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# Predictors of Alcohol Relapse Following Liver Transplantation for Alcohol-Induced Liver Failure. Consideration of “A–D” Selection Criteria

Authors' Contribution:  
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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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Demonstrated abstinence from alcohol for over six months and successful completion of a formal alcohol addictions program are two commonly employed criteria for determining whether an alcoholic patient with liver failure should proceed to liver transplantation.

In this systematic review of the medical literature, we review the justification for these criteria and consider other variables that have also been reported to be of predictive value.

While abstinence from alcohol for over six months is supported by the medical literature, data are more limited regarding the value of formal alcohol addictions program as selection criteria for proceeding towards liver transplantation. Positive family histories of alcoholism, co-inhabitants drinking alcohol in the presence of the patient and concurrent drug dependencies are more robust predictor variables of post-transplant recidivism. Based on the findings of this review, we propose a simple A–D transplantation selection criteria wherein “A” refers to demonstrated abstention from alcohol for over six months, “B” biology (a negative family history for alcoholism), “C”, co-inhabitants not consuming alcohol in the presence of the patient; and “D”, no concurrent drug dependency.

**MeSH Keywords:** Alcohol • Liver Diseases • Liver Transplantation

**Abbreviations:** **AASLD** – American Association for the Study of Liver Diseases; **A-B-C** – abstinence, biology, co-inhabitant; **DUI** – driving under the influence; **HCC** – hepatocellular carcinoma; **HRAR** – High Risk Alcoholism Relapse

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## Background

Alcohol-induced liver disease is one of the most common causes of liver disease seen by hepatologists [1]. Yet relatively few patients with alcohol-induced liver failure proceed to liver transplantation [2]. The explanation for this paradoxical finding is multi-factorial; however, concerns regarding post-transplant alcohol relapse are thought to play an important role.

In an effort to limit the number of patients with alcohol-induced liver failure who are likely to relapse post-transplantation, most transplant centers and the American Association for the Study of Liver Diseases (AASLD) guidelines stipulate that transplant candidates must be abstinent from all alcohol consumption for a minimum of six months and have successfully completed a formal, outpatient substance abuse program [3,4]. Despite implementation of these criteria, relapse rates in patients transplanted for alcohol-induced liver failure have been reported to range between 10% and 50% [5,6]. Thus, patients who presumably have met these criteria and were subsequently transplanted might not have undergone the procedure had more stringent criteria been in place. Alternatively, some patients who might have benefitted from liver transplantation and not relapsed will have succumbed to liver failure prior to meeting the present selection criteria. For these patients, less stringent criteria would have been appropriate.

The principal purpose of this review was to examine the basis for those variables that have been proposed as predictors of alcohol relapse in patients with alcohol-induced liver failure. A secondary purpose was to stimulate further research in this area and thereby, develop optimal criteria that should be in place for patients with alcohol-induced liver failure who might benefit from liver transplantation.

## Material

The search criteria for this review involved the use of PubMed and Google Scholar databases. The primary keywords were “alcohol, liver transplantation and recidivism”. Inclusion criteria of “cirrhosis”, “hepatitis” and “recidivism” were implemented. Studies that were powered to specifically address the issue of predicting alcohol relapse post-transplantation as the primary outcome measure were selected for review. There were no time limitations to the reports considered.

## Results

Seventeen of 80 reports satisfied the selection criteria (Table 1). In this review, we present the findings of those reports in order of patient sample size from largest to smallest number of

patients. Unless otherwise indicated, each study employed a retrospective study design and relapses were defined as self-reported consumption or laboratory detection of any amount of alcohol post-transplantation.

The largest study reported to date on predicting alcohol relapse post-liver transplantation was published by De Gottardi et al. [7]. In their study of 387 patients, the authors identified a diagnosis of anxiety or depressive disorder ( $p < 0.001$ ), no life partner ( $p < 0.001$ ), abstinence less than six months before liver transplantation ( $p < 0.001$ ), older age ( $p < 0.001$ ), year of liver transplant ( $p < 0.05$ ), and scores of 4 to 6 on the High-risk Alcoholism Relapse (HRAR) scale ( $p < 0.001$ ) as significant individual predictors of alcoholic relapse. The HRAR scale is a point-based system that considers duration of heavy drinking, typical number of daily drinks, and number of prior inpatient treatments for alcoholism in each patient. However, following multivariate logistic regression analysis, only psychiatric comorbidity ( $p < 0.001$ ), HRAR scores ( $p < 0.005$ ), and abstinence less than six months ( $p = 0.02$ ) were significant predictor variables. The authors also reported that 13/272 patients (5%) relapsed if they had none; 16/92 (18%) relapsed if they had one; 14/22 (64%) two, and 3/3 (100%) if they had all three of the risk factors prior to transplantation.

In another large study of 300 patients, Pfitzmann et al. identified abstinence prior to liver transplantation ( $p = 0.0001$ ), poor psychosomatic prognosis ( $p = 0.002$ ), underage children ( $p = 0.01$ ), social support ( $p = 0.02$ ), and younger age ( $p = 0.03$ ) as significant predictors of alcohol relapse post-transplantation [8]. A multivariate analysis via logistic regression in their study demonstrated that poor psychosomatic prognosis ( $p = 0.001$ ), duration of sobriety ( $p = 0.002$ ), poor social support ( $p = 0.002$ ), and presence of underage children ( $p = 0.02$ ) were all significant. In the study, the duration of sobriety was divided into three categories: less than six months, six to <12 months, and 12 months or longer. As the length of sobriety increased, risk of relapse decreased. Social support was similarly divided into three categories: single or widowed, married or companionship, and divorced or separated. Those who were divorced or separated had a greater chance of relapse than those who were single or widowed. Interestingly, this finding was contrary to those described by De Gottardi et al., Karman et al., and Kelly et al., wherein patients who were married or in companionship had the highest rates of relapse [7,9,10]. Possible explanations for the discrepancy include the small sample sizes for single/widowed ( $n = 26$ ) and divorced/separated ( $n = 20$ ) cohorts. The presence of underage children as a predictor of relapse was interpreted as representing major stressors to patients. A similar finding was reported by Foster et al. [11].

In a more limited study of 147 patients, Gedaly et al. found that length of sobriety ( $p = 0.009$ ), abstinence less than 12 months ( $p = 0.019$ ), and no alcohol rehabilitation prior to liver

transplantation ( $p=0.026$ ) were significant predictors of alcohol relapse [12]. However, multivariate analysis revealed that only abstinence less than 12 months predicted relapse ( $p=0.037$ ).

In a Canadian study, Tandon et al. assessed 171 patients for both first-time alcohol use and problem drinking post-transplantation [13]. The authors found in both univariate and multivariate analyses, length of abstinence was a significant predictor of alcohol relapse in patients with problem drinking ( $p=0.015$  and  $p=0.03$ , respectively).

A similar size study by DiMartini et al. of 167 patients revealed that the length of abstinence ( $p=0.005$ ), diagnosed with alcohol dependence ( $p=0.007$ ), completion of alcohol rehabilitation ( $p=0.008$ ), and comorbid substance use ( $p=0.04$ ) were all significant predictors of first-time alcohol relapse and binge use in a univariate analysis [14]. Following multivariate analysis, for first-time alcohol use; length of abstinence ( $p=0.001$ ), diagnosed with alcohol dependence ( $p=0.03$ ), and depression ( $p=0.04$ ) were significant predictor variables. For patients engaged in binge use following transplantation; length of abstinence ( $p=0.01$ ) and no stable partner ( $p=0.05$ ) were statistically significant.

Egawa et al. reviewed 140 patients for any alcohol use and 139 patients for harmful relapse (defined as drinking that resulted in physical or mental damage) post-transplantation [15]. In their univariate analysis for patients with any alcohol use, treatment for psychiatric comorbidity ( $p<0.01$ ), non-compliance with clinic visits post-transplantation ( $p<0.01$ ), post-transplant smoking ( $p<0.01$ ), and marital status ( $p=0.04$ ) were significant predictors of alcohol relapse. Multivariate analysis revealed that treatment for psychiatric comorbidity ( $p=0.02$ ) and post-transplant smoking ( $p=0.05$ ) were significant predictors of alcohol relapse. Conversely, the univariate analysis for patients who had harmful relapses found that living arrangements ( $p=0.03$ ), marital status ( $p=0.03$ ), and non-compliance ( $p=0.03$ ) were significant. Multivariate analysis for these patients revealed non-compliance with clinic visits ( $p=0.004$ ), treatment for psychiatric comorbidity ( $p=0.02$ ), and post-transplant smoking ( $p=0.05$ ) were significant predictors. In this study, living arrangements were categorized into living with family and living alone. Living alone was predictive of alcohol relapse. Additionally, marital status was categorized into stable partner, widowed or divorced, and no marital history. Individuals with no marital history were more likely to relapse.

Bellamy et al. reviewed 123 transplant recipients and found that pre-transplant daily alcohol consumption significantly predicted alcohol relapse post-transplantation in ( $p=0.03$ ) [16]. They speculated that such consumption reflects the severity of addiction to alcohol. It should be noted that if three patients in whom investigators were only suspicious of a relapse were excluded, daily ethanol consumption was no longer significant.

Hartl et al. examined 120 patients for risk of alcohol relapse, which in their study was defined as alcohol consumption of  $>30$  g/day for females and  $>60$  g/day for males, and found that non-acceptance of having an alcohol problem prior to transplantation ( $p=0.001$ ) and abstinence of less than three months ( $p=0.012$ ) were significant predictors [17].

In a review of 118 patients, Rodrigue et al. found that no hepatocellular carcinoma ( $p<0.001$ ), abstinence less than twelve months ( $p<0.001$ ), continued alcohol use after diagnosis ( $p<0.001$ ), low motivation for relapse prevention ( $p < 0.001$ ), poor insight or non-acceptance of alcohol dependency ( $p<0.001$ ), no substitute activities ( $p<0.001$ ), poor stress management ( $p<0.001$ ), no rehabilitation relationship ( $p<0.001$ ), no nonmedical behavioral consequences after alcohol relapse ( $p<0.001$ ), participation in social drinking events ( $p<0.001$ ), alcohol as a primary cause of liver disease ( $p=0.003$ ), abstinence less than six months ( $p=0.004$ ), prior tobacco dependency ( $p=0.006$ ), prior unsuccessful alcohol intervention ( $p=0.007$ ), low hope or self-esteem ( $p=0.02$ ), poor social support ( $p=0.02$ ), and non-adherence to liver disease management ( $p=0.03$ ) were all significant predictors of increased alcohol relapse on univariate analysis [18]. On multivariate analysis, nine of the above variables were significantly associated with an increased risk of relapse and the regression model accounted for 73% of variance in the outcome ( $p<0.001$ ). The nine predictors included no hepatocellular carcinoma ( $p<0.001$ ), continued alcohol use after diagnosis ( $p<0.001$ ), tobacco dependency ( $p=0.01$ ), low motivation for relapse prevention ( $p=0.02$ ), poor social support ( $p=0.03$ ), poor stress management ( $p=0.04$ ), and lack of a rehabilitation program ( $p=0.04$ ).

In a study by Jauhar et al. a family history of alcoholism was the most significant predictor for alcohol relapse ( $p=0.003$ ) in 111 patients [19]. This finding was confirmed on multivariate analysis ( $p=0.03$ ). The authors posited that a family history of alcoholism indicates shared genetic risk factors and environmental conditions that could encourage alcohol consumption in the post-liver transplantation period.

In their multivariate analysis of 99 patients Karman et al. reported that no alcohol rehabilitation prior to liver transplant ( $p=0.001$ ), unfavorable living arrangements ( $p=0.006$ ), history of hospitalization due to alcohol ( $p=0.01$ ), refusal of alcohol rehabilitation during assessment by a liver specialist ( $p=0.01$ ), and history of suicidal ideation ( $p=0.03$ ) were all significant predictors of alcohol relapse [9]. Living arrangements were divided into those who lived alone or with family, and those who lived within a community or with friends. Those who lived alone or with family were more likely to relapse than those living within a community or with friends. The authors speculated that living alone or with a family that shares a similar lifestyle could reinforce negative habits such as heavy drinking. Refusal to attend an alcohol rehabilitation program could reflect poor compliance

**Table 1.** Significant predictors of alcohol relapse in 17 published retrospective studies.

Author	Year	N	Univariate analysis		Multivariate analysis	
			Predictors	p	Predictors	p
De Gottardi et al.	2007	387	Psychiatric comorbidity	<.001	Psychiatric comorbidity	<.001
			No life partner	<.001	HRAR, 4–6	<.005
			Abstinence <6 mo	<.001	Abstinence <6 mo	.02
			Older age	<.001		
			HRAR, 4–6	<.001		
			Year of transplant	<.05		
Pfitzmann et al.	2007	300	Length of abstinence	.0001	Length of abstinence	.002
			Poor psychosomatic prognosis	.002	Poor psychosomatic prognosis	.002
			Underage children	.01	Poor social support	.002
			Poor social support	.02	Underage children	.02
			Younger age	<.03		
Tandon et al.	2009	171	Length of abstinence	.015	Length of abstinence	.03
DiMartini et al.*	2006	167	Length of abstinence	.005	Length of abstinence	.001
			Alcohol dependence	.007	Alcohol dependence	.03
			No alcohol rehab	.008	Depression	.04
			Comorbid substance use	.04	Length of abstinence	.01
					No stable partner	.05
Gedaly et al.	2008	147	Length of abstinence	.009	Abstinence <12 mo	.037
			Abstinence <12 mo	.019		
			No alcohol rehab	.026		
Egawa et al.	2014	140	Psychiatric comorbidity treatment	<.01	Psychiatric comorbidity treatment	.02
			Non-compliance	<.01	Smoking	.05
			Smoking	<.01		
			Marital status	.04		
Egawa et al.	2014	139	Living arrangements	.03	Non-compliance	.004
			Marital status	.03	Psychiatric comorbidity treatment	.02
			Non-compliance	.03	Smoking	.05
Bellamy et al.	2001	123	Daily alcohol consumption	.03	n/a	n/a
Hartl et al.	2011	120	Non-acceptance of alcohol problem	.001	n/a	n/a
			Abstinence <3 mo	.012		
Rodrigue et al.	2013	118	Abstinence <12 mo	<.001	No HCC	<.001
			No HCC	<.001	Continued alcohol use	<.001
			Continued alcohol use	<.001	Social drinking events	<.001
			Low motivation	<.001	Tobacco dependency	.01
			Poor insight	<.001	No behavioural consequences	.01
			Poor stress management	<.001	Low motivation	.02
			No rehab	<.001	Poor social support	.03
			No behavioural consequences	<.001	No rehab	.04
			Social drinking events	.003	Poor stress management	.049
			No substitute activities	.004		
			Alcohol as primary cause	.006		
			Abstinence <6 mo	.007		
			Tobacco dependency	.02		
			Prior unsuccessful intervention	.02		
			Low hope/self-esteem	.03		
			Poor social support			
Non-adherence to liver management						
Jauhar et al.	2004	111	Family history of alcoholism	n/a	Family history of alcoholism	.03

**Table 1 continued.** Significant predictors of alcohol relapse in 17 published retrospective studies.

Author	Year	N	Univariate analysis		Multivariate analysis	
			Predictors	p	Predictors	p
Karman et al.	2001	99	n/a	n/a	No alcohol rehab	.001
					Unfavourable living arrangements	.006
					Alcohol hospitalization	.01
					Refused alcohol rehab	.03
					Suicidal ideation	
Kelly et al.	2006	90	No stable partner	.002	No life partner	.002
			Mental disorder	.011	No family/friends support	.011
			Daily tobacco use	.026	Daily tobacco use	.016
					Poor insight	.019
Karim et al.	2010	80	Length of abstinence	<.001	Abstinence <6 mo	.013
			Younger age	.004	Females	.043
			Abstinence <6 mo	.006		
			Psychiatric comorbidity	.018		
			Abstinence <12 mo	.019		
			Females	.021		
			Personal stressors	.05		
Foster et al.	1997	63	Comorbid drug use	.00034	n/a	n/a
			No life insurance	.001		
			Younger age	.009		
			Alcoholic sisters	.01		
			Length of abstinence	.024		
			DUI	.033		
Miguet et al.	2004	51	Abstinence <6 mo	.0003	Abstinence <6 mo	.02
Osorio et al.	1994	37	Abstinence <6 mo	.03	n/a	n/a

\* First multivariate analysis considered patients who had a first-time alcohol relapse. Second multivariate analysis considered patients who binge used alcohol.

with medical protocols, which could lead to an increased risk of alcohol relapse. Finally, a history of suicidal ideation could imply poor stress management or lack of perceived support, both of which would increase the risk of alcohol relapse.

Kelly et al. differed from most other investigators by defining alcohol relapse not as any alcohol consumption post-liver transplant, but as harmful drinking (more than 140 g of ethanol per week) or drinking with medical or social implications [10]. They hypothesized that those who engage in social drinking (or alcoholic slips) were not at the same risk of hepatotoxicity as those who engage in harmful drinking. In their analysis of 90 patients, the diagnosis of a mental disorder (uniformly depression) ( $p=0.011$ ), no stable partner ( $p=0.019$ ), and daily tobacco use ( $p=0.026$ ) were significant predictors of alcohol relapse. Multivariate analysis via step-wise logistic regression identified several variables that influenced alcohol relapse, namely no stable partner ( $p=0.002$ ), no support from family or friends ( $p=0.011$ ), daily tobacco use ( $p=0.016$ ), and poor insight into alcohol as the etiology for their liver disease ( $p=0.019$ ). This model accounted for 52% of variance in patient outcome.

Karim et al. analyzed 80 patients in their study, and demonstrated that length of abstinence ( $p<0.001$ ), younger age ( $p=0.004$ ), abstinence less than six months ( $p=0.006$ ), psychiatric comorbidity ( $p=0.018$ ), abstinence less than 12 months ( $p=0.019$ ), female ( $p=0.021$ ), and increased personal stressors ( $p=0.05$ ) significantly predicted alcohol relapse post-liver transplantation [20]. A stepwise, multivariate logistic regression revealed that abstinence less than six months ( $p=0.033$ ) and female sex ( $p=0.043$ ) were significant predictor variables. This model accounted for 61% of variance in patient relapse ( $p=0.033$ ). Although females were at higher risk for alcohol relapse post-transplant, the authors speculated that because females are more likely to suffer from depressive or anxiety disorders, this result could be confounded.

In a relatively small study of 63 patients, Foster et al. identified comorbid drug use disorder ( $p=0.00034$ ), no active life insurance ( $p=0.001$ ), presence of alcoholic sisters ( $p=0.01$ ), a younger age at transplantation ( $p=0.009$ ), history of driving under the influence (DUI) ( $p=0.033$ ) and shorter lengths of abstinence before liver transplant ( $p=0.024$ ) as predictors of relapse [11].

Based on these findings, the authors proposed that comorbid drug abuse was an important predictor. They interpreted the history of DUI as reflecting the severity of drinking in the patient, and their general compliance with the law; physicians could then extrapolate that lack of compliance to compliance with medical protocols. Active life insurance was included in the analysis because life insurance requires a beneficiary (usually a life partner), and infers steady income and social responsibility with payments – all indicators of an individual who was socially supported, and responsible with their drinking habits. Alcoholic sisters were considered because their presence would implicate both genetics and environmental conditions that could increase the chances of alcohol relapse. The study did not include brothers because the authors reasoned that females were less likely to harmfully drink than males; therefore, if sisters exhibited alcoholism, presumably the factors contributing to drinking were strong. Length of abstinence before liver transplant was also assessed; although those who relapsed were on average sober for a shorter number of months, the criteria of six months was not significant. Finally, younger patients were considered more likely to relapse.

Miguet et al. reviewed 51 post-liver transplantation patients and found that abstinence less than six months prior to transplantation was the most significant predictor of alcohol relapse ( $p=0.0003$ ) [21]. In their study, relapse rates were higher during follow-ups done 24 months after the transplant, in comparison to follow-ups of 12 months.

Finally, Osorio et al. completed a study of 37 patients, and identified the period of abstinence prior to liver transplantation to be predictive of abstinence post-transplantation [22]. Specifically, abstinence less than six months was a statistically significant predictor of relapse post-transplantation ( $p=0.03$ ).

## Discussion

The results of this review support in part the present policy that patients with alcohol-induced liver failure must be abstinent from alcohol for a period of over six months prior to liver transplantation. Five of the 13 reviewed studies in which multivariate analyses was performed, identified abstinence (or lack thereof) as a strong predictor of alcohol relapse following liver transplantation. However, the precise duration of abstinence that need be in place remains unclear.

Unlike the provision regarding abstinence, successful completion of a formal, outpatient substance abuse program was not identified as a robust predictor of alcohol relapse in the majority of studies reviewed. Indeed, only the studies by Karman et al.

and Rodrigue et al. identified this variable as being of predictive value [18,20]. The explanation for why substance abuse programs were not identified in other studies may reflect the tendency of investigators to not include this variable in their study design and analyses. Moreover, the Karman et al. and Rodrigue et al. studies were performed at centers where such rehabilitation programs are an integral part of the patient care map and therefore, staffing and infrastructure support at their sites may exceed that available to other transplant centers.

Other less “patient driven” but frequently identified predictor variables that emerged from this review included family histories of alcoholism, companion drinking habits, and concurrent drug dependencies. Unfortunately, these variables were defined differently by the various investigators and therefore, inter-study comparisons and consistencies that might have existed were difficult to ascertain.

Overall, based on this review, a defined six month period of abstinence (A); favorable biology (B) i.e., a negative family history of alcoholism; absence of a co-inhabitant (C) who consumes alcohol in the presence of the patient and as per current transplant exclusion criteria of patients with liver failure regardless of etiology; no concurrent addiction to drugs (D) may serve as more robust selection criteria for patients with alcohol-induced liver failure who are being considered for liver transplantation. Clearly, the value of this simple A–D selection criteria will need to be established in prospective multi-center trials wherein the duration of abstinence, definition of positive “family history” and “alcoholism”, distinction between co-inhabitants drinking alcohol *per se* or merely not drinking in the presence of the patient and which drugs/medications contribute to higher relapse rates post-transplantation, are clearly defined.

## Conclusions

Based on the results of previous studies, the proposed “A–D” selection criteria could serve as a simple, consistent and perhaps more robust means of selecting alcoholic patients for liver transplantation.

## Conflicts of interest

None.

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