Liver elastometry and alcohol withdrawal: Median-term follow-up in a psychiatric unit

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Short Title : Liver stiffness evolution after alcohol withdrawal

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Abstract

The measurement of liver stiffness (LS) show promise as a follow-up tool after alcohol withdrawal but has mainly been studied in the early phase or in patients with severe liver disease. A six-month ancillary study of a specific psychiatric cohort of alcoholic patients without known liver disease followed after withdrawal was conducted (Clinical Trial NCT01491347). Clinical and biological data and LS values were collected every two months. A total of 129 patients were included in the study, 93 had a LS assessment within the first seven days and 37 had all four LS measurements. Only seven (7.5%) patients had an initial LS > 12.1 kPa, the threshold used to define severe fibrosis. Abstinence was not associated with changes in LS at the various median-term follow-up periods. However, LS of abstinent subjects decreased significantly relative to that of non-abstinent subjects between M0 and M2. CAP^{TM} values were not associated with abstinence.

The systematical median-term follow-up of withdrawn patients does not appear to be contributory. However, LS could help to detect relapse in the first two months after withdrawal for subjects treated in a psychiatric hospital for dependence. It thus could serve as a motivation tool. Prospective studies with various and higher baseline LS values are warranted for simultaneous longitudinal assessment, including for very short- and long-term LS after withdrawal.

Key words : alcohol consumption, liver stiffness, motivation, alcohol withdrawal, liver fibrosis.

Introduction

Chronic and excessive alcohol consumption leads to a major risk of chronic liver disease. Alcohol accounts for 50 to 75% of all cases of cirrhosis in western countries ((European Association for the Study of Liver, 2012). Cirrhosis, the ultimate stage of the evolution of liver fibrosis, exposes individuals to potentially serious and lethal complications. This risk correlates with the degree of alcohol consumption. Recently, Shah et al. showed that alcoholic liver diseases in the United States are diagnosed later than liver disease due to other major causes (2017).

Screening, in particular early screening, for the impact of alcohol consumption on the liver is crucial. Various methods can be used for liver fibrosis staging. Histology is still the gold standard but liver biopsy requires hospitalization and may, although rarely, expose patients to severe complications (Mueller et al., 2014). Over the last 10 years, non-invasive methods have been developed to avoid the constraints and risks of liver biopsy, including biological algorithms and liver stiffness (LS) : serum markers (Eyles et al., 2013; Cook et al., 2015; Mueller et al., 2017), LS measure alone (Harris et al., 2019) or combined in algorithm with liver function markers (Harman et al., 2015)…. They were first validated for chronic viral hepatitis and then extended to the other major chronic liver diseases. Elastometry, based on the measurement of LS, is easily available and reproducible: specific ranges have been proposed for determining the stage of fibrosis (Nguyen-Khac et al., 2008, 2018). Specific guidelines have been proposed and this tool is an option for the management of alcoholic patients (EASL, 2012; 2015). Liver elastometry is highly recommended for the management of patients who inject drugs (PWID) for hepatitis screening, in addition to rapid diagnostic tests (RDTs), but has been marginally studied and used in routine clinical practice for the management of alcoholic patients (Lahmek et al., 2014). This tool could also be used to

screen the general population for chronic liver diseases, specifically targeting alcoholic liver diseases due to their high prevalence in western countries (Baba et al., 2011).

LS has been linked to the amount of alcohol consumed and, more specifically, to the time since the last consumption (Trabut et al., 2012; Bardou-Jacquet et al., 2013; Lahmek et al., 2014). A decrease in LS values appears to reflect an improvement of the liver status after a decrease in alcohol consumption (in link to a probable improvement of acute histological lesions, such as necrosis, inflammation, and early fibrosis). The evolution of LS during alcohol consumption and after withdrawal could be key for the screening and management of these patients, particularly affecting their long-term motivation. An improvement of LS has been specifically studied within the first seven days after the cessation of consumption. It clearly drops in the first days following alcohol withdrawal in patients with very severe liver disease, but information on the evolution in subjects with as yet undetected liver disease after this initial period is absent (Mueller et al., 2014; Girard et al., 2017), especially at the moment of relapse. Indeed, some subjects may alternateabstinent and non-abstinent periods over the months after withdrawal (Nubukpo et al., 2016). Whether the somatic modifications associated with alcohol consumption are immediately perturbed is yet to be determined.

We aimed to assess the LS values according to the abstinence status at 2, 4, and 6 months after alcohol withdrawal, and characterize the evolution of LS throughout the follow-up period, associated with the clinical characteristics of the subjects. The evolution of the risk of fibrosis risk was assessed, and the relationship between LS scores and alcohol abuse markers (declared alcohol consumption, gamma-glutamyl-transferase- GGT, and carbohydrate-deficient transferrin-CDT) was also explored.

Method

Patients and data

We conducted a six-month ancillary study using a specific cohort (clinical trial NCT01491347) established from 2011 in a psychiatric hospital in Limoges, France, among patients with alcohol-use disorder (AUD) hospitalized for alcohol detoxification according to DSM-IV-TR criteria. The studies received legal, administrative, and ethical authorizations from the French Committee for the Protection of Persons and the National Agency for the Security of Drugs and Health Products. All included subjects gave their written informed consent. The study was registered with theClinicalTrials.gov identifier: NCT02202148. Inclusion criteria were a diagnosis of alcohol dependence, according to the DSM-IV-TR criteria, and coming to the psychiatric hospital to request treatment to quit drinking. Subjects with a neurologically characterized illness (Korsakoff syndrome), severe somatic illness (pancreatitis, chronic decompensated liver disease, etc.), anti-retroviral therapy, or chronic viral hepatitis and any known liver disease were not included. Other exclusion criteria were an age of under 18 years, the absence of informed written consent, inability to understand questionnaires in French, absence of a permanent address, leaving the area during the first months after the beginning of the study, pregnancy, hospitalization without consent, participation to another study, and the existence of an active implantable device (previous contraindication to FibroScan.). The only inclusion criterion for this study was participation in the main study.

At baseline, and the 2-, 4-, and 6-month follow-up, subjects participating in the study underwent a clinical evaluation, blood tests, and a LS measurement. Clinical examination at inclusion consisted of a semi-standardized interview to collect data on age, gender, duration of the disease (years), number of previous treatments in alcohol detoxification programs, tobacco and/or illicit drug consumption (cannabis use at least once a week), mean number of cups of coffee consumed per day, and total alcohol consumption characteristics based on the results of the Alcohol Timeline Follow-Back (TLFB) (mean standard drinks during the

previous two months, number of days of consumption, time since the last alcoholic drink) (Cervantes et al., 1994; Grant et al., 1995). Psychiatric comorbidities (schizophrenia and related disorders, bipolar disorders, and depression and anxiety disorders) were determined according to the DSM-IV TR criteria by the referent psychiatrist. Information on psychotropic treatments (antipsychotics, antidepressants, anxiolytics, and mood stabilizers) was also collected, with a specific attention to antidepressant and neuroleptic treatments which may have a potential effect on the liver, and to their recent introduction (Carrier et al., 2016).

At each visit, the following data were registered:

- Mean alcohol consumption, based on the participant's declarations (to keep independent from biological markers, which are representative of alcohol toxicity and only change after approximately two weeks). Subjects were considered to be abstinent if they declared the absence of any alcohol consumption since the previous follow-up. Partial relapse (partially abstinent) was defined as a consumption of alcohol in a regular or intermittent manner (less than five consecutive days) or less than four to five standard drinks each time. Total relapse (non-abstinent) corresponded to repeated alcohol consumption for at least five consecutive days between two follow-ups or more than four to five standard drinks each time (heavy drinking days) (Belgherbi et al., 2015). The overall status of the participants during the six-month period following withdrawal was defined as total abstinence (all follow-ups), no abstinence (relapse at M2 until M6), or intermittent (more than one follow-up with abstinence).
- The length of psychiatric follow-up, the number of previous withdrawals, the number of days on which alcohol was consumed, the number of standard alcoholic drinks per day.
- GGT, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) serum concentrations for the routine clinical evaluation at baseline and follow-ups.

LS (elastometry measurement) was determined at least three hours after food intake (FibroScan®, EchoSens, Paris.). Ten consecutive inter-costal measurements were required to validate the examination, and the median was considered for LS values. Liver steatosis was also specifically evaluated by the CAP^{TM} (controlled attenuation parameter), which was calculated by EchoSens (de Lédinghen et al., 2014). The threshold chosen for advanced fibrosis (equivalent METAVIR F3, cirrhosis corresponding to F4) was an elasticity > 12.1 kPa. Numerous LS thresholds have been proposed in the literature for alcoholic disease (De Franchis et al., 2015, Thiele et al., 2018). The threshold of 12.1 KPa is based on a large recently published meta-analysis that showed an area under the receiver operating characteristic curve of 0.90 for the diagnosis of advanced fibrosis. The mean variation of elasticity was calculated between M0 and each follow-up date and defined as below: (LS at follow-up – LS at M0) / LS at M0 (17).

Statistical analysis

Quantitative variables are described as the means ± standard deviation, and medians and 95% confidence interval. Qualitative variables are described as percentages and numbers (n). Comparisons between groups were performed using non-parametric the Mann Whitney test for quantitative variables, and Chi² test or Fischer exact test for qualitative variables. The non-parametric paired Wilcoxon test was used to compare quantitative variables between M0 and the follow-up times. Repeated measures ANOVA was used to explore the overall evolution of LS over time with either inter-subject variables or co-variables and to verify the absence of changes in BMI over time and the absence of gender effect (Magdaleno et al., 2017) (and discard the need to adjust data on BMI values or gender). The results are handled as exploratory thus without correction of type I error (Jouan-Flahault et al., 2004).

Lost-to follow-up subjects were not considered as being more at risk of relapse, as already observed in a previous cohort (Nubukpo et al., 2016) where the absence of link between care and abstinence status was verified. Missing data are thus considered to be random, because the reasons for lack of follow-up are not related to variables that may influence the main objective : change of residence, exclusion from the study for lack of more than 1 monitoring, the absence of transport solution, the impossibility to be contacted (the patients do often have disruption in telephone subscription for example), etc...The population with follow-ups is therefore considered representative of the overall sample, we considered our data as Missing Completely At Random (MCAR) or as Missing Completely At Random, and did not use any technic to account for missing data.

All statistical analyses were performed using SPSS® software (version 20.0) (SPSS. Inc., Chicago, IL, USA).

Results

Population at inclusion

A total of 129 patients were included in this study, mostly men (104). Among them, 115 experienced alcohol withdrawal at the time of the study and 113 had psychiatric comorbidity. LS was determined within the first week of withdrawal for 93 participants (M0), who constituted the study population. Some patients could miss one follow-up and thus sixty-six patients could be evaluated at M2, 81 at M4, and 87 at M6. Only 37 participants among the initial 93 participants had LS measurement at all four timepoints.

The patient characteristics and their evolution are shown in Table 1. They consumed a large amount of alcohol and were chronic consumers, considering the number of previous withdrawals and the long duration of care in psychiatry.

Risk factors that may have influenced LS at the time of withdrawal, *e.g.* cannabis and coffee consumption, declined after inclusion and then remained stable. The proportion of smokers remained stable throughout the follow-up.

The mean BMI remained below the first grade for being overweight (mean 24.5 kg/m², median 24.09, 17 to 40.9 kg/m²). Repeated measures modeling indicated the absence of any significant change in BMI during the six months of the study ($F = 0.186$, $p = 0.831$) and the absence of gender effect ($F = 0.897$, $p = 0.349$).

Nearly half of the subjects were receiving a psychotropic treatment, either antidepressant or neuroleptic. A new psychotropic treatment (antidepressant) was introduced within the last three months for one third of the subjects.

Biological results and liver stiffness

Mean hepatic enzyme levels were close to normal at the time of withdrawal (AST: 32 UI/L, GPT: 28 UI/L).

Mean LS values corresponded to the absence of significant fibrosis (median 5.25 [5.14 – 9.8] kPa at M0, 4.90 [4.96 – 6.96] kPa at M2; 4.7 [5.05 – 7.70] kPa at M4; and 4.9 [4.96 – 6.86] kPa at M6), and very few participants exhibited suspicious severe fibrosis: only seven (7.5%) had a LS score ≥ 12.1kPa at M0. Mean elasticity values in the entire population appeared to remain stable over time after withdrawal (Table 1) (Figure 1) and still favored the absence of severe fibrosis (< 12.1 kPa). The mean difference in LS between each follow-up and M0 demonstrated an overall decrease of mean elasticity ($p = 0.197$ between M0 and M2, $p = 0.111$ between M0 and M4, and $p = 0.165$ between M0 and M6). The proportion of subjects at risk of severe fibrosis remained stable throughout the follow-up period. The distribution of the number of subjects at risk of advanced fibrosis was however different between M0 and M2 ($p = 0.002$), M0 and M4 ($p < 0.001$), and M0 and M6 ($p = 0.001$): the LS values decreased from “severe fibrosis risk” to a lesser risk for four subjects (LS < 12.1 kPa), and

three subjects remained in the same risk category. At M4, four subjects were still at "risk of advanced fibrosis" compared to M0, three had a decreased risk and one had an increased risk of advanced fibrosis. Three subjects had an increased risk of fibrosis between M2 and M4. At M6, three subjects remained at risk of advanced fibrosis, two had a decreased risk, and one an increased risk. Only two subjects remained at risk for advanced fibrosis throughout the six months.

LS values and potential association with clinical and paraclinical factors at each follow-up

LS values did not differ according to coffee or cannabis consumption, the existence of previous alcohol withdrawals, the time since the last consumption of alcohol, antidepressant or neuroleptic treatment, or the recent introduction of antidepressant treatment at any follow-up.

LS values also did not vary according to the abstinence status, regardless of the time of follow-up; only a trend was found at M2 for total relapsers, who exhibited a higher elasticity value ($p = 0.051$) (Table 2).

CAP^{TM} values may interfere with LS values, but they add information about steatosis. Thus, CAP^{TM} values were retrospectively calculated: they were not associated with the abstinence status and did not change between M0 and the other follow-up timepoints ($p = 0.695$ for M0 *vs* M2, $p = 0.500$ for M0 *vs* M4, and $p = 0.577$ for M0 *vs* M6) (Table 2). However, there was a trend towards a significant increase in the group of total relapsers relative to abstainers at six months, indicating a potential difference in the kinetics of variation.

There was no difference in LS between abstinent subjects and partial relapsers. However, the evolution of LS values differed between abstinent subjects and total relapsers between M0 and M2 (Table 3). The introduction of antidepressant treatment at the time of severence or the introduction of a neuroleptic treatment in the previous month was not associated with LS

values at follow-up (Table 2). Subjects initiating a new antidepressant treatment during the month before alcohol withdrawal experienced a significant change in LS between inclusion and two months (M2) (Table 3).

Evolution of LS during the six-month period after alcohol withdrawal and associated factors

Repeated measures modelling was applied alone or with the introduction of inter-subject variables to evaluate their influence on LS values (table 4). LS values were not found to vary significantly over time. Tobacco use at M0 and the duration of the disease were found to interfere with the evolution of LS over time. However, only nine non-smoking subjects were included in the analysis and they exhibited an initially higher value of LS which did not decrease over time.

LS and biological markers of alcohol consumption

Finally, we explored a potential correlation between hepatic enzyme levels and LS values at each follow-up. A positive threshold value of CDT, which reflects alcohol consumption within the last two weeks, was not linked to LS. GGT levels correlated with LS at each date ($r = 0.610$, $p = 0.01$ at M0, $r = 0.460$, $p = 0.001$ at M2, $r = 0.502$, $p = 0.001$ at M4; and $r = 0.567$, $p = 0.001$ at M6). AST levels correlated with liver elasticity only at M2 ($r = 0.319$, $p = 0.042$), M4 ($r = 0.401$, $p = 0.006$), and M6 ($r = 0.558$, $p = 0.001$), as well as ALT levels ($r = 0.370$, $p = 0.017$ at M2, $r = 0.249$, $p = 0.051$ at M4; and $r = 0.826$, $p = 0.001$ at M6).

Discussion

There is little data concerning the medium- and long-term effects of the management of patients with alcohol consumption on LS (Bardou-Jacquet et al., 2013). Our study suggests that LS is not affected by alcohol withdrawal in the medium-term. The results should be interpreted according to the epidemiological profile of our quite young patients (mean age 45

years) with a low median LS score at M0, a characteristic which may have decreased the amplitude of variations in LS over time. There was a significant difference in LS between abstinent patients and total relapsers at M2, suggesting an impact of the amount of alcohol consumed. LS could help to differentiate between the two categories of relapse within the first months. Furthermore, the slight decrease in the proportion of patients with severe fibrosis can be explained by regression of the fibrosis and, in particular, the partial disappearance of inflammation.

The alcohol-drinking status was based on the declaration of the subjects in the absence of an available alternative sensitive tool to evaluate abstinence. The abstinent group may thus have included some subjects with low alcohol consumption. We assume that this small number of patients may have slightly, but probably not significantly, modified the results.

However, our patients correspond to the usual epidemiological profile of patients hospitalized for alcohol detoxification in many psychiatric units. Somatic complications due to alcohol consumption appear often later than in the early fifth decade (Askgaard et al., 2015). Conflicting results have been highlighted by Bardou-Jacquet et al. (2013), whose population consisted of patients hospitalized in an hepato-gastroenterology department who had acute alcoholic hepatitis (elevation of the median AST > 4N and gamma GT > 11N) and more advanced underlying liver disease than in units attending addiction. Moreover, a previously identified liver disease was an exclusion criterion in our study.

A short-term effect of withdrawal on LS has been described within the first seven days, allowing a rapid decrease of elasticity values and suggesting that LS may be a useful tool in the early management of withdrawal (Mueller et al., 2010; Gelsi et al., 2011; Trabut et al., 2012; Lahmek et al., 2014; Gianni et al., 2017). The design of our study, in which we determined the first LS value in the first seven days after withdrawal did not allow us to assess this very early effect in the absence of a reference LS value (within the first two to four

days) before withdrawal. As almost all subjects were examined within the first three days after withdrawal, we cannot exclude a potential significant decrease of LS between the first day of withdrawal and the first assessment of LS. This may also partially explain the subsequent weak global median effect of withdrawal on LS in this study.

The delta of the LS values between M0 and M2 was significantly different between abstainers and relapsers, indirectly confirming the early impact of relapse on LS. The early impact of withdrawal on LS is probably not related to a reduction of fibrosis but rather to a reduction in inflammatory processes (Sagir et al., 2008; Mueller et al., 2014). A recent meta-analysis highlighted the link between LS and the histological features of asymptomatic and non-severe alcoholic hepatitis (Nguyen-Khac et al., 2018). In our study, CAP^{TM} values were not associated with abstinence status and did not change significantly between M0 and the different time points of follow-up. Recently, Thiele et al. (2018) showed that CAP^{TM} had good diagnostic accuracy for diagnosing severe alcoholic liver steatosis and that CAP^{TM} values rapidly declined after alcohol withdrawal within less than seven days. These findings focusing on the very early impact of withdrawal are not incompatible with those of our studies that focused on the medium-term impact of CAP^{TM} monitoring (Thiele et al., 2018). However, CAP^{TM} values at withdrawal were not elevated and this in itself limits the possibility of observing large variations during the follow-up. Once again, it is likely that the patients attending addiction units do not have the same profile of liver disease as those attending hepato-gastroenterology units, where most studies are conducted. Moreover, we cannot exclude a significant decrease of CAP^{TM} between the first day of withdrawal and the first assessment of CAP^{TM}, using the same rationale as for LS.

In our study, we defined the alcohol drinking status of patients using qualitative variables: abstinence, non-abstinence, and partial abstinence. Among the biological variables, only GGT was associated with LS. We had already stated that GGT levels are not in direct link with

abstinence status, as they depends also on the level of hepathic damages in a pathological context (Nubukpo et al., 2016). LS is associated to the liver state at a precise time, as are GGT levels, and are not in direct link with alcohol consumption status. However, GGT levels correlated with LS values. In the literature, a relationship has been established between AST and LS in the first days, attributable to specific inflammation related to acute alcoholic hepatitis (Bardou-Jacquet et al., 2013). Some authors proposed that the assessment of fibrosis by FibroScan during alcohol withdrawal would only be accurate when AST is at least under 100 U/mL (Baba et al., 2011). As our aim was to study the data in link with LS and its changes, we did not controle for hepatic enzymes, thus allowing to evaluate LS independently.

An original finding of our study is the proposed relationship between taking antidepressants and the evolution of LS in these patients. Psychotropic drugs, mainly neuroleptics, have been described to influence elasticity values, but this observation is less well established for antidepressants (Carrier et al., 2016), with a lack of data in the literature. The potential relationship of antidepressant use and the evolution of LS has to be further studied, as our sample size is not enough to discard a potential effect of the variance of basal LS and its evolution, and only the newly prescribed molecules, and not the overall use were explored. Psychiatric illnesses themselves are associated with the risk of metabolic syndrome and steatosis and psychiatric drugs themselves can potentially contribute to liver disease. This risk is thus not directly associated with alcohol consumption alone. The specific role of psychiatric illnesses and illness-associated treatments should be more precisely investigated. Cannabis consumption did not appear to significantly affect LS in our study, even if paradoxical effects have been previously described in the literature: a deleterious effect on liver fibrosis (Hezode et al., 2005; Pateria et al., 2013), but a more recently reported protective effect against NAFLD (Adejumo et al., 2017).

Another potentially important factor is the influence of tobacco consumption over time. Tobacco consumption is traditionally associated with heavy drinkers and alcohol relapse (Cooney et al., 2007; Dawson et al., 2007; Joseph et al., 2014).

Making successive measurements of LS during withdrawal induce a motivational role of the FibroScan examination, which aims to change patient behavior (Lahmek et al., 2014). It has been shown in PWID that FibroScan plays a key role in the detection of viral hepatitis including hepatitis C, as well as other potential liver comorbidities (Pateria et al., 2013; Marshall et al., 2015). It is very well accepted and provides the patient with his/her real time "liver status". Nevertheless, the results must be cautiously interpreted and explained to the patients in the context of withdrawal, considering the time since alcohol withdrawal.

The main limitation of our study was the non-exhaustive nature of the data, as only a small number of patients had LS measurements at all expected times. However, the compliance of participants with alcohol use disorder (AUD), even after withdrawal, also fluctuated in many other studies. We also can not exclude a “floor effect” of the data, as the selection criteria of the subjects included the absence of known identified hepatic disease, and LS values as a consequence are not elevated and thus not subjected to important variations. Specific studies are needed with the specific objectives to explore the combined influence on LS of abstinence and other factors, as AD prescription for example.

We did not have histological samples in this study and thus the stage of fibrosis could not be confirmed. However, our aim was not to assess the efficacy of Fibroscan to assess the severity of fibrosis, but to study long-term changes in elasticity after alcohol withdrawal, independently of histological data.

Finally, we suggest investigating LS, first very early, in the first days following abstinence, with a strict pre-withdrawal referent assessment, and in the longer term. The longitudinal

investigation of non-invasive biological markers of fibrosis also merits consideration (Naveau et al., 2009; Chrostek et al., 2014).

In conclusion, LS should probably be assessed early after alcohol withdrawal, especially in heavy drinkers with biological signs of acute alcoholic hepatitis, to confirm withdrawal, as the LS values would change rapidly within the first two or three weeks after withdrawal in case of LS alteration and identified difference with the normal LS values.. It is also essential after the normalization of AST to accurately assess liver fibrosis. Moreover, it appears that its use as a motivational tool would also be helpful in this indication within the first two months after withdrawal.

The impact of inflammatory phenomena on LS of patients who have low baseline LS, which is often the case in the psychiatric population, is more difficult to assess, and it may not be wise to systematically recommend medium-term follow-up of these patients if the aim is to assess withdrawal at the medium term.

Based on our results, FibroScan is not a good tool to assess alcohol withdrawal and cannot replace the use of alcohol biomarkers for the detection of relapse. However, the simultaneous assessment of very early and long-term LS and the evolution of other fibrosis scores and its impact on motivation should be performed in prospective cohorts of patients with varying severity of baseline fibrosis.

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Tables

Table 1. Population characteristics at inclusion (M0) and at 2, 4, and 6 months (M2, M4, M6) after alcohol withdrawal.

	M0 (n = 93)	M2 (n = 65)	M4 (n = 66)	M6 (n = 57)
Age (years) (mean (SD))	45.8 (9.3)	-	-	-
Sex (male/female)	75/18	-	-	-
Previous withdrawals N (%)	84 (90.3)	-	-	-
Number of Previous withdrawals (mean (SD))	3.6 (4.7)	-	-	-
Duration of disease (mean (SD))	7.8 (9.3)	-	-	-
Tobacco use n (%)	80 (86)	53 (90.3)	52 (85.5)	50 (84.7)
Cannabis use n (%)	17 (18.3)	7.0 (11.3)	6 (9.7)	6 (10.2)
Coffee consumption (mean cups	4.2 (4.1)	4.1 (3.6)	6.1 (4.5)	4.5 (2.9)

(SD))				
abstinent / non-abstinent		28 / 37	20 / 46	21 / 40
Abstinent / partial relapse		28 / 20	28 / 26	21 / 15
Abstinent / total relapser		28 / 17	20 / 20	21 / 21
Mean time since the last drink (mean (SD))	4.4 (2.1)	28.0 (29.3)	44.0 (51.3)	54.3 (69)
Mean alcohol consumption during the last 2 months(mean (SD))	16 (11.2)	4.7 (7.5)	6.5 (8.2)	5.1 (6.6)
Mean number of days of alcohol consumption(mean (SD))	49.4 (16.4)	9.1 (13)	16.9 (22.9)	23.8 (34.3)
BMI (kg/m²) (mean (SD))	24.5 (4.7)	25.0 (4.6)	25.3 (4.6)	25.6 (4.5)
Biology (UI/L) (mean (SD))				
GGT	156.6 (244.7)	68.6 (93.2)	81.5 (137.7)	153 (465.1)
AST	43.5 (32.2)	28.2 (20.5)	33.5 (41.4)	29.7 (24.8)
ALT	38.5 (26.5)	24.9 (16.6)	18.5 (35.8)	25.8 (20.0)
CDT positive	57 (61.3)	18 (27.7)	20 (30.3)	18 (30.5)

Elasticity (kPa) (mean (SD))	6.9 (7.7)	5.8 (3.0)	6.0 (4.5)	6.9 (6.0)
LS Difference between M0 and follow-up (M0 - follow-up) (mean ± SD)	-	1.042 (5.428)	1.437 (6.908)	1.190 (7.440)
CAP™ (dB) (mean ± SD)	247.7 (58.0)	249.3 (53.6)	245.8 (69.7)	248.5 (66.3)
steatosis stages	46 (51.1) 28 (31.1) 16 (17.8)	30 (54.5) 17 (30.9) 8 (14.5)	27 (19.1) 18 (32.7) 10 (18.2)	31 (53.4) 15 (25.9) 12 (20.7)
Fibrosis risk n (%) > 12.1 kPa	7 (7.5)	3 (3.2)	5 (5.4)	4 (4.3)
New AD before M0	34 (36.6)	-	- -	
AD at M0	42 (45.2)	-	- -	
NL at M0	51 (54.8)	- -	- -	

AD: antidepressant; AST: aspartate amino transferase; ALT: alanine aminotransferase; CAP: control attenuation parameter; CDT: carbohydrate deficient transferase; GGT: gamma glutamyl transferase; LS: liver stiffness; NL: neuroleptic

Table 2. LS and CAP™ values at inclusion (M0) and at 2, 4, and 6 months (M2, M4, M6) after withdrawal according to the presence (+) or absence (-) of different types of relapse and risk factors

Elasticity (kPa) (SD) (n)	M0			M2			M4			M6		
	+	-	p	+	-	*p*	+	-	*p*	+	-	*p*
Non-abstinence	-	-		5.4 (2.8)	6.0 (3.2)	*0.173*	6.1 (4.5)	5.9 (4.7)	*0.851*	7.1 (7.8)	6.8 (5.0)	*0.568*
Partial relapse	-	-		5.4 (2.7)	5.4 (2.7)	*0.696*	5.6 (3.6)	5.9 (4.7)	*0.903*	5.7 (2.5)	7.1 (7.8)	*1.000*
Total relapse	-	-		6.7 (3.7)	5.4 (2.8)	*0.051*	7.0 (5.4)	5.9 (4.7)	*0.351*	7.9 (6.1)	7.1 (7.7)	*0.187*
Coffee consumption	7.2 (5.9)	6.1 (6.3)	0.240	5.0 (1.8)	6.8 (3.9)	*0.87*	5.6 (3.9)	6.7 (5.6)	*0.825*	6.9 (6.3)	6.7 (3.1)	*0.410*
Cannabis use	6.7 (6.7)	5.1 (2.1)	0.093	5.6 (1.3)	5.8 (3.2)	*0.513*	6.0 (2.1)	6.1 (4.7)	*0.309*	7.0 (2.7)	6.8 (6.3)	*0.160*
Previous withdrawals	6.9 (4.1)	6.9 (8.0)	0.300	5.5 (2.5)	7.3 (5.3)	*0.482*	6.0 (4.3)	6.2 (6.2)	*0.867*	6.9 (6.1)	6.6 (4.9)	*0.889*
New AD treatment introduction before M0	6.3 (4.1)	7.8 (11.54)	0.083	5.9 (3.2)	5.7 (3.0)	*0.757*	5.6 (4.0)	6.4 (5.0)	*0.460*	7.2 (7.4)	6.7 (5.2)	*0.776*
AD treatment	5.8 (3.1)	8.2 (10.9)	0.717	5.8 (2.7)	5.8 (3.6)	*0.724*	5.8 (4.3)	5.9 (4.1)	*0.217*	6.9 (6)	6.8 (6.0)	*0.980*
CAP™ (dB) (SD)												
Non-abstinence				247.9 (46.7)	251.6 (64.3)	*0.835*	247.9 (76.1)	240.7 (52.4)	*0.643*	257.3 (63.5)	234.5 (70.9)	*0.157*
Partial relapse				236.2 (30.7)	251.5 (64.3)	*0.379*	233.8 (71.5)	240.7 (52.4)	*0.728*	240.2 (80.2)	266.8 (98.1)	*0.732*
Total relapse				261.3 (58.0)	251.6 (64.3)	*0.554*	264.3 (80.0)	240.7 (52.5)	*0.211*	270.8 (49.9)	234.5 (70.9)	*0.054*

AD: antidepressant; CAP: control attenuation parameter

Table 3. Variation in elasticity values between M0 and the various follow-ups after withdrawal ((LS at follow-up – LS at M0) / LS at M0) according to the presence (+) / absence (-) of different types of relapse and the introduction of a new antidepressant treatment.

Variation in elasticity values between M0 and follow-up ((LS at follow-up – LS at M0) / LS at M0)	M0 M2			M0 M4			M0 M6		
Mean (SD)	+	-	*p*	+	-	*p*	+	-	*p*
Abstinence / non-abstinence	1.085 (0.448)	0.956 (0.490)	*0.325*	1.045 (0.586)	0.862 (0.353)	*0.395*	1.168 (0.930)	0.925 (0.386)	*0.272*
Abstinence / partial relapse	0.980 (0.415)	0.956 (0.490)	*0.765*	1.044 (0.734)	0.862 (0.353)	*0.742*	0.9976 (0.620)	0.925 (0.387)	*0.957*
Abstinence /	1.200 (0.466)	0.956 (0.490)	***0.042***	1.045 (0.353)	0.862 (0.353)	*0.235*	1.322 (1.116)	0.925 (0.387)	*0.074*

total relapse									
New antidepressant treatment	1.212 (0.558)	0.927 (0.394)	***0.011***	1.095 (0.430)	0.950 (0.557)	*0.095*	1.195 (0.674)	1.074 (0.862)	*0.183*

Table 4. ANOVA in repeated measures for the evaluation of LS evolution at withdrawal and the follow-up at 2, 4, and 6 months

	F	p
Time effect	1.932	0.162
x Abstinence status over the 6-month period after withdrawal	0.482	0.621
x New antidepressant treatment in the 3 months before withdrawal	0.091	0.765
x Antidepressant at withdrawal	0.051	0.808
x Neuroleptic prescription at withdrawal	0.231	0.633
x Coffee consumption	0.363	0.954
x Cannabis consumption	0.879	0.354
x Tobacco consumption	11.630	0.001
x BMI	0.334	0.566
x Number of previous alcohol withdrawals	0.602	0.850
x Any previous withdrawals	0.289	0.594
x Years of disease	0.341	0.562

Figure 1. Evolution of LS values at M2, M4 and M6 after alcohol withdrawal (M0).