Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease?

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Keywords
alcohol consumption, alcohol dependence, alcoholic cirrhosis, liver transplantation, relapse.

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Received: 11 May 2005
Revision requested: 8 June 2005
Accepted: 27 July 2005

doi:10.1111/j.1432-2277.2005.00208.x

Summary

Predictive factors for alcoholic relapse after liver transplantation (LT) performed for alcoholic liver disease (ALD) have been assessed in numerous studies, often with contradictory results. The aim of the study was to assess pretransplantation alcohol consumption characteristics on alcoholic relapse after LT. Patients transplanted for ALD for at least 6 months were included. An anonymous questionnaire assessed socio-demographic characteristics, medical history, and alcohol consumption before and after LT. Relapse was defined as any alcohol use after LT. Severe relapse was defined by heavy drinking: more than 21 units/week for males and 14 units/week for females. A total of 61 patients were studied. The mean follow up after LT was 49 ± 34 months. Alcoholic relapse occurred in 32 of 61 patients (52%) and severe relapse in eight of 61 patients (13%). Risk factors for severe relapse were: length of abstinence before LT ($P = 0.0001$), more than one alcohol withdrawal before LT ($P = 0.001$), alcohol dependence ($P = 0.05$), alcohol abuse in first relatives ($P = 0.05$), and younger age ($P = 0.05$). Information on previous alcohol consumption (dependence, number of withdrawals, family history) helps to predict severe relapse after LT in patients with ALD, allowing early awareness and specific postoperative care.

Introduction

In 1988, Starzl *et al.* [1], demonstrated that alcoholic cirrhosis is a good indication for liver transplantation (LT). Since this first publication, alcoholic liver disease (ALD) became a leading cause of LT and now represents the second common indication for LT in the USA and in Europe [2]. However, one major issue is the likelihood of relapse, because it is the possibility of recurring alcohol abuse after LT that separates patients with ALD from those with other forms of chronic liver disease. Alcohol consumption after LT occurs frequently and thereby, many studies assessed the risk factors of alcoholic relapse after LT starting from the patient characteristics before the LT [3–15]. The mean incidence of relapse is among one-thirds of the patients [16], but the published studies have given very variable results that ranged from <10% until more than 90% [17,18]. One of the main reasons explaining these very important variations is probably the lack of consensus about the definition of relapse which could be define by drinking only one unit or by a regular and huge consumption with histologic damage.

The impact of these studies on clinical practice could be discussed because until recently short-term outcome studies and United Network for Organ Sharing (UNOS) database have consistently showed that patients with ALD

have similar graft and patient survival outcomes as patients who undergo transplantation for non-ALD [16,19]. However, it seems that mild relapse and severe relapse correspond to very different patient groups [20], with significant risk to develop liver damage for the latter group. It appears recently that prolonged exposure to tobacco and alcohol could worsen the survival beyond 5–7 years in alcoholic cirrhotic transplants [21]. Using the follow up of 4000 patients who underwent LT, Jain and Jung recently confirmed these results. In their cohort, the survival of alcoholic patients was comparable with nonalcoholic recipients in the first 7 years, but significantly decreased thereafter [22].

Under these conditions, the main goal is not actually to improve patient selection procedures, but rather to detect the severe relapsers who are individuals with poorer survival, to targeting specific interventions after LT [2]. It is also necessary to improve the monitoring strategy used preoperatively to assess alcoholic disease [23]. Indeed, alcoholic transplant recipients are not a homogenous population but could be alcohol abusers, alcohol-dependent patients, or patients suffering from associated psychiatric disorders [24,25]. Although the latter point could be an important confusing factor for the relapse studies, the characteristics of alcohol consumption are generally poorly assessed.

Therefore, the aim of this study was to assess the risk factors of relapse and severe relapse after LT, including previously reported major factors, and the characteristics of pretransplant alcohol consumption behavior.

Patients and methods

This retrospective study was performed in our liver transplant unit, from June 2001 to June 2002. We included all consecutive patients seen at the outpatient clinic for at least 6 months after transplantation for pure ALD. The exclusion criteria were: psychiatric disorder, making the interview unreliable; patient refusing to take part in the study; other causes of liver disease. These other causes were: nonalcoholic steatohepatitis; chronic viral hepatitis B or C; autoimmune hepatitis; primary or secondary biliary cirrhosis; primary sclerosing cholangitis; hemochromatosis; Wilson's disease.

Patients were asked about their alcohol consumption both before and after LT. An anonymous questionnaire was completed by an independent interviewer (psychologist) not belonging to the transplant team, and who did not ensure the follow up of the liver transplant recipients. Various items were sought by the questionnaire: sociodemographic characteristics (age at the time of the LT; sex; school degree; professional status; social instability as defined by frequent changes of employment, marital status or place of residence); tenant or owner of their housing; marital status (single, married, divorced, widowed). Personal and family medical history included: history of drug-addiction (oral, intravenous, sniff); diagnosis of psychiatric disorders; hospitalization or outpatient follow up in a psychiatric center; suicide attempt; psychiatric treatment; chronic alcohol consumption among first-degree relatives.

The questions about alcohol consumption before the LT addressed: age of the first alcohol drinking; age of alcohol withdrawal; total duration of alcohol consumption; number of alcohol withdrawals with institutionalized treatment; duration of abstinence; number of alcohol units per week; mean time of the first alcohol absorption during the day; diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual (DSM)-IV criteria. Questions about alcohol consumption after the LT addressed: alcohol consumption or not; time of the relapse (if any) after the LT; number of alcohol units per week. The patients were classified according to their alcohol consumption after LT: abstinence defined as no alcohol use; relapse defined as any alcohol use. Among the relapsers, we studied a subgroup of severe relapsers (heavy drinkers) defined as more than 21 units/week for males and more than 14 units/week for females.

Statistics

For categorical variables, the percentage comparisons were made with the chi-squared analysis, or with Fisher's correction where the chi-squared test was not valid. Except for the age of LT, the distribution of the variables was not normal. So, descriptive statistics were made using median, range, mean values and standard deviations. These variables of relapse (partial and severe) were compared by a nonparametric method, the Mann–Whitney test. Correlations between numerous variables were performed using Spearman rank coefficient (nonparametric) method. For statistical analysis, the statistical software SAS version 6.12/UNIX (SAS Institute, Cary, NC, USA; PROC FREQ, PROC UNIVARIATE, PROC NPAR1WAY, PROC LOGISTIC) was used.

Results

From 1990 to 2002, 282 patients underwent LT in our center. Among them, 171 patients were transplanted for alcoholic cirrhosis. All patients seen at the outpatient clinic and fulfilling the inclusion criteria during the inclusion period agreed to complete the anonymous questionnaire, which represented 61 patients: 46 males and 15 females (mean age 54 ± 7 years). No patient in our institution had alcohol relapse that may have been responsible for early graft loss and death in the first 6 months.

Before LT

The social characteristics were as follows: employment: 23 patients (38%); social instability: 11 patients (18%). Twenty-seven patients (47%) were tenants while 30 (53%) were owners of their housing. The marital status was: single people and widowers: eight of 61 (13%); divorced 15 of 61 (25%); married 38 of 61 (62%). There was intravenous drug-addiction in four patients (6.7%), one or more depressive episodes in 16 cases (27%), one or more suicide attempts in five cases (8.3%). A family history of excessive alcohol consumption was described by 24 patients (40%). Alcohol dependence was diagnosed in 31 of the 61 patients (52%) according to the DSM-IV criteria, whereas the other 30 patients were considered as abusers without dependence (48%).

After LT

The mean duration of the follow up after the LT was 49 ± 34 months (range: 6–126; Fig. 1). After the LT, 32 of 61 patients (52%) consumed at least one unit of alcohol (relapsers). Eight of 61 patients were considered as severe relapsers: the mean consumption was 67 units/week (range: 34–140). In these eight patients, liver biopsies were performed because of abnormal liver enzyme tests. The histologic examination revealed the following lesions: steatosis in three cases; nonalcoholic steatohepatitis in three cases; acute alcoholic hepatitis and acute rejection related to a poor compliance with the immunosuppressive treatment in one case; cirrhosis in one case. The graft biopsies carried out among patients who did not have severe relapse did not show any abnormalities suggestive of acute alcoholic hepatitis or cirrhosis. Six of the eight patients with severe relapse accepted a specific inpatient antialcoholic treatment: two of these six patients are currently abstinent, and two have a very moderate consumption.

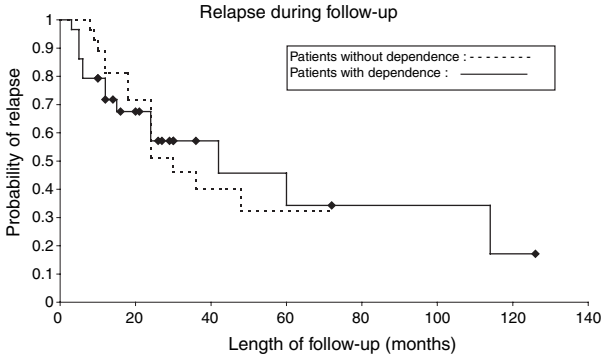

Figure 1 Follow up after the liver transplantation and relapse rate of alcohol consumption.

Risk factors for alcoholic relapse after LT

Three risk factors correlated significantly with relapse in univariate analysis: the mean delay from the LT ($P < 0.002$), a longer time increasing the risk; the time of the first alcohol consumption in the daytime (0.03), mean time of the beginning was 10.8 ± 3 AM for patients who relapsed vs. 12.2 ± 3 for those who did not; more than one alcoholic withdrawal before the LT ($P = 0.02$; Table 1). The relapse risk according to the time of the first alcohol intake was 68% for a first glass of alcohol between 6 and 10 AM, 57% between 11 and 12 AM, 41% between 0 and 1 PM, 33% between 2 and 8 PM. Two factors were significant in multivariate analysis: the delay from LT [OR/year of follow up 1.45 (95% CI: 1.13–1.86), $P = 0.002$] and more than one withdrawal before LT [OR 6.6 (95% CI: 1.6–36), $P < 0.01$].

Risk factors of severe relapse after LT

Eight of the 61 patients had a severe relapse after LT (13%; Table 2). Five risk factors of severe relapse were significant in univariate analysis (Table 2): shorter length of abstinence before the LT ($P = 0.001$); more than one alcohol withdrawal before the LT (0.001); dependence on alcohol before the LT ($P = 0.05$); existence of alcohol abusers in first-degree relatives ($P = 0.05$), and younger age at the time of LT ($P = 0.05$). There was a significant correlation between alcohol dependence and two other variables: more than one alcohol withdrawal before LT ($P = 0.0001$) and short duration of the abstinence before LT ($P < 0.01$).

Discussion

Alcohol relapse after LT for ALD is an ethical and medical issue. In our center, alcoholic cirrhosis has been recognized as a good indication for LT for a long time, and represents about 50% of all LTs. Most studies have failed to predict drinking behavior after transplant. We have previously emphasized the need to distinguish the different patterns of alcohol consumption after LT [20]. This study indicated that among patients who relapsed, only those who resumed heavy alcohol consumption had severe graft injury and death risk related to alcohol. Thus, one of the unresolved questions is whether or not the risk factors of relapse are similar, whether the alcohol consumption is mild or heavy. Moreover, it recently appeared that chronic alcohol consumption after LT significantly decreases the long-term survival [22]. Thus, the main goal is actually to detect the severe relapsers and to propose a specific treatment to these patients.

Table 1. Risk factors for relapse after liver transplantation (LT).

Risk factor	No relapse, *n* (%)	Relapse, *n* (%)	*P*-value (univariate analysis)	OR (95% CI)	*P*-value (multivariate analysis)
Mean delay from LT (months)	34 ± 30	61 ± 32	<0.002		0.002
More than one withdrawal	3/29 (10)	11/30 (37)	<0.02	6.6 (1.6–36)	<0.01
Time of the first alcohol intake (am)	12.2 ± 3	10.8 ± 3	0.03		
Male gender	19/29 (66)	27/32 (84)	0.09		
Age at the time of LT (years)	49 ± 8	50 ± 6	0.38		
Employment	12/29 (41)	10/31 (32)	0.46		
Social instability	4/27 (15)	6/31 (19)	0.65		
Owner of housing	14/28 (50)	17/30 (57)	0.61		
History of drug-addiction	2/29 (7)	2/32 (6)	0.92		
History of depressive episodes	9/29 (31)	8/32 (25)	0.6		
Alcohol abuse in first-degree relatives	11/29 (38)	14/32 (44)	0.64		
Length of alcohol consumption (years)	23 ± 11	26 ± 11	0.28		
Length of abstinence (months)	19 ± 14	20 ± 26	0.92		
Alcohol dependence before LT	15/29 (52)	16/32 (50)	0.89		

Table 2. Risk factors for severe relapse after liver transplantation (LT).

	No severe relapse, *n* (%)	Severe relapse, *n* (%)	*P*-value
Length of abstinence before LT (months)	21 ± 22	6 ± 3	0.0001
More than one withdrawal	7/51 (14)	7/8 (88)	0.001
Alcohol dependence before LT	24/53 (45)	7/8 (88)	0.05
Alcohol abuse in first-degree relatives	19/53 (36)	6/8 (75)	0.05
Age at the time of LT (years)	51 ± 7	45 ± 4	0.05

In the present study, 52% of patients relapsed after LT, and 13% were considered as heavy relapsers. The risk factors in these two groups were not similar. When all were considered, whatever their level of alcohol consumption, three risk factors were identified, two of which remained significant after multivariate analysis: delay from LT, more than one alcohol withdrawal before LT. The delay from LT is a well known risk factor [26,27]. Indeed, the longer the time from LT, the more patients are likely to have consumed at least one unit. This confirms that long-term follow up is necessary to assess drinking behavior after LT [26,27]. The time of the first alcohol intake during the day seems to be an interesting criterion, although only significant in univariate analysis. For the included patients, the relapse risk was inversely proportional to the time of the first alcohol intake. For instance, the risk of relapse was nearly 70% in the group of patients who begin to drink between 6 and 10 AM.

The patients with severe relapse are probably the most important group to study because of the risk of morbidity due to alcohol consumption. Five significant pretransplant risk factors were isolated by univariate analysis. Length of abstinence before LT is frequently discussed, with some heterogenous results. For many teams, a 6-month cut-off is a significantly predictive factor of relapse [9–11,14,15]. For others, the 6-month cut-off is poorly predictive [4,5,25,28,29], and can be fatal for patients with a short life-expectancy [30]. In our series, as well as Foster *et al.*'s [11], the length of abstinence before LT was a significant factor, even if the 6-month cut-off was not discriminate. Moreover, our results are very similar to those of Foster *et al.* [11]: the mean length of abstinence was 5.6 months in the latter study for severe relapsers (6 months in the present study), against 22 months for the other patients (21 months in the present study). The number of withdrawals before LT is described as a relapse risk factor for the first time. This was correlated to alcohol dependence in severe relapser patients. Although it is common practice to evaluate alcohol dependence in patients on the waiting list with the DSM-IV criteria [31], this criteria is generally not assessed in studies about relapse after LT. Indeed, the criteria for LT are related to hepatic function and not to the degree of dependence. In the present study, seven of eight patients who experienced a severe relapse were dependent before LT, according to the DSM-IV criteria, demonstrating the importance of this factor. The number of withdrawals appeared to be significantly associated with dependence, because among the seven dependent patients before LT who had a severe relapse, six underwent several

withdrawals. Alcohol abuse in first-degree relatives was also a significant factor, which may be compared with the familial history previously evaluated [11]. Young age at the time of LT was a risk factor for severe relapse in our patients and in earlier studies [11,15]. Similar results have been reported in nontransplanted patients [32], probably because alcoholism in young adults is often associated with early personality difficulties and unsatisfactory school experiences [33]. Thus, the youngest patients must be followed very closely because they represent a subgroup of higher risk of relapse and are probably more susceptible to a severe fibrosis relapse. Interestingly, in the patients of Foster *et al.*, who developed terminal hepatic insufficiency, the relapsers were significantly younger than those who were not [11].

One of the bias of this retrospective study could be an underestimation of the amount of alcohol consumed as well as the degree of alcohol dependence before the LT. The risk is probably more important among patients having been transplanted many years before the study. In addition to the 'memory bias, we must take into account the difficulty to speak about alcohol consumption to the transplant team [18]. Therefore, the interview was performed by an independent investigator for this study who compare (when it was possible) the patient assertions to the family report, the doctor reports, and the medical file.

On the contrary, almost all of the relapse studies were retrospective [2] and therefore allowed the inclusion of a significant number of patients and a long follow up, two important criteria to assess risk of relapse [26,27]. Moreover, the patients included did not have any cognitive disorder at the time of the investigation, although their statements during the pretransplant training course were not very reliable, often because of hepatic encephalopathy [34].

Alcohol relapse after LT is not always synonymous of graft dysfunction [15]. Furthermore, it is difficult to follow all patients exhaustively. Therefore, it seems preferable to concentrate the monitoring on those likely to have serious complications associated with serious chronic consumption. A complex scale allowing a rational approach for patient selection [23] was tested, but unfortunately, it did not appear very predictive of relapse [5]. We need simple tests that are easy to use during the pretransplant period and that are standardized to isolate a high-risk subgroup. We think that criteria such as the DSM-IV dependence scale and the number of alcohol withdrawals have these characteristics. For example, in our series, the use of the criterion 'more than one withdrawal before the LT' would allow detection of seven of the eight severe relapsers (88%), while following only 14 of the 61 patients (23%).

In conclusion, alcohol consumption occurs in many patients who have been transplanted for ALD, but severe relapse is not frequent. Although the size of included patients may restrict evidence, the data strongly suggest that the characteristics of pretransplant alcohol consumption are a useful tool to detect patients with high risk of severe alcohol relpase after LT. Therefore, the alcohol dependence is not only useful to evaluate potential candidates for LT, but also to focus on the early management of high-risk patients after LT.

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