Research Article
NAFLD and Alcohol-Related Liver Diseases

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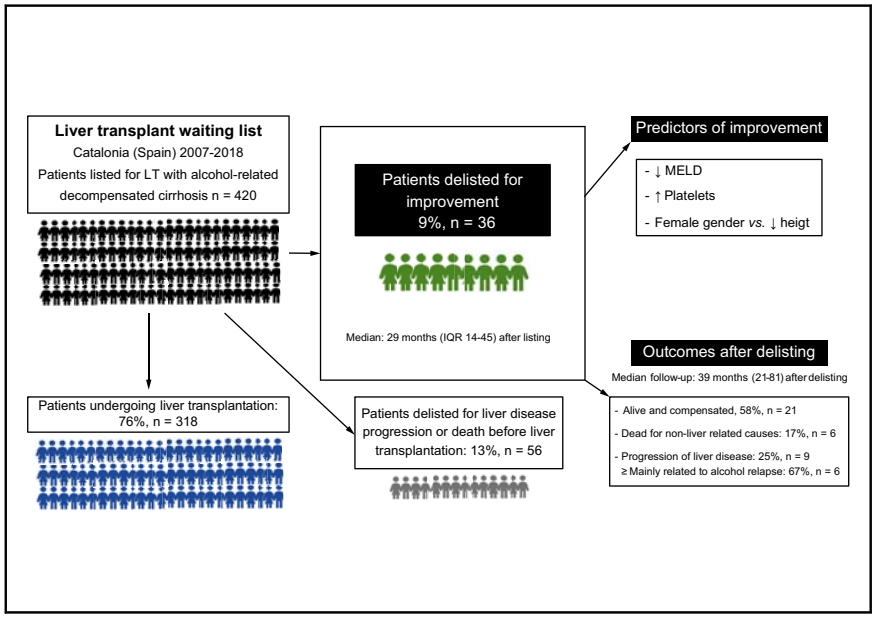
A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement

Graphical abstract



Highlights

- Around 9% of patients with alcohol-related cirrhosis are delisted for improvement.
- MELD score is the main determinant of improvement.
- Women have higher probabilities of being delisted for improvement.
- Outcomes after delisting are globally favorable and affected by alcohol relapse.

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Lay summary

Patients with alcohol-related cirrhosis can improve until being delisted in approximately 9% of cases. Low model for end-stage liver disease score and high platelet levels at admission predict delisting after improvement, and women have higher probabilities of being delisted due to improvement. Long-term outcomes after delisting are generally favorable.

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Research Article
NAFLD and Alcohol-Related Liver Diseases

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A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement

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Background & Aims: To what extent patients with alcohol-related decompensated cirrhosis can improve until recovery from decompensation remains unclear. We aimed to investigate the probability of recovery and delisting due to improvement in patients with alcohol-related decompensated cirrhosis on the waiting list (WL) for liver transplantation (LT).

Methods: We conducted a registry-based, multicenter, retrospective study including all patients admitted to the LT WL in Catalonia (Spain) with the indication of alcohol-, HCV-, cholestasis- or non-alcoholic steatohepatitis-related decompensated cirrhosis between January 2007 and December 2018. Competing-risk analysis was used to investigate variables associated with delisting due to improvement in patients with alcohol-related decompensated cirrhosis. Criteria for delisting after improvement were not predefined. Outcomes of patients after delisting were also studied.

Results: One-thousand and one patients were included, 420 (37%) with alcohol-related decompensated cirrhosis. Thirty-six (8.6%) patients with alcohol-related decompensated cirrhosis were delisted after improvement at a median time of 29 months after WL admission. Lower model for end-stage liver disease (MELD) score, higher platelets and either female sex or lower height were independently associated with delisting due to improvement, while time of abstinence did not reach statistical significance in multivariate analysis ($p = 0.055$). Five years after delisting, the cumulative probability of remaining free from liver-related death or LT was 76%, similar to patients with HCV-related decompensated cirrhosis delisted after improvement.

Conclusions: A significant proportion of LT candidates with alcohol-related cirrhosis can be delisted due to improvement, which is predicted by low MELD score and higher platelet count at WL admission. Women also have a higher probability of being delisted after improvement, partially due to reduced early access to LT for height discrepancies. Early identification of patients with potential for improvement may avoid unnecessary transplants.

Lay summary: Patients with alcohol-related cirrhosis can improve until being delisted in approximately 9% of cases. Low model for end-stage liver disease score and high platelet levels at admission predict delisting after improvement, and women have higher probabilities of being delisted due to improvement. Long-term outcomes after delisting are generally favorable.

Introduction

Decompensated cirrhosis is the final stage of chronic liver diseases, and liver transplantation (LT) is the only treatment that improves the prognosis of these patients. Nevertheless, several studies have demonstrated that successful treatment of the aetiological agent of liver injury can have beneficial effects on the progression of liver disease.[1–3] Indeed, removal from the LT waiting list (WL) due to improvement has been described in a significant number of patients with HCV-related decompensated cirrhosis after treatment with direct-acting antivirals (DAAs).[4,5]

The efficacy of DAA has led to several changes in the characteristics of patients awaiting LT. First, alcohol is the leading aetiology of liver disease among patients listed for LT in the US and Europe,[6–8] and this is expected to continue because the incidence of alcohol-related liver disease (ArLD) is increasing despite efforts to prevent alcohol use disorder (AUD).[9,10] In addition, the overall number of patients listed for LT has decreased or stabilized in many geographical areas as a consequence of the dramatic decrease in patients with decompensated HCV-related cirrhosis.[11] In this setting, the relevance of relative contraindications for LT is being challenged, and there is also an increasing interest in expanding the indications of LT.[12] For instance, alcoholic hepatitis has evolved from being considered a contraindication to a growing indication of LT.[12–15]

Abstinence from alcohol is the main driver of long-term prognosis in ArLD. Beneficial effects of abstinence have been shown even in advanced stages like alcoholic hepatitis and decompensated cirrhosis.[16–19] In fact, the effect of time of

Keywords: alcohol; HCV; delisting; recompensation; liver transplant.
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abstinence in clinical outcomes is one of the bases of the so-called "6 month rule", which advocates a 6-month abstinence before admitting patients with ArLD to the LT WL. In theory, this period of time may permit recovery from decompensation in some patients, thus avoiding the necessity of LT. However, such recovery may occur later than these 6 months of abstinence. This may be important, as the increased availability of organs and reduced waiting times could lead to unnecessary LT in some patients with ArLD who will improve at a later point.

While 2 recent studies from North America reported delisting for improvement in 2–16% of patients with alcohol-related decompensated cirrhosis,[20,21] there is a lack of information about the outcomes on the WL in patients with alcohol-related cirrhosis from European countries. Consequently, we designed a registry-based multicenter study to describe and analyze the incidence of delisting for improvement in patients with alcohol-related decompensated cirrhosis.

Patients and methods

Design of the study and inclusion/exclusion criteria

This is an OCATT (Organització Catalana de Trasplantaments) registry-based study of patients listed for LT in Catalonia (north-east of Spain, 7.5 million inhabitants). OCATT is a public institution dependent upon the Catalan Health Department, which is responsible for the organization, management and coordination of organ procurement and distribution. Information about the allocation and prioritization system is given in the supplementary methods. We obtained permission from the OCATT to use the anonimized database in order to perform this study.

We considered all patients admitted in the adult elective LT WL with the indication of decompensated cirrhosis between January 1st 2007 and December 31st 2018. Patients with an indication for LT other than decompensated cirrhosis (*i.e.* hepatocellular carcinoma [HCC]) and patients with prior transplantation were excluded. The aetiology of liver disease was extracted from the data files of the patients provided by the centers at WL inclusion, and categorized into 4 main aetiologies: alcohol, HCV, cholestatic diseases and NASH (including also patients with the diagnosis of cryptogenic cirrhosis). Patients with other aetiologies were excluded from the analysis. Patients with more than 1 aetiological diagnosis including alcohol were included in the non-alcohol aetiology (*i.e.* patients with HCV-alcohol cirrhosis were categorized as "HCV") in order to have a pure cohort of patients with ArLD.

Definitions and variables

During the study period, the indication for LT in patients with decompensated cirrhosis remained the same: any decompensations of cirrhosis and a model for end-stage liver disease (MELD) score ≥12 and/or a Child-Pugh score ≥8 points. Alcoholic hepatitis was a contraindication for LT during the study period. With regard to the evaluation of AUD, reported alcohol abstinence was required to be at least 6 months during the study period. All patients were seen by hospital addiction specialists before admission to the WL. Management of addiction and control of abstinence while on the WL relied either on the Liver Transplant Unit addiction specialists or on primary care addiction units. With respect to biomarkers of alcohol intake, 1 of the centers (VH) has been using urine ethanol until present; another center (HC) used urine ethanol until 2017 and changed to ethyl glucuronide (ETG), and the remaining center (HUB) used urine or saliva ethanol until 2009 and then started using ETG. Frequency of biomarker determination varied depending on the addiction specialist involved and the characteristics of the patient. In case of alcohol relapse, the patient was placed in inactive status for 6 months and then readmitted once abstinence was under control.

Outcomes in the WL were classified as follows: LT, death, worsening of clinical status leading to contraindication for LT (these 2 grouped together as death/worsening), improvement, and others (*i.e.* change to a WL in a different region, alcohol relapse or voluntary withdrawal). Patients remaining on the WL at the end of the study period were excluded from the main analysis. However, a sensitivity analysis including these patients censored at the end of the study period (December 31st 2018) was also performed to confirm the results. Delisting due to improvement was decided by the medical team at each center. Although there are no pre-established criteria to consider delisting due to improvement, absence or easy control of decompensations and a significant improvement in liver function tests were considered the basis to withdraw patients after recompensation for any aetiology of liver disease.

Variables registered at the time of admission in the WL were age, sex, weight, height, BMI, laboratory values and liver decompensations. In addition, we retrospectively collected other variables, at admission to the WL (including time of abstinence before being admitted to the WL for patients with AUD), as well as the evolution of laboratory values and liver decompensations every 6 months whilst on the WL. Finally, we retrospectively reviewed and registered the outcomes after delisting for improvement in patients with alcohol and HCV-related decompensated cirrhosis, including the date of last follow-up and the clinical status of the patients.

Statistical analysis

Quantitative variables are expressed as mean (SD) and categorical variables as absolute count and percentages. Differences between aetiological groups were studied with Chi square test or ANOVA. Predictive factors for delisting were studied with uni- and multivariate competing-risk regression analysis (Fine and Gray method). Variables with a p value <0.1 in the univariate analysis, as well as those clinically relevant (time of abstinence) were included in the multivariate analysis. Time to delisting due to improvement was considered as the primary endpoint while LT and death/worsening were considered as competing endpoints.

A composite endpoint (liver disease progression) including LT or liver-related death was defined to evaluate the outcomes of patients that had been delisted due to improvement, and its cumulative incidence was studied using Kaplan-Meier curves and the log-rank test. Statistical analysis was performed by SPSS statistical package version 20; competing-risk analysis was performed with the command extension *"UAB Competing Risks"* (Applied Biostatistics Laboratory, Autonomous University of Barcelona). A p value <0.05 was considered statistically significant for all statistical tests.

Results

Patients

During the study period, 2,316 patients were included in the OCATT elective WL. After excluding patients with indications other than decompensated cirrhosis and patients with previous LT, 1,170 patients were considered for the study. One-hundred and forty-one of these patients had been listed for different aetiologies to the main 4 groups and 28 were still awaiting LT at the end of

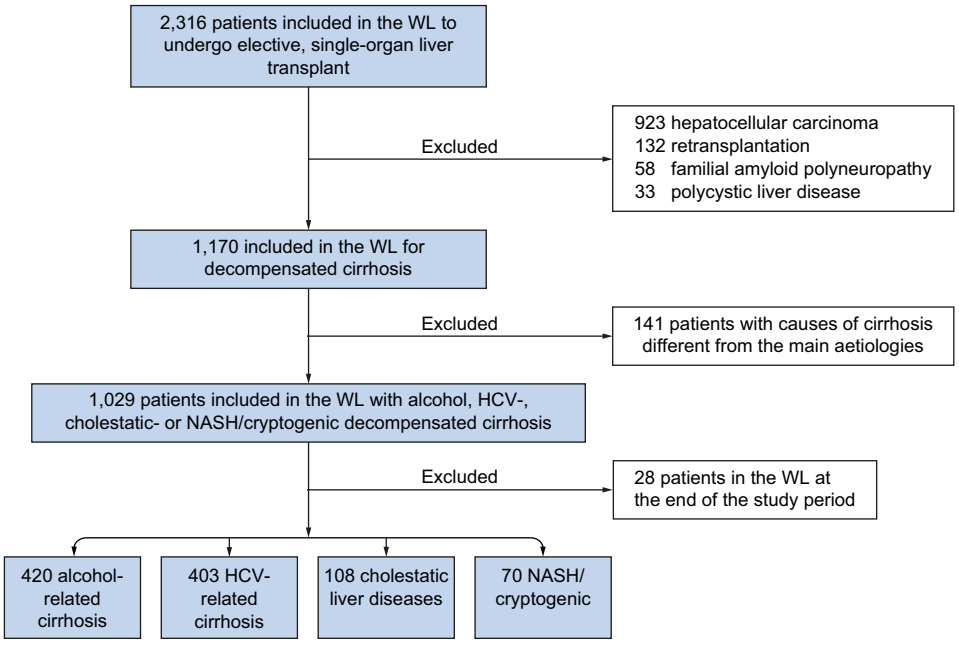


Fig. 1. Flow-chart of the study. NASH, non-alcoholic steatohepatitis; WL, waiting list.

the study period, so the final cohort comprised 1,001 patients admitted to the LT WL with alcohol-, HCV-, cholestasis- or NASH/cryptogenic-related decompensated cirrhosis. A flow-chart of the patients' disposition is shown in Fig. 1. Characteristics of the whole cohort and according to the aetiology are shown in Table 1.

Global outcomes after admission to the waiting list

Most patients admitted to the WL underwent LT (n = 775, 77%) (Fig. 2), while 135 (13%) patients were delisted for death/worsening and 70 (7%) were delisted due to improvement. The cumulative incidence of delisting after improvement was 1.4% at 12 months, 4.8% at 36 months and 6.5% at 60 months after listing.

The probability of delisting due to improvement was different depending on the cause of cirrhosis (Fig. 3), being more frequent in patients with alcohol-related and HCV-cirrhosis compared to other etiologies ($p = 0.04$). Cumulative incidence of delisting after LT, death/worsening, improvement or other reasons according to the aetiology are shown in Fig. S1A-D.

Characteristics, evolution while in the WL and outcomes of patients with alcohol-related cirrhosis delisted after improvement

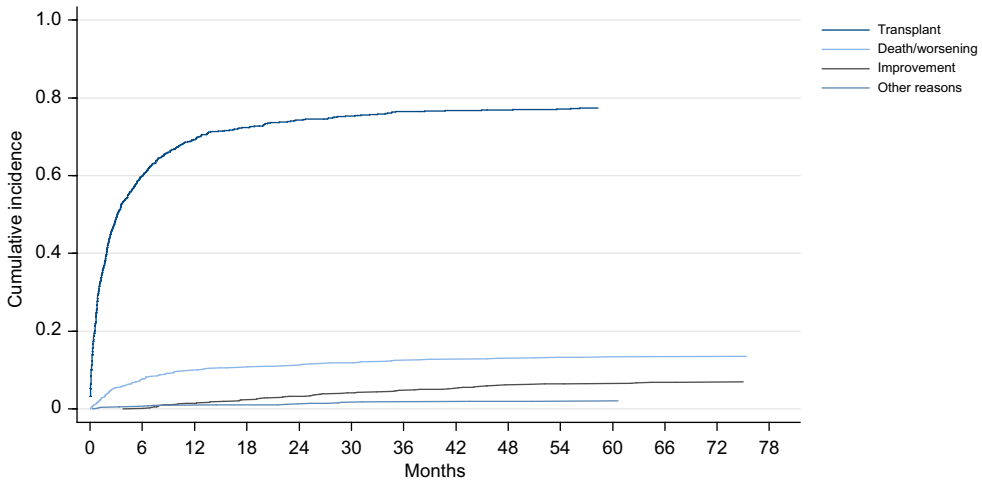
Among the 420 patients with alcohol-related decompensated cirrhosis, 36 (8.6%) were delisted due to improvement at a median time of 29 months (IQR 14-45) after inclusion in the WL, while 56 were delisted after death/worsening and 10 for other reasons; in 3 of these latter 10 patients, the cause of delisting was persistent alcohol relapse. No patient apart from these 3 was diagnosed with alcohol relapse during their time on the WL. Thirteen patients with alcohol-related decompensated cirrhosis remained on the WL at the end of the study period.

At baseline, patients with alcohol-related decompensated cirrhosis that would eventually be delisted after improvement had lower MELD scores and bilirubin levels and higher platelet count and serum sodium than patients who would undergo LT or be delisted due to worsening/death (Table 2). In addition, patients delisted after improvement were more frequently female compared to the rest of the groups. In univariate competing-risk regression analysis, baseline variables associated with delisting due to improvement were lower MELD, BMI and height; higher platelets and albumin levels; and female sex. In the multivariate analysis, female sex, lower MELD score and higher platelet count were independently associated with delisting due to improvement; while time of abstinence (forced into the model due to clinical significance) was at the limit of statistical significance. Interestingly, sex and height were highly co-lineal (Pearson coefficient 0.562, p <0.001). In this regard, when height was included in the multivariate analysis instead of sex it was also an independent predictor, along with MELD and platelets, that maintained the same coefficients as for the analysis including sex

Table 1. Baseline characteristics of the patients included, in the entire cohort and according to the aetiology of liver disease.

	Total cohort (n = 1,001)	Alcohol (n = 420)	HCV (n = 403)	Cholestatic (n = 108)	NASH/cryptogenic (n = 70)	*p* value
Age (years)	54 (10)	56 (7)	54 (8)	51 (12)	59 (9)	0.001
Sex (male)	700 (70)	354 (84)	287 (71)	42 (39)	40 (57)	0.001
MELD score	19 (6)	20 (6)	18 (5)	18 (5)	20 (6)	0.001
Bilirubin (mg/dl)	5.1 (6.3)	5.1 (5.3)	4.2 (4.6)	8.3 (7.5)	5.9 (9.3)	0.001
Creatinine (mg/dl)	1.3 (1.1)	1.3 (1.0)	1.2 (1.0)	1.2 (1.3)	1.4 (0.9)	0.284
Albumin (g/L)	26 (12)	25 (12)	25 (11)	28 (12)	24 (14)	0.003

Differences were analyzed using ANOVA or Chi square tests. MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.



N° at risk	1,001	317	185	100	45	20	7	0
N°of events in the previous interval								
Transplant		600	94	50	21	5	5	0
Improvement		1	13	18	16	14	3	5
Death/progression		76	23	13	13	5	4	1
Other		7	2	4	5	1	1	1

Fig. 2. Kaplan-Meier curves showing the cumulative incidence of removal from the waiting list.

(Table 3). In a sensitivity analysis including the 13 patients that remained on the WL at the end of the study period, the independent predictive factors were the same (Table S1). The cumulative incidence of delisting due to LT, improvement death/worsening and others according to sex in alcohol-related decompensated cirrhosis is shown in Fig. S2. In this regard, 61% of women and 65% of men had undergone LT 6 months after WL admssion, while figures for 12 month-access to LT were 67% and 71%, respectively (p = 0.14).

Considering these results, we aimed to further describe the impact of sex and MELD score on WL outcomes. The probability of delisting due to improvement, LT or death/progression according to MELD score quintiles in the whole population, and in men and women separately is shown in Fig. 4A-C, respectively. As depicted in the Figure, no patient with a baseline MELD score >20 was delisted after improvement and, indeed, the probability of delisting after improvement was inversely related with MELD score at listing. This was particularly remarkable in women with MELD score 15-17, in whom the probability of delisting due to improvement (37%) was very similar to that of undergoing LT (50%). On the other hand, the probability of delisting after improvement in men with MELD score 15-17 was much lower (7%) than the actual probability of undergoing LT (73%).

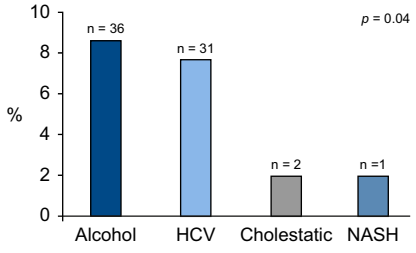


Fig. 3. Proportion of patients delisted after improvement according to the aetiology of liver disease. p = 0.04 (Chi square test). NASH, non-alcoholic steatohepatitis.

Before being delisted, a significant improvement of MELD score was experienced in these patients, already noticeable 6 months after WL admission (Fig. S3). Similarly, at the time of WL admission most patients had ascites that required diuretic treatment or large volume paracentesis, and 60% of them had had episodes of overt hepatic encephalopathy in the previous 3 months. On the contrary, at delisting, most patients had no ascites or it was easily controlled with low-dose diuretics, and only 3% of patients had had hepatic encephalopathy within the 3 previous months (Fig. S4). Improvement in complications of cirrhosis occurred gradually during follow-up, although signs of improvement were already present 6 months after admission.

Patients were followed for a median of 39 months (IQR 21-81) after being delisted due to improvement. Most patients were alive at the end of follow-up (24/36, 67%), and 12 (33%) patients had died. Six patients (50% of deaths) died due to liver-related causes: 3 of them due to HCC and the remaining 3 due to decompensations of cirrhosis. In the remaining 6 patients, causes of death were extrahepatic neoplasia in 4 patients, and mesenteric vein thrombosis and post-endoscopic retrograde cholangiography bleeding in the remaining 2 patients.

Twenty-one of the 24 patients (87%) that were alive at the end of the follow-up period had compensated cirrhosis, 2 patients were relisted for LT following the reappearance of decompensated cirrhosis (at 48 and 120 months after previous delisting) and finally underwent LT, and the remaining patient had decompensated cirrhosis with active alcohol consumption. Indeed, among the 9 patients with progression of liver disease after delisting (6 dead due to liver-related causes, 2 transplanted and 1 alive and decompensated), alcohol relapse was documented in 6 patients (67%).

Table 2. Baseline characteristics of wait-listed patients with alcohol-related decompensated cirrhosis according to waiting list outcome.

	Transplant (n = 318)	Delisting for death/ progression (n = 56)	Delisting for improvement (n = 36)	*p* value
Age (years)	56 (7)	57 (7)	58 (6)	0.452
Sex (male)	273 (86)	48 (86)	24 (67)	0.025
MELD score	21 (5)	18 (7)	14 (3)	0.001
Bilirubin (mg/dl)	5.6 (5.6)	5.6 (3.2)	2.1 (1.2)	0.001
Creatinine (mg/dl)	1.3 (1.0)	1.1 (1.3)	1.0 (0.4)	0.294
Albumin (g/L)	25 (12)	23 (14)	26 (14)	0.441
BMI (kg/m^2)	28 (4.2)	27 (4.8)	26 (3.9)	0.157
Height (cm)	168 (7.6)	168 (9.1)	164 (8.4)	0.020
Duration of alcohol abstinence before listing (months)	29 (23)	38 (46)	23 (22)	0.220
AST (U/L)	52 (27)	49 (28)	45 (17)	0.515
ALT (U/L)	32 (22)	32 (21)	28 (14)	0.682
Platelets (10^9/L)	74 (73)	76 (63)	119 (148)	0.019
Na (mEq/L)	134 (5)	133 (5)	135 (5)	0.018

Ten patients who were delisted due to other causes were not included in this comparison. Differences were analyzed using ANOVA or Chi square tests. ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, model for end-stage liver disease.

Comparison to patients with HCV-related decompensated cirrhosis

Thirty-one of the 403 WL patients with HCV-related decompensated cirrhosis were delisted due to improvement (7.6%). Among the 403 patients, 108 (27%) had a dual diagnosis of HCV and alcohol-related decompensated cirrhosis. The probability of delisting after improvement was 7% in only-HCV and 9.2% in HCV + alcohol patients (p = 0.405). As expected, delisting after improvement was significantly higher in the post-DAA era (4% in the 2007-2013 period and 15% in the 2014-2018 period, p = 0.005), and in this period, 88% of delisted patients had received antiviral therapy with DAAs. In the 2014-2018 period, 51% of patients with HCV-related decompensated cirrhosis received antiviral therapy while on the WL, and 27% of treated patients were eventually delisted after improvement.

Characteristics at delisting and the time between WL admission and delisting were similar in patients with HCV- and alcohol-related decompensated cirrhosis delisted after improvement (Table S2). Of the 31 patients with HCV delisted due to improvement, after a median follow-up of 32 months (IQR 22-56), 22 (71%) were alive (20 compensated, 1 decompensated with contraindications for LT and another having eventually undergone LT), and 9 had died, 6 of whom (67%) died of liver-related causes. The outcomes after delisting were similar in patients with alcohol- and HCV-related cirrhosis: 5 years after delisting, 76% and 74%, respectively, were free from progression of liver disease, defined as liver-related death or LT (Fig. 5).

Discussion

In this study we describe, for the first time in a multicenter European cohort, the phenomenon of delisting from the LT WL after improvement in patients with alcohol-related decompensated cirrhosis. This has been previously described after treatment with DAAs in patients with HCV-related cirrhosis.[4] However, to date, only a registry study from the US and a Canadian cohort have described delisting in patients with alcohol-related cirrhosis.[20,21] These studies had some limitations derived from the registry-based nature of the US study and the single-center design of the Canadian one, where there was also a very high access to living liver donation. In contrast, our cohort merges both approaches: it is a registry-based study with a larger sample size and centralized data control, while the fact

Table 3. Competing-risk uni- and multivariate analysis of factors associated with delisting for improvement in patients with alcohol-related decompensated cirrhosis.

Variable	Uni sHR (95%CI)	*p* value	Multi sHR (95%CI)	*p* value
Sex (female)	2.820 (1.42–5.6)	0.003	**2.289 (1.07–4.89)**	**0.032****
Age (years)	1.035 (0.99–1.08)	0.136		
Duration of alcohol abstinence before listing (months)	0.992 (0.98–1.00)	0.145	0.986 (0.97–1.00)	0.055
BMI (kg/m^2)	0.926 (0.86–0.99)	0.040		
Height (cm)	0.943 (0.91–0.98)	<0.001	**0.957 (0.92–0.992)**	**0.018***
MELD score	0.766 (0.72–0.82)	<0.001	**0.784 (0.73–0.83)**	**<0.001**
Albumin (g/L)	1.085 (1.03–1.15)	0.004	1.031 (0.96–1.10)	0.375
AST (U/L)	0.990 (0.98–1.002)	0.106		
ALT (U/L)	0.989 (0.97–1.006)	0.208		
Platelets (10^9/L)	1.004 (1.001–1.004)	0.003	**1.004 (1.002–1.006)**	**0.006**
Na (mEq/L)	1.063 (0.98–1.15)	0.124		
Year of wait-listing	0.917 (0.84–1.01)	0.067	0.956 (0.88–1.04)	0.269
Era (pre-DAA)	0.751 (0.36–1.551)	0.440		
Center	0.702 (0.475–1.038)	0.076	0.747 (0.488–1.144)	0.180

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAAs, direct-acting antivirals; MELD, model for end-stage liver disease; sHR, subdistribution hazard ratio.
*p value of height when included in the multivariate model with the variables with a p value <0.1 (except for sex) and time of abstinence.
**p value of sex when included in the multivariate model with the variables with a p value <0.1 (except for height) and time of abstinence. In these analyses, p value of MELD and platelets, as well as the corresponding sHR, remained the same. When both sex and height were included in the model, only MELD and platelets remained as independently associated with delisting for improvement. When the analysis was performed including BMI instead of height; sex, platelets and MELD score remained as significant in the multivariate analysis.

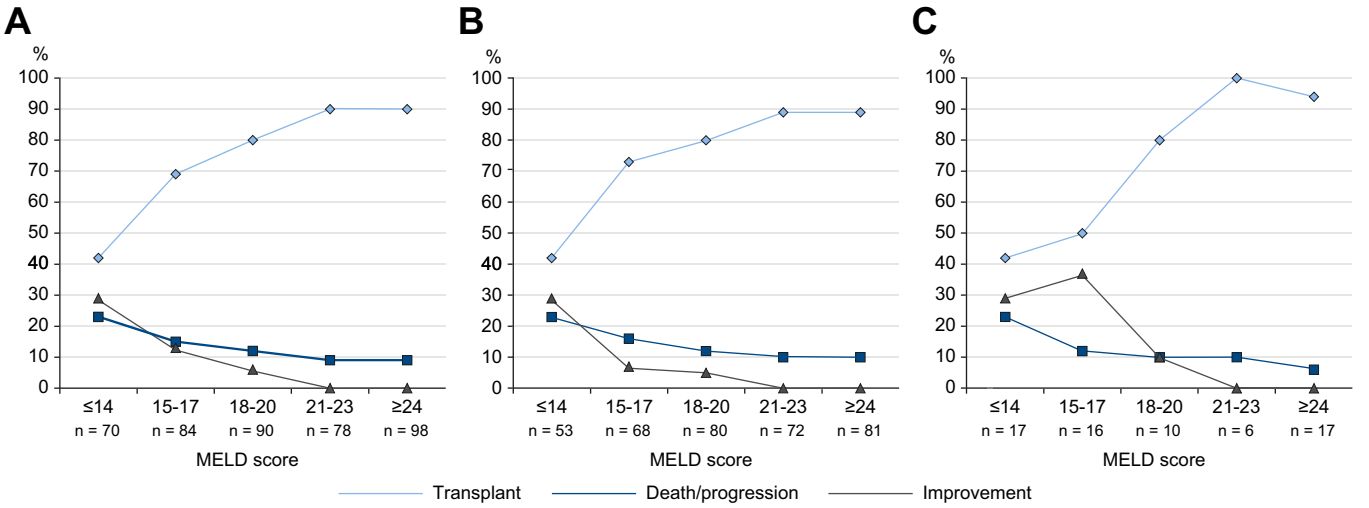
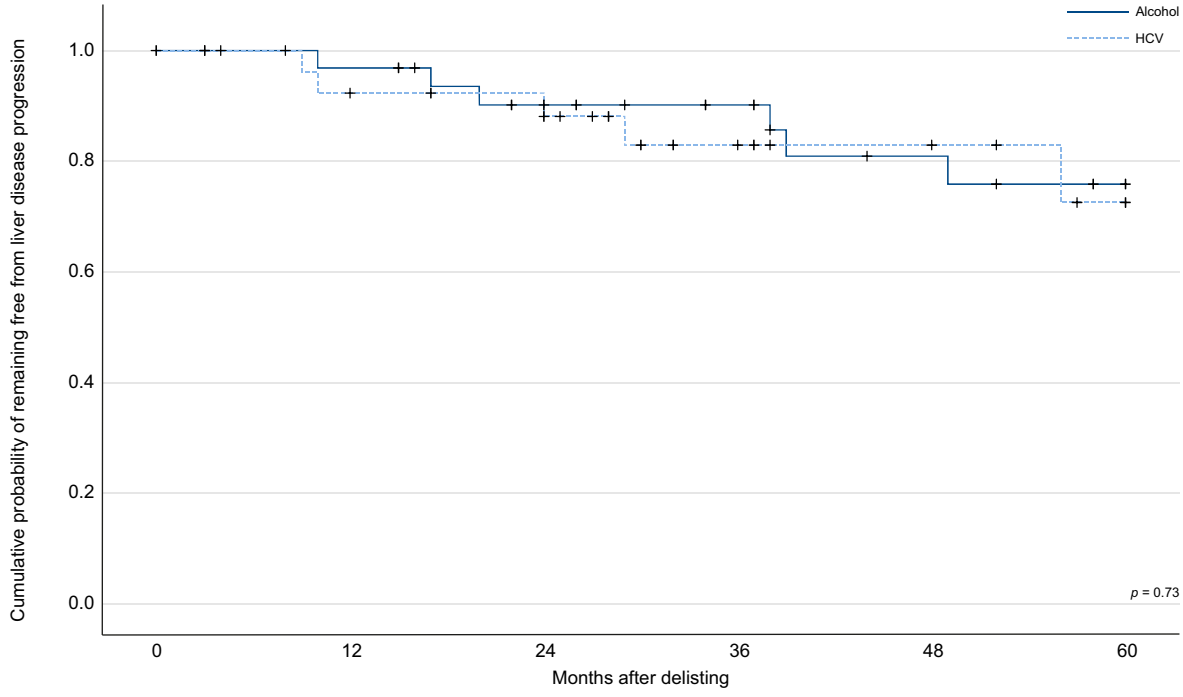


Fig. 4. Proportion of patients delisted after LT, death/progression or improvement according to MELD score in quintiles. (A) The whole population; (B) men and (C) women. LT, liver transplantation; MELD, model for end-stage liver disease.

that only centers with common listing criteria are involved in the registry improves the quality and granularity of the data.

The LT WL composition has changed significantly in the last years, and ArLD is now the main cause of LT for decompensated cirrhosis in Europe and the US.[7,10] This situation will probably be accentuated in the coming years, and the profound changes driven by anti-HCV DAAs has created the possibility for new LT indications and diminished the importance of relative contraindications, provided the survival benefit remains and the principles of justice and equity are followed. In the case of patients with alcohol-related cirrhosis, this may lead to shorter abstinence requirements for inclusion on the WL. Indeed, LT for alcoholic hepatitis has become a standard-of-care in some centers, showing promising results if an accurate selection of patients can be performed.[22–25]

On the other hand, it is well known that abstinence can lead to clinical improvements in patients with decompensated cirrhosis and eventually make LT unnecessary. In our study, a



N° at risk	Delisting					
Alcohol	36	31	25	21	16	13
HCV	31	24	22	14	10	6

Fig. 5. Kaplan-Meier curves showing the probability of remaining free from progression of liver disease (liver disease-related death or need for LT) in patients delisted for improvement with alcohol- and HCV-related cirrhosis. $p = 0.73$ (log-rank test).

non-negligible percentage of patients with alcohol-related cirrhosis experienced a significant improvement of liver function and clinical decompensations and were delisted. It must be stressed, however, that improvement until delisting is infrequent and these patients more frequently evolve to progression and death than to improvement.

Identification of patients that can improve after alcohol abstinence in the setting of the LT WL is of major relevance, given that delisting for improvement may not be possible before LT is performed if expected WL times are short. In studies in patients with decompensated cirrhosis, outside the setting of the WL, variables found to be associated with improvement are mainly abstinence, liver function and presence of decompensations of cirrhosis, or histological parameters such as percentage of fibrosis in liver biopsy or histological signs of alcoholic hepatitis.[16–18] Accordingly, in our study we show that the more advanced the liver disease (as assessed by MELD and platelets), the lower the probability of delisting after improvement. In addition, time of abstinence was at the limit of statistical significance in multivariate analysis, supporting the beneficial effects of abstinence even in the long-term. Indeed, the inverse association between the time of abstinence and the probability of improvement suggests that patients with shorter abstinence may benefit from having more time on the WL to improve, provided their MELD score is low enough that they do not qualify for LT; while patients included in the WL after a longer period of abstinence may already be out of the timeframe for improvement at the moment of WL admission. These results may raise the debate of whether potential LT candidates with low MELD score (albeit with a clinical indication for LT) and short abstinence would be good candidates for surveillance and close follow-up before considering their inclusion in the LT WL. It is clear that such a decision may have important implications, as some of these patients with low MELD scores may still worsen; thus, further studies to validate criteria that predict improvement are needed.

A very relevant aspect that needs to be considered when interpreting our results is the actual access to transplant of patients on the WL, which determines the MELD score required to undergo LT in each specific site or country. It is well known that the access to LT in Spain is relatively easy compared to other countries, in the setting of a high donation rate.[26] In our cohort, median MELD at transplant ranged between 19 and 21 during the study period and the median time between WL admission and LT was 1.1 months, with 75% of transplanted patients receiving a graft in the first 3 months after being admitted to the WL. This rapid access to LT probably determines the probabilities of delisting after improvement and at least in part justifies the fact that no patient with a MELD score >20 was delisted due to improvement. This fact affects the generalizability of our results, and we encourage studies from countries with different allocation and donation systems.

In our cohort, women had higher probabilities of being delisted after improvement. Interestingly, this was also suggested in the other 2 studies looking at this topic. In the study from Aravinthan *et al.*,[20] male sex was associated with an odds ratio of 0.43 (0.17-1.06) for delisting after improvement in the multivariate logistic regression analysis, with a p value of 0.07; and in the study from Giard *et al.*,[21] women with alcohol-related decompensated cirrhosis were more likely than men to be removed from the WL, because of either clinical improvement or deterioration/death, using competing-risk regression analysis. The sex differences in WL outcomes have been largely described, and the potential explanations for such disparities include differential weighting of renal dysfunction by MELD according to sex, as well as donor/recipient size mismatch.[27–29] These facts would account for a more difficult access to LT and could justify worse WL outcomes in women. Looking at our data, a plausible hypothesis would be that a lower access to LT in women, mainly derived from donor/recipient height disparities, may in turn permit a proportion of them (those with lower MELD score) to have enough time to recompensate and be delisted after improvement.

There are some differences between our study and the previously published works. In terms of results, the incidence of delisting due to improvement ranged from 2% in the US study to 16% in the Canadian study, being 8.6% in our population, with median time to delisting ranging between 14 and 29 months. As mentioned above, the different designs of the studies potentially explain some of the differences, while there are also differences related to the health systems involved. Importantly, the fact that only 3 centers with the same criteria for transplantation are involved increases the granularity and consistency of our data, even in the setting of a large registry-based study. In addition, our study includes an homogeneous population with an in-depth description of clinical outcomes and long-term follow-up.

We could describe the outcomes of patients with alcohol-related decompensated cirrhosis delisted due to improvement after a relatively long follow-up from delisting. Importantly, we observed that the prognosis of these patients is not always favorable after delisting, and indeed liver disease progressed in a proportion of them after the initial improvement of liver function, though alcohol relapse after delisting largely contributed to the poor outcomes of these patients. Thus, like wait-listed patients, these patients will still require strict follow-up involving an addiction diseases specialist. It is also important to acknowledge that only 50% of the liver-related deaths were due to new decompensations and the remaining 3 patients died from HCC in the setting of otherwise compensated cirrhosis. In addition, it is also remarkable that 50% of deaths in patients with alcohol-related cirrhosis delisted after improvement were unrelated to liver disease, and among them, extrahepatic cancer was the most frequent. This underlies the importance of alcohol as a factor associated with an increased risk of several types of neoplasia,[30] also suggested by the higher incidence of post-LT *de novo* neoplasia in LT recipients with previous ArLD.[31,32] Finally, even though a proportion of patients progressed, most patients were alive and compensated after a long follow-up. Indeed, nearly 80% of the cohort was free from progression of liver disease 5 years after being delisted; thus, a significant number of transplants could be avoided without adversely impacting prognosis.[33,34] However, as stated, delisted patients are still at risk of re-decompensation and thus require strict follow-up and management of AUD.

We considered that comparing the outcomes of these patients with those of patients with HCV-related decompensated cirrhosis could be of interest. Several studies have shown that DAAs can induce improvement and delisting in many patients with HCV-related cirrhosis.[4–6,11] Although patients with HCV were not the primary focus of our study, we showed a clear impact of DAAs on the possibility of delisting. In fact, the probability of delisting due to improvement in patients with alcohol-

related decompensated cirrhosis seems higher than that of patients with HCV-related cirrhosis without effective therapy (*i.e.* before DAAs), but lower than that of HCV-patients once highly effective DAAs were available. Importantly, the outcome of both groups after delisting seems comparable.

Our study has some limitations that need to be acknowledged. First, we assumed that delisting was the consequence of long-term alcohol abstinence. However, the fact that abstinence was not monitored in the same manner in the 3 centers precludes us from definitely attributing improvement to maintained abstinence, which would anyway be the most plausible explanation for our findings. Second, our study was focused in patients actually listed for LT, and we did not consider those candidates that were not listed because of recompensation during pre-LT assessment, so the full scope of the situation cannot be provided. Third, as stated, access to LT in each center/country may determine the probability of delisting due to improvement. Finally, decisions on when to list or delist a patient for LT are made according to established criteria but on an individual basis; as such, there may be subtle characteristics that physicians consider when making such decisions that may be confounders in our study.

In conclusion, our data show for the first time in a European cohort that approximately 9% of wait-listed patients with alcohol-related decompensated cirrhosis may be delisted due to improvement, and that the grade of liver disease (MELD, platelets) and female sex are associated with this outcome. Although liver disease progresses in a proportion of these patients, outcomes after delisting are generally favorable and comparable to those of patients with HCV-related cirrhosis delisted for improvement.

Abbreviations

ArLD, alcohol-related liver disease; AUD, alcohol use disorder; DAA, direct-acting antiviral; ETG, ethyl glucuronide; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; WL, waiting list.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

EP: study concept and design, acquisition of data; analysis and interpretation of data, drafting of the manuscript. AT: acquisition of data, statistical analysis, critical review of the manuscript. ER: acquisition of data, statistical analysis, critical review of the manuscript. VP-C: acquisition of data, critical review of the manuscript. IC-V: acquisition of data, critical review of the manuscript. EA: acquisition of data, critical review of the manuscript. JG-G: acquisition of data, critical review of the manuscript. JC: acquisition of data, critical review of the manuscript. LC: acquisition of data, critical review of the manuscript. JC: acquisition of data, critical review of the manuscript. JT: acquisition of data, critical review of the manuscript. PG: study concept and design, acquisition of data, critical review of the manuscript. GC: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript.

Data availability statement

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

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Supplementary data

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Author names in bold designate shared co-authorship

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