

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

Word Count: 4085

Abstract Count: 262

Tables: 4

Figures: 1

Supplementary material: 4

References: 44

**Treatment retention in a specialized alcohol programme after an episode
of alcoholic hepatitis: impact on alcohol relapse**

Running head: Treatment retention after an alcoholic hepatitis

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

^aGrup Recerca Addicions Clínic (GRAC-GRE). Department of Psychiatry,
Clinical Institute of Neuroscience. Hospital Clínic i Universitari de Barcelona.
Universitat de Barcelona. Villarroel, 170, 08036, Barcelona, Catalonia, Spain.

^bInstitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Rosselló,
149, 08036, Barcelona, Catalonia, Spain.

^cRed de Trastornos Adictivos. RETICS. C/ Sinesio Delgado, 4, 28029 Madrid,
Spain.

Do not disseminate or use without explicit permission from ¹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

^dLiver Unit. Hospital Clinic. Universitat de Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD).

^e Pittsburgh Liver Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

*Joint last authorship.

Corresponding author: Hugo López-Pelayo. Medical Doctor and PhD student.

Hospital Clínic i Universitari de Barcelona.

Villarroel 170, escalera 9 planta 6, 08036, Barcelona, Catalonia, Spain.

Telephone number: +34 932271719. Fax number: +34932275548 Email:

hlopez@clinic.cat

Conflicts of Interest and Source of Funding

Hugo López-Pelayo has received honouraria from Lundbeck, Teva and Janssen and travel grants from Lilly, Pfizer, Otsuka, Lundbeck and Janssen. Laia Miquel has received honouraria from Lundbeck. Antoni Gual has received financial support from Lundbeck, D&A Pharma and TEVA and was paid fees by Lundbeck, D&A Pharma and Abbvie that were unconnected to the research conducted while carrying out this study. Ramon Bataller has received lecture fees from Echosens. None of this support represents a conflict of interest with regard to the information provided in this study. The rest of the authors have no conflicts of interest to disclose.

Do not disseminate or use without explicit permission from ²
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

This work is also supported by the RD12/0028/0016 project, Plan Nacional de I+D+I and was financed jointly with ISCII-Subdirección General de Evaluación y Fondo Europeo de Desarrollo Regional (FEDER). This grant was received by AG.

Contributors

HLP, AL, JA, TG RM and LO designed the study. HLP and LM wrote the first draft of the manuscript. All other authors contributed to the editing and final review of the manuscript. All authors have approved the final article.

Acknowledgements

This work is supported by the following institutions: Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Hospital Clínic i Universitari de Barcelona and CERCA Programme / Generalitat de Catalunya

RB is a recipient of National Institute of Alcohol Abuse and Alcoholism (NIAAA) grants U01AA021908 and U01AA020821

JA wishes to express his gratitude to the Mexican National Council of Science and Technology (CONACyT, Mexico City, Mexico) for partially supporting his predoctoral stay at IDIBAPS

We would like to thank Fleur Braddick, Alvaro Castañon and Chrysanthi Blithikioti for their writing assistance.

Do not disseminate or use without explicit permission from ³
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

Abstract

Aims: Alcoholic hepatitis (AH) is a life-threatening complication of alcohol use disorder (AUD). Alcohol abstinence is the main predictor of the long-term prognosis of AH. It is unknown whether AUD treatment retention (TR) after an AH episode impacts alcohol relapse and mortality or what baseline factors influence TR.

Methods: Design: case-control study; *Study population:* hospitalized patients (1999 -2012) with an episode of biopsy-proven AH were included (n=120); *Assessment:* demographic and clinical data, the High-Risk Alcoholism Relapse (HRAR) scale, mortality and alcohol relapse were assessed through clinical records and telephone or personal interviews; *Follow-up period:* short-term and long-term TRs were assessed at 12 and 24 months, respectively.

Results: The overall short-term and long-term TRs were 37% and 27.8%, respectively. The severity of liver disease at baseline predicted both short-term and long-term TR (OR 3.7 and 3.3, respectively), whereas HRAR >3 and a history of psychiatric disorders predicted long-term TR (OR 2.9 and 2.6, respectively). Moreover, HRAR >3 (OR 3.0) and previous treatment for AUD (OR 2.9) increased the risk of relapse in the short term. Importantly, receiving alcohol therapy in a centre different from the hospital where the patient was admitted was associated with increased risk of alcohol relapse over the long-term (OR 5.4).

Do not disseminate or use without explicit permission from ⁴
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c,*}

Conclusion: Experiencing an alcohol-related life-threatening complication is insufficient motivation to seek treatment for AUD. AUD treatment after an episode of AH is suboptimal, with a low TR rate, high risk of alcohol relapse and poor impact of treatment on alcohol relapse.

Keywords: alcohol, alcoholic hepatitis, alcohol use disorder, treatment retention, abstinence

Abbreviations

AUD: Alcohol Use Disorders; OR: Odds Ratio; TR: Treatment Retention; MELD: Model End-Stage Liver Disease; AH: Alcoholic Hepatitis; HRAR: High-Risk Alcoholism Relapse; ALD: Alcoholic Liver Disease; AU: Addictions Unit

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

1. Introduction

Excessive alcohol intake is a well-documented risk factor for approximately 200 medical conditions, including alcoholic liver disease (ALD). Recent data from the World Health Organization indicate that alcohol use accounts for 50% of cirrhosis worldwide[1]. ALD includes a spectrum of disorders from steatohepatitis to cirrhosis and hepatocellular carcinoma. Moreover, patients with underlying ALD and continuing alcohol consumption can develop an episode of alcoholic hepatitis (AH), one of the most deadly alcohol-related medical conditions, with a short-term mortality of 20-35%[2]. According to the Alcoholic Hepatitis Consortia of the NIAAA[3], AH is defined as “a clinical entity with rapid onset of jaundice with elevated serum aspartate transaminase, arising on the background of heavy alcohol use”. The impact of AH is relevant in terms of public health, e.g., there are 4.5 hospitalizations for AH per 100,000 persons each year in Denmark[4], and on an individual basis, e.g., the 4-year mortality in the USA is 42%[5].

We recently showed that in patients surviving an index episode of AH, alcohol abstinence is the most important factor influencing long-term prognosis[6]. Therefore, effective treatment of the underlying alcohol use disorder (AUD) could prevent alcohol relapse and positively impact patient outcomes. In addition, “salvage” or early transplantation has been recently proposed for these patients, meaning that prevention of further alcohol relapse is necessary to

Do not disseminate or use without explicit permission from ⁶
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

prevent graft loss. Unfortunately, there are very few studies assessing AUD treatment in patients with AH[7–10].

Treatment retention in an AUD setting – covering both consultations and medication – has been shown to be a good predictor of abstinence[11–13].

Although few studies focus on patients who previously received a liver transplantation, the impact of treatment retention in AUD settings among patients with severe forms of ALD is largely unknown[14,15]. In particular, there are no data on AUD treatment retention in patients who survive an episode of AH and its impact on alcohol relapse. The current study was undertaken to fill this knowledge gap. In our centre, all patients hospitalized due to decompensated ALD and active drinking (including those with AH) are visited by a specialized alcohol psychiatrist and are offered AUD treatment, meaning that they do not initially request alcohol therapy. It could be argued that, compared to patients attending an alcohol clinic, AH patients may differ in two ways: on the one hand, their organic condition may act as a reinforcement for abstinence, and, on the other hand, they may be less prone to see themselves as having an addiction problem and therefore be less willing to accept treatment for their AUD.

In summary, the impact of AUD treatment retention after an episode of AH has not been previously addressed and is potentially relevant for the prognosis of this patient population. Using a large series of biopsy-proven AH, which has been used extensively in prospective clinical studies[16], we assessed the rate

Do not disseminate or use without explicit permission from ⁷
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

of treatment retention in a specialized AUD treatment programme after an episode of AH and its impact on alcohol relapse and mortality. Predictive factors associated with treatment retention were also explored.

NO COPIAR

Do not disseminate or use without explicit permission from ⁸
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

2. Patients and Methods

2.1. Study design: In this case-control study, we performed a post hoc analysis of a large subset of patients who received therapeutic intervention (n=120) out of a cohort of 142 patients with biopsy-proven AH admitted to inpatient treatment[6]. The clinical protocol of the management of patients with AH in our centre includes a first appointment with a psychologist or a psychiatrist in the first month after discharge and at least one appointment every two months during the first and second years.

2.2. Study population: Patients admitted to the Liver Unit of the Hospital Clinic of Barcelona from 1999 to 2012 with an episode of AH were included, as described previously[6]. Briefly, the inclusion criteria were as follows: 1) biopsy-proven AH (hepatocellular ballooning and presence of Mallory bodies, inflammatory infiltrate being predominantly polymorphonuclear cells and pericellular fibrosis), according to NIAAA Alcoholic Hepatitis Consortia, all these patients have the diagnosis of definite AH; 2) at least one appointment with a psychiatrist during admission; 3) high risk of alcohol consumption (>60 g/day) at least 2 years prior to admission; 4) moderately elevated aminotransferases: aspartate aminotransferase (AST) > alanine aminotransferase (ALT); 5) high gamma-glutamyl transpeptidase (GGT); and 6) high bilirubin serum levels (>3 mg/dL). The exclusion criteria were as follows: 1) hepatocellular carcinoma; 2) any other potential cause of liver disease; and 3) death during index admission. The entire sample was assessed by a specialist of the addictions unit who

Do not disseminate or use without explicit permission from ⁹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

carried out a brief intervention and provided referrals for outpatient specialized treatment. Upon hospitalization, the local clinical protocol in the Hospital Clinic of Barcelona includes a consultation for an alcohol addiction specialist.

2.3. Assessment

All patients were evaluated within 72 hours of admission. Parameters obtained during the index admission were as follows: 1) anthropometric data; 2) High-Risk Alcoholism Relapse (HRAR) scale, a 3-item questionnaire (scores range from 0-6 points) that allows patient stratification into two alcohol relapse risk categories (low risk ≤ 3 - and high risk > 3 -) [17]; 3) alcohol consumption before the episode of AH (grams/day), assessed using the Systematic Interview of Alcohol Consumption (SIAC)[18]; 4) diagnosis of a current or past psychiatric disorder according to DSM IV-TR criteria [19]; 5) the severity of liver disease based on the Model End-Stage Liver Disease (MELD) and Maddrey DF [20,21]; and 6) a clinical diagnosis of Alcohol Liver Disease (ALD) before admission. All patients were assessed through clinical records; fifteen patients were also assessed through face-to-face interviews, seventeen through telephone and twenty-one through interviews of their relatives. Sixty-six patients (55%) provided urine sample regularly until the end of the study or drop-out and the results were registered in clinical records. Interviews (face-to-face or telephone) were conducted by AL, and clinical records were reviewed by HLP and AL. These data were retrieved in the 24th month after admission.

Do not disseminate or use without explicit permission from¹⁰
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

2.3.1. Definition of treatment retention in an alcohol programme: Based on the clinical practice, we defined three categories: 1) attendance to the first appointment in an Addictions Unit (AU) with a psychiatrist or a psychologist; 2) short-term treatment retention, i.e., at least one appointment with a psychologist or a psychiatrist during the last six months (first year); and 3) and long-term treatment retention, i.e., at least one appointment with a psychologist or a psychiatrist during the last six months (second year). Those who died before the assessment point (first or second year) were considered in treatment or not, according to their last status (See Figure 1). The majority of patients followed an AUD treatment programme in the same hospital where the liver disease was treated. For geographical and transportation reasons, 16.7% were treated in a different specialized centre within the community.

The integrated treatment offered for alcoholism followed the national guidelines[22]. This multicomponent and flexible treatment was based on shared decision making and relapse prevention (cognitive-behaviour theory). We also offered medication and group therapy if applicable. We treated comorbid conditions if present (e.g., antidepressants for Major Depression Disorder). Several strategies for improving the engagement of the patients in alcohol treatment were used: e.g., the liver specialist encouraged alcohol treatment and referred patients to the Addictions Unit if they accepted. If the patient was already engaged with alcohol treatment, he/she would receive an e-mail reminder one week before the appointment. If the patient did not attend to

Do not disseminate or use without explicit permission from¹¹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

the addictions appointment, the liver specialist would be informed to facilitate re-engagement.

2.3.2. Outcome data: Mortality in the first and second years was retrieved from clinical records. Data on alcohol consumption after the AH episode was retrospectively collected considering different sources of information: 1) self-report via telephone or personal interview of the patient and/or patient's relatives, 2) clinical records and/or 3) an alcohol urine test for those attending the hospital AU[6]. Alcohol relapse was defined as any amount of alcohol consumed after admission. We used a very strict definition of relapse, including one-time consumption, because of the severity of the underlying liver disease and the potential detrimental effects of any alcohol intake on liver function. Two types of alcohol relapse were considered: moderate (<40 grams of pure alcohol per day for women and <60 grams of pure alcohol per day in men) and heavy use (≥60 grams of pure alcohol per day for men and ≥40 grams of pure alcohol per day for women). Two relapse points were considered: short-term relapse (at 1 year) and long-term relapse (at 2 years).

2.4. Statistical analysis: Continuous variables were described in terms of the mean and the standard deviation. Categorical variables were described in terms of the count and the percentage. *Univariate analysis:* Differences between categorical variables were assessed by the Chi-squared test or Fisher's exact test according to the distribution. Differences between continuous variables were assessed by Student's t test. The p-values of the univariate tests were not

Do not disseminate or use without explicit permission from¹²
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

corrected for multiple testing, because those tests were taken as exploratory. To analyse the impact of treatment retention in an addictions unit on alcohol relapse, we ran a logistic regression considering short-term treatment retention (1-year) and long-term treatment retention (2-years) as independent variables and short-term alcohol relapse and long-term alcohol relapse as dependent variables. We considered as potential co-variables baseline clinical and demographic factors such as age, sex, tobacco consumption, previous treatment for AUD, treatment for AUD in the same centre as treatment for liver disease, HRAR >3, MELD ≥21, Maddrey DF ≥32, alcohol consumption prior to admission, previous diagnosis of ALD, and any psychiatric disorder. We included in multivariate analyses only those variables that showed p<0.10 in the univariate analysis or were clinically significant. In the univariate analyses, we included variables that have shown an impact on clinical outcomes of alcohol liver disease, alcohol use disorders or both[11,14,23–25] and could be recollected accurately in our study. The results of the multivariable logistic regression analysis (odds ratio –OR-) were considered to be the main outcome, as it addresses those variables independently associated with the outcome. For the inferential analysis, those who died during the follow-up period were considered as retention in treatment if the last status before death was retention in treatment and non-retention in treatment if the last status was non-retention. We also assessed the impact of AUD treatment retention in mortality through Kaplan-Meier curves and univariate analysis. We did not conduct a Cox

Do not disseminate or use without explicit permission from¹³
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

regression or logistic regression because of a lack of findings in the univariate analysis. Baseline clinical and demographic factors were also assessed by univariate and logistic regression (for those variables that showed $p < 0.1$ in the univariate analysis) to identify predictors of treatment retention (dependent variables short-term treatment retention and long-term treatment retention). The statistical package SPSS (SPSS Inc., version 15.0, Chicago, IL) was used for all analyses.

2.6. Ethical issues

The protocol was approved by the Ethics Committee of the Hospital Clinic according to Declaration of Helsinki and national legislation. All patients gave written informed consent (CEIC 2011/707).

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

3. Results

3.1. Patient characteristics.

Baseline characteristics of the series are depicted in Table 1. Briefly, 120 patients with biopsy-proven AH who survived the index hospitalization and were assessed by a psychiatrist during hospitalization were included. The mean alcohol consumption was 116.3±59 g/day. One hundred and four patients (86.7%) had a history of at least 11 years of heavy alcohol use, 87 (72.5%) drank at least 110 grams of pure alcohol per day and 72 patients (60%) had not received previously treatment for AUD. According to HRAR, thirty patients (25%) had a high risk of alcohol relapse. A psychiatric disorder was identified in forty-one patients (34.2%). Tobacco users were eighty-two (68.3%). Six patients were cannabis users (5.0%), two patients were non-prescribed benzodiazepine users (1.7%) and five patients were cocaine users (4.2%). Thirty-two patients suffered an Axis I disorder, with 29 patients showing Depressive Disorders (including Major Depression Disorder, Dysthymia and Non-specified Disorder) and three patients showing Anxiety Disorders (Panic disorder, Generalized Anxiety Disorder, Non-specified Anxiety Disorder). Eleven patients suffered a Personality Disorder (in two cases, they had comorbid Anxiety Disorder). Three patients (2.5%) received medication to prevent relapse (disulfiram or cyanamide), and ten patients were included in group therapy and completed 24 months of weekly group therapy, except one who passed away before the end. Most of them (80%) were in the group of integrated treatment.

Do not disseminate or use without explicit permission from¹⁵
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

3.2. Treatment retention in alcohol specialized units during the follow-up.

We first analysed the percentage of patients who were followed up on in the addiction unit. Seventy patients (58.3%) attended the first appointment, 40 (37%) continued in treatment after 12 months and 27 (27.3%) did so after 24 months. According to our definitions (see methods), patients were stratified into short-term non-retained (n=77, 64.2%) and long-term non-retained (n=85, 70.8%). Those who died before the first assessment point were considered retained or non-retained according to their last status. Figure 1 shows recruitment and TR data.

3.3. Predictors of alcohol use disorder treatment retention at admission.

Next, we analysed the predictive value of the parameters obtained at admission on treatment retention to an alcohol programme. The univariate analysis identified that presence of psychiatric disorders, an HRAR scale >3, previous treatments for AUD and the MELD score were associated with retention to alcohol therapy during follow-up (see Table 4). Multivariate analyses (Supplementary material: Table 5 and 6) showed that higher MELD was independently associated with short-term TR (OR 3.7, CI 95% 1.6-8.7), whereas higher MELD (OR 3.3, CI 95% 1.3-8.0), HRAR >3 (2.9, CI 95% 1.1-7.3) and the presence of psychiatric disorders (OR 2.6, CI 95% 1.1-6.3) were independently associated with long-term TR. Severe patients—because of psychiatry comorbidities, AUD severity or more advanced liver disease—were most likely to be in alcohol treatment after two years. Treatment retention was

Do not disseminate or use without explicit permission from¹⁶
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

not associated with substance use (short-term $p=0.62$; long-term $p=0.37$) or tobacco use (short-term $p=0.38$; long-term $p=0.19$). Axis I disorder was not associated with short-term retention to treatment ($p=0.28$), but it was associated with long-term retention to treatment ($p=0.01$) Axis II disorder was not associated with short-term retention ($p=0.60$) or long-term retention to treatment ($p=0.32$).

3.4. Impact of alcohol use disorder treatment retention and clinical/demographic co-variables in short-term and long-term alcohol relapse.

We next assessed the impact of TR to an alcohol programme on relapse. Sixty-two (51.7%) patients relapsed during the first year, and 85 patients (70.8%) did so during the first two years. Seventy-three percent of those who relapsed long term did so in the first year. Importantly, nearly half of the patients who relapsed ($n=42$, 42.5%) did so with a pattern of heavy alcohol consumption. Table 1 shows the results of the univariate analyses. For short-term relapse, a HRAR scale > 3 ($p=0.02$), the grams of pure alcohol per day prior to the treatment ($p=0.09$) and previous treatment for AUD showed sufficient statistical significance ($p<0.10$) to be included in multivariate analyses. For long-term relapse, age ($p=0.049$), treatment in a different alcohol specialized unit ($p=0.04$) and previous treatment for AUD ($p=0.04$) showed sufficient statistical significance ($p<0.10$) to be included in multivariate analyses. The multivariate

Do not disseminate or use without explicit permission from¹⁷
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

analysis (Table 2 and 3) showed that an HRAR scale >3 was independently associated with an increased risk of alcohol relapse (OR 3.0 CI 95% 1.2-7.5) at one year. Moreover, previous treatment of AUD increased the risk of relapse in the short term (OR 2.9 CI 95% 1.3-6.7). Importantly, treatment retention in the short and long terms was not associated with short- and long-term alcohol relapse. However, having alcohol therapy in a centre different from the index hospital was associated with an increased the risk of alcohol relapse long term (OR 5.4 CI 95% 1.1-26.5).

Relapse to alcohol use was not associated with substance use (short-term p=0.12; long-term p=0.62) or tobacco use (short-term p=0.30; long-term p=0.73).

Axis I disorder was not associated with short-term relapse (p=0.53) or long-term relapse (p=0.55). Axis II disorder was not associated with short-term relapse (p=0.84) or long-term relapse (p=0.60).

3.5. Impact of alcohol treatment retention and clinical/demographic co-variables on short-term and long-term mortality.

Finally, we studied the impact of TR to alcohol programme as well as other variables on patient mortality. The cumulative mortality of patients surviving the index episode of AH was 10% (n=12) and 17.5% (n=21) during the first and second years, respectively. Fifty-seven percent of all deaths occurred during the first year. The main cause of death was multiorgan failure after liver

Do not disseminate or use without explicit permission from¹⁸
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

decomposition (n=6, 28.6%), followed by upper gastrointestinal bleeding (n=5, 23.8%) and septic shock (n=5; 23.8%). In two cases, the cause of death was respiratory failure (9.5%). Only three deaths were not related to liver disease (14.3%) –lung cancer, mouth cancer and severe traumatic injury. Early mortality and two years cumulative mortality were not associated with any socio-demographic or clinical characteristic or with treatment retention in the univariate analysis (data not shown). Finally, Kaplan-Meier analyses showed no differences between short-term retention and non-retention, or between long-term retention and non-retention on patients' survival (Supplementary Material: Figure 2 and 3).

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

4. Discussion.

We recently demonstrated that alcohol abstinence is the main determinant of long-term prognosis in patients surviving an episode of AH. Unfortunately, there are no studies assessing the usefulness and feasibility of different interventions to reduce alcohol relapse among this patient population. Our results indicate that the location of the alcohol therapy, rather than TR, influences the rate of alcohol relapse. These intriguing results strongly suggest that integrated care is important for the prognosis of AUD after an episode of AH. The first year after an episode of AH is crucial because mortality (57.1%) and alcohol relapses (72.9%) are concentrated in this period of time. However, TR throughout this first year period is low. In fact, more than 40% of patients do not attend their first appointment to the AU; and one year after the episode of AH, 63% patients have not been enrolled in AUD treatment. Having received previous treatment for AUD predicts short-term alcohol relapse. The High-Risk Alcoholism Relapse scale (HRAR) is a potentially useful instrument for predicting short-term alcohol relapse in this population but does not predict long-term alcohol relapse. Long-term alcohol relapse was predicted by following AUD treatment in a centre different to that of the liver disease treatment.

4.1. Integrated treatment versus parallel treatment

Patients treated for AUD and liver disease in the same centre relapsed less.

This finding suggests that integrated care, combining treatments from the liver

Do not disseminate or use without explicit permission from²⁰
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

unit and the addictions unit in the same centre[26], is helpful in reducing long-term relapse in AH. Integrated care may enhance the patients' perception of both treatments as complementary and may improve the skills of both psychiatrists and hepatologists, who are able to work together in those teams.

4.2. Low TR to AUD treatment after an episode of AH

Before the episode of AH, 60% of patients had not previously received any alcohol treatment; and after the episode, 40% did not engage in alcohol therapy. These results are not surprising if we consider that AUD is a mental disorder with one of the widest treatment gaps[27]. Even if patients received psychiatric intervention aimed at increasing alcohol treatment engagement during their admission for an AH, most of them did not enroll in such treatment. Stigma, attitudinal barriers and insufficient readiness to change can partially explain this treatment gap. Various treatment approaches, such as motivational interviewing[28,29] and shared decision making[30], have been demonstrated to be effective in the contexts of several medical pathways to increase engagement (e.g., alcohol liver disease or diabetes mellitus in primary care), but evidence in the area of AH is scarce.

Remarkably, patients who were affected by severe organic (MELD) or alcoholic (HRAR, psychiatric comorbidities) diseases tended to be more likely to be retained in alcohol treatment. The fact that more severe cases of AUD exist in those who access treatment is well known[31]. These data might be interpreted

Do not disseminate or use without explicit permission from²¹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

as those who are “less ill” having less insight into AUD and -therefore not seeking treatment. A lower severity of alcohol-related problems was already found to be a predictor of low adherence to psychological treatment[32]. At the same time, in treating the most severe patients, we can expect lower success rates.

The low retention in our sample should be understood taking into account that patients with alcohol liver disease tend to either not meet criteria for alcohol use disorder (e.g., only 26% suffered from alcohol dependence) or meet them at low severity levels[33].

4.3. Limited impact of AUD treatment retention on alcohol relapse

Reducing alcohol consumption is insufficient alone to improve prognosis [6,34]. Compared with a cohort of alcohol-dependent patients treated in our environment (38% of alcohol relapses at 5-year of follow-up), patients who have suffered an AH have higher relapse rates, despite being in treatment (59.7%-72.9%)[35]. In addition, there were no differences between those who attended treatment and those who did not regarding alcohol relapse rates and mortality. Low treatment efficacy might be explained by the scarcity of specific AUD treatment for this population[36] [37], including the fact that they did not actively seek treatment. For these reasons, new evidence-based treatment approaches are required, and alternatives aiming to increase the treatment retention and

Do not disseminate or use without explicit permission from²²
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

motivation of these patients through brief intervention or motivational interviewing[38] should be considered. Further studies of this population are necessary.

Previous attempts to deal with alcohol problems lead to lower success in subsequent treatments[15]. This relationship might be explained by two reasons. First, people who fail in previous rehabilitation have low levels of self-efficacy, meaning that they fail to achieve the goal of abstinence in the future[39,40];second, unsuccessfulness is a marker of severity[15].

In terms of alcohol relapses, the lack of differences between the groups regarding treatment retention is the main concern resulting from this study, as previous evidence in addiction treatment shows the opposite[11]. Again, evidence-based treatments for this population are urgently required to improve their efficacy.

4.4. Limitations and Strengths

Our study has several limitations. First, retrospective collection of relapses and follow-up data might introduce a recall bias. Second, the single-centre study design hinders the generalization of the results. However, both limitations are acceptable in the early stages of research in a specific field, as in our case.

Third, psychiatrist intervention during and after hospital admission is not standardized, so it is difficult to generalize the results. However, the intervention of mental health professionals represents common clinical practice in our

Do not disseminate or use without explicit permission from²³
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

environment, based on Spanish guidelines (medical care, combined psychotherapy - both group based and individual based - and pharmacotherapy, individualized treatment)[22]. Fourth, desirability bias is an intrinsic limitation of self-reporting in addictions field, but they remain used in very sensitive studies such as drug trials[41,42]. Fifth, our study does not allow the validation of HRAR, this being beyond the scope of our study's aims and design, but the results show that the HRAR is promising in predicting short-term relapse, which is the most critical period. Regarding the current trend to increase therapy alternatives for severe cases of AH –especially liver transplantation[43]–the validation of this and other instruments in patients with AH seems essential. Sixth, potential cofounders related to the decision of where a patient was treated for alcoholism that could not be analysed include the following: the type of alcohol treatment, rural areas *versus* urban areas (which might translate into differential access to treatment), and conditions that reduce mobility. Seventh, in our sample, only three patients (2.5%) received medication to prevent relapse. Alcoholism treatment in patients after an episode of alcoholic hepatitis is challenging because the effectiveness of anti-relapse drugs either is not clear (e.g., baclofen, topiramate, oxibate) or is directly contraindicated (disulfiram, naltrexone)[44]. Further studies are required to develop safe and effective treatments for this population. In contrast, our study has several strengths. First, the naturalistic approach of the study is a main strength because it is a reflection of clinical practice. Second, our AH diagnosis criteria

Do not disseminate or use without explicit permission from²⁴
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

were very strict, so the sample of AH was reliable. Third, the sample size is adequate despite the strict diagnosis criteria of AH. Fourth, a two-year follow-up is an appropriate period of time regarding the course of the disease. Finally, the psychosocial evaluation and chart/telephone follow-up descriptions are detailed, precise and state of the art.

Do not disseminate or use without explicit permission from²⁵
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

5. Conclusion

Integrated care in survivors after an episode of AH is promising. An extreme alcohol-related life-event, such as an episode of AH, is not enough to motivate patients to give up alcohol intake and seek treatment for AUD. The current format of AUD treatment after an episode of AH is not appropriate, as evidenced by the low treatment retention, high risk of alcohol relapse and null impact of treatment in alcohol relapse. An episode of AH may represent a good opportunity to intervene in non-previously treated patients.

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

References

- [1] E. Stein, M. Cruz-Lemini, J. Altamirano, N. Ndugga, D. Couper, J.G. Abraldes, R. Bataller, Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide, *J. Hepatol.* 65 (2016) 998–1005. doi:10.1016/j.jhep.2016.06.018.
- [2] A.J. McCullough, J.F.B. O' Connor, Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology, *Am. J. Gastroenterol.* 93 (1998) 2022–2036. doi:10.1111/j.1572-0241.1998.00587.x.
- [3] D.W. Crabb, R. Bataller, N.P. Chalasani, P.S. Kamath, M. Lucey, P. Mathurin, C. McClain, A. McCullough, M.C. Mitchell, T.R. Morgan, L. Nagy, S. Radaeva, A. Sanyal, V. Shah, G. Szabo, NIAAA Alcoholic Hepatitis Consortia, Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia., *Gastroenterology.* 150 (2016) 785–90. doi:10.1053/j.gastro.2016.02.042.
- [4] T.D. Sandahl, P. Jepsen, K.L. Thomsen, H. Vilstrup, Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study., *J. Hepatol.* 54 (2011) 760–4. doi:10.1016/j.jhep.2010.07.016.
- [5] C.L. Mendenhall, T.E. Moritz, G.A. Roselle, T.R. Morgan, B.A. Nemchausky, C.H. Tamburro, E.R. Schiff, C.J. McClain, L.S. Marsano, J.I. Allen, A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic

Do not disseminate or use without explicit permission from²⁷
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

hepatitis: results of a Department of Veterans Affairs cooperative study.,
Hepatology. 17 (1993) 564–76. <http://www.ncbi.nlm.nih.gov/pubmed/8477961>
(accessed January 2, 2017).

- [6] J. Altamirano, H. López-Pelayo, J. Michelena, P.D. Jones, L. Ortega, P. Ginés, J. Caballería, A. Gual, R. Bataller, A. Lligoña, Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival, *Hepatology*. (2017). doi:10.1002/hep.29338.
- [7] G.Y. Im, M.R. Lucey, Practical Concerns and Controversies in the Management of Alcoholic Hepatitis., *Gastroenterol. Hepatol. (N. Y)*. 12 (2016) 478–489. <http://www.ncbi.nlm.nih.gov/pubmed/27917083> (accessed January 2, 2017).
- [8] J. Casanova, R. Bataller, Alcoholic hepatitis: Prognosis and treatment, *Gastroenterol. Hepatol*. 37 (2014) 262–268. doi:10.1016/j.gastrohep.2014.02.001.
- [9] J. Altamirano, J. Michelena, V. Prado, J. Caballería, R. Bataller, Trasplante hepático temprano en hepatitis alcohólica: una opción en el tratamiento del paciente no respondedor a corticoides, *Gastroenterol. Hepatol*. 35 (2012) 457–459. doi:10.1016/j.gastrohep.2012.04.001.
- [10] V. Donckier, V. Lucidi, T. Gustot, C. Moreno, Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy, *J. Hepatol*. 60 (2014) 866–871. doi:10.1016/j.jhep.2013.11.015.

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

- [11] P. Aguiar, D. Neto, R. Lambaz, J. Chick, P. Ferrinho, Prognostic Factors During Outpatient Treatment for Alcohol Dependence: Cohort Study with 6 months of Treatment Follow-up, *Alcohol Alcohol.* 47 (2012) 702–710.
doi:10.1093/alcalc/ags097.
- [12] K. Lohit, C. Kulkarni, R. Galgali, Factors influencing adherence to anti-craving medications and drinking outcomes in patients with alcohol dependence: A hospital-based study, *J. Pharmacol. Pharmacother.* 7 (2016) 72.
doi:10.4103/0976-500X.184770.
- [13] A. Zweben, H.M. Pettinati, R.D. Weiss, M. Youngblood, C.E. Cox, M.E. Mattson, P. Gorroochurn, D. Ciraulo, Relationship Between Medication Adherence and Treatment Outcomes: The COMBINE Study, *Alcohol. Clin. Exp. Res.* 32 (2008) 1661–1669. doi:10.1111/j.1530-0277.2008.00743.x.
- [14] D. Telles-Correia, I. Mega, Candidates for liver transplantation with alcoholic liver disease: Psychosocial aspects., *World J. Gastroenterol.* 21 (2015) 11027–33. doi:10.3748/wjg.v21.i39.11027.
- [15] M.B. Terra, H.M.T. Barros, A.T. Stein, I. Figueira, L.D. Athayde, D.R. Ott, R. de C.S. de Azambuja, D.X. da Silveira, Predictors of relapse in 300 Brazilian alcoholic patients: a 6-month follow-up study., *Subst. Use Misuse.* 43 (2008) 403–11. doi:10.1080/10826080701202999.
- [16] P. Sancho-Bru, J. Altamirano, D. Rodrigo-Torres, M. Coll, C. Millán, J. José Lozano, R. Miquel, V. Arroyo, J. Caballería, P. Ginès, R. Bataller, Liver progenitor cell markers correlate with liver damage and predict short-term

Do not disseminate or use without explicit permission from²⁹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

mortality in patients with alcoholic hepatitis, *Hepatology*. 55 (2012) 1931–1941.
doi:10.1002/hep.25614.

- [17] A. DiMartini, J. Magill, M.G. Fitzgerald, A. Jain, W. Irish, G. Khera, W. Yates,
Use of a high-risk alcohol relapse scale in evaluating liver transplant candidates.,
Alcohol. Clin. Exp. Res. 24 (2000) 1198–201.
<http://www.ncbi.nlm.nih.gov/pubmed/10968657> (accessed August 18, 2015).
- [18] A. Gual, M. Contel, L. Segura, A. Ribas, J. Colom, [The ISCA (Systematic
Interview of Alcohol Consumption), a new instrument to detect risky drinking].,
Med. Clin. (Barc). 117 (2001) 685–9.
<http://www.ncbi.nlm.nih.gov/pubmed/11730629> (accessed August 4, 2015).
- [19] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental
Disorders*, 2000.
- [20] M.O. Farooq, R. Bataller, Pathogenesis and Management of Alcoholic Liver
Disease., *Dig. Dis.* 34 (2016) 347–55. doi:10.1159/000444545.
- [21] W.C. Maddrey, J.K. Boitnott, M.S. Bedine, F.L. Weber, E. Mezey, R.I. White,
Corticosteroid therapy of alcoholic hepatitis., *Gastroenterology*. 75 (1978) 193–9.
<http://www.ncbi.nlm.nih.gov/pubmed/352788> (accessed January 10, 2017).
- [22] Socidrogalcohol, *Guías Clínicas SOCIDROGALCOHOL basadas en la
EVIDENCIA CIENTÍFICA: Alcoholismo*, 2014.
- [23] J. Altamirano, R. Bataller, A. Cardenas, J. Michelena, N. Freixa, M. Monrás, J.
Ríos, A. Liccioni, J. Caballería, A. Gual, A. Lligoña, Predictive factors of

Do not disseminate or use without explicit permission from³⁰
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

abstinence in patients undergoing liver transplantation for alcoholic liver
disease., *Ann. Hepatol.* 11 213–21.

<http://www.ncbi.nlm.nih.gov/pubmed/22345338> (accessed August 18, 2015).

- [24] J. Altamirano, H. López-Pelayo, J. Michelena, P.D. Jones, L. Ortega, P. Ginès, J. Caballería, A. Gual, R. Bataller, A. Lligoña, Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival, *Hepatology.* 66 (2017). doi:10.1002/hep.29338.
- [25] B.P. Lee, N. Mehta, L. Platt, A. Gurakar, J.P. Rice, M.R. Lucey, G.Y. Im, G. Therapondos, H. Han, D.W. Victor, O.K. Fix, L. Dinges, D. Dronamraju, C. Hsu, M.D. Voigt, M.E. Rinella, H. Maddur, S. Eswaran, J. Hause, D. Foley, R.M. Ghobrial, J.L. Dodge, Z. Li, N.A. Terrault, Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis, *Gastroenterology.* 155 (2018) 422–430.e1. doi:10.1053/J.GASTRO.2018.04.009.
- [26] G. Addolorato, A. Mirijello, L. Leggio, A. Ferrulli, C. D'Angelo, G. Vassallo, A. Cossari, G. Gasbarrini, R. Landolfi, S. Agnes, A. Gasbarrini, Gemelli OLT Group, Liver Transplantation in Alcoholic Patients: Impact of an Alcohol Addiction Unit Within a Liver Transplant Center, *Alcohol. Clin. Exp. Res.* 37 (2013) 1601–1608. doi:10.1111/acer.12117.
- [27] K. Robert, S. Saxena, I. Levav, B. Saraceno, The treatment gap in mental health care, 2004.
- [28] B. Lundahl, T. Moleni, B.L. Burke, R. Butters, D. Tollefson, C. Butler, S. Rollnick, Motivational interviewing in medical care settings: a systematic review and meta-

Do not disseminate or use without explicit permission from³¹
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c,*}

analysis of randomized controlled trials., *Patient Educ. Couns.* 93 (2013) 157–
68. doi:10.1016/j.pec.2013.07.012.

- [29] A. Palacio, D. Garay, B. Langer, J. Taylor, B.A. Wood, L. Tamariz, Motivational Interviewing Improves Medication Adherence: a Systematic Review and Meta-analysis., *J. Gen. Intern. Med.* (2016). doi:10.1007/s11606-016-3685-3.
- [30] K.A. Bradley, D.R. Kivlahan, Bringing patient-centered care to patients with alcohol use disorders., *JAMA.* 311 (2014) 1861–2. doi:10.1001/jama.2014.3629.
- [31] J. Rehm, A. Allamani, H.-J. Aubin, R. Della Vedova, Z. Elekes, U. Frick, A. Jakubczyk, N. Kostogianni, I. Landsmane, J. Manthey, L. Miquel, F. Paille, L. Pieper, C. Probst, F. Scafuri, K.D. Shield, S. Snikere, P. Struzzo, M. Trapencieris, F. Voller, H.-U. Wittchen, A. Gual, M. Wojnar, People with Alcohol Use Disorders in Specialized Care in Eight Different European Countries, *Alcohol Alcohol.* 50 (2015) 310–318. doi:10.1093/alcalc/agv009.
- [32] S. Vuoristo-Myllys, J. Lahti, H. Alho, J. Julkunen, Predictors of dropout in an outpatient treatment for problem drinkers including cognitive-behavioral therapy and the opioid antagonist naltrexone., *J. Stud. Alcohol Drugs.* 74 (2013) 894–901. <http://www.ncbi.nlm.nih.gov/pubmed/24172116> (accessed June 7, 2017).
- [33] D. Gleeson, J.S. Jones, E. McFarlane, R. Francis, C. Gellion, M.P. Bradley, R.J. Peck, Severity of Alcohol Dependence in Decompensated Alcoholic Liver Disease: Comparison with Heavy Drinkers without Liver Disease and Relationship to Family Drinking History, *Alcohol Alcohol.* 44 (2009) 392–397. doi:10.1093/alcalc/agp008.

Do not disseminate or use without explicit permission from³²
the authors

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

- [34] J.R. Potts, S. Goubet, M.A. Heneghan, S. Verma, Determinants of long-term outcome in severe alcoholic hepatitis, *Aliment. Pharmacol. Ther.* 38 (2013) 584–595. doi:10.1111/apt.12427.
- [35] A. Gual, F. Bravo, A. Lligoña, J. Colom, Treatment for Alcohol Dependence in Catalonia: Health Outcomes and Stability of Drinking Patterns over 20 Years in 850 Patients, *Alcohol Alcohol.* 44 (2009).
- [36] G. Addolorato, A. Mirijello, P. Barrio, A. Gual, Treatment of alcohol use disorders in patients with alcoholic liver disease., *J. Hepatol.* (2016). doi:10.1016/j.jhep.2016.04.029.
- [37] A. Khan, A. Tansel, D.L. White, W.T. Kayani, S. Bano, J. Lindsay, H.B. El-Serag, F. Kanwal, Efficacy of Psychosocial Interventions in Inducing and Maintaining Alcohol Abstinence in Patients With Chronic Liver Disease: A Systematic Review., *Clin. Gastroenterol. Hepatol.* 14 (2016) 191–202.e4. doi:10.1016/j.cgh.2015.07.047.
- [38] N. Bertholet, J.-B. Daepfen, V. Wietlisbach, M. Fleming, B. Burnand, Reduction of Alcohol Consumption by Brief Alcohol Intervention in Primary Care, *Arch. Intern. Med.* 165 (2005) 986. doi:10.1001/archinte.165.9.986.
- [39] S.F. Greenfield, M.R. Hufford, L.M. Vagge, L.R. Muenz, M.E. Costello, R.D. Weiss, The relationship of self-efficacy expectancies to relapse among alcohol dependent men and women: a prospective study., *J. Stud. Alcohol.* 61 (2000) 345–351. doi:10.15288/jsa.2000.61.345.

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluïsa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c *}, Antoni Gual MD PhD ^{a,b,c*}

[40] R.M. Kadden, M.D. Litt, The role of self-efficacy in the treatment of substance use disorders, *Addict. Behav.* 36 (2011) 1120–1126.

doi:10.1016/j.addbeh.2011.07.032.

[41] New drug to treat alcoholism., *FDA Consum.* 38 3.

<http://www.ncbi.nlm.nih.gov/pubmed/15595128> (accessed June 15, 2015).

[42] EMA, Development of medicinal products for the treatment of alcohol dependence, 2010.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf.

[43] P. Mathurin, C. Moreno, D. Samuel, J. Dumortier, J. Salleron, F. Durand, H. Castel, A. Duhamel, G.-P. Pageaux, V. Leroy, S. Dharancy, A. Louvet, E. Boleslawski, V. Lucidi, T. Gustot, C. Francoz, C. Letoublon, D. Castaing, J. Belghiti, V. Donckier, F.-R. Pruvot, J.-C. Duclos-Vallée, Early Liver Transplantation for Severe Alcoholic Hepatitis, *N. Engl. J. Med.* 365 (2011) 1790–1800. doi:10.1056/NEJMoa1105703.

[44] D. Fuster, J.H. Samet, Alcohol Use in Patients with Chronic Liver Disease, *N. Engl. J. Med.* 379 (2018) 1251–1261. doi:10.1056/NEJMra1715733.

Hugo López-Pelayo MD ^{a,b,c}, Laia Miquel MD^{a,b,c}, José Altamirano MD MsC^b,
Ramon Bataller MD PhD^e, Joan Caballeria MD PhD^d, Lluisa Ortega MD ^{a, c},
Anna Lligoña MD ^{a, c} *, Antoni Gual MD PhD ^{a,b,c*}

NO COPIAR

Do not disseminate or use without explicit permission from³⁵
the authors