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Liver transplantation in alcoholic patients: impact of an Alcohol Addiction Unit within a liver transplant center

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Abstract

Background—Many concerns about liver transplantation in alcoholic patients are related to the risk of alcohol recidivism. Starting from 2002, an Alcohol Addiction Unit was formed within the Liver Transplant Centre for the management of alcoholic patients affected by end-stage liver disease and included in the waiting list for transplantation. We evaluated retrospectively the impact of the Alcohol Addiction Unit on alcohol recidivism after transplantation. The relationship between alcohol recidivism and the duration of alcohol abstinence before transplant was evaluated as well.

Methods—Between 1995 and 2010, 92 cirrhotic alcoholic patients underwent liver transplantation. Clinical evaluation and management of alcohol use in these patients was provided by psychiatrists with expertise in addiction medicine not affiliated to the Liver Transplant Centre before 2002 (n=37; group A), or by the clinical staff of the Alcohol Addiction Unit within the Liver Transplant Centre starting from 2002 (n=55; group B).

Results—Group B, as compared to group A, showed a significantly lower prevalence of alcohol recidivism (16.4% vs. 35.1%; p=0.038) and a significantly lower mortality (14.5% vs. 37.8%;

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p=0.01). Furthermore, an analysis of group B patients with either ≥6 months or <6 months of alcohol abstinence before transplantation showed no difference in the rate of alcohol recidivism (21.1% vs. 15.4%; p=ns).

Conclusions—The presence of an Alcohol Addiction Unit within a Liver Transplant Centre reduces the risk of alcohol recidivism after transplantation. A pre-transplant abstinence period <6 months might be considered, at least in selected patients managed by an Alcohol Addiction Unit.

Keywords

alcohol dependence; alcoholism; Alcohol Addiction Unit; alcohol recidivism; OLT

Introduction

Alcohol use disorder represents the first cause of liver cirrhosis in the Western Countries (Tilg & Day, 2007). The persistence of alcohol consumption in patients with alcoholic liver disease (ALD) is associated with a significant risk ratio of death (Pessione et al., 2003; Yates et al., 1998). The primary effective strategy for patients with ALD is represented by total alcohol abstinence, since medical and surgical treatments for ALD and its complications have limited success when drinking continues (Yates et al., 1998). When even total alcohol abstinence does not result in a significant improvement of liver function, orthotopic liver transplantation (OLT) represents the *gold standard* treatment for end-stage alcoholic liver disease (Varma et al., 2010; Addolorato et al., 2013).

However many concerns about the usefulness of OLT in alcoholic patients are still present, including the unwillingness of the transplant team to transplant patients at risk of recidivism (Kotylar et al., 2008). Moreover, alcohol use disorder is still often considered a “self-inflicted disease” (Gramenzi et al, 2011), and part of the society considers alcoholic individuals as patients not deserving an OLT (Neuberger, 2007). Thus, the risk of recidivism is often reported as the major justification against OLT eligibility, also considering the issue of organ shortage (Hartl et al, 2011), the long-term survival reduction and the graft loss in recidivistic patients (Cuadrado et al., 2005). On the other hand, patient survival rates for ALD are significantly higher than those of patients transplanted for other aetiologies (Burra et al., 2010), in particular when recidivism does not occur.

There is a highly variable rate of recidivism in alcoholic patients after OLT, with a percentage ranging from 10 to 95% (Lim & Keeffe, 2004; Björnsson et al., 2005), probably due to several factors, including different approaches to manage these patients and the lack of consensus on the definition and classification of alcohol consumption (e.g. recidivism, lapse and relapse) after OLT (Gramenzi et al, 2011).

At present, although predictors of post-OLT recidivism have not been clearly identified (Mackie et al., 2001), a requirement of at least 6 months of total alcohol abstinence before OLT is generally adopted (Neuberger, 2007). However the validity of the ‘6-month rule’ has been questioned and deemed arbitrary (Gramenzi et al., 2011). Moreover, a higher number of alcoholic patients is likely to achieve long-term total alcohol abstinence, if they are followed by a specialized clinical team that can provide a comprehensive evaluation of the

patients' alcohol use or misuse, and plan specific therapeutic approaches, including for example multimodal approaches that include both a psychological and a pharmacological component (Addolorato et al., 2005; O'Shea et al., 2010; EASL, 2012). However, most of the transplant centres use an external team of psychiatrists, social workers and psychologists to evaluate alcohol use in patients undergoing OLT (Kotlyar et al., 2008), and the presence of a specialized Alcohol Addiction Unit (AAU) within a transplant centre is not routinary (Björnsson et al., 2005).

In the Departments of Internal Medicine and Surgery at the Gemelli Hospital (Rome, Italy), patients undergoing OLT received an external psychiatric evaluation for their alcohol use before 2002. Starting from 2002, an Alcohol Addiction Unit (AAU) was formed and its clinical staff works within the Gemelli OLT group to provide the clinical evaluation and management of alcohol use in patients undergoing OLT.

The main goal of the present retrospective study was to evaluate the impact of the presence of an AAU within the Liver Transplantation Centre, on the prevalence of alcohol recidivism in alcoholic patients who underwent OLT. Specifically, these variables were evaluated comparing patients who underwent OLT before or after 2002 (i.e. when the AAU was integrated into the Liver Transplantation Centre). Finally, difference in the rate of alcohol recidivism considering the length of alcohol abstinence before OLT was evaluated.

Patients and Methods

Alcohol Addiction Unit (AAU)

The AAU was formed in 1998 in the Department of Internal Medicine of Gemelli Hospital, Catholic University of Rome. The AAU is dedicated to the clinical evaluation, management and treatment of patients affected by alcohol use disorder. Clinicians working in this unit are board-certified internists, physicians in training and psychologists, with expertise in alcoholism, hepatology and neuroscience. Patients are usually evaluated as outpatients, but hospitalization is available as the clinical situation may dictate. The clinical staff of the AAU joined the Liver Transplantation Centre Group of the Gemelli Hospital in 2002 in order to provide expert clinical support in the evaluation, management and treatment of patients with alcohol use disorder affected by end stage ALD. Staff of the AAU provides a multimodal approach to help patients achieving and maintaining alcohol abstinence; monitors abstinence in those patients on the OLT waiting list; offers therapeutic support to prevent recidivism before and after OLT. Members of the AAU participate to weekly meetings with all the other members of the Gemelli OLT group and play a key role in the final decision of those issues related to patients' alcohol use, such as, for example, including or removing patients from the OLT waiting list, as well as approving in some specific cases the inclusion in the waiting list of patients with < 6 months of total alcohol abstinence. Members of the AAU follow-up patients in the OLT waiting list or under consideration for inclusion on a weekly basis during the first month, then every other week during the second and third month, and finally every month.

Patients

Between 1995 and 2010, a total of 297 patients affected by cirrhosis underwent OLT at the Gemelli Hospital Liver Transplantation Centre. Indications for OLT are shown in figure 1. A total of 92 patients who underwent OLT had a diagnosis of alcoholism; an increase of OLT for alcoholic cirrhosis was observed between 2001–2009 (figure 1). Sociodemographic characteristics of patients are shown in table 1. The medical records of these patients were reviewed retrospectively. The diagnosis of alcoholism was made based on either the DSM-IIIR or the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 3rd or 4th revision). The diagnosis of cirrhosis was made on the basis of histological findings, physical examination, or both, biochemical laboratory tests, and diagnostic imaging. Severity of cirrhosis was classified according to the Child-Pugh and the model of end-stage liver disease (MELD) scores.

Patients (n=92) were divided into two subgroups: patients who were followed-up by the AAU (n=55, 60%); and patients who were not followed-up by the AAU (n=37, 40%) because OLT was performed before 2002.

Treatment

Patients followed-up at the AAU received a multimodal treatment, in particular clinical and medical management, including counselling, and pharmacological treatment. Counselling sessions were provided by the same trained professional staff in individual sessions of up to 30 minutes and focused on craving evaluation, and identification of risk factors for possible relapse (Addolorato et al., 2007). Craving was evaluated by visual analogic scale and/or by the Italian version of the obsessive compulsive drinking scale (OCDS) (Janiri et al., 2004). Attendance to support groups (e.g. Alcoholics Anonymous) was strongly recommended but not mandatory. Pharmacological treatment consisted in the administration of the GABAb receptor agonist baclofen (10 mg t.i.d), a medication that has shown to be useful in reducing alcohol craving and drinking and safe in cirrhotic patients (Addolorato et al., 2007). Baclofen was prescribed to patients who did not show any contraindication, as previously described (Addolorato et al., 2007). In particular, all (n=55) patients seen at the AAU received clinical and medical management including counselling, 24 patients attended support groups, and 9 patients received treatment with baclofen.

Alcoholic patients transplanted before 2002 were seen by a team of consultant psychiatrists with expertise in addiction medicine external in the Liver Transplantation Centre, which provided psychological support every month. The consultant participated monthly to the Gemelli OLT Group meeting. They expressed a formal opinion on the effective abstinence of patients.

Evaluation of alcohol abstinence before OLT

Abstinence from alcohol was assessed in all patients using a clinical interview based on patients' self-report and interviews with family members (Addolorato et al., 2002; Dumortier et al., 2007). Where reports conflicted, the highest estimate was considered. In case of recidivism, information about the number of standard drinks consumed was collected (a standard drink was considered equal to 12 g of absolute alcohol). The main biomarkers of

alcohol consumption [γ-glutamyltransferase (GGT), Mean Cellular Volume (MCV), Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) >2] were evaluated in all patients, even considering their poor specificity rate in the pre-OLT period (EASL, 2012). Breath alcohol concentration and, starting from 2007, carbohydrate deficient transferrin (CDT) were also evaluated in patients followed at the AAU.

Alcohol Recidivism after OLT

Since total alcohol abstinence is required after OLT, alcohol recidivism was defined as any alcohol intake after liver transplantation (EASL, 2012). Recidivism includes both alcohol relapse and lapse. Alcohol relapse was defined as a daily alcohol intake of more than four drinks or an overall consumption of 14 drinks or more per week during at least 4 weeks (Dumortier et al, 2007). We deemed alcohol lapse as any episode of alcohol consumption not classified as relapse. Alcohol recidivism (lapse and/or relapse) was evaluated at each follow-up visit as described before.

Outcome

The primary outcome of the study was the difference in alcohol recidivism, between patients followed at the AAU since 2002 and those not followed because seen before 2002. Difference in mortality rate was also evaluated between the two groups of patients.

The secondary outcome was the difference in alcohol recidivism between patients with a pre-OLT alcohol abstinence ≥6 months vs. those <6 months in patients followed by the AAU. No patients with abstinence < 6 months were transplanted among those not followed at the AAU.

Statistical analysis

Several techniques were used to analyze the available data. First, a purely descriptive analysis was carried out to summarize each variable studied, both numerical and categorical, through a number of common procedures such as tabular and/or graphical displays and standard measures of data location (mean, quantiles) and dispersion (standard deviation). Moreover, possible relationships among the variables were preliminarily explored by the use of Pearson correlation coefficient (for couples of numerical variables) and contingency tables (in the case of categorical variables). Then, standard two-sample *t*-tests were performed to compare mean values of the various numerical variables for two specific groups of patients, for instance those followed by the AAU and those not followed. In the case of categorical variables, comparisons of proportions (e.g. proportions of deceased patients) between the two groups selected were made by running two-sample tests for the difference of proportions. In order to study further some categorical variables of interest, a logistic regression approach (based on the logit function) was adopted to model the probability of success (for example the probability of recidivism, or that of survival) in relation to a number of possible predictors, both categorical and numerical. Such approach was primarily used to supplement previous analyses based on two-sample tests for proportions; in all these cases, the logistic regression analysis has supported the conclusions derived previously, as reported in the Results section, also adding some valuable information through, for example, the related odds ratios. Finally, the probability of survival for two

groups of primary interest, that is those followed by the AAU and those not followed, was studied through the use of a Kaplan-Meier model, supplemented with results from log-rank tests performed at different times. Conclusions from such study are drawn in the Results section, both graphically and analytically.

All the computations needed to carry out the various analyses were done by using the free software R (R Development Core Team, 2012).

Results

Among 92 alcoholic patients who underwent OLT, 22 (23.9%) patients showed alcohol recidivism after OLT, 22 (23.9%) patients died after OLT, 2 (2.1%) patients were lost-to-follow-up. Characteristics of alcohol abuse in recidivistic and non-recidivistic patients are reported in table 2 and the main causes of death are reported in table 3.

There were no differences in the mean age, mean MELD score, mean pre-OLT length of alcohol abstinence and mean alcohol intake before OLT between deceased and survived patients.

Analyzing variables before OLT, there was an inverse correlation between duration of alcohol abuse and survival time after OLT (95% CI: −0.62: −0.17; p=0.002). There was an inverse correlation between MELD score and survival time after OLT (95% CI: −0.67: −0.33; p=0.000001). No significant correlation between MELD score and alcohol intake (p=0.128) was found.

There was no significant correlation between the duration of alcohol abuse and MELD score (p=0.707), alcohol intake (p=0.543), pre-OLT length of alcohol abstinence (p=0.808).

Impact of AAU on OLT-related outcomes

Of the 55 patients followed at the AAU since 2002, 9 (16.4%) patients had alcohol recidivism, one (1.8%) patient was lost-to-follow-up and 8 (14.5%) patients died after OLT.

Of the 37 patients who were seen before 2002, thus not followed-up at the AAU, 13 (35.1%) patients had alcohol recidivism, one (2.7%) patient was lost-to-follow-up and 14 (37.8%) patients died after OLT.

Use of t-tests showed no differences between the two groups regarding the mean age, mean MELD score, mean time of abstinence before OLT and mean alcohol intake (table 4).

A two-sample test for the difference of proportions revealed that, comparing the two groups of patients, those followed at the AAU showed a significantly lower prevalence of alcohol recidivism (16.4% vs. 35.1%; p=0.038) after OLT; this difference remained statistically significant also after excluding the 18 deceased patients (7 among the patients followed by the AAU and 11 among the remaining patients) together with the 2 drop-out patients (1 in the AAU group and 1 in the other one) (19.1% vs 52%; p=0.005) (figure 2).

A subsequent logistic regression analysis reinforced this conclusion, showing the impact of the AAU on the probability of recidivism; in fact, patients followed at the AAU showed a significantly lower probability to have alcohol recidivism (OR: 0.23; p=0.007) when compared to patients not followed.

Moreover, patients followed at the AAU showed, through a test for the difference of proportions, a significantly lower prevalence of death with respect of those patients who were not followed-up at the AAU (14.5% vs. 37.8%; p=0.01). Logistic regression confirmed that patients followed by AAU showed a significantly lower probability to die after OLT with respect to patients not followed (OR: 0.28; p=0.013).

The analysis by the Kaplan-Meier model is summarized in figure 3a, where estimated survival probability curves are plotted for each of the two groups of patients, those followed at the AAU and those not followed. A visual inspection of this plot suggests that the two curves tend to clearly diverge until the time of 2000–2200 days, equivalent to about 5–6 years. Firmer conclusions are drawn by performing formal log-rank tests for different times of interest, as reported by p values in figure 3a showing the higher estimated survival probability in patients followed at the AAU. Further insights are given from figure 3b, which displays the difference of the estimated survival probabilities of the two groups of patients, along with the related confidence bands; clearly, this supplemental plot gives results consistent with those provided by the previous analyses.

Finally, patients followed at the AAU were divided into two groups on the basis of the pre-OLT length of alcohol abstinence, using 6-month as the cut-off. In order to study alcohol recidivism properly, the 2 patients with missing abstinence time, together with 7 deceased patients and a single drop-out were excluded from the analysis, resulting in a final group of 45 patients. A total of 19 patients (42.2%) showed a pre-OLT length of alcohol abstinence <6 months (4.10±1.66 months) while 26 patients (57.8%) showed an pre-OLT length of alcohol abstinence ≥6 months (23.00±15.96 months). There were no significant differences in term of alcohol recidivism [4/19 (21.1%) vs. 4/26 (15.4%); p=0.623] after OLT between the 2 groups (figure 4). This conclusion was supported by a logistic regression analysis, showing no significant impact of alcohol abstinence time before OLT on alcohol recidivism (p=0.624), after OLT. Moreover, a two-sample test for proportions showed no significant difference in mortality after OLT between the two groups [3/22 (13.6%) vs. 4/31 (12.9%); p=0.94] (figure 4). In this case, 2 patients with missing abstinence time were excluded from the total group of patients followed in the AAU.

Of the 9 patients treated with baclofen, none showed alcohol recidivism after OLT. There were no differences in terms of mean age, mean MELD score, mean alcohol intake, pre-OLT length of alcohol abstinence between patients who received baclofen and those who did not receive the drug.

Patients with co-infection(s) and complications

Of the 92 alcoholic patients, 33 (35.9%) also had a diagnosis of chronic viral infection. In particular, 22 (23.9%) patients presented with HCV infection, 7 (7.6%) with HBV infection, and 4 (4.3%) with HBV and HCV co-infection.

A total of 13 (14.1%) alcoholic patients were complicated by Hepatocellular Carcinoma (HCC); of these, 4 (4.3%) had HCV coinfection and 1 (1.1%) had HBV coinfection. All HCC patients met Milan's criteria for eligibility to OLT.

Two-sample t-tests revealed that patients affected by chronic viral infection, and in particular those affected by HCV, showed a significantly lower duration of alcohol abuse (p=0.044; p=0.0397 respectively), a significantly lower age (p=0.044; p=0.029 respectively) and a significantly higher quantity of mean alcohol intake (p=0.059; p=0.035 respectively) with respect to patients with only an alcoholic aetiology of the liver disease. No other significant relationships emerged between viral infections and/or HCC and the other variables considered.

Discussion

The present study shows that the presence of an Alcohol Addiction Unit within a Liver Transplant Centre reduces alcohol recidivism in alcoholic patients after OLT.

Many issues on the appropriateness of OLT in alcoholic patients are still present. Most of the concerns are related to the risk of alcohol recidivism often reported as the major argument against OLT eligibility (Gramenzi et al., 2011; Neuberger et al., 2007; Burra et al., 2000). Data from literature show, however, a high variability of recidivism prevalence (Gramenzi et al., 2011; Burra et al., 2010; Björnsson et al., 2005) and this variability could be related to the different management of patients, provided by different professional figures and to different referral settings (i.e. hepatology, surgery or psychiatry outpatients).

In the present study, the prevalence of alcohol recidivism after OLT in our Liver Transplantation Centre was 35.1% (50.0% excluding deceased patients) until 2001; this percentage is consistent with data from other Italian and European Liver Transplant Centre (Burra et al., 2000; Burra et al., 2010). The establishment of an AAU within our Liver Transplant Centre determined both an increase of the number of OLTs for alcoholic cirrhosis (figure 1) and a significant reduction of the prevalence of alcohol recidivism after OLT. The presence of a specialized staff as in the AAU might have reduced surgeons' reluctance to transplant alcoholic patients, and provided patients with a specific clinical support able to increase their ability to achieve and maintain the total alcohol abstinence.

There are several aspects related to alcohol recidivism after OLT that play a very important role. In fact, alcohol recidivism affects survival of these patients (Faure et al., 2012) due to hepatic damage and pulmonary and pancreatic complications (Lucey et al., 1997; Pageaux et al., 2003). Alcohol recidivism is also associated with a higher incidence of graft loss due to poor compliance to the immunosuppressive therapy (Pageaux et al., 2003), and to an increased number of complications that require hospitalization and may even determine the loss of the transplanted organ (Lucey et al., 1997). All of these factors result in a significant increase of social and economic costs. Furthermore, alcohol recidivism could be a reason of public disquiet over distribution of donor livers to those with ALD and could affect organ donation (Neuberger, 2007) worsening the organ shortage and lowering the priority for access to OLT for patients with ALD.

Several approaches have been evaluated to reduce alcohol recidivism in alcoholic patients after OLT, but there is no a standardized approach, and available data are few and often controversial. In some liver transplant centres, alcoholic patients are encouraged to attend support groups, even if data on the efficacy of such treatment in this cluster of patients are at present lacking. In a pilot study, Georgiou and colleagues (Georgiou et al., 2003) reported that psychosocial interventions could be a valid approach to support motivation in these patients. However, this study was conducted on a limited number of patients and the efficacy of this intervention on alcohol recidivism after OLT was not evaluated. Bjornsson and colleagues (Bjornsson et al., 2005) evaluated the impact of the management of alcoholic patients by addiction psychiatrists, social workers and tutors in the period before OLT, and reported a 22% prevalence of alcohol recidivism in the treated group vs. 48% in the untreated group (Bjornsson et al., 2005). Erim and colleagues (Erim et al., 2006) evaluated the impact of psycho-educational therapy in this cluster of patients, showing low rates of alcohol recidivism. However alcohol abstinence was only evaluated using breath alcohol concentration (BAC) determinations (Erim et al., 2006). In a recent trial, Weinrieb and colleagues (Weinrieb et al., 2011) evaluated the impact of motivational therapy vs. standard treatment (counselling or support groups) in alcoholic patients waiting for OLT. A modest effect of the motivational treatment was shown (Weinrieb et al., 2011).

The presence of an Alcohol Addiction Unit within a Liver Transplantation Centre is not usual, but our study suggests its utility in reducing alcohol recidivism after OLT in alcoholic patients.

In the present study, a significantly lower prevalence of mortality was found in patients followed at the AAU with respect to patients not followed at the AAU. This observation could be related to several factors not related to the presence of AAU, i.e. the improvement of surgical techniques, the increased practice with liver transplantation procedures, intensive care management and immunosuppressive therapies over time, even considering that some deaths happened peri-operatively. However, this result could be at least partially related to the decrease of alcohol recidivism in patients followed at the AAU, a conclusion consistent with previous data showing that alcohol relapse impairs long-term post-OLT survival (Cuadrado et al., 2005; Faure et al., 2012).

An analysis of the subgroup of patients followed at the AAU indicated no significant differences in alcohol recidivism, and mortality between patients transplanted with a pre-OLT length of alcohol abstinence <6 months or ≥6 months.

At present, the “6-month rule” is generally used in order to reduce the risk of recidivism risk after OLT (Lucey et al., 1997; Lucey et al., 1998); however this approach has been questioned and deemed arbitrary and not-evidence-based (Gramenzi et al., 2011). Some studies report that reducing this time could increase the recidivism risk after OLT (Tandon et al., 2009), therefore patients with an alcohol abstinence time shorter than 6 months (including patients affected by alcoholic hepatitis) should be excluded from transplantation programmes. There is growing evidence, however, that the “6-month rule” is unable to predict alcohol recidivism risk (Kelly et al., 2006; DiMartini et al., 2006). Alcohol abstinence time usually produces an improvement of liver function and a period of total

alcohol abstinence is a mandatory criterion for the eligibility to OLT. However, in some patients, the overall clinical status does not allow for a 6 months waiting time, i.e. patients with severe alcoholic hepatitis (Mathurin et al, 2011; Brown, 2011) or advanced liver disease. With the limits of the retrospective design, the present study suggests that the pre-OLT abstinence time could be shortened, at least in selected patients followed-up in a specialized AAU. In this regard, some reports already support this hypothesis (Neuberger, 2007; Lucey, 2002) and some investigators suggest that the cut-off could be reduced to >3 months in selected patients (Hartl et al., 2011). Future prospective studies are needed, however, to shed light on this point.

A small sub-group of patients received a pharmacological treatment with baclofen as part of the multimodal treatment provided at the AAU. No patients in this subgroup showed alcohol recidivism after OLT. This preliminary observation is consistent with the ability of baclofen to reduce alcohol craving and drinking and promote abstinence in patients with severe liver disease (Addolorato et al., 2007), and tentatively suggest the use of baclofen in alcoholic patients undergoing OLT. Larger prospective studies will be needed to evaluate the potential use of baclofen before and after OLT to prevent alcohol recidivism.

In conclusion, the present study, with the limitations of the retrospective monocentric design and of the small sample size, indicates that the presence of an Alcohol Addiction Unit within a liver transplantation centre reduces alcohol recidivism after OLT. Based on this observation, future prospective multicenter studies using a validated and standardized method are needed to further explore this clinical approach that has the potential to significantly reduce the social and economic costs of alcohol recidivism after OLT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol. 2002; 37:504–508. [PubMed: 12217947]

Addolorato G, Abenavoli L, Leggio L, Gasbarrini G. How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review. Neuropsychobiol. 2005; 51:59–66.

Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007; 370:1915–1922. [PubMed: 18068515]

Addolorato G, Mirijello A, Leggio L, Ferrulli A, Landolfi R. Management of alcohol dependence in patients with liver disease. CNS Drugs. 2013; in press. doi: 10.1007/s40263-013-0043-4

Björnsson E, Olsson J, Rydell A, Fredriksson K, Eriksson C, Sjöberg C, Olausson M, Bäckman L, Castedal M, Friman S. Long-term follow-up of patients with alcoholic liver disease after liver

transplantation in Sweden: impact of structured management on recidivism. Scand J Gastroenterol. 2005; 40:206–216. [PubMed: 15764153]

Brown RS Jr. Transplantation for alcoholic hepatitis--time to rethink the 6-month “rule”. N Engl J Med. 2011; 365:1836–1838. [PubMed: 22070481]

Burra P, Mioni D, Cillo U, Fagiuoli S, Senzolo M, Naccarato R, Martines D. Long-term medical and psycho-social evaluation of patients undergoing orthotopic liver transplantation for alcoholic liver disease. Transpl Int. 2000; 13:s174–178. [PubMed: 11111991]

Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, Neuberger J. ELITA; ELTR Liver Transplant Centers. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant. 2010; 10:138–148. [PubMed: 19951276]

Cuadrado A, Fábrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl. 2005; 11:420–426. [PubMed: 15776421]

DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, Fung JJ, Fontes P. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl. 2006; 12:813–820. [PubMed: 16528710]

Dumortier J, Guillaud O, Adham M, Boucaud C, Delafosse B, Bouffard Y, Paliard P, Scoazec JY, Boillot O. Negative impact of de novo malignancies rather than alcohol relapse on survival after liver transplantation for alcoholic cirrhosis: a retrospective analysis of 305 patients in a single center. Am J Gastroenterol. 2007; 102:1032–1041. [PubMed: 17313502]

Erim Y, Beckmann M, Tagay S, Beckebaum S, Gerken G, Broelsch CE, Senf W. Stabilisation of abstinence by means of psychoeducation for patients with alcoholic liver disease awaiting liver transplantation. Psychosom Med Psychoter. 2006; 52:341–357.

European Association for the Study of the Liver (EASL). Clinical Practice Guidelines: Management of Alcoholic Liver Disease. J Hepatol. 2012; 57:399–420. [PubMed: 22633836]

Faure S, Herrero A, Jung B, Duny Y, Daures JP, Mura T, Assenat E, Bismuth M, Bouyabrine H, Donnadieu-Rigole H, Navarro F, Jaber S, Larrey D, Pageaux GP. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. J Hepatol. 2012; 57:306–312. [PubMed: 22521352]

Georgiou G, Webb K, Griggs K, Copello A, Neuberger J, Day E. First report of a psychosocial intervention for patients with alcohol-related liver disease undergoing liver transplantation. Liver Transpl. 2003; 9:772–775. [PubMed: 12827568]

Gramenzi A, Gitto S, Caputo F, Biselli M, Lorenzini S, Bernardi M, Andreone P. Liver transplantation for patients with alcoholic liver disease: an open question. Dig Liver Dis. 2011; 43:843–849. [PubMed: 21550324]

Hartl J, Scherer MN, Loss M, Schnitzbauer A, Farkas S, Baier L, Szecsey A, Schoelmerich J, Schlitt HJ, Kirchner GI. Strong predictors for alcohol recidivism after liver transplantation: non-acceptance of the alcohol problem and abstinence of <3 months. Scand J Gastroenterol. 2011; 46:1257–1266. [PubMed: 21815863]

Janiri L, Calvosa F, Dario T, Pozzi G, Ruggeri A, Addolorato G, Di Giannantonio M, De Risio S. The Italian version of the Obsessive-Compulsive Drinking Scale: validation, comparison with the other versions, and difference between type 1- and type 2-like alcoholics. Drug Alcohol Depend. 2004; 74:187–195. [PubMed: 15099662]

Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley J, McCaughan GW, Haber PS. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol. 2006; 41:278–283. [PubMed: 16476764]

Kotlyar DS, Burke A, Campbell MS, Weinrieb RM. A critical review of candidacy for orthotopic liver transplantation in alcoholic liver disease. Am J Gastroenterol. 2008; 103:734–743. [PubMed: 18081918]

Lim JK, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. Liver Transpl. 2004; 10:S31–38. [PubMed: 15382288]

Lucey MR, Carr K, Beresford TP, Fisher LR, Shieck V, Brown KA, Campbell DA, Appelman HD. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. Hepatology. 1997; 25:1223–1227. [PubMed: 9141441]

Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keefe EB, Kneteman NM, Lake JR, Martin P, Rakela J, Shiffman ML, So S, Wiesner RH. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Transplantation. 1998; 66:956–962. [PubMed: 9798717]

Lucey MR. Is liver transplantation an appropriate treatment for acute alcoholic hepatitis? J Hepatol. 2002; 36:829–831. [PubMed: 12044536]

Mackie J, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, Neuberger J. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. Liver Transpl. 2001; 7:418–427. [PubMed: 11349262]

Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011; 365:1790–1800. [PubMed: 22070476]

Neuberger J. Public and professional attitudes to transplanting alcoholic patients. Liver Transpl. 2007; 13:S65–68. [PubMed: 17969090]

O'Shea RS, Dasarathy S, McCullough AJ. Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. Hepatology. 2010; 51:307–328. [PubMed: 20034030]

Pageaux, Gp; Bismuth, M.; Perney, P.; Costes, V.; Jaber, S.; Possoz, P.; Fabre, JM.; Navarro, F.; Blanc, P.; Domergue, J.; Eledjam, JJ.; Larrey, D. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? J Hepatol. 2003; 38:629–634. [PubMed: 12713874]

Pessione F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int. 2003; 23:45–53. [PubMed: 12640727]

R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2012. http://www.R-project.org/

Tandon P, Goodman KJ, Ma MM, Wong WW, Mason AL. A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation. Am J Gastroenterol. 2009; 104:1700–1706. [PubMed: 19471253]

Tilg H, Day CP. Management strategies in alcoholic liver disease. Nat Clin Pract Gastroenterol Hepatol. 2007; 4:24–34. [PubMed: 17203086]

Varma V, Webb K, Mirza D. Liver transplantation for alcoholic liver disease. World J Gastroenterol. 2010; 16:4377–4393. [PubMed: 20845504]

Weinrieb, Rm; Van Horn, Dh; Lynch, Kg; Lucey, MR. A Randomized, Controlled Study of Treatment for Alcohol Dependence in Patients awaiting Liver Transplantation. Liver Transpl. 2011; 17:539–547. [PubMed: 21506242]

Yates WR, Labrecque DR, Pfab D. The reliability of alcoholism history in patients with alcohol-related cirrhosis. Alcohol Alcohol. 1998; 33:488–494. [PubMed: 9811201]

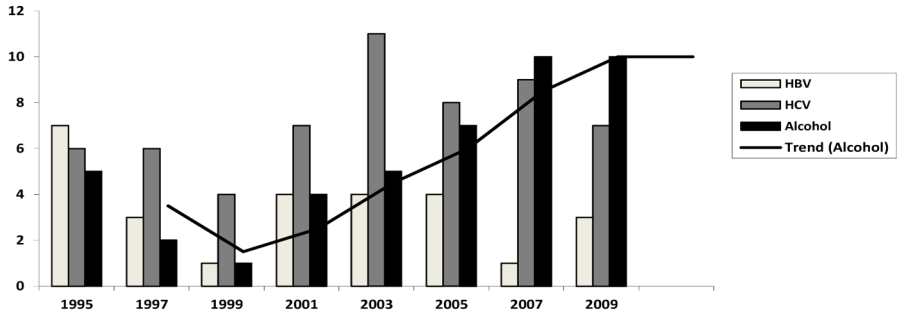

Figure 1.

Number of patients, divided by etiologies, who underwent liver transplantation between 1995 and 2009. Trend of transplantation for alcoholic cirrhosis.

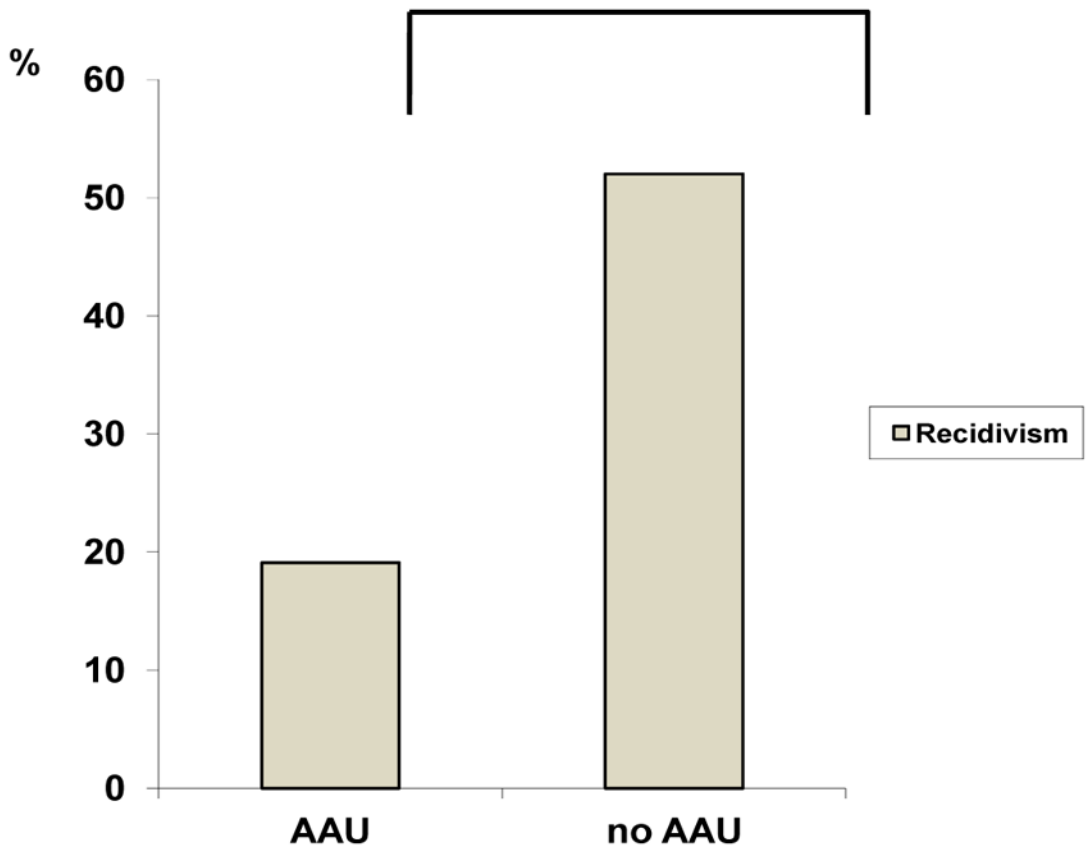

Figure 2.
Percentage of patients who showed recidivism after liver transplantation, and statistical comparison (p=0.005). (AAU= Alcohol Addiction Unit).

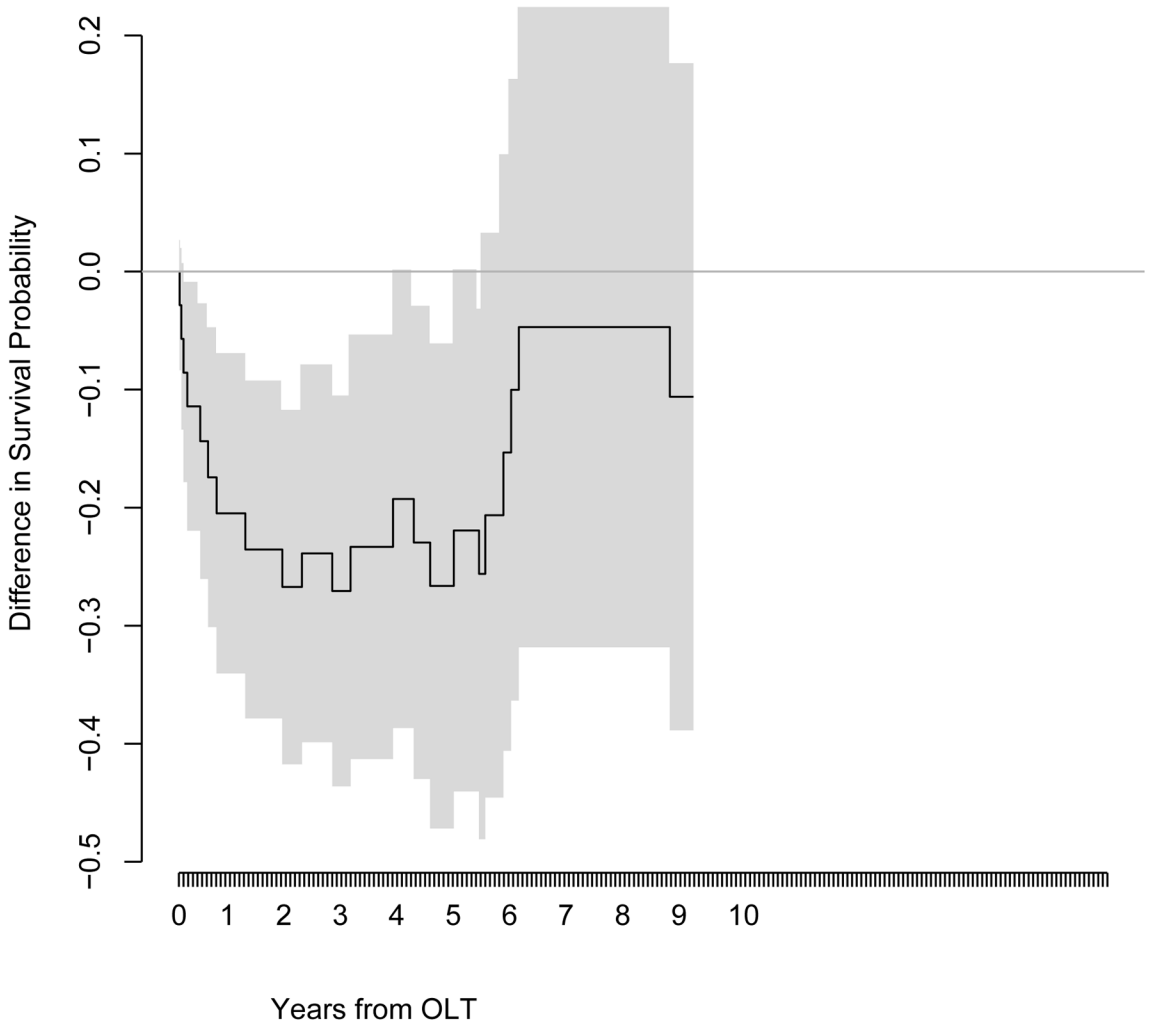

Figure 3.

Kaplan–Meier survival analysis of the two groups of patients, followed and not followed at the Alcohol Addiction Unit.

Figure 3a: Results from Kaplan-Meier analysis. Estimated survival probability curves for patients followed and not followed at the Alcohol Addiction Unit, together with p-values from log-rank tests at different times of observation. (AAU: Alcohol Addiction Unit; OLT: Orthotopic Liver Transplantation).

Figure 3b: Difference in the estimated survival probability for patients followed and not followed at the Alcohol Addiction Unit, along with the related confidence bands. (OLT: Orthotopic Liver Transplantation).

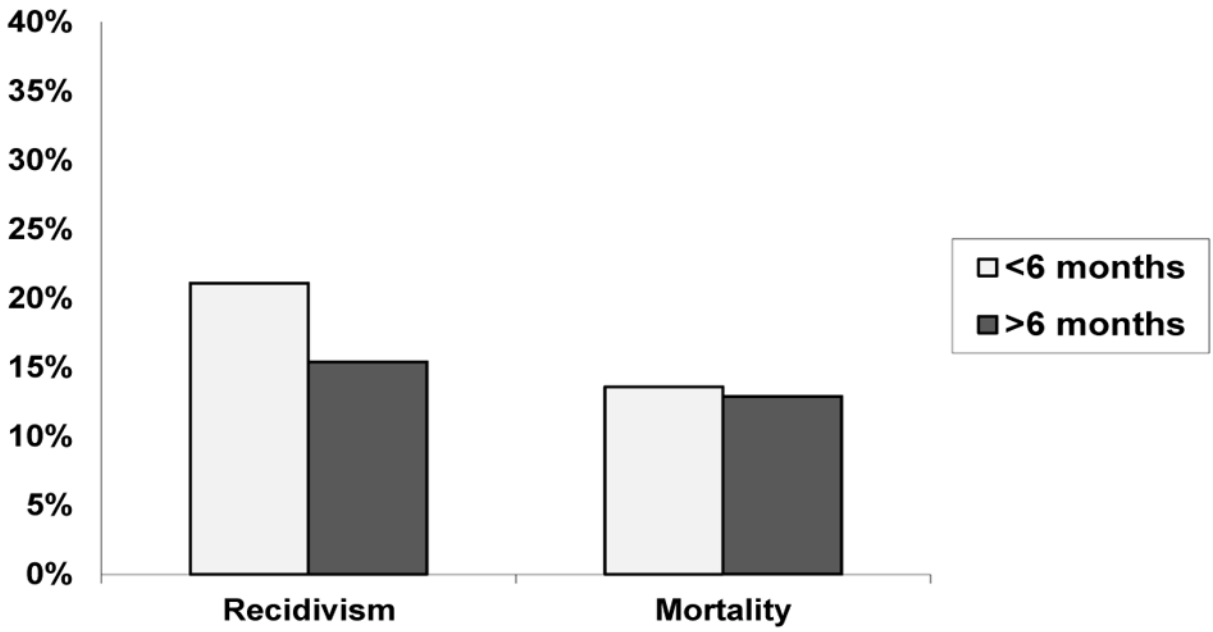

Figure 4.

Percentage of patients, followed at the Alcohol Addiction Unit, who showed recidivism, lapse, relapse and mortality after liver transplantation, grouped on the basis of the pre-transplant length of alcohol abstinence (>/< 6 months). (p=ns).

Table 1

Socio-demographic and clinical characteristics of the 92 patients who underwent liver transplantation with a diagnosis of alcoholism. (HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HCC: HepatoCellular Carcinoma)

Male: n. (%)	82 (89%)
Female: n. (%)	10 (11%)
Age: mean±SD; range	49.39±7.68; 28–69
MELD score: mean±SD; range	18.68±6.93; 8–33
Child-Pugh score: mean±SD; range	9.73±3.12; 5–14
Duration of alcohol abuse: years±SD; range	22.94±10.06; 1–45
Daily alcohol consumption (grams) mean±SD; range	190.54±100.99; 50–550
Family history of alcoholism: n. (%)	5 (5.4%)
Tobacco smoking	51 (55.4%)
Employed	40 (43.5%)
Married	68 (73.9%)
Education (>13 years)	36 (39.1%)
HCV infection	22 (23.9%)
HBV infection	7 (7.6%)
HBV and HCV coinfection	4 (4.3%)
HCC	13 (14.1%)

Table 2

Characteristics of alcohol abuse in recidivistic (lapse or relapse) and non-recidivistic patients. Numerical comparison together with the corresponding p-value.

	No recidivism	Recidivism	p-value
Duration of alcohol abuse (years): mean (SD)	22.88 (10.14)	23.20 (10.27)	0.92
Age (years): mean (SD)	50.16 (7.08)	46.95 (9.10)	0.09
MELD score: mean (SD)	18.60 (7.17)	19.00 (6.13)	0.84
Daily alcohol intake (grams): mean (SD)	193.98 (106.34)	172.22 (67.23)	0.56
Pre-OLT length of alcohol abstinence (months): mean (SD)	17.16 (16.64)	13.37 (10.56)	0.39

Table 3

Causes of death in patients (all pts=22), divided by follow-up at the Alcohol Addiction Unit (AAU: Alcohol Addiction Unit) (no AAU=14; AAU=8).

	All pts.	No AAU	AAU
Cardiac arrest	3	2	1
Sepsis	8	4	4
Neoplasm	4	2	2
Perioperative mortality	4	4	0
HCV recidivism	1	1	0
Hepatic artery thrombosis	1	0	1
Portal Vein Thrombosis	1	1	0

Table 4

Characteristics of alcohol abuse in patients followed and not followed at the Alcohol Addiction Unit. Numerical comparison together with the corresponding p-value. (AAU: Alcohol Addiction Unit).

	No AAU (n.37)	AAU (n. 55)	p-value
Duration of alcohol abuse (years): mean (SD)	18.00 (12.34)	23.46 (9.80)	0.252
Age (years): mean (SD)	47.97 (8.43)	50.34 (7.05)	0.147
MELD score: mean (SD)	17.63 (6.65)	19.11 (7.06)	0.404
Daily alcohol intake (grams): mean (SD)	235.71 (95.54)	184.22 (101.03)	0.209
Pre-OLT length of alcohol abstinence (months): mean (SD)	17.25 (12.89)	15.98 (16.77)	0.743