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Alcohol Use after Liver Transplantation is Independent of Liver Disease Etiology

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Abstract

Aim: To assess alcohol use after liver transplantation (LT) and compare liver transplant recipients for alcoholic liver disease (ALD) with recipients for non-ALD causes.
Methods: National Institute of Diabetes and Digestive and Kidney Diseases liver transplant database stratified to ALD and non-ALD causes.
Results: Among 488 LT recipients reporting pre-transplant alcohol use (147 ALD), proportion of LT recipients reporting alcohol use was similar comparing ALD and non-ALD transplants (25.4% vs. 27.2%; $P = 0.56$). Among ALD transplants, of 31 with alcohol use, 23 (74%) relapsed at ≥2 year, 25 (80%) reported intermittent drinking and 4 (13%) reported heavy drinking. Among Non-ALD recipients, alcohol use was equally distributed to within 2, 2–5 and after 5 years of LT with 82% reporting intermittent drinking and 9% heavy drinking. Patients with pre-transplant drinking of >20 years and abstinence duration of <2 years were over 2.5-fold likely to report post-transplant alcohol use compared to drinking of >20 years and abstinence of >2 years, 2.56 [95% CI: 1.41–4.67]. Etiology (ALD vs. non-ALD) did not predict post-transplant alcohol use. Of 139 ALD patients with follow-up biopsy data, 13 (7 with post-transplant alcohol use) had steatohepatitis. Histology on 319 non-ALD recipients showed recurrent disease in 91, none due to alcohol. Overall survival was similar between drinkers and abstainers (71% vs. 66%; $P = 0.35$). Recurrent ALD was cause of death in one ALD and none of non-ALD patients.
Conclusion: Alcohol use after LT is independent of LT indication. Patients with non-ALD etiology should be carefully screened for alcohol use prior to LT to identify those at risk for post-LT alcohol use.

INTRODUCTION

Alcoholic liver disease (ALD) is a common indication for liver transplantation (LT) (Singal *et al.*, 2013b). Most transplant centers require minimum 6 months of abstinence prior to evaluating for LT. About 10–60% of transplant recipients for ALD use alcohol after LT (Singal *et al.*, 2013a). However, data on predictors of alcohol use after LT and its impact on survival remain controversial. About 60–65% of the US population consumes some amount of alcohol (Singal *et al.*, 2013a). Data on post-transplant alcohol use among patients receiving LT for causes other than alcohol (non-ALD) are scanty. We performed this study with specific aims to (a) determine prevalence and predictors of alcohol use among LT recipients, (b) examine whether indication of transplantation (ALD or non-ALD) impacts post-transplant alcohol use and (c) assess the impact of alcohol use on the liver graft and patient survival.

RESULTS

Study population

Of 1563 candidates evaluated for LT (Methods outlined in the supplementary file), 714 of 916 LT performed between 1990 and 1994 were analyzed (Fig. 1). Of 147 LT for ALD, 47 (32%) had concomitant hepatitis C virus (HCV) infection. Indications amongst non-ALD transplants were primary biliary cirrhosis or primary sclerosing cholangitis ($n = 198$), HCV ($n = 117$), cryptogenic cirrhosis ($n = 74$), autoimmune hepatitis ($n = 41$), miscellaneous causes ($n = 32$), hepatitis B virus ($n = 31$) infection, fulminant hepatic failure ($n = 30$), metabolic causes ($n = 25$) and malignancy ($n = 19$).

Pre-transplant drinking history

Of 129 transplants with ALD as primary diagnosis, pre-transplant alcohol use was reported heavy in 109 (84%) and light in 5 (4%), with unavailable data in 15 (12%) patients. Of 18 ALD transplants with HCV as primary diagnosis, 13 reported heavy drinking and data were unavailable in 5. Of 567 non-ALD transplants, 341 (60%) reporting alcohol use prior to transplantation were included in analysis. Of these, 251 with information on alcohol use prior to LT, 192 (76%) were light and 59 (24%) heavy drinkers.

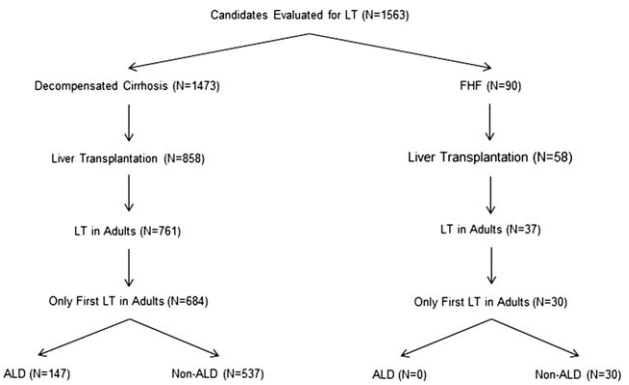

Fig. 1. Study population.
Note: Of non-ALD transplant recipients, only 341 with pre-transplant alcohol use were analyzed.

Prevalence of post-transplant alcohol use

Of 413 (122 ALD) recipients, 113 (27%) reported use of alcohol after LT, with similar prevalence comparing ALD and non-ALD transplants (31 of 122 [25%] vs. 82 of 291 [28%]; $P = 0.56$), and similar probability on median follow-up of about 3 years (Supplementary Figure 1). Of 31 ALD transplants with post-LT alcohol use, 4 were heavy and 16 light drinkers, with unavailable data in 11. About 74% (23 of 31) relapsed after 2 years of LT and 14 of these relapsing after 5 years. Majority were intermittent drinkers with only 6 of 31 reported continuous drinking (Fig. 2A). Of non-ALD transplants, 7 of 80 (9%) reported heavy drinking. About 82% (67of 82) were intermittent drinkers and were equally distributed for time to relapse with 31, 25 and 26 patients within 2, 2–5 and after 5 years of LT (Fig. 2B).

Predictors of relapse to alcohol use

Patients with post-transplant alcohol use ($n = 113$) compared to 300 abstainers had similar duration of pre-transplant drinking; however, they were abstinent for a shorter duration (Table 1). Patients with post-transplant alcohol use were more likely to report pre-transplant drinking of >20 years and abstinence of <2 years compared to abstainers (Table 1). Further, alcohol users were more likely to lack social support (Table 1). On multivariable Cox regression modeling, compared to pre-transplant drinking of ≤20 years and abstinence of >2 years, patients with drinking history of >20 years and abstinence of ≤2 years were over 2.5-fold more likely to engage in recidivism. Younger age also tended to predict post-transplant alcohol use. Liver disease etiology (ALD vs. non-ALD) did not predict use of alcohol after LT (Table 2).

Impact of post-transplant alcohol use on liver graft and patient survival

A total of 458 patients had information on liver histology after LT. Of 139 ALD patients, 13 (alcohol relapse in 7) revealed steatohepatitis with cirrhosis in 1 patient. Of 319 non-ALD transplants, 91 (48 with HCV transplants) developed recurrent disease, without impact of drinking on development of recurrent liver disease (data not shown). Among 413 reporting alcohol use, 102 of 300 (34%) abstainers and 33 of 113 (29%) alcohol users died, ($P = 0.35$). After excluding 130 patients with concomitant HCV, survival comparing

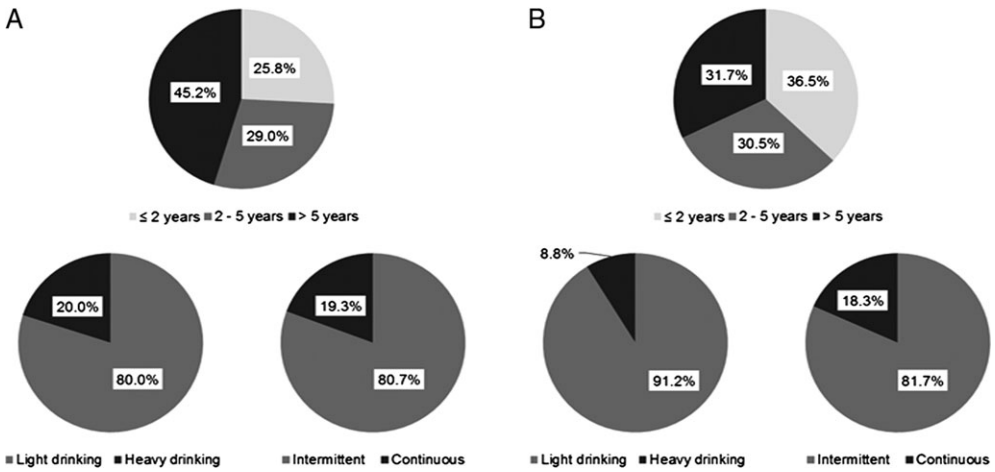

Fig. 2. Pattern of alcohol use after LT among transplanted patients with ALD (left panel) or with non-ALDs (right panel).

199 abstainers and 84 drinkers was similar (68 vs. 73%; $P = 0.13$) (Supplementary Figure 2). Impact of amount of drinking on survival could not be analyzed as only eight patients reported heavy drinking with two deaths, one from recurrent cirrhosis and second patient died from an unknown cause. Of 23 deaths with light drinking, 6 died from recurrent disease (none with recurrent ALD), 3 from cardiovascular causes, and 2 from malignancy, 5 from multi-organ failure or infections and 7 from unknown cause. Similar data among 102 deaths in abstainers were available for 59 patients with 10 deaths due to recurrent disease (none with ALD), 20 from malignancy, 10 from infections, 5 from cardiovascular causes and 14 from multi-organ failure. On multivariable Cox regression modeling, younger age and male gender but not the post-transplant alcohol use impacted survival (Supplementary Table).

Table 1. Patient characteristic at LT comparing recipients based on reported post-transplant alcohol use after LT[a]

Characteristic	Stratum	Drinkers ($N = 113$)	Abstainers ($N = 300$)	P value
Age in years		47.6 ± 10.5	49.2 ± 10.4	0.07
% Males		58.4	64.0	0.30
	Caucasian	86.7	82.0	
% Race	Blacks	1.8	4.8	0.40
	Hispanics	8.0	7.3	
	Others	3.5	6.0	
% HCV infection		25.7	33.7	0.12
Drinking years		22.2 ± 10.0	20.9 ± 11.0	0.33
Abstinence years		3.4 ± 4.7	5.4 ± 6.7	<0.01
% Smokers		67.0	65.7	0.81
% Married		71.8	72.5	0.88
No. of people in household		1.6 ± 1.1	1.9 ± 1.5	0.02
% Social support[b]		79.6	87.8	0.04
Education years		13.9 ± 3.1	13.3 ± 3.1	0.13
% Employed		39.3	33.8	0.35
	Good	25.0	19.3	
% Socioeconomic status[c]	Average	40.2	32.6	0.09
	Poor	34.8	48.1	
% Psychiatric symptoms		90.1	94.0	0.22

[a]For continuous variables, the corresponding mean ± standard deviation was presented.

[b]Social support was defined as either married or more than one household people.

[c]Socioeconomic status was stratified to good (above high school education with employment), average (above high school education or employed) and poor (high school or lower education and unemployed).

DISCUSSION

Main findings of our study are that alcohol use after LT (a) occurs in about 27% patients with equal frequency among LT for ALD or non-ALD indication, (b) is not predicted by etiology and (c) impacts allograft with recurrent ALD, without affecting post-transplant survival.

Major factor that influences use of alcohol after LT is duration of follow-up, with 5.7% per 100 person-years for any alcohol use and 2.5% for heavy drinking (Dew *et al.*, 2008). About 60–65% of people in the US report some alcohol use with about 8–10% engaging in heavy drinking. In one study, 10 patients transplanted for alcoholic cirrhosis had higher rates of alcohol use compared to 48 transplants for cirrhosis other than that related to alcohol abuse (50 vs. 2%; $P < 0.0001$) (Abosh *et al.*, 2000). Data from a single center, small sample size and chart review design compared to our larger database study may explain these divergent results.

Data on duration of pre-transplant abstinence as a predictor of relapse remain controversial. In a systematic review of 26 studies, pre-transplant abstinence from alcohol predicted alcohol use in only two of eight studies examining this variable (McCallum and Masterton, 2006). More consistent predictors of post-transplant alcohol use in this systematic review were younger age of the patient, poor social support and psychiatric comorbidities similar to findings from our analysis.

Steatohepatitis on allograft biopsy in six cases without history of alcohol use in our analysis may be due to non-alcoholic fatty liver

Table 2. Multivariable Cox regression analysis to determine predictors of post-transplant alcohol use

	Model 1		Model 2		Model 3[a]		Model 4[a]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ALD vs. non-ALD etiology	0.99	0.65–1.50	1.01	0.66–1.54	1.01	0.65–1.56	1.02	0.65–1.60
Age			0.99	0.97–1.00	0.99	0.97–1.01	0.98	0.96–1.00
Non-Caucasians vs. Caucasians			0.93	0.54–1.61	0.94	0.54–1.64	0.92	0.52–1.63
Females vs. males			1.12	0.76–1.65	1.11	0.75–1.65	1.23	0.82–1.83
Poor social support					1.40	0.87–2.24	1.29	0.78–2.16
Social economic status								
Good					Ref.	–	Ref.	–
Average					1.03	0.61–1.74	1.01	0.60–1.72
Poor					0.72	0.42–1.25	0.65	0.37–1.13
Status of drinking and abstinence[b]								
Drinking ≤ 20, abstinence > 2							Ref.	–
Drinking ≤ 20, abstinence ≤ 2							1.27	0.63–2.53
Drinking > 20, abstinence > 2							1.47	0.71–3.06
Drinking > 20, abstinence ≤ 2							2.56	1.41–4.67

[a]Patients having unknown social economic status, unknown social support status and unknown status of drinking and abstinence at the pre-transplantation were included. The results for unknown categories were not reported.

[b]Status of drinking and of abstinence was created by using medians of drinking years and duration of abstinence.

disease in the allograft (Watt and Charlton, 2010), or inaccurate report by the recipient on alcohol use. Graft loss from alcohol use is rare except among patients with recurrent cirrhosis in the graft, which can occur in about one-third of patients with harmful alcohol relapse after LT and 3% of the original cohort transplanted for alcoholic cirrhosis (Dumortier *et al.*, 2015). Five-year survival among patients transplanted for liver diseases other than hepatitis C is about 70–80%, similar to 73% in our study (Singal *et al.*, 2013b). Alcohol use has been shown to impact long-term survival after LT (Singal *et al.*, 2013a; Dumortier *et al.*, 2015). Different results in our analysis are likely due to inclusion of transplants in an earlier era (1990–1994) and relatively shorter follow-up of about 5 years.

Analysis of the National Institute of Diabetes and Digestive and Kidney Diseases database with large sample size is a strength of our study. However, our study suffers from limitations of retrospective study design, data analyzed from relatively earlier era and self-reported alcohol use. In conclusion, alcohol use after LT is not predicted by indication of LT, but relates more to the drinking history prior to LT. It highlights the importance of taking detailed alcohol use history in every patient with liver disease coming for LT evaluation irrespective of etiology. Prospective multicenter data on large samples are needed to more clearly define impact of post-transplant alcohol use on the liver graft and on patient survival.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Alcohol* and *Alcoholism* online.

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CONFLICT ON INTEREST STATEMENT

None declared.

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