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Predicting Pre-transplant Abstinence in Patients with Alcohol-Induced Liver Disease

Abstract

Background: Some patients with alcohol-induced liver failure will succumb to their disease prior to demonstrating compliance with the six months abstinence rule for liver transplantation.

Purpose: The purpose of this study was to determine whether a patient's self-reported, longest period of abstinence predicts subsequent abstinence.

Methods: Adult patients (n=63) with alcohol-induced liver disease were asked to recall their longest period of abstinence prior to their initial hepatology visit. Compliance with instructions to remain abstinent was then documented.

Results: Nineteen patients (30%) achieved abstinence and 44 (70%) relapsed within six months of seeing their hepatologist. Relapses were more common in patients who self-reported previous periods of abstinence exceeding six months (19/44, 43%) compared with 2/19 (11%) in those with periods of less than six months (p=0.01). Serum albumin levels were lower in relapsers but other tests of liver function (bilirubin level and international ratio of prothrombin time) and predictors of post-transplant recidivism did not associate with relapses. On multivariate analysis, self-reported abstinence (OR: 0.11, 95% CI: 0.02-0.57, p=0.008) and serum albumin levels (regression coefficient 0.113, p=0.02) predicted relapses.

Conclusions: A self-reported period of abstinence in excess of six months was associated with an increased risk of subsequent relapse following a hepatologist's instructions to remain abstinent. These counter-intuitive findings should be confirmed by larger, prospective studies.

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The majority of liver transplant programs in North America and Europe require patients with alcohol-induced, advanced liver disease to demonstrate abstinence from alcohol for a minimum of six months prior to being considered for liver transplantation [1-3]. While such a policy has been effective in decreasing rates of recidivism post-transplant and enables some patients to recover from liver failure to a point where transplantation is no longer required, other patients who might benefit from transplantation and would have remained abstinent in the post-transplant period may succumb to their liver disease prior to being able to demonstrate compliance with the six month abstinence rule. For these patients and for clinicians involved in the care of patients with alcohol-induced liver disease, more immediate predictors of subsequent recidivism are required.

In this retrospective study we tested the hypothesis that a patient's self-declared, longest period of abstinence, from the onset of his/her problem drinking to being told to abstain from alcohol by their consulting Hepatologist, predicts subsequent abstinence for beyond six months (i.e., a high probability of successfully completing the six months abstinence rule). We also determined whether other variables, which have been previously reported to predict recidivism in the post-transplant setting, are of value in predicting relapses in the pre-transplant setting.

Methods

Patients were identified for this study by accessing a computerized patient database maintained by the Section of Hepatology at the Health Sciences Centre in Winnipeg, Manitoba, Canada. Search terms consisted of "alcoholic hepatitis" and "alcoholic cirrhosis". Potential study subjects were invited to participate and consented by telephone or at the time of their next outpatient liver clinic assessment. All consenting subjects were asked to complete the study questionnaire (Appendix 1, available on request from author).. Answers to the questionnaire were provided by the patient and no attempt was made to verify the accuracy of the responses. Subsequent periods of abstinence were measured from the time of the patient's first visit to the consulting hepatologist where they were instructed to abstain from alcohol (T=0) to their next self-reported consumption of any amount of alcohol. Follow-up care was provided every 3-6 months during which patients were asked if they had experienced any "slips" (i.e., consumption of any amount of alcohol). Blood alcohol and urine ethyl glucuronide levels were not measured during the follow-up period.

Statistics

The Chi-square test of association was used to examine differences in demographic features and clinical variables. Continuous variables were assessed using Student's t-test or analysis of variance. Univariate and multivariate logistic regression analyses were conducted for predicting whether a patient subsequently relapsed. All statistical analyses were carried out using the SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina).

Results

A total of 294 patients were identified in the liver diseases outpatient database as having alcoholic hepatitis (N=118) or alcoholic cirrhosis (N=176). Sixty-three of these patients were successfully contacted and agreed to participate in the study (42 by telephone and 21 at a subsequent office visit). Of the 63 patients, 19 (30%) achieved abstinence for a period beyond six months and 44 (70%) relapsed within that time period after being told by their hepatologist to abstain from alcohol.

As shown in Table I and Figure 1, a higher percent of patients who self-reported being abstinent for in excess of six months previously subsequently relapsed (43% versus 11%, respectively, $p=0.01$). There were no differences between the two cohorts with respect to previous participation in formal alcohol rehabilitation programs, alcohol related hospitalizations, alcoholic parents or siblings, concurrent alcohol consumption by the patient's partner/co-inhabitant or comorbid drug use.

Clinical features of those who abstained, relapsed and the combined study population are also provided in Table I. There were no gender differences between abstainers and relapsers (79% versus 59% males, respectively, $p=0.13$). The mean ages were also similar in the two cohorts (52 ± 11 versus 52 ± 9 years, respectively, $p=0.97$). Although serum albumin levels were lower (32 ± 7.5 versus 36 ± 6.1 g/L, respectively), international ratio of prothrombin times (INR) more prolonged (1.5 ± 0.6 versus 1.2 ± 0.3 , respectively) and bilirubin levels higher in abstainers compared to relapsers, only the difference in serum albumin levels reached statistical significance ($p=0.04$, 0.06 and 0.11 , respectively).

Univariate analysis was performed to determine whether the adjusted relationship between the predictor and outcome differed from the raw (unadjusted) relationship. The results are provided in Table II. Only self-reported previous abstinence for a period of less than six months (OR: 0.155, CI: 0.03-0.75, $p=0.02$), low serum albumin and prolonged INR

TABLE I. Demographic Features, Risks of Recidivism and Liver Function Tests in Alcoholic Patients who Remained Abstinent or Relapsed During the Six Months After Being Instructed to Abstain from Alcohol

	Abstinent (N=19)	Relapsed (N=44)	Total (N=63)	P-value
Variable	Mean $\pm$ SD.	Mean $\pm$ SD.	Mean $\pm$ SD.	
Phone/interview (% phone)	15 (78.95)	27 (61.36)	42 (66.67)	0.17
Gender (% males)	15 (79)	26 (59)	41 (65)	0.13
Males	15 (37%)	26 (63%)	41	
Females	4 (18%)	18 (82%)	22	
Age (years)	52.3 $\pm$ 10.5	52.4 $\pm$ 9.0	53.3 $\pm$ 9.4	0.97
Individuals with prior length of abstinence $\pm$ 6 months (%)	2 (10.53)	19 (43.18)	21 (33.33)	0.012
Alcohol rehab (% yes)	4 (21)	19 (43)	23 (36)	0.09
Alcohol hospitalization (% yes)	4 (21)	14 (32)	18 (29)	0.38
Alcoholic relative (% yes)	9 (47)	25 (57)	34 (54)	0.49
Alcoholic parents (% yes)	7 (37)	15 (34)	22 (35)	0.83
Alcoholic siblings (% yes)	5 (26)	19 (43)	24 (38)	0.21
Drinking co-inhabitants (% yes)	7 (37)	21 (48)	28 (44)	0.42
Partner drinks (% yes)	7 (37)	18 (41)	25 (40)	0.76
Housemates drink (% yes)	6 (32)	20 (45)	26 (41)	0.30
Comorbid drug use (% yes)	7 (37)	14 (32)	21 (33)	0.70
Albumin	32.3 $\pm$ 7.5	36.1 $\pm$ 6.1	34.9 $\pm$ 6.8	0.04
Total bilirubin	60.1 $\pm$ 82.4	26.5 $\pm$ 42.7	36.7 $\pm$ 59	0.11
INR	1.50 $\pm$ 0.64	1.19 $\pm$ 0.27	1.29 $\pm$ 0.44	0.06

Abbreviation: INR, international ratio of prothrombin times

values (regression coefficients of 0.08 and -1.74, $p=0.04$ respectively) were associated with subsequent abstinence.

All variables identified as being significant from univariate analyses and selected demographic variables were employed in the multivariate analyses. The results revealed that a previous period of abstinence shorter than six months and lower serum albumin levels were associated with subsequent abstinence (Table 2).

Discussion

The results of this study could be considered somewhat counter intuitive in that alcoholics who had previously demonstrated their ability to remain abstinent for in excess of

six months were less likely to subsequently achieve abstinence when instructed to do so by their hepatologist than those who had previously been abstinent for shorter periods of time. The results also indicate that previously-described predictive variables for recidivism in the post-transplant setting, such as a positive family history of alcoholism, participation in formal alcohol rehabilitation programs, hospitalization for alcohol related disorders, ongoing consumption of alcohol by the patients partner or co-inhabitant and comorbid drug use, fail to predict subsequent abstinence in the pre-transplant setting [4]. However, the presence of more advanced liver disease, as reflected by low serum albumin and high INR values, predicted subsequent abstinence on univariate analysis and serum albumin remained significant on multivariate analysis.

TABLE 2. Logistic Regression Analyses for Predicting Recidivism During the “Six Month Rule” in 63 Alcoholic Liver Disease Patients

Variable	Univariate				Multivariate			
	Regression coefficient	OR	95% CL	P	Regression coefficient	OR	95% CL	P
Albumin	0.085			0.04	0.113			0.02
INR	-1.75			0.04				
Prior abstinence <6 months		0.155	0.03 - 0.75	0.02		0.11	0.02 - 0.57	0.008
Age (years)	0.0012			0.97				
Bilirubin	-0.009			0.07				
Female gender		2.60	0.74 - 9.12	0.14				
Prior alcohol rehabilitation		2.85	0.81 - 9.98	0.10				
Alcohol related hospitalization		1.75	0.50 - 6.25	0.39				
Family history of alcoholism		1.46	0.50 - 4.31	0.49				
- Alcoholic parents		0.73	0.21 - 2.48	0.61				
- Alcoholic siblings		1.13	0.37 - 3.46	0.83				
Stable partner		0.52	0.15 - 1.83	0.31				
Drinking housemates		1.81	0.58 - 5.62	0.31				
- Partner drinks		1.19	0.39 - 3.60	0.76				
- Co-habitant drinks		1.57	0.52 - 4.72	0.43				
Comorbid drug use		0.80	0.26 - 2.47	0.70				
MODEL					R ² =0.19			0.001

Abbreviation: INR, international ratio of prothrombin times

This is the first published study where the issue of predicting abstinence for beyond six months in pre-transplant patients with advanced liver disease has been addressed; therefore, the results of the present study cannot be compared to other reports in the medical literature. Although numerous studies have identified various predictor variables for recidivism in patients who have already undergone liver transplantation, these studies involved patients who had been preselected by virtue of having already demonstrated six months of abstinence prior to transplantation [4]. Similarly, previous studies designed to identify predictor variables of abstinence in the general alcoholic population would have consisted of study populations wherein only a minority of subjects will have had advanced liver disease. Thus, at this time it is unclear whether our findings are in keeping with or

contrary to those that might be derived from other, similar study populations.

Why patients with a self-reported history of previous abstinence for in excess of six months are less likely to remain abstinent within six months of being instructed to do so by their hepatologist remains to be determined. It is conceivable that some of these patients were aware of the six month rule for liver transplantation and inaccurately calculated their longest previous period of abstinence in an effort to maximize their chances of being selected a transplant candidate if the procedure were to be required in the future; however, such an explanation would not reconcile with why the same patients would self-report alcohol consumption after being instructed by their hepatologist to remain abstinent. It is also conceivable these patients had a different and more liberal impression as to when their period of alcohol abuse began; for example, some

FIGURE 1. Length of previous abstinence and subsequent outcome. Patients who claimed to have been previously abstinent for in excess of six months were more likely to relapse within six months of being instructed to abstain from alcohol than those with a history of less than six months abstinence.

may have included a period of abstinence for in excess of six months that occurred prior to their drinking becoming truly problematic. Additional studies are required to confirm this finding and determine whether the reasons for previous abstinence in this cohort of relapsers were similar to those of the remaining study population.

Although many studies have documented a variety of additional predictors of recidivism following liver transplantation, these variables were not of value in this pre-transplant patient population [5-10]. Perhaps the most likely explanation for this finding relates to differences in the extent of the liver disease in the study populations. The present study consisted of patients with alcoholic hepatitis or cirrhosis and, for the most part, were not being considered for liver transplantation. Thus, the patients themselves and/or their co-inhabitants may not have appreciated the importance of achieving complete abstinence. This explanation is supported by the finding that patients with biochemical evidence of more advanced disease were more likely to remain abstinent.

There are a number of limitations to this study beyond those already outlined. First, this was a retrospective study with a limited study population. Second, of the 294 patients with alcohol-induced liver disease only 63 were successfully contacted and agreed to participate in the study. Thus, a

selection bias must be considered. Third, attempts were not made to confirm the patients self-reported longest period of abstinence. Fourth, the timing of the longest period of abstinence in relation to the initial clinic visit was not documented. Fifth, differences in how instructions to be abstinent were delivered by the various hepatologists attending the clinics, could not be ascertained. Sixth, relapses were self-reported and not documented by blood or urine tests for alcohol and/or its metabolites. Finally, the study population did not include inpatients with liver failure who constitute the majority of alcoholic patients in whom a decision regarding transplantation must be made expeditiously [11].

In conclusion, alcoholic patients attending an urban outpatient clinic who self-report previous abstinence for in excess of six months prior to being instructed by their hepatologist to be abstinent are less likely than those who have been abstinent for shorter periods of time to comply with those instructions. In addition, predictor variables for relapses in the post-liver transplant setting do not predict relapses in this patient population. Finally, patients with biochemical evidence of advanced liver disease are more likely to achieve abstinence than those with less advanced disease. These findings highlight the need for prospective studies involving larger patient populations to identify variables that will predict

compliance with the six month abstinence rule or ideally, post-transplant abstinence and, thereby, limit the risk of patients succumbing to their liver disease before transplantation can be offered.

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