aspartate (AST) and alanine (ALT) aminotransferase were 53.6 and 43.8 U/L, respectively.

FIB-4 in the study population

Using the FIB-4 index cutoff at 2.67, we found that 117 (19.3%) patients had values suggestive of advanced fibrosis with an average FIB-4 value of 5.4. Patients with and without advanced fibrosis had a comparable DSM-5 score (8.4 vs. 8.2, $p = 0.55$), age of onset for alcohol consumption (15.3 ± 4.4 vs. 16 ± 6.1, $p = 0.14$), and SDU per week (131 ± 83.2 vs. 121 ± 83.4 SDU, $p = 0.22$). Patients with FIB-4 ≥2.67 had a significantly higher binge drinking pattern (75.4% vs. 66%, $p = 0.05$) but less cocaine (31.6% vs. 47.5%, $p < 0.01$) and cannabis (12.8% vs. 22.5%, $p = 0.01$) use. Being single (16.3% vs. 30%; $p < 0.01$) and being employed (32.7% vs. 41.8%; $p = 0.03$) were the least frequent social conditions for patients with FIB-4 ≥2.67. Table 1 describes the sociodemographic characteristics and consumption of alcohol and other substances in the two groups according to the FIB-4 index.

Hemoglobin levels (13.8 vs. 14.5 g/dL, $p < 0.01$), leukocyte (6.0 vs. 7.9 × 10^9 cells/L, $p < 0.01$), and platelet counts (153.3 vs. 253 × 10^9 cells/L, $p < 0.01$) were significantly lower in those with FIB-4 ≥ 2.67. The proportion of patients with anemia and leukopenia among those with FIB-4 ≥ 2.67 was significantly higher than among those with FIB-4 ≤2.67 (24.1% vs. 8.8%, $p < 0.01$ and 12.1% vs. 1.6%, $p < 0.01$; respectively). Patients with FIB-4 ≥ 2.67 also had higher serum total bilirubin (1.1 vs. 0.7 mg/dL, $p < 0.01$), AST (129 vs. 35.3 U/L, $p < 0.01$), ALT (79.4 vs. 35.2, $p < 0.01$), and erythrocyte sedimentation rate (ESR, 24.5 vs. 15.2 mm/h, $p < 0.01$). The proportion of high ESR (20 mm/h) was significantly higher among these patients (46% vs. 26.4%, $p < 0.01$). Detailed information on the laboratory parameters is shown in Table 2.

Associations of high FIB-4 ≥ 2.67

To analyze associations of FIB-4 ≥ 2.67 we first performed univariate analyses on the variables that were observed to have a significantly different distribution according to FIB-4 index. The variables included in the FIB-4 index; that is, age, AST and ALT levels, and platelet count, were not included in the multivariate analyses. We found that a history of binge drinking (OR 1.9, 95% CI, 1.05–3.47), evidence of anemia (OR 2.95, 95% CI, 1.42–6.11–0.98), leukopenia (OR 7.46, 95% CI, 2.07 to −26.8), and total bilirubin >1 mg/dL (OR 6.46, 95% CI, 3.57–11.7) were factors independently associated with FIB-4 index ≥2.67 among patients with AUD. Table 3 includes the univariate and multivariate logistic regression analysis.

DISCUSSION

We found that 19% of patients with AUD had FIB-4 index values suggestive of advanced liver fibrosis even after excluding patients with underlying or decompensated liver cirrhosis. This prevalence aligns with previous research in patients with early ALD, highlighting the significant burden of advanced fibrosis in this population (Thiele et al., 2016). Patients with FIB-4 values suggestive of advanced fibrosis were older, and had a higher proportion of binge drinking patterns and a lower proportion of self-reported cannabis and cocaine use when compared to those without advanced fibrosis.

Our study provided valuable insights into the relationship between binge drinking patterns and the development of advanced ALD, as indicated by FIB-4 values suggestive of advanced liver fibrosis. This association underscores the importance of considering not only the quantity (Anstee et al., 2016) but also the pattern of alcohol consumption in assessing the risk of ALD progression among individuals with AUD (Mathurin et al., 2007). Mechanistically, binge

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

TABLE 1 Baseline characteristics of 604 patients according to FIB-4 value.

	Total ($N=604$)	FIB-4 < 2.67 ($N=487$)	FIB-4 ≥ 2.67 ($N=117$)	*p*-value
Age at admission (years)	48.2 ± 11	46.9 ± 10.8	53.8 ± 10.2	<0.01
Gender, M (*N*, %)	410 (67%)	327 (67%)	83 (71%)	0.43
Body Mass Index (kg/m^2)	25.8 ± 5	25.8 ± 4.8	25.7 ± 5.4	0.86
Current smokers (*N*, %)	501 (84%)	408 (85%)	93 (80%)	0.17
Marital status* (*N*, %)				
Single	165 (27.4%)	146 (30%)	19 (16.3%)	<0.01
Married	214 (35.5%)	163 (33.4%)	51 (44%)	
Widower/Separated/Divorced	223 (37%)	177 (36.2%)	46 (39.6%)	
Education ** (*N*, %)				
Cannot read or write	7 (1.2%)	3 (0.85%)	2 (2.6%)	0.36
Primary school	119 (20.3%)	92 (19.4%)	27 (24.1%)	
Secondary school	353 (60.4%)	291 (61.6%)	62 (55.3%)	
University/Graduate	104 (17.8%)	84 (17.8%)	20 (17.8%)	
Employment *** (*N*, %)				
Currently employed	241 (40.1%)	203 (41.8%)	38 (32.7%)	0.03
Part-time work/unemployed	255 (42.4%)	206 (42.4%)	49 (42.2%)	
Disability/Pensioner/Housewife	105 (17.4%)	76 (15.6%)	29 (25%)	
Alcohol consumption and other substance use				
DSM-5 severity score	8.3 ± 2	8.2 ± 2.1	8.4 ± 1.8	0.55
Severe AUD (*N*, %)	464 (81.6%)	373 (80.5%)	91 (86.6%)	0.14
Age at starting alcohol consumption	16 ± 5.8	16 ± 6.1	15.3 ± 4.4	0.25
Age at starting regular alcohol consumption	25 ± 11.4	25.2 ± 11	26.1 ± 13	0.44
Family history of AUD (*N*, %)	371 (64.3)	306 (65.3%)	65 (59.6%)	0.25
Standard drink unit/week (last month)	123 ± 83.4	121 ± 83.4	131 ± 83.2	0.22
Binge drinking (*N*, %)[a]	390 (67.8%)	307 (66%)	83 (75.4%)	0.05
Cocaine use (*N*, %)	268 (44.4%)	231 (47.5%)	37 (31.6%)	<0.01
Cannabis use (*N*, %)	125 (20.7%)	110 (22.5%)	15 (12.8%)	0.01

Note: Data available in *602, **583, and ***601 patients respectively.

[a] More than five Standard Drink Units in a period of less than 2 h and for six or more days per week.

drinking leads to an increase in serum lipopolysaccharide levels, a key inflammatory driver during ALD pathogenesis (Bala et al., 2014). A population-based study demonstrated a near-linear association between binge-drinking frequency and liver disease risk, even after adjusting for average daily alcohol intake and age (Åberg et al., 2017). The clinical implications of these findings are substantial. First, they provide compelling evidence linking binge drinking patterns to the development of advanced ALD, emphasizing the need for targeted interventions aimed at reducing binge drinking behaviors among individuals with AUD. Second, they underscore the importance of collecting detailed information on both the quantity and pattern of alcohol consumption in primary care settings for risk stratification of ALD. Patients with a history of binge drinking may be at heightened risk of developing advanced liver disease and could benefit from early referral to hepatologists or consideration of diagnostic tests such as elastography for further evaluation and management.

The results of our study show the potential utility of laboratory-based tests, particularly leukopenia, anemia, and bilirubin levels, in identifying patients with AUD who may have advanced liver fibrosis, as indicated by higher FIB-4 values. This is especially valuable in primary care settings where access to elastography may be limited. Our findings suggest that routine laboratory tests commonly obtained in primary care settings could serve as effective screening tools for identifying individuals with possible advanced liver disease. Notably, the association between anemia and elevated FIB-4 values, particularly in patients with a normal mean corpuscular volume (MCV), suggests an inflammatory state driven by alcohol toxicity in the hemopoietic system (Ballard, 1997). This underscores the importance of considering anemia with a normal MCV as a potential marker of inflammation and chronic medical illnesses, which have been associated with mortality in AUD (Fuster et al., 2015). Furthermore, the association between leukopenia and elevated FIB-4 values

TABLE 2 Baseline laboratory parameters in 604 patients with AUD according to FIB-4 values.

	Total (*N* = 604)	FIB-4 < 2.67 (*N* = 487)	FIB-4 ≥ 2.67 (*N* = 117)	*p*-value	Normal values
FIB-4	2 ± 2.1	1.1 ± 0.5	5.4 ± 2.9	<0.01	
Hemoglobin (g/dL)	14.4 ± 1.7	14.5 ± 1.6	13.8 ± 1.8	<0.01	13.5–17.5
Anemia[a] (*N*, %)	71 (11.7%)	43 (8.8%)	28 (24.1%)	<0.01	
Leucocytes ($\times 10^9$/L)	7.5 ± 2.5	7.9 ± 2.4	6 ± 1.9	<0.01	4.0–11.0
Leucopenia[b] (*N*, %)	22 (3.68%)	8 (1.6%)	14 (12.1%)	<0.01	
Platelet count	233.8 ± 74.8	253.2 ± 66.1	153.3 ± 52	<0.01	150–400
Urea (mg/dL)	25.4 ± 9.2	26.2 ± 9	22.2 ± 9.6	<0.01	22–52
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.13	0.7–1.2
Total bilirubin (mg/dL)	0.7 ± 0.5	0.7 ± 0.3	1.1 ± 0.8	<0.01	0.1–1
Total bilirubin >1 mg/dL (*N*, %)	86 (15%)	42 (9.1%)	44 (39.2%)	<0.01	
Aspartate aminotransferase (AST, U/L)	53.6 ± 61.3	35.5 ± 28.3	129 ± 95.1	<0.01	5–40
Alanine aminotransferase (ALT, U/L)	43.8 ± 50.3	35.2 ± 36.6	79.4 ± 77	<0.01	5–41
Albumin (g/dL)	42.1 ± 7.6	42.7 ± 7	39.7 ± 9.2	<0.01	35–52
Total proteins (g/dL)	70.6 ± 5.7	70.6 ± 5.3	70.9 ± 7.3	0.61	64–83
Fasting glucose (mg/dL)	97.7 ± 28.7	97 ± 29.5	100.4 ± 25.2	0.25	68–100
Cholesterol (mg/dL)	209.4 ± 50.2	208.8 ± 46.7	211.7 ± 63.2	0.58	69–200
Triglyceride (mg/dL)	165 ± 169	165.5 ± 161	162.5 ± 202.3	0.86	<150
Erythrocyte sedimentation rate (ESR, mm/h)	17 ± 17	15.2 ± 14.5	24.5 ± 24.4	<0.01	0–20
ESR >20 mm/h (*N*, %)	161 (30%)	116 (26.4%)	45 (46%)	<0.01	

[a] Hemoglobin <12 mg/dL in women and <13 mg/dL in men.

[b] Leucocytes <4.000 × 10^9xL.

TABLE 3 Univariate and multivariate analysis of FIB-4 values suggestive of advanced liver fibrosis in patients with AUD.

Variable	Univariate (OR and 95% CI)	*p*-value	Multivariate (OR and 95% CI)	*p*-value
Marital status (compared to being single)	0.45 (0.25–0.77)	<0.01	0.64 (0.34–1.22)	0.18
Employment (compared to currently employed)	0.67 (0.44–1.03)	0.07	–	–
Binge drinking	1.58 (0.98–2.54)	0.05	1.9 (1.05–3.47)	0.03
Cocaine use	0.51 (0.33–0.78)	<0.01	0.61 (0.34–1.12)	0.10
Cannabis use	0.50 (0.28–0.90)	0.02	0.94 (0.46–1.94)	0.87
Anemia	3.28 (1.93–5.57)	<0.01	2.95 (1.42–6.11)	<0.01
Leukopenia	8.23 (3.36–20.13)	<0.01	7.46 (2.07–26.8)	<0.01
Total bilirubin >1 mg/dL	6.45 (3.93–10.58)	<0.01	6.46 (3.57–11.7)	<0.01
ESR > 20 mm/h	2.35 (1.5–3.69)	<0.01	1.52 (0.87–2.65)	0.13

may indicate the presence of portal hypertension (Liangpunsakul et al., 2003). Leukopenia is a common finding in patients with compensated liver cirrhosis and has been identified as a predictor of disease progression and mortality, particularly due to liver decompensation and bacterial infections (Qamar et al., 2009). Treatments aimed at improving granulopoietic activity and response, such as colony-stimulating growth factor (G-CSF), have shown promise in improving survival in patients with severe forms of ALD (Singh et al., 2018).

The challenge of diagnosing ALD in patients with AUD lies in the fact that many patients are diagnosed only when their liver disease has progressed to a decompensated state, indicating a significant period of asymptomatic fibrosis or compensated cirrhosis (Shah et al., 2019). This underscores the importance of screening for underlying ALD, particularly in those at risk for advanced disease or fibrosis. Patients who develop ALD require treatment for underlying AUD, with the primary goal of achieving abstinence (Ting et al., 2020). Approximately 10%–15% of AUD patients

develop alcohol-associated cirrhosis and the mortality rate from alcohol-associated cirrhosis only affects a subset of patients with AUD (Schwantes-An et al., 2021). Taken together, it is necessary to screen for underlying ALD especially those who are at risk for advanced disease or fibrosis. However, screening for ALD in the general AUD population presents challenges due to the low prevalence of ALD among a large population of at-risk individuals, making cost-effective screening more difficult (Israelsen et al., 2024; Liangpunsakul & Crabb, 2016). Risk stratification may offer a solution by targeting screening efforts toward individuals at higher risk for advanced liver disease (Israelsen et al., 2024). Tools such as transient elastography and 2-dimensional shear wave elastography have shown promise in screening individuals at risk for liver fibrosis due to alcohol consumption (Thiele et al., 2016). However, the availability of these tools, particularly in primary care settings where most patients with AUD are seen, may be limited.

Our study has several strengths, including a relatively large sample size of patients with AUD seeking treatment for the first time. This population represents an important cohort for assessing the disorder comprehensively. However, it is essential to acknowledge and discuss the limitations of the study, which can provide context for interpreting the findings. One notable limitation is the absence of liver biopsy or elastography examinations to confirm the presence of advanced fibrosis. While these diagnostic tests are considered gold standards for assessing liver fibrosis, they may not be clinically feasible, particularly in primary care settings where patients with AUD are often seen. In such settings, the use of the FIB-4 index serves as a practical alternative, especially considering its high diagnostic performance in predicting advanced fibrosis in patients with ALD, as demonstrated in previous studies (Chrostek et al., 2019; Nguyen-Khac et al., 2018). Nevertheless, incorporating transient elastography into the evaluation of patients with AUD in primary care settings could enhance the assessment of liver fibrosis and disease severity (Israelsen et al., 2024). The lack of data on ascites or encephalopathy limits the ability to assess disease severity using traditional scoring systems like the Child–Pugh score. Furthermore, the absence of information on the prevalence of diabetes or metabolic syndrome, which are known risk factors for liver disease, could impact the interpretation of study findings.

In conclusion, our study highlights the potential utility of detailed alcohol consumption history, particularly binge drinking, as well as laboratory parameters such as anemia, leukopenia, and bilirubin levels, in screening patients with AUD for the presence of advanced fibrosis. We recommend incorporating a basic laboratory panel, in addition to a thorough clinical evaluation, in the primary care setting to identify patients with AUD at risk of alcohol-related liver disease. Leukopenia, in particular, may serve as an early indicator of liver fibrosis, even in patients without clinical manifestations of ALD. Understanding the pathophysiological mechanisms underlying binge drinking and exploring the social and cultural factors associated with this consumption pattern is crucial for developing targeted interventions. Early identification of patients with AUD will be clinically important if the providers can influence their drinking behavior with either cognitive or pharmacologic treatments (Liangpunsakul & Crabb, 2016). The cornerstone of treatment for patients with AUD is reducing alcohol consumption and achieving abstinence, which can help prevent the progression of liver injury or advanced liver disease.

AUTHOR CONTRIBUTION

P.Z., D.F., and R.M. conceived and designed the study. P.Z., D.F., and R.M. obtained research funding. P.Z., D.F., R.B., A.H.R., L.M., M.T., G.R., F.B., EAD, and R.M. undertook recruitment of patients. P.Z. and R.M. undertook the statistical analysis. P.Z., D.F., and L.M. reviewed the literature and made contributions to the interpretation of data. All authors (P.Z., D.F., S.L., A.H.R., L.M., M.T., G.R., F.B., F.R.F., and R.M.) contributed substantially to its revision. All the authors have revised and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

FUNDING INFORMATION

Ministry of Economy and Competitiveness, Institute of Health Carlos III, Spain (RD21/0009/0004; Programa Juan Rodes JR20/00016; Programa Sara Borrell CD19/00019; grant number PI20/00883); the National Plan on Drugs, Spain (grant no 2020/024); and the Agency for Management of University and Research Grants, Government of Catalonia (2021-SGR-00945).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Paola Zuluaga https://orcid.org/0000-0002-0247-0351
Daniel Fuster https://orcid.org/0000-0003-1262-5860
Anna Hernández-Rubio https://orcid.org/0000-0001-8612-7827
Laia Miquel https://orcid.org/0000-0002-1248-4626
Marta Torrens https://orcid.org/0000-0001-6222-4761
Gabriel Rubio https://orcid.org/0000-0002-1171-1508
Ferrán Bolao https://orcid.org/0000-0002-9104-6615
Suthat Liangpunsakul https://orcid.org/0000-0002-6504-8123
Enric Abellí-Deulofeu https://orcid.org/0000-0002-5403-8755
Fernando Rodriguez de Fonseca https://orcid.org/0000-0002-4516-5795
Robert Muga https://orcid.org/0000-0001-6301-431X

REFERENCES

Åberg, F., Helenius-Hietala, J., Puukka, P. & Jula, A. (2017) Binge drinking and the risk of liver events: a population-based cohort study. *Liver International*, 37, 1373–1381.

American Psychiatric Association. (2013) *Diagnostic and statistical manual of mental disorders*, 5th edition. Washington, DC: American Psychiatric Association.

Anstee, Q.M., Seth, D. & Day, C.P. (2016) Genetic factors that affect risk of alcoholic and nonalcoholic fatty liver disease. *Gastroenterology*, 150, 1728–1744.e7.

Bala, S., Marcos, M., Gattu, A., Catalano, D. & Szabo, G. (2014) Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. *PLoS One*, 9, e96864.

Ballard, H.S. (1997) The hematological complications of alcoholism. *Alcohol Health and Research World*, 21, 42–52.

Chang, B., Huang, A., Saxena, R., Sun, Y., Liu, S., Zhou, G. et al. (2021) Hepatic histopathology among excessive drinkers without advanced liver disease. *Alcohol and Alcoholism*, 56, 669–677.

Chrostek, L., Przekop, D., Gruszewska, E., Gudowska-Sawczuk, M., Cylwik, B. & Caputo, F. (2019) Noninvasive indirect markers of liver fibrosis in alcoholics. *BioMed Research International*, 2019, 3646975.

Devarbhavi, H., Asrani, S.K., Arab, J.P., Nartey, Y.A., Pose, E. & Kamath, P.S. (2023) Global burden of liver disease: 2023 update. *Journal of Hepatology*, 79, 516–537.

Fuster, D., Sanvisens, A., Bolao, F., Zuluaga, P., Rivas, I., Tor, J. et al. (2015) Markers of inflammation and mortality in a cohort of patients with alcohol dependence. *Medicine*, 94, e607.

Gual, A., Martos, A.R., Lligoña, A. & Llopis, J.J. (1999) Does the concept of a standard drink apply to viticultural societies? *Alcohol and Alcoholism*, 34, 153–160.

Hagström, H., Talbäck, M., Andreasson, A., Walldius, G. & Hammar, N. (2020) Ability of noninvasive scoring systems to identify individuals in the population at risk for severe liver disease. *Gastroenterology*, 158, 200–214.

Israelsen, M., Rungratanawanich, W., Thiele, M. & Liangpunsakul, S. (2024) Non-invasive tests for alcohol-associated liver disease. *Hepatology*. https://doi.org/10.1097/HEP.0000000000000885

Kranzler, H.R. & Soyka, M. (2018) Diagnosis and pharmacotherapy of alcohol use disorder a review. *JAMA*, 320, 815–824.

Lackner, C., Spindelboeck, W., Haybaeck, J., Douschan, P., Rainer, F., Terracciano, L. et al. (2017) Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. *Journal of Hepatology*, 66, 610–618.

Liangpunsakul, S. & Crabb, D.W. (2016) Early detection of alcoholic liver disease: are we a step closer? *Gastroenterology*, 150, 29–31.

Liangpunsakul, S., Ulmer, B.J. & Chalasani, N. (2003) Predictors and implications of severe hypersplenism in patients with cirrhosis. *The American Journal of the Medical Sciences*, 326, 111–116.

Mathurin, P., Beuzin, F., Louvet, A., Carrié-Ganne, N., Balian, A., Trinchet, J.C. et al. (2007) Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. *Alimentary Pharmacology & Therapeutics*, 25, 1047–1054.

Nguyen-Khac, E., Thiele, M., Voican, C., Nahon, P., Moreno, C., Boursier, J. et al. (2018) Non-invasive diagnosis of liver fibrosis in patients with alcohol-related liver disease by transient elastography: an individual patient data meta-analysis. *The Lancet Gastroenterology & Hepatology*, 3, 614–625.

Qamar, A.A., Grace, N.D., Groszmann, R.J., Garcia-Tsao, G., Bosch, J., Burroughs, A.K. et al. (2009) Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clinical Gastroenterology and Hepatology*, 7, 689–695.

Rasmussen, D.N., Thiele, M., Johansen, S., Kjærgaard, M., Lindvig, K.P., Israelsen, M. et al. (2021) Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. *Journal of Hepatology*, 75, 1017–1025.

Rathod, S.D., Roberts, T., Medhin, G., Murhar, V., Samudre, S., Luitel, N.P. et al. (2018) Detection and treatment initiation for depression and alcohol use disorders: facility-based cross-sectional studies in five low-income and middle-income country districts. *BMJ Open*, 8, e023421.

Rehm, J., Allamani, A., Della, V.R., Elekes, Z., Jakubczyk, A., Landsmane, I. et al. (2015) General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 European countries. *Annals of Family Medicine*, 13, 28–32.

Rhodes, F.A., Trembling, P., Panovska-Griffiths, J., Tanwar, S., Westbrook, R.H., Rodger, A. et al. (2021) Systematic review: investigating the prognostic performance of four non-invasive tests in alcohol-related liver disease. *Journal of Gastroenterology and Hepatology*, 36, 1435–1449.

Rossow, I., Amundsen, E.J. & Samuelsen, S.O. (2021) Socio-economic differences in all-cause mortality in people with alcohol use disorder: a prospective cohort study. *Addiction*, 116, 53–59.

Sanvisens, A., Zuluaga, P., Rivas, I., Rubio, G., Gual, A., Torrens, M. et al. (2018) Pacientes con trastorno por uso de alcohol: resultados iniciales de un registro multicéntrico en la Red de Trastornos Adictivos-RTA. Estudio CohRTA. *Adicciones*, 30, 292–300.

Schwantes-An, T.H., Darlay, R., Mathurin, P., Masson, S., Liangpunsakul, S., Mueller, S. et al. (2021) Genome-wide association study and meta-analysis on alcohol-associated liver cirrhosis identifies genetic risk factors. *Hepatology*, 73, 1920–1931.

Seitz, H.K., Bataller, R., Cortez-Pinto, H., Gao, B., Gual, A., Lackner, C. et al. (2018) Alcoholic liver disease. *Nature Reviews Disease Primers*, 4, 16.

Shah, A.G., Lydecker, A., Murray, K., Tetri, B.N., Contos, M.J., Sanyal, A.J. et al. (2009) Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology*, 7, 1104–1112.

Shah, N.D., Ventura-Cots, M., Abraldes, J.G., Alboraie, M., Alfadhli, A., Argemi, J. et al. (2019) Alcohol-related liver disease is rarely detected at early stages compared with liver diseases of other etiologies worldwide. *Clinical Gastroenterology and Hepatology*, 17, 2320–2329.e12.

Singh, V., Keisham, A., Bhalla, A., Sharma, N., Agarwal, R., Sharma, R. et al. (2018) Efficacy of granulocyte colony-stimulating factor and N-acetylcysteine therapies in patients with severe alcoholic hepatitis. *Clinical Gastroenterology and Hepatology*, 16, 1650–1656.e2.

Thiele, M., Detlefsen, S., Sevelsted Møller, L., Madsen, B.S., Fuglsang Hansen, J., Fialla, A.D. et al. (2016) Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology*, 150, 123–133.

Ting, P.S., Wheatley, J. & Chen, P.H. (2020) Behavioral treatment for patients with alcohol-related liver disease: a primer for hepatologists. *Clinical Liver Disease*, 15, 31–35.

World Health Organization. (2011) Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-111

World Health Organization. (2018) *Global status report on alcohol and health 2018*. World Health Organization. https://www.who.int/publications/i/item/9789241565639

How to cite this article: Zuluaga, P., Fuster, D., Blanes, R., Hernández-Rubio, A., Miquel, L., Torrens, M. et al. (2024) Clinical features of individuals with laboratory values suggestive of advanced liver fibrosis when first treated for alcohol use disorder. *Alcohol: Clinical and Experimental Research*, 00, 1–9. Available from: https://doi.org/10.1111/acer.15345

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

APPENDIX 1

CohRTA Study. Spanish Network on Addictive Disorders, Alcohol Program.

Coordinating Center: Department of Internal Medicine. Hospital Universitari Germans Trias i Pujol, Badalona, Spain.

CohRTA centers and researchers as of February 1, 2022:

Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol/IGTP, Badalona, Spain: Arantza Sanvisens, Paola Zuluaga, Daniel Fuster, Anna Hernández-Rubio, Magí Farré, Esther Papasseit, Clara Pérez-Mañá, Lourdes Poyatos, Nuria García-Marchena, Enric Abellí-Deulofeu, Robert Muga.

Department of Psychiatry, Alcohol Unit, Hospital Universitari Son Espases/IdISPa, Palma de Mallorca, Spain: Catalina Moranta, Rafael Blanes, Raimer C. Oberguggenberger.

Department of Psychiatry, Hospital Universitario 12 de Octubre, i+12, Madrid, Spain: Gabriel Rubio, Ana Sion.

Department of Psychiatry, Hospital Clínic de Barcelona/IDIBAPS, Barcelona, Spain: Laia Miquel, Lluisa Ortega, Pol Bruguera, Elsa Caballeria, Ana Messeguer.

Department of Neuropsychiatry and Addictions, Parc de Salut Mar/IMIM, Barcelona, Spain: Marta Torrens, Francina Fonseca, Joan Ignasi Mestre-Pinto, María Alías, Fernando Dinamarca.

Department of Internal Medicine, Hospital Universitari de Bellvitge/IDIBELL, L'Hospitalet de Llobregat, Spain: Ferran Bolao.

Biomedical Research Institute/IBIMA, Málaga, Spain: Fernando Rodríguez-Fonseca, Francisco Javier Pavón-Morón.

Department of Internal Medicine, Hospital Universitario de Salamanca/IBSAL, Salamanca, Spain: Miguel Marcos.

Department of Internal Medicine, Hospital Universitario de Canarias/HUGCDN, Santa Cruz de Tenerife, Spain: Candelaria Martín, Onán Pérez-Hernández.

CohRTA Biobank: Department of Neurosciences, Miguel Hernández University, San Juan de Alicante, Spain: Jorge Manzanares, Francisco Navarrete, Ani Gasparyan.