

# Follow-Up of Alcohol Consumption After Liver Transplantation: Interest of an Addiction Team?

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**Background:** Alcohol relapses after liver transplantation (LT) constitute a critical issue. Because there is no widely accepted definition of LT, its prevalence varies from 7 to 95% across studies. Only a severe relapse, the frequency of which is estimated to be 11 to 26%, decreases life expectancy after 5 years of LT and requires specific care. To improve the early identification of alcohol consumption among transplanted patients, liver transplant teams may be helped by input from an addiction team. Nevertheless, added benefit of involvement by addiction specialists in treating posttransplant patients has not been demonstrated. Thus, the aim of this study was to compare the evaluation of the alcohol consumption after LT performed routinely during the transplant consultation or obtained from a specific addiction consultation.

**Methods:** This was a prospective single-site study. Patients were seen consecutively by their hepatologist and by an addiction specialist, and they completed the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C). Thus, the patient's alcohol status was assessed using 3 different sources of information: the hepatologist's interview, the AUDIT-C score, and the addiction specialist visit.

**Results:** One hundred forty-one patients were consecutively evaluated. Alcohol consumption was identified by the hepatologist in 31 patients (21.9%), in 52 (36.8%) using the AUDIT-C questionnaire, and in 58 (41.1%) by the addiction specialist. The 31 patients concerned reported an average of 6.5 alcohol units/wk to the transplant physician, a number which was significantly greater ( $p = 0.001$ ) by 8.6 units/wk when they were interviewed by the addiction specialist.

**Conclusions:** This study highlights the clinical utility of a systematic addiction consultation among liver transplant patients, irrespective of the reason for transplantation.

**Key Words:** Liver Transplantation, Alcohol Relapse, Addiction Team.

LIVER TRANSPLANTATION (LT) is the gold standard curative treatment for end-stage liver diseases and hepatocellular carcinoma (HCC) at an early stage. One thousand LTs are performed yearly in France, and the survival rates in Europe are 75 and 68% at 5 and 10 years, respectively (Burra et al., 2010).

In the United States, the primary indication is hepatitis C although alcoholic liver disease is the leading cause in Europe (Shukla et al., 2013). Moreover, alcohol consumption is

often present in transplant candidates even if primary indication is not an alcoholic liver disease. LT treatment is intended to improve both the quality and the life expectancy, and results for quality of life or for survival after a LT in patients with alcoholic liver disease are similar to those in patients with other cirrhosis etiologies (Iruzubieta et al., 2013) the first 5 years of follow-up. However, alcohol relapses after LT constitutes a critical issue (Lucey, 2014).

The definition of alcohol relapse remains heterogeneous, and therefore, its frequency varies depending on studies from 7 to 95% (Dew et al., 2008; Lim and Keeffe, 2004; Lucey et al., 1997; Neuberger and Tang, 1997). Some authors consider that the least consumption as recidivism although others think that “slip” cannot be considered as a relapse (Tome and Lucey, 2003). Severe relapse after LT is often defined by a consumption of more than 14 units per week for women and more than 21 glasses per week for men or more than 4 drinks on a single occasion (Dumortier et al., 2015).

This severe relapse decreases the life expectancy after 5 years of LT regardless of the primary indication of surgery (Faure et al., 2012; Lucey, 2014; Rice et al., 2013) and requires specific care (Rice et al., 2013). Frequency of severe relapse is estimated from 11 to 26% (Kotlyar et al., 2008).

Many studies have identified risk factors of alcohol relapse as pretransplantation abstinence duration, male gender, presence of psychiatric comorbidities, polyaddiction, social

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Received for publication July 19, 2016; accepted October 24, 2016.

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DOI: 10.1111/acer.13276

isolation (Karim et al., 2010; Pageaux et al., 2003; Perney et al., 2005; Rodriguez et al., 2013). One liver transplantation team has tried to define an “alcohol contract” (Masson et al., 2014). In this contract, patients who were listed for liver transplantation confirmed in writing their commitment to abstinence. There was no evidence that the introduction of this contract has had a significant effect on alcohol consumption after LT.

Under these conditions, the prevention and the diagnosis of alcohol relapse represent an important issue after LT (Marroni, 2015). Biological markers (Berlakovich et al., 1999) and validated questionnaires (Girela et al., 1994) for alcohol abuse seem to be effective, but their use in daily clinical practice remains limited. In a study using an anonymous urinalysis test, a positive toxicological test was found in 30% of the patients (alcohol or illicit drug), whereas only 4% of the patients reported alcohol or illicit drug use (Webzell et al., 2011). This study shows that it may be very uncomfortable for a transplanted patient to speak about his relapse with the transplant team.

A retrospective study showed that including an alcohol addiction unit within a liver transplant center is associated with a decrease in the post-LT alcohol relapse rate and an improvement in the first 5 years of mortality in patients transplanted for alcoholic cirrhosis (Addolorato et al., 2013). However, the availability of an internal addiction unit is a kind of luxury out of reach of several liver transplant centers so a first screening by the transplant team before directing the patient toward the addiction unit could be a good arrangement, subjected alcohol consumption could be reliably evaluated.

Nevertheless, as abstinence was an absolute condition both required for LT and highly recommended afterward by the hepatologist, one may wonder whether any patient having lapse or relapse might be ready to tell that to the LT team. Therefore, we designed a prospective study to compare the evaluation of the alcohol consumption after LT assessed by the hepatologist during a routine follow-up visit transplant consultation and by an external specialist in addiction.

## MATERIALS AND METHODS

This was a prospective monocentric study conducted from November 2013 to November 2014 in the liver transplantation center of Montpellier. This center performs about 70 to 80 liver transplantations annually.

### *Patients*

The inclusion criteria were to be liver transplanted for more than 2 months regardless of primary indication and regardless of their present clinical or biological status. Patients had to be aged above 18 years. The aim and the methodology of the protocol were clearly explained, and they have to give an oral informed consent of participation. Exclusion criteria were patients with psychiatric conditions or cognitive dysfunction not allowing reliable answers.

### *Methods*

The LT patients visited first the hepatologist and thereafter the addiction specialist during a usual monitoring visit. The hepatologist performed his routine visit and was asked to evaluate the patient's alcohol consumption using his own method. He also classified the patient into 1 of 4 following categories: (i) abstinence defined by a total absence of alcohol consumption; (ii) occasional drinker defined by <4 glasses on a single occasion and not regular; (iii) regular drinker defined by <14 glasses per week for women, <21 glasses per week for men, and <4 glasses on a single occasion; and (iv) excessive drinker corresponding to a consumption of more than 14 units per week for women and more than 21 units per week for men or more than 4 drinks on a single occasion.

Then, the patients had a visit with the addiction specialist. In the waiting room, they were asked to complete the short Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) (Saunders et al., 1993), a widely used screening instrument for hazardous and harmful alcohol consumption. Following this test, patient was classified in 1 of 4 alcohol consumption categories depending on the frequency and quantity of alcohol drunk per week. The following AUDIT-C cutoffs were used: abstinence 0; occasional  $\leq 2$ ; regular 3 to 5; excessive  $\geq 6$ .

The patient gave the completed AUDIT-C to the addiction specialist who remained blind of the results until the end of the visit. The addiction specialist first confirmed to the patient that the interview will be confidential and that no information will be forwarded to the hepatologist; then, he made his specific interview but was blind of the patient's medical record related to LT and of the hepatologist's appreciation of the alcohol status. The interview was not structured. Sociodemographic data (age, gender), primary indication for liver transplantation, stated by patients were noted. Declarative alcohol consumption during the last month was collected using the timeline followback method (Sobell et al., 1979). Following this interview, physician classed patients into 1 of the 4 categories of alcohol consumption listed above. Then, he was allowed to compare his results with those of the AUDIT-C. Thus, the alcohol status was assessed using 3 different sources: the hepatologist interview, the AUDIT-C, and the addiction specialist visit.

Biology, clinical, and radiology data usually performed for LT surveillance were available. The absence of currently running liver injury was defined as no hepatitis C virus or autoimmune disease recurrence; no infection; no rejection; no biliary tract or liver lesion diagnosed by radiology exams (ultrasonography, CT scan, or MRI). Biological abnormal values of aspartate transaminase (ASAT), gamma-glutamyltransferase (GGT), or values of mean globular volume (VGM) were considered to be alcohol-related when they were observed in the absence of current liver injury.

### *Statistical Analysis*

Main characteristics of the studied population were described using frequencies for qualitative parameters and mean  $\pm$  SD for quantitative one. Differences between the repartition of drinking status were evaluated using the McNemar test; quantitative values were compared using nonparametric test (Wilcoxon). Analyses were performed using the SPSS software v 23 (IBM SPSS, Chicago, IL).

## RESULTS

### *Demographics Data*

One hundred and forty-one patients were consecutively included from November 2013 to November 2014. There were 100 men (70.9%) and 41 women (29.7%) with a mean

age of  $56 \pm 11$  years (median 58 years). The mean time between transplantation and inclusion in the study was  $6.1 \pm 5.4$  years (median 5 years).

### Primary Indication of Liver Transplantation

The primary indication of liver transplantation according to the medical record was alcoholic cirrhosis in 80 patients (56.7%), HCC in 23 (16.3%), and hepatitis C in the remaining 21 (14.9%).

However, when the indications of transplantation for alcoholic cirrhosis collected in the medical files were crossed with those reported by the patients, the concordance was low ( $p = 0.004$ , McNemar test) with 22 patients (27.8%; 19 men and 3 women) denying having been transplanted for alcoholic cirrhosis (Table 1).

### Alcohol Consumption After Liver Transplantation

Alcohol consumption was identified in 31 patients (21.9%) by the hepatologist, in 52 (36.8%) using the AUDIT-C questionnaire, and in 58 (41.1%) by the addiction specialist (Table 2). The repartition of the drinking status according to the 3 different evaluations (hepatologist/AUDIT-C/addiction specialist) was significantly different (hepatologist vs. AUDIT-C,  $p < 0.001$ ; hepatologist vs. addiction specialist,  $p < 0.001$ ; AUDIT-C vs. addiction specialist,  $p < 0.001$ ) (Table 2).

The detailed patient's classification according to the 3 methods is showed in Table 3. In 98 patients (69.5%), there was a complete concordance between the 3 methods, while in the remaining 43 (30.5%), discordance between either 2 or 3 methods was observed.

In 31 patients (21.9% of the whole sample), the alcohol status estimated by the hepatologist differed from that provided by the AUDIT-C. In most cases, the hepatologist underscored the status. Indeed, among the 21 patients he considered as abstinent, 18 were reclassified as occasional and 3 as regular drinkers using the AUDIT-C. One regular drinker was moved to the excessive group while an excessive was reclassified as regular.

Following the patient interview, the addiction specialist classification differed from that of the AUDIT-C in 17 cases (12.1% of the whole sample). Six abstinent patients were moved to the occasional drinker category, 6 occasional

**Table 2.** Agreement Between the Alcohol Consumption Classifications Obtained from the 3 Different Evaluations

Drinking status (N, %)	Hepatologist	AUDIT-C	Addiction specialist
Abstinent	110 (78.1)	89 (63.1)	83 (58.9)
Drinker	31 (21.9)	52 (36.8)	58 (41.1)
Occasional	22 (15.6)	33 (23.4)	33 (23.4)
Regular	7 (4.9)	16 (11.3)	15 (10.6)
Excessive	2 (1.4)	3 (2.1)	10 (7.1)
Total (abstinent + drinker)	141	141	141

**Table 3.** Details of the Drinking Classification Using the 3 Methods in the 141 Patients

	Hepatologist	AUDIT-C	Addiction specialist	N
Concordance	Abs	Abs	Abs	83
	Occ	Occ	Occ	11
	Reg	Reg	Reg	3
	Exc	Exc	Exc	1
				98 (69.5%)
Discordance	Abs	Abs	Occ	6
	Abs	Occ	Occ	16
	Abs	Occ	Reg	1
	Abs	Occ	Exc	1
	Abs	Reg	Reg	3
	Occ	Occ	Reg	3
	Occ	Occ	Exc	1
	Occ	Reg	Reg	5
	Occ	Reg	Exc	2
	Reg	Reg	Exc	2
	Reg	Exc	Exc	2
	Exc	Reg	Exc	1
			43 (30.5%)	

Abs: abstinent; Occ: occasional; Reg: regular; Exc: excessive.

drinkers were reclassified in 4 regular and 2 excessive drinkers, respectively, and finally, the 5 regular drinkers were classified as excessive.

The addiction specialist repartition differed from that of the hepatologist in 42 cases (29.8%). Twenty-seven abstinent drinkers were reclassified into 22 occasional, 4 regular, and 1 excessive drinker. Eleven occasional drinkers were moved to regular and excessive drinking categories in 8 and 3 cases, respectively. Finally 4 regular drinkers were reclassified as excessive.

Thus, the discordance rate between the 3 methods was in decreasing order: hepatologist versus addiction specialist (29.8%), hepatologist versus AUDIT-C (21.9%), addiction specialist versus AUDIT-C (12.1%).

Altogether, if only the excessive drinking was considered to worsen the prognostic of the liver transplantation, 10 patients (12.6% of those transplanted for alcoholic cirrhosis) were concerned. The hepatologist diagnosed 1 case (10%), the AUDIT-C score 2 supplementary cases ( $N = 3$ ; 30%), and the addiction specialist 7 supplementary cases ( $N = 10$ , 100%). Therefore, the sensitivity of AUDIT-C to detect excessive drinking in our sample was 30% (3 cases detected among 10), and its specificity was 94.6%.

**Table 1.** Concordance Between Patient and Medical Record About Alcoholic Cirrhosis in Primary Indication of Liver Transplantation

Liver transplantation due to alcoholic cirrhosis		According to the patient		
		No	Yes	Total
According to the medical file	No	56 (90.3%)	6 (9.7%)	62
	Yes	22 (27.8%)*	57 (72.2%)	79
	Total	78	63	141

McNemar test, \* $p = 0.004$ .

The main reason for the low performance of the hepatologist was the underreporting of the alcohol consumption during their interview. Indeed, the 31 patients concerned reported an average of 6.5 alcohol units/wk to the hepatologist, a number that significantly increased ( $p = 0.001$ ) to 8.6 units/wk when the addiction specialist interviewed them.

The 10 patients who were excessive drinkers were mostly of male sex (9 of 10), their mean age was 58 years, and they had been transplanted 6 years ago on average. Seven of them had been transplanted for alcoholic cirrhosis, but 4 denied it. There was no difference in the posttransplantation delay nor in disturbance of liver function tests.

#### *Interest of Liver Tests for the Diagnosis of Alcohol Relapse*

The rate of patients with abnormal biological test and the presence of a liver injury is presented in Table 4. These rates were not significantly different according to the category of drinking. However, when abstinence and occasional drinking were merged in a low drinking category, and regular and excessive drinking in a high one, steatosis was more frequent ( $p = 0.045$ ) in the high drinker and it was the same, although not significantly ( $p = 0.06$ ) for the existence of a liver injury. However, no biological differences were observed between the low and high drinker.

Five patients had laboratory abnormalities that could suggest alcohol relapse, that is, increase in serums aminotransferase and GGT without signs of liver injury. Among these 5 patients, 3 were abstinent, 1 had occasional consumption, and 1 had regular alcohol consumption. Their alcohol status was concordant between the hepatologist and the addiction specialist.

## DISCUSSION

Many studies suggest that severe alcohol relapse leads to decrease in both graft and patient survival (Iruzubieta et al., 2013) that justifies early diagnosis. Our hypothesis was that patients may have difficulties in speaking about alcohol consumption with their transplant physician and that a specific addiction consultation during the posttransplantation period warranted evaluation.

Our series resembles liver transplanted patients in Europe, with 70% men, a mean age of 56 years, and a primary indication of alcohol and hepatitis C. Moreover, the mean

follow-up was long enough (6 years) to validate conclusions (DiMartini et al., 2010). Finally, the rate of alcohol drinking in our sample was similar to that reported in transplanted patients of the same geographical area (Pageaux et al., 2003; Perney et al., 2005).

Interestingly, the primary indications given by patients differed from those reported in the medical records. Indeed, 17 patients transplanted for alcoholic cirrhosis declared their liver disease had a nonalcoholic origin. This difference might reflect alcoholic disease denial, the belief that other hepatotoxic factors were involved or that HCC was prioritized. Not recognizing, or minimizing, alcohol consumption could in itself be an alcohol relapse risk factor. Among the 10 patients identified as excessive drinkers after LT, 4 did not declare alcohol as the primary indication of their LT although it was actually the case.

The assessment of alcohol consumption after LT using 3 different methods has given valuable information by demonstrating that the method used is of particular importance.

Thus, the prevalence and quantity of alcohol consumed post-LT were greater when assessed by an addiction specialist. Talking to a caregiver who does not belong to the transplant team helps improve identification of alcohol relapse. In addition, medical consultations based exclusively on alcohol consumption and using specific tools to detect addiction help to identify more subjects who have suffered a relapse. Similarly, the quantity of alcohol consumed is reported more accurately.

If we consider alcohol intake diagnosis by the addiction specialist as the gold standard, the diagnosis by the hepatologist was discordant in 29.8% of the cases, leading to a sensitivity of 70.2%. However, as soon as laboratory abnormalities were present, the hepatologist identified the drinkers as well as the addiction specialist; this reflects the vigilance of transplant physician for graft functions. Conversely, patients without laboratory abnormalities were relatively poorly identified. These differences could be explained in several ways. On the one hand, the addiction specialist interview focused on alcohol consumption and used validated tests to record alcohol consumption.

On the other hand, the hepatologist had many parameters to consider such as immunosuppressive treatment, graft function, renal dysfunction, metabolic syndrome (Gelb and Feng, 2009). Moreover, the hepatologist had a specific relationship with the patient, and we can consider the notion of "double denial" between them. The transplant physician finds it difficult to diagnose an alcohol relapse, and the patient is embarrassed to admit it.

Patients with severe relapse according to the addiction specialist were predominantly men grafted 6 years ago. In a recent study, severe alcoholic relapse occurred after a median period of 25 months (Dumortier et al., 2015). Perhaps our patients had a severe relapse, which was not diagnosed before the addiction consultation.

Only 3 of these 10 patients had been transplanted for reasons other than alcoholic cirrhosis. These results confirm

**Table 4.** Biological Abnormalities and Liver Injury According to the Drinking Status

Drinking status	N	Abnormal value (%)			Presence (%) of liver injury
		ASAT	GGT	VGM	
Abstinent	83	10.0	16.3	7.5	6.3
Occasional	33	12.9	22.6	3.2	9.7
Regular	15	20.0	40.0	20.0	26.7
Excessive	10	0.0	20.0	20.0	10.0
Total	141	11.0	20.6	8.8	9.6

that post-LT alcohol relapse is not correlated with the primary indication (Faure et al., 2012).

The AUDIT-C is a self-administered test for identifying excessive alcohol consumption with sensitivity ranging from 51 to 97% and specificity from 78 to 96% (Conigrave et al., 1995; Fiellin et al., 2000) in the general population. Although we find a similar specificity when AUDIT-C was administered in our population, its sensitivity was far low, 30%. Therefore, using this questionnaire improved screening but only marginally.

Indeed, the addiction specialist moved 7 patients from the regular drinker category to the excessive drinker category according to the information gathered during the interview, demonstrating that clinical experience enhances the performance of questionnaires. Moreover, the recipient of the AUDIT-C was the addiction specialist, and one cannot be sure that it would have been completed similarly had the recipient been the hepatologist.

Our work has some limits. First, alcohol consumption was declarative. However, measuring alcohol consumption is always a complicated challenge, and this is even more difficult in patients having been liver transplanted. Indeed, liver graft may suffer from various problems, which per se can modify the clinical examination and the biological function tests, and this was the case in our series. Therefore, interview and screening test still are the reference. Second, the low prevalence of patients transplanted for HCV-related cirrhosis and for HCC hampered analyzing our results according to the etiology. Indeed, one cannot exclude that the etiology modifies the quality of the relation between the patient and his physician so the former might be more or less prone to tell the truth regarding his alcohol consumption. Finally, if we consider that only excessive drinking impairs the graft or the patient survival, then our series was short as our comparison between the 3 methods was carried out on 10 patients only.

In conclusion, our results confirm that post-LT alcohol relapse is common and difficult to detect during standard posttransplant consultations. A questionnaire such as the AUDIT-C could improve screening but only moderately for excessive drinking. Screening is really improved by systematic addiction consultation, regardless of the primary indication for LT and any abnormal laboratory findings.

### CONFLICT OF INTEREST

Authors declare they do not have any conflict of interest.

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