Received: 14 October 2023 | Accepted: 6 February 2024

DOI: 10.1097/HEP.0000000000000825

ORIGINAL ARTICLE

Recurrent alcohol-associated hepatitis is common and is associated with increased mortality

Jordi Gratacós-Ginès[1,2,3] | Pilar Ruz-Zafra[4] | Miriam Celada-Sendino[5] | Aina Martí-Carretero[6] | Clàudia Pujol[7] | Rosa Martín-Mateos[8] | Víctor Echavarría[9] | Luis E. Frisancho[10] | Sonia García[11] | Mónica Barreales[12] | Javier Tejedor-Tejada[13] | Sergio Vázquez-Rodríguez[14] | Nuria Cañete[15] | Carlos Fernández-Carrillo[16] | María Valenzuela[17] | David Martí-Aguado[18] | Diana Horta[19] | Marta Quiñones[20] | Vanesa Bernal-Monterde[21] | Silvia Acosta[22] | Tomás Artaza[23] | José Pinazo[24] | Carmen Villar-Lucas[25] | Ana Clemente-Sánchez[26] | Ester Badia-Aranda[27] | Álvaro Giráldez-Gallego[4] | Manuel Rodríguez[5] | Pau Sancho-Bru[2] | Joaquín Cabezas[9] | Meritxell Ventura-Cots[3,6] | Conrado Fernández-Rodríguez[20,28] | Victoria Aguilera[3,11] | Santiago Tomé[29] | Ramon Bataller[1,3] | Juan Caballería[1,2,3] | Elisa Pose[1,2,3] | REHALC Registry investigators

[1]Department of Liver Diseases, Hospital Clínic de Barcelona, Barcelona, Spain

[2]Liver, Digestive System and Metabolism Department Institut d'Investigacions Biomèdiques August Pi i Sunyer, IDIBAPS, Barcelona, Spain

[3]Department of Liver Injury, Progression of Cirrhosis and Liver Transplantation, Centro de Investigación Biomédica En Red de Enfermedades Hepáticas y Digestivas, CIBERehd, Madrid, Spain

[4]Department of Digestive Diseases, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[5]Department of Liver Diseases, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain

[6]Department of Liver Diseases, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Research, Universitat Autònoma de Barcelona, Barcelona, Spain

[7]Department of Gastroenterology, Hospital Santa Creu i Sant Pau, Barcelona, Spain

[8]Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, Madrid, Spain

[9]Department of Gastroenterology and Hepatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[10]Department of Liver Diseases, Hospital Parc Taulí, Sabadell, Spain

[11]Department of Hepatology and Liver Transplant, Hospital Universitari i Politècnic La Fe, IISLa FE, Valencia, Spain

[12]Department of Liver Diseases, Hospital Universitario 12 de Octubre, Madrid, Spain

[13]Department of Gastroenterology, Hospital Universitario de Cabueñes, Gijón, Spain

[14]Department of Gastroenterology. Xerencia Xestion Integrada de Vigo Research Group in Digestive Diseases, Galicia Sur Health Research Institute (IIS Galicia Sur), SERGAS-UVIGO, SERGAS, Vigo, Spain

[15]Liver Section, Department of Gastroenterology, Hospital del Mar, Barcelona, Spain

[16]Department of Gastroenterology and Hepatology, Hospital Universitario Puerta de Hierro, Madrid, Spain

[17]Department of Gastroenterology and Hepatology, Hospital Universitari Dr. Josep Trueta, Girona, Spain

[18]Digestive Disease Department, Clínic University Hospital, Biomedical Research Institute INCLIVA, Valencia, Spain

[19]Department of Digestive Diseases, Hospital Universitari Mútua Terrassa, Terrassa, Spain

[20]Gastroenterology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain

[21]Department of Digestive Diseases, Hospital Universitario Miguel Servet, Zaragoza, Spain

[22]Department of Digestive Diseases, Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain

[23]Department of Digestive Diseases, Hospital Universitario de Toledo, Toledo, Spain

[24]Department of Gastroenterology, Hospital Virgen de la Victoria, Málaga, Spain

[25]Department of Digestive Diseases, Hospital Universitario de Salamanca, Salamanca, Spain

[26]Department of Liver Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[27]Department of Digestive Diseases, Hospital Universitario de Burgos, Burgos, Spain

[28]Department of Medicine, Universidad Rey Juan Carlos, Madrid, Spain

[29]Department of Liver Diseases, Hospital Universitario de Santiago, Santiago de Compostela, Spain

Correspondence
Elisa Pose, Liver Unit, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
Email: epose@clinic.cat

Abstract

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

Approach and Results: A registry-based study was done 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 tests. A total of 1118 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%. The 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 U/d, and history of liver decompensation. RAH was clinically more severe compared to the first AH (higher MELD, more frequent ACLF, and HE). 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.

Abbreviations: ACLF, acute-on-chronic liver failure; AEEH, *Asociación Española para el Estudio del Hígado*; AH, alcohol-associated hepatitis; EASL, European Association for the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver, Chronic Liver Failure; MAH, moderate alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis; SAH, severe alcohol-associated hepatitis.

Presented at 47 Congreso Anual de la Asociación Española para el Estudio del Hígado (May 2022, Madrid, Spain) and the International Liver Congress 2022, EASL Congress (June 2022, London, UK).

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepjournal.com.

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 the 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]

AH 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% to 20% at 1 year in moderate alcohol-associated hepatitis (MAH)[3–5] to >30% at 28 days in severe alcohol-associated hepatitis (SAH) and nonresponse to corticosteroids.[6–9] Finally, health expenditures associated with AH are high due to the frequent development of complications requiring a high amount of resources and the need for readmissions 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 that has been termed as recurrent alcohol-associated hepatitis (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.

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 1, 2014, and December 31, 2021. Patients with International Classification of Diseases, 10th revision 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 a history of AH prior to 2014 were not included in the study. AH was defined 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 (Supplemental Table S1, http://links.lww.com/HEP/I308). First AH was defined as an episode of "probable" or "definite" AH in a patient with no history of AH. RAH was defined as any episode of "probable" or "definite" AH occurring at least 3 months after a previous episode in a patient with a 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 (1) HCC exceeding the Milan criteria; (2) previous liver transplant; or (3) severe extrahepatic disease, including extrahepatic neoplasia, with a life expectancy of <6 months.

For the purpose of the study, we performed 2 types of main analyses:

(1) Patients alive after first AH, comparing those who presented RAH during follow-up versus 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 versus all RAH, as well as paired episodes: first AH versus 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 (1) SAH versus MAH; and (2) RAH presenting before versus after the start of the COVID-19 pandemic in Spain (March 2020).

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

Data collection

A careful review of the patients' medical records was performed by all participant centers. Data on demographics, substance use, comorbidities, history of liver disease, clinical presentation, and laboratory tests at admission were collected. Acute kidney injury was defined following the European Association for the Study of the Liver (EASL) Guidelines on Decompensated Cirrhosis.[20] ACLF was defined according to the

European Association for the Study of the Liver, Chronic Liver Failure (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 for endotracheal intubation in the absence of West Haven grade 3 and 4 HE.[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) 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 nonabstinent on an assumption of a worst-case scenario regarding missing data.

Data collected for each episode of AH were 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 (Jordi Gratacós-Ginès) 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-squared or Fischer tests. Quantitative variables were expressed as the median and interquartile range (25th–75 percentile) and were analyzed using *t* test (normal distribution), Mann-Whitney test (non-normal distribution), or Wilcoxon. Factors associated with the recurrence of AH and death were studied with Cox regression analysis and expressed as 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 (ie, 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 the 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 the 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, 1285 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 the patient analysis was death during first admission (n = 154), to include only patients at risk of RAH. Of the remaining 1118 patients, 125 (11%) presented RAH during follow-up (Figure 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 the 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, and had a higher proportion of psychiatric comorbidity as well as history of hepatic decompensations. Ascites was the most frequent previous liver decompensation (34%), followed by overt HE (13%).

Out of the 1118 patients included, 439 (39%) had a specialized follow-up in an addiction unit (ethyl glucuronide 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% of the 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% (Figure 2). In this subgroup of patients, baseline characteristics were similar to those of the total study cohort (Supplemental Table S2, http://links.lww.com/HEP/I308).

Out of the 1118 patients with AH, 690 (62%) presented with SAH, and of these, 72 (10%) presented

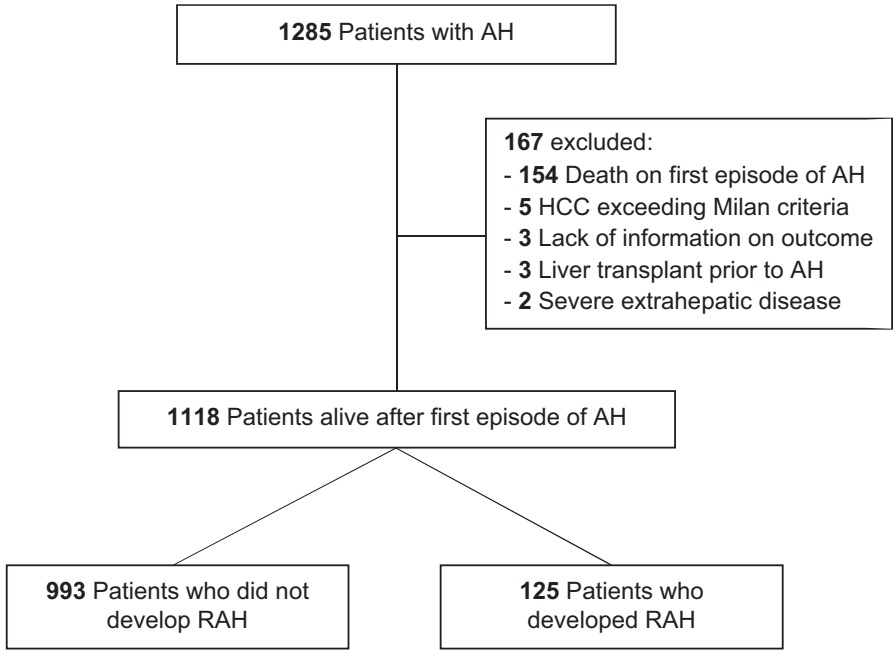

FIGURE 1 Study flowchart. Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

recurrent SAH during follow-up. The demographics and history of these patients were highly comparable to those of the total cohort (Supplemental Table S3, http://links.lww.com/HEP/I308).

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 with 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 /d, 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 U/d (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 (Supplemental Table S4, http://links.lww.com/HEP/I308).

In the subgroup of patients with SAH, factors independently associated with 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 versus RAH episodes

We next compared the characteristics of all first versus all RAH 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 1275 (88.2%) as first AH. Median follow-up was 11 [3–24] months after RAH and 15 [6–32] months after the 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 discriminant function, MELD and Child-Pugh scores, lower platelet count, and higher international normalized ratio. We also found a higher proportion of ACLF at admission, with no significant differences in the percentages of individual organ failures (Supplemental Table S5, http://links.lww.com/HEP/I308). In addition, the development of overt HE during hospitalization was also more frequent when being admitted for RAH.

The analysis of paired episodes of the first AH and first RAH revealed very similar findings (Supplemental Table S6, http://links.lww.com/HEP/I308); admissions due to RAH had a higher Maddrey discriminant function, plus higher MELD and Child-Pugh scores. Moreover, a greater impairment in liver function was shown with every further recurrence (Supplemental Table S7, http://links.lww.com/HEP/I308). A nonstatistically significant trend toward a higher proportion of ACLF at admission in RAH was also observed when analyzing paired episodes. In this analysis, recurrent admissions had a higher percentage

TABLE 1 Baseline demographics and history of patients included in the study, divided into 2 groups depending on the status of recurrence at the end of follow-up

	Patients without RAH during follow-up (n = 993)	Patients with RAH during follow-up (n = 125)	*p*
Age (y)	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 (U/d)	10 (6–13)	10 (7–15)	0.174
Duration of alcohol use (y)	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 HE	47 (5)	16 (13)	< **0.001**
Bleeding due to PHT	52 (5)	13 (10)	**0.018**

Bold values indicate statistically significant differences.
[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: PHT, portal hypertension; RAH; recurrent alcohol-associated hepatitis.

of renal failure, as well as trends toward a greater proportion of organ failure in the remaining systems (Supplemental Table S8, http://links.lww.com/HEP/I308).

Interestingly, the probability of maintaining alcohol abstinence throughout the follow-up period was notably lower after an episode of RAH than after the 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 was associated with alcohol abstinence, although there was a trend toward 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 the first and RAH episodes. Of note, the development of HE during hospitalization was significantly more common in RAH (31% vs. 44%, $p = 0.003$). With respect 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 Supplemental Table S9, http://links.lww.com/HEP/I308.

We performed a subanalysis of RAH from the prepandemic versus pandemic periods. Interestingly, we found no differences in liver function tests and prevalence of decompensation and ACLF (Supplemental Table S10, http://links.lww.com/HEP/I308). Survival of RAH was not significantly different when comparing patients diagnosed in the prepandemic versus

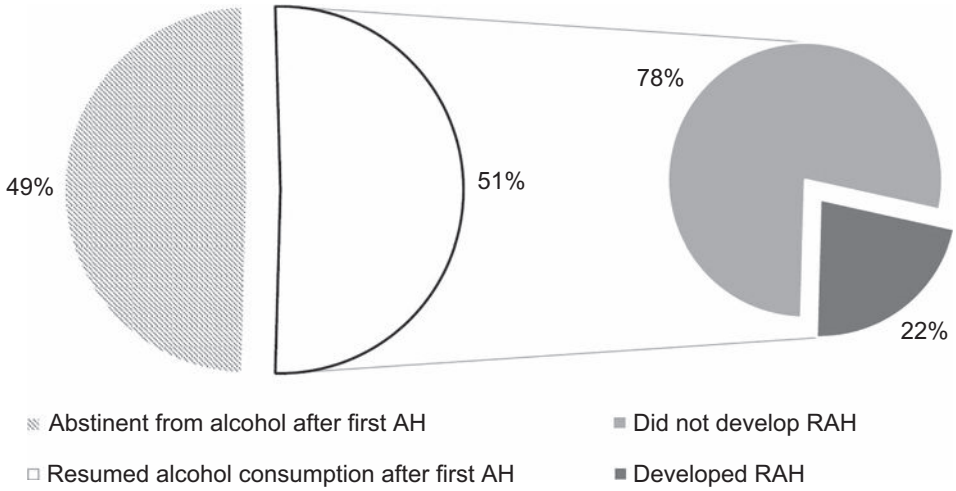

FIGURE 2 Incidence of RAH in patients who resumed alcohol consumption after surviving a first AH. Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

pandemic periods (78% vs. 65% at 1 year, $p = 0.084$). Furthermore, the time of presentation was not associated with higher alcohol abstinence (OR for the 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 ($p = 0.026$) (Figure 3). Causes of death in both groups are listed in Supplemental Table S11, http://links.lww.com/HEP/I308. Fifty-five (5%) patients underwent liver transplantation during follow-up, 50 in the group of patients without RAH and 5 in the group with RAH. A trend toward 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 the 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 an RAH. Notably, survival was lower after RAH compared to the 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, C, respectively. In SAH, survival was lower after RAH compared to the 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

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

	Univariate analysis			Multivariate analysis		
Variable	**HR**	***p***	**95% CI**	**HR**	***p***	**95% CI**
Age < 50 (y)	**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 U/d	**1.591**	**0.010**	**1.117-2.266**	**1.583**	**0.016**	**1.091-2.297**
Duration of alcohol use (y)	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**

Bold values indicate statistically significant differences.

TABLE 3 Main characteristics of first AH and RAH episodes

	First AH (n = 1275)	Recurrent AH (n = 171)	*p*
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 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 HE	292 (23)	61 (36)	< **0.001**
Bleeding due to PHT	76 (6)	14 (8)	0.262
Bacterial infection	361 (28)	53 (31)	0.478

Values are median (± IQR) or absolute count (percentage).
Bold values indicate statistically significant differences.
Abbreviations: ABIC, age-bilirubin-INR-creatinine; AH, alcohol-associated hepatitis; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; PHT, portal hypertension; SAH: severe alcohol-associated hepatitis.

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 below 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

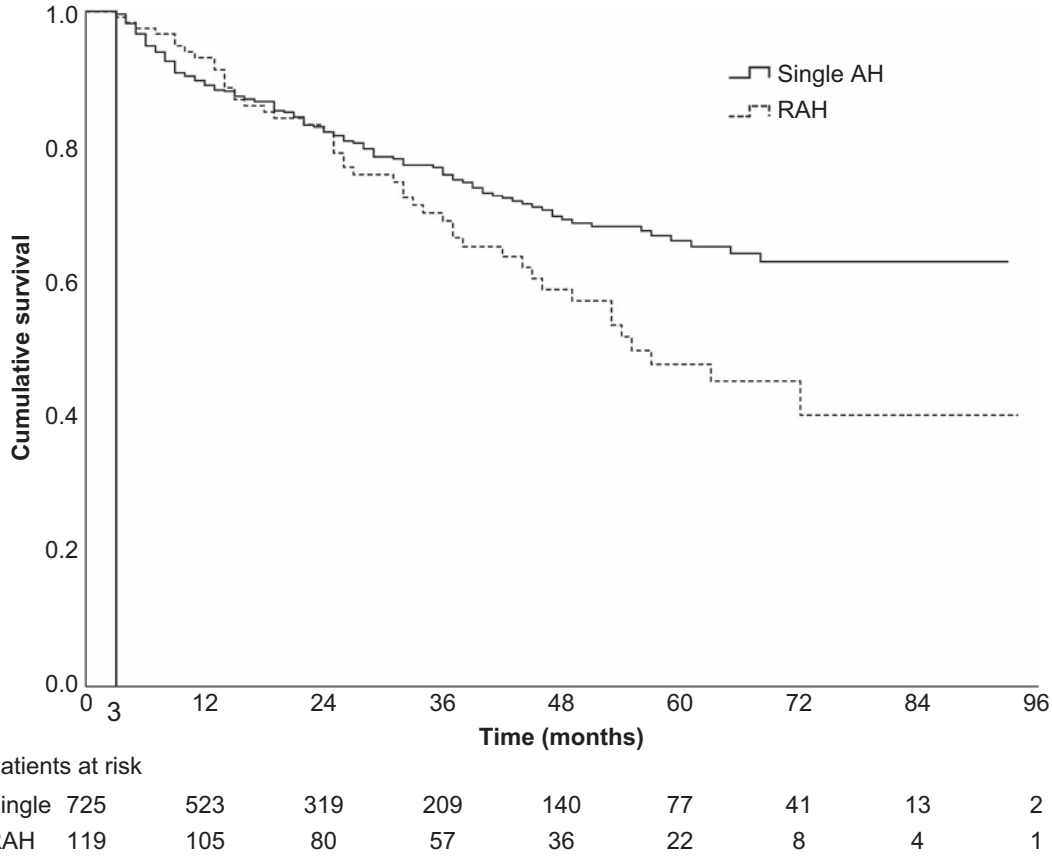

FIGURE 3 Kaplan-Meier curves showing the survival of patients who did not develop RAH during follow-up (single AH) and patients who did develop RAH (RAH group). $p = 0.026$ (log-rank test). Abbreviations: AH, alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis.

recurrence suggests that patients with more advanced liver disease are at higher risk of recurrence. Furthermore, studies in patients post-liver transplantation have also found an association between previous decompensations of liver disease and harmful use of alcohol,[24] which may at least in part explain the higher risk of recurrence in this population. 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 been 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 platelet levels, as an indirect marker of more severe portal hypertension. Moreover, patients admitted for RAH were more prone to developing HE 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

TABLE 4 Survival rates at different time points after an episode of first AH versus RAH in (A) the total cohort; (B) the subgroup of SAH episodes; and (C) the subgroup of MAH

(A)	First AH (n = 1218)[a]	Recurrent AH (n = 162)[a]	p[c]
Alive at 1 mo	1093 (90)	140 (86)	0.198
Alive at 3 mo	1013 (83)	132 (82)	0.591
Alive at 6 mo	973 (80)	120 (74)	0.077
Alive at 12 mo	897 (75)	104 (64)	**0.008**
Alive at 24 mo	823 (70)	87 (54)	**< 0.001**
Alive at 36 mo	775 (67)	84 (52)	**< 0.001**
(B)	**First SAH (n = 812)[a]**	**Recurrent SAH (n = 125)[a]**	p[c]
Alive at 1 mo	692 (85)	103 (82)	0.413
Alive at 3 mo	619 (76)	95 (76)	0.995
Alive at 6 mo	586 (72)	84 (67)	0.252
Alive at 12 mo	528 (66)	73 (58)	0.105
Alive at 24 mo	473 (60)	60 (48)	**0.010**
Alive at 36 mo	441 (57)	58 (46)	**0.025**
(C)	**First MAH (n = 401)[b]**	**Recurrent MAH (n = 37)[b]**	p[c]
Alive at 1 mo	396 (99)	37 (100)	1.000
Alive at 3 mo	390 (97)	37 (100)	0.610
Alive at 6 mo	383 (96)	36 (97)	1.000
Alive at 12 mo	365 (92)	32 (87)	0.217
Alive at 24 mo	346 (89)	28 (76)	**0.031**
Alive at 36 mo	330 (88)	27 (73)	**0.021**

First AH episodes were censored at the time of recurrence.
Bold values indicate statistically significant differences.
[a]Information on outcome missing in <5%.
[b]Information on outcome missing in 5%–10%.
[c]Chi-square test.
Abbreviations: AH, alcohol-associated hepatitis; MAH, moderate alcohol-associated hepatitis; RAH, recurrent alcohol-associated hepatitis; SAH, severe alcohol-associated hepatitis.

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 International Classification of Diseases, 10th revision 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, the 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 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 the 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 the 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.

TABLE 5 Univariate and multivariate analysis of baseline risk factors of mortality

	Univariate analysis			Multivariate analysis		
Variable	**HR**	***p***	**95% CI**	**HR**	***p***	**95% CI**
Age (y)	**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 U/d	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**

Note: Presenting with an episode of RAH was an independent risk factor for death.
Bold values indicate statistically significant differences.
Abbreviations: ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

AUTHOR CONTRIBUTIONS

Jordi Gratacós-Ginès: conceptualization, methodology, formal analysis, investigation, writing original draft, and visualization. Juan Caballería: conceptualization, supervision. Elisa Pose: conceptualization, methodology, writing original draft, and project administration. All the other authors contributed to patient and data recruitment, as well as manuscript review and editing.

ACKNOWLEDGMENTS

The authors thank the *Asociación Española para el Estudio del Hígado (AEEH)* and *Centro de Investigación Biomédica en Red (CIBER)* del Instituto de Salud Carlos III for the support. The authors thank Carolina Jiménez-González for technical assistance and Juan G. Abraldes, Miquel Serra-Burriel, Adrià Juanola, and Octavi Bassegoda for the support with the statistical analyses.

FUNDING INFORMATION

Jordi Gratacós-Ginès has a Contrato Río Hortega grant (CM21/00095), Instituto de Salud Carlos III (ISCIII)—Acción Estratégica en Salud (AES) and has received financial support from *Asociación Española para el Estudio del Hígado* (AEEH). David Martí-Aguado is the recipient of a Joan Rodés award (JR22/00002), ISCIII. Elisa Pose has the grant PI022/00910 (Proyectos de Investigación en Salud, proyectos FIS—AES).

CONFLICTS OF INTEREST

Ramon Bataller consults for GlaxoSmithKline, Novo Nordisk and Boehringer Ingelheim. He is on the speakers' bureau for AbbVie and Gilead. Sergio Vázquez-Rodríguez received grants from Roche. Manuel Rodríguez is on the speakers' bureau of Gilead and Advanz. Joaquín Cabezas advises, is on the speakers' bureau and received grants from AbbVie and Gilead. The remaining authors have no conflicts to report.

REHALC REGISTRY INVESTIGATORS

Edilmar Alvarado, María Pilar Ballester, Federico Cáceres, María Del Barrio, Inmaculada Fernández-Vázquez, Montserrat García-Retortillo, Concepción Gómez-Medina, Queralt Herms, Helena Hernández-Évole, Lorena Jara, Esther Maderuelo, Dalia Morales, Olga Ramos Barriga, Mercè Roget, Jordi Sánchez, Germán Soriano, Ares Villagrasa, Joana Villaverde.

REFERENCES

1. Bataller R, Arab JP, Shah VH. Alcohol-associated hepatitis. N Engl J Med. 2022;387:2436–48.
2. Singal AK, Arsalan A, Dunn W, Arab JP, Wong RJ, Kuo YF, et al. Alcohol-associated liver disease in the United States is associated with severe forms of disease among young, females and Hispanics. Aliment Pharmacol Ther. 2021;54:451–61.
3. Degré D, Stauber RE, Englebert G, Sarocchi F, Verset L, Rainer F, et al. Long-term outcomes in patients with decompensated alcohol-related liver disease, steatohepatitis and Maddrey's discriminant function. J Hepatol. 2020;72:636–42.
4. Bennett K, Enki DG, Thursz M, Cramp ME, Dhanda AD. Systematic review with meta-analysis: High mortality in patients with non-severe alcoholic hepatitis. Aliment Pharmacol Ther. 2019;50:249–57.
5. Daniel KE, Lucey MR. Editorial: Moderate alcoholic hepatitis-hiding in plain sight. Aliment Pharmacol Ther. 2019;50:608–9.
6. Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015;372:1619–28.
7. Dominguez M, Rincón D, Abraldes JG, Miquel R, Colmenero J, Bellot P, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol. 2008;103:2747–56.
8. Louvet A, Labreuche J, Artru F, Boursier J, Kim DJ, O'Grady J, et al. Combining data from liver disease scoring systems better predicts outcomes of patients with alcoholic hepatitis. Gastroenterology. 2015;149:398–406.e8.
9. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KVN, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology. 2005;41:353–8.
10. Jinjuvadia R, Liangpunsakul S. Trends in alcoholic hepatitis-related hospitalizations, financial burden, and mortality in the United States. J Clin Gastroenterol. 2015;49:506–11.
11. Thompson JA, Martinson N, Martinson M. Mortality and costs associated with alcoholic hepatitis: A claims analysis of a commercially insured population. Alcohol. 2018;71:57–63.
12. Peeraphatdit TB, Kamath PS, Karpyak VM, Davis B, Desai V, Liangpunsakul S, et al. Alcohol rehabilitation within 30 days of hospital discharge is associated with reduced readmission, relapse, and death in patients with alcoholic hepatitis. Clin Gastroenterol Hepatol. 2020;18:477–85.e5.
13. Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol. 2017;66:610–8.
14. Louvet A, Labreuche J, Artru F, Bouthors A, Rolland B, Saffers P, et al. Main drivers of outcome differ between short term and long term in severe alcoholic hepatitis: A prospective study. Hepatology. 2017;66:1464–73.
15. Potts JR, Goubet S, Heneghan MA, Verma S. Determinants of long-term outcome in severe alcoholic hepatitis. Aliment Pharmacol Ther. 2013;38:584–95.
16. Altamirano J, López-Pelayo H, Michelena J, Jones PD, Ortega L, Ginès P, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival. Hepatology. 2017;66:1842–53.
17. Parés A, Caballería J, Bruguera M, Torres M, Rodés J. Histological course of alcoholic hepatitis. Influence of abstinence, sex and extent of hepatic damage. J Hepatol. 1986;2:33–42.
18. Chedid A, Mendenhall CL, Gartside P, French SW, Chen TRL. Prognostic factors in alcoholic liver disease. VA Cooperative Study Group. Am J Gastroenterol. 1991;86:210–6.
19. Potts JR, Howard MR, Verma S. Recurrent severe alcoholic hepatitis: Clinical characteristics and outcomes. Eur J Gastroenterol Hepatol. 2013;25:659–4.
20. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406–60.
21. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37, 1437.e1-9.
22. Mahmud N, Chapin S, Goldberg DS, Reddy KR, Taddei TH, Kaplan DE. Statin exposure is associated with reduced development of acute-on-chronic liver failure in a Veterans Affairs cohort. J Hepatol. 2022;76:1100–8.
23. Ball SA. Type A and type B alcoholism: Applicability across subpopulations and treatment settings. Alcohol Heal Res World. 1996;20:30–5.
24. Weinberg EM, Dukewich M, Jakhete N, Stonesifer E, Im GY, Lucey MR, et al. Early liver transplantation for severe alcohol-associated hepatitis and a history of prior liver decompensation. Am J Gastroenterol. 2022;117:1990–8.
25. Gratacós-Ginès J, Bruguera P, Pérez-Guasch M, López-Lazcano A, Borràs R, Hernández-Évole H, et al. Medications for alcohol use disorder promote abstinence in alcohol-related cirrhosis: results from a systematic review and meta-analysis. Hepatology. 2024;79:368–79.
26. Patidar KR, Belcher JM, Regner KR St, Hillien SA, Simonetto DA, Asrani SK, et al. Incidence and outcomes of acute kidney injury including hepatorenal syndrome in hospitalized patients with cirrhosis in the US. J Hepatol. 2023;79:1408–7.
27. Jepsen P, Kraglund F, West J, Villadsen GE, Sørensen HT, Vilstrup H. Risk of hepatocellular carcinoma in Danish outpatients with alcohol-related cirrhosis. J Hepatol. 2020;73:1030–6.
28. Arab JP, Díaz LA, Baeza N, Idalsoaga F, Fuentes-López E, Arnold J, et al. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: A worldwide study. J Hepatol. 2021;75:1026–33.
29. Alexander JF, Lischner MW, Galambos J. Natural history of alcoholic hepatitis. II. The long-term prognosis. Am J Gastroenterol. 1971;56:515–25.
30. Veldt BJ, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: Quantitative evaluation and optimal timing. J Hepatol. 2002;36:93–8.

How to cite this article: Gratacós-Ginès J, Ruz-Zafra P, Celada-Sendino M, Martí-Carretero A, Pujol C, Martín-Mateos R, et al. Recurrent alcohol-associated hepatitis is common and is associated with increased mortality. Hepatology. 2024;80:621–632. https://doi.org/10.1097/HEP.0000000000000825