Polysubstance Abuse in Liver Transplant Patients and Its Impact on Survival Outcome

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Background: **Alcohol-related end-stage liver disease was the most common reason for liver transplant in the 1990s. Currently, hepatitis C virus (HCV) is the most common reason for transplant. The major HCV risk factor is intravenous drug abuse, which often includes other forms of substance abuse. It is important to understand posttransplant survival outcomes in patients with multiple substance abuse and pretransplant factors that predict relapse.**

Methods: **The medical records of patients referred to the transplant psychiatrist were retrospectively reviewed to identify posttransplant patients with pretransplant multisubstance abuse issues including cannabis, cocaine, opioids, and alcohol. Survival outcomes and drug relapse were assessed in relation to demographic variables including age, race, sex, legal history, psychiatric diagnoses or need for psychiatric hospitalization, and substance abuse diagnosis.**

Results: **Twenty-seven patients with polysubstance abuse disorders were identified: substance abuse (n=41), substance dependence (n=33), and other (n=8); a mean of 3.03 substances was used per patient. Eight patients relapsed (29.6%) and 10 patients died (33%) between 2 and 60 months after transplant. Patients were divided into relapse and no-relapse groups, and 1-year patient survival rates in patients were 100% and 83.9%, respectively. No between-group differences were found for age, race, sex, legal history, psychiatric diagnoses or need for psychiatric hospitalization, or having first-degree relatives with substance abuse issues.**

Conclusions: **The rate of recidivism was 26.9%; however, it did not affect survival. No predictors of relapse were identified. Patients with polysubstance abuse issues should not be categorically denied access to liver transplant. Further research regarding these issues is essential.**

Key words: *Substance dependence, Alcohol, Cannabis, Cocaine, Heroin*

Alcohol-related end-stage liver disease was, for many years, the most common reason for liver transplant (1). Years ago, when such patients sought transplant, moral or ethical judgments were not uncommonly part of the evaluation. Should patients with alcohol-induced end-stage liver disease have a lower priority for receiving a liver transplant than those with non–self-induced liver illnesses? Social worth or social value judgments were debated as a basis for organ allocation (2-5). However, evidence began to emerge that patients with alcoholic liver disease had comparable survival outcomes after transplant when compared with persons who had received liver transplants for other reasons (6, 7). Regarding assessment of these patients, a shift began away from value judgments or social worth determinations toward evidence-based medical outcomes. However, concerns remained about the potential for relapse, and hence, graft or patient loss, after transplant. Efforts then began to discern those factors that predicted which patients with end-stage liver disease due to alcohol use were at higher risks of graft or survival failure because of relapse on alcohol (8-11). Identifying patients at high risk of relapse can then improve selection of transplant candidates with alcoholic liver disease. This avoids stereotyping such patients and rejecting them for transplant.

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Liver transplant for alcoholic liver disease is now established (12). Along with this has been an expanding of the criteria for liver transplant in patients with multiple substance abuse issues. This perhaps is due in large part to the facts that end-stage liver disease due to HCV is now the most common reason for liver transplant (13), the major risk factor for infection with HCV is intravenous drug abuse (14, 15), and intravenous drug abuse is often accompanied by other forms of substance abuse (16, 17). As such, more patients with histories of nonalcohol substance abuse or polysubstance abuse including alcohol are presenting to liver transplant centers for evaluation. Not dissimilar to the early years of assessing patients with alcoholic liver disease, some patients with nonalcohol substance abuse issues may have been refused transplant based on moral or ethical grounds (18). However, in assessing patients with multiple substance abuse issues who present for transplant, as in those with alcohol-related end-stage liver disease, candidate selection based on moral or ethical judgments should give way to evidence-based outcomes research.

To date, there is a small amount of data about general outcomes in opioid-dependent patients (19). However, there are no studies about posttransplant survival outcomes in patients with end-stage liver disease with histories of polysubstance abuse with or without alcohol abuse. Further, there are no known factors that might predict relapse in patients in this population.

Aim

The aim of this study is to examine the effect of pretransplant polysubstance abuse and posttransplant rate of recidivism on patient and graft survival following transplant. An additional aim of the study is to begin identifying predictors of relapse after transplant.

Methods

All patients with a history of substance abuse at our institution undergo psychiatric evaluation by the same psychiatrist who has a special interest in transplant. The selection committee carefully examines the findings of the psychiatrist before listing patients for liver transplant on the waiting list. Patients considered to be at high risk for relapse are usually not listed until they successfully complete a rehabilitation program. By retrospectively reviewing the charts of the transplant psychiatrist, we found 27 patients with end-stage liver disease who underwent transplant between 1999 and 2004 who had been referred for pretransplant psychiatric assessment. Of those charts, patients who had undergone transplant and had diagnoses of more than 1 substance abuse or dependence disorder, but not exclusively alcohol abuse or dependence, were selected. The study protocol was approved by the institutional review board.

Substance abuse and dependence were classified according to American Psychiatric Association criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (20). Substance abuse was defined as a maladaptive pattern of use causing clinically significant impairment or distress manifested by 1 or more of the following in a 12-month period: failure to fulfill role obligations (eg, during work, at school, or at home), use during potentially hazardous circumstances (eg, while driving an automobile or using machinery), alcohol-related legal problems, and continued use despite persisting social problems caused by the alcohol. Substance dependence was defined as a maladaptive pattern of use causing clinically significant impairment or distress manifested by 3 or more of the following in a 12-month period: tolerance, markedly increased amounts to achieve intoxication, and markedly diminished effect with the same amount of use.

Patient survival outcomes were assessed through an existing survival database. Post-transplant relapse was assessed by reviewing the patients' medical and laboratory records for positive urine toxicology screens or notes indicating relapse. To discern those factors that predicted relapse, several variables were analyzed. These variables included the demographic characteristics of age, race, and sex; social factors such as marital status, presence of first-degree relatives with substance abuse issues, and history of legal convictions; psychiatric diagnoses; history of any psychiatric hospitalizations; and substance abuse diagnoses.

Statistical analyses

Values are presented as means plus or minus standard deviations. Mean values between the groups were compared using the t test, and categorical values between the groups were compared using the chi-square test. Survival rates were calculated using the Kaplan-Meier test and compared using the log-rank test. A P value $< .05$ was considered statistically significant. Statistical analyses were performed using SPSS software (Statistical Product and Services Solutions, version 15.0, SPSS Inc, Chicago, IL, USA).

Table 2. Substance abuse / dependence in relation to relapse

Case No.	Age (y)	Sex	Substance abuse						Substance dependence						Follow-up (months)	Posttransplant recidivism	Death (months posttransplant)
			ETOH	THC	Cocaine	Opioid	Other	Total	ETOH	THC	Cocaine	Opioid	Other	Total		Relapse (Y/N)	
1	48	M			Y	Y		2	Y					1	36.3	N	
2	53	M		Y				1	Y					1	37.1	Y	
3	45	F		Y				1	Y		Y			2	60.0	N	60.0
4	48	M			Y			1	Y					1	15.4	Y	15.4
5	49	M					Y	1	Y	Y				2	46.9	N	
6	58	M	Y	Y	Y	Y		4						0	3.8	N	3.8
7	41	M					Y	1	Y	Y	Y			3	38.0	N	
8	48	M						0	Y		Y	Y		3	17.5	Y	
9	46	M		Y	Y	Y	Y	4	Y					1	14.4	Y	
10	53	F		Y				1				Y		1	10.1	Y	
11	54	M		Y	Y			2	Y					1	12.8	N	12.8
12	44	F		Y	Y			2	Y					1	8.4	N	
13	53	M	Y	Y	Y		Y	4						0	24.3	N	
14	42	M		Y			Y	2	Y		Y	Y		3	7.5	N	7.5
15	49	M	Y	Y				2						0	12.5	N	12.5
16	47	M	Y		Y			2		Y				1	20.6	N	
17	48	M						0	Y		Y			2	21.9	N	
18	48	M		Y				1	Y					1	2.1	N	2.1
19	53	M				Y		1						0	23.2	N	
20	56	M					Y	1	Y		Y			2	73.0	Y	
21	49	M	Y		Y		Y	3		Y				1	43.9	N	
22	61	F			Y	Y		2	Y					1	17.9	N	
23	48	M		Y	Y			2						0	5.9	N	
24	44	M		Y	Y			2	Y				Y	2	23.4	Y	23.4
25	44	M		Y				1	Y		Y			2	20.4	Y	20.4
26	36	M		Y	Y	Y		3	Y					1	21.5	N	
27	53	M		Y	Y			2	Y					1	12.3	N	12.3
Total	**(mean age = 48.8)**		**5**	**16**	**14**	**6**	**7**	**48**	**19**	**4**	**7**	**3**	**1**	**34**	**(mean = 23.4)**	**Y=8**	**10**

Abbreviations: ETOH, alcohol; F, female; M, male; N, no.; THC, tetrahydrocannabinol; Y, yes; Others, amphetamines, benzodiazepines, lysergic acid diethylamide

Results

The records of 27 patients that met the diagnostic criteria were identified and screened for poly-substance abuse (Table 1). Of these, 24 patients had alcohol and nonalcohol substance abuse issues or dependence, and 3 had nonalcohol substance abuse disorders (Table 2). The diagnoses of substance abuse disorders included alcohol dependence and abuse, cannabis dependence and abuse, cocaine dependence and abuse, opioid dependence and abuse, and amphetamine and hallucinogen abuse. The mean number of substances abused per patient was 3.03. The etiologies of end-stage liver disease included 1 patient with Laënnec's cirrhosis, 1 with hemochromatosis, and 25 with HCV infection (Table 2). Of the 25 patients with HCV, 1 had concurrent hemochromatosis and 2 had hepatocellular carcinoma. On detailed examination of the family and psychosocial history of the patients, 24 had children and 17 were married at the time of transplant. Fifteen patients were using antidepressant medications, 2 were using benzodiazepines, 3 were using mood-stabilizing medications, and 3 were using antipsychotic medications. The mean time between transplant and the time of study was 19.01 months (range, 2.1-60.0 months).

Table 2. Patient distribution and diagnoses

Substance	Abuse	Dependence	Total
ETOH	5	19	24
THC	16	4	20
Cocaine	14	7	21
Opioid	6	3	9
Other*	7	1	8
Total	48	34	82
Diagnosis			
Hepatitis C viral infection (HCV)†			25
Alcohol-induced liver cirrhosis			1
Hemochromatosis			1

*Amphetamines, benzodiazepines, lysergic acid diethylamide.
†Two patients with HCV also had hepatocellular carcinoma and 1 had hemochromatosis.
Abbreviations: ETOH, alcohol; THC, tetrahydrocannabinol

Relapse

Of 27 patients, 8 (29.6%) relapsed after transplant. The chemicals used included tetrahydrocannabinol (n=5 patients), cocaine (n=6 patients), opioids (n=3 patients), alcohol (n=7 patients), and other substances (n=3). Patients relapsed on a mean of 3.0 substances (Table 3). Among the patients who relapsed with tetrahydrocannabinol, 5 had a diagnosis of abuse, and none had a diagnosis of dependence. Among those who relapsed with cocaine, 3 had a diagnosis of

abuse, and 3 had a diagnosis of dependence. Among the patients who relapsed on opioids, 1 had a diagnosis of abuse, and 2 had a diagnosis of dependence. And among those who relapsed on alcohol, none had a diagnosis of abuse, and 7 had a diagnosis of dependence. In the pretransplant setting, of the 2 patients who had been using tetrahydrocannabinol who relapsed, 1 had been dependent and 1 had been abstinent; 1 patient on cocaine and 2 patients on opioids had been dependent, and the 3 patients on alcohol had been abstinent for less than 6 months. The distribution of patients with a diagnosis of abuse or dependence who did not relapse on various substances after transplant is shown in Table 3.

Demographic variables in relation to relapse (Table 4)

Age: The average age at the time of transplant for the entire sample was 48.8 years. Age was not a significant factor for predicting relapse. The average age of those who relapsed was 49.0 years, and for those who did not relapse, the average age was 48.74 years ($P = .911$).

Sex: One out of 4 women (25%) and 7 out of 20 men (28.5%) relapsed ($P = .826$).

Race: Twenty patients were white, 4 were African American, 2 were Hispanic, and 1 was of an unknown race. Seven white and 1 of unknown race relapsed. Race was not a significant predictor of relapse ($P = .159$).

Family history of substance abuse: Thirteen patients had first-degree relatives with alcohol or substance abuse issues. A family history of alcohol or substance abuse was not a significant predictor of relapse. Four of the 8 patients that relapsed had first-degree relatives with substance abuse problems, and 4 did not ($P = .901$).

Legal convictions: Eleven patients (40.7%) had legal convictions for possession and probable use; 2 (25.0%) of these patients relapsed and 9 (47.3%) did not ($P = .318$).

Table 3. Distribution of substances for relapse and nonrelapse

	THC	Cocaine	Opioid	ETOH	Other*
Relapse (n=8)					
Abuse	5	3	1	0	2
Dependence	0	3	2	7	1
Total	5	6	3	7	3
No relapse (n=19)					
Abuse	11	11	5	5	5
Dependence	4	4	1	12	0
Total	15	15	6	17	5

*Other: amphetamines, benzodiazepines, lysergic acid diethylamide.
Abbreviations: ETOH, alcohol; THC, tetrahydrocannabinol

Table 4. Demographic and psychiatric variables in relation to relapse

	Relapse (n=8)	No relapse (n=19)	*P* value
Demographic variable			
Mean age (y)	49.0	48.7	.911
Sex	Men: 7, Women: 1	Men: 16, Women: 3	.826
Race	White: 7, Unknown: 1	White: 13, African American: 4, Hispanic: 2	.159
Family history of substance abuse	4	9	.901
Legal convictions (average number per patient)	2	9	.318
Psychiatric variables			
Anxiety	4	3	.064
Depression	1	1	.512
Personality disorder	1	2	.882
Adjustment disorder	1	3	.302
Psychiatric hospitalization	1	6	.121

Psychiatric variables

Psychiatric diagnoses: Seven patients had anxiety disorders, 2 had depressive disorders, 3 had personality disorders, and 4 had other psychiatric diagnosis. None was diagnosed with more than 1 psychiatric diagnosis in addition to the substance abuse diagnoses. Psychiatric diagnoses did not differ between relapsers and nonrelapsers (Table 3).

Psychiatric hospitalizations: Seven patients had prior psychiatric hospitalizations, 1 relapsed and 6 did not ($P = .121$).

Substance abuse variables

Nineteen of the 24 patients with alcohol abuse issues had a diagnosis of alcohol dependence with other substance abuse diagnoses; the remaining 5 patients had a diagnosis of alcohol abuse. Three patients had substance abuse issues that did not involve alcohol; 1 had a diagnosis of opioid dependence, another had a diagnosis of opioid dependence plus cannabis abuse, and 1 had a diagnosis of cocaine abuse plus cannabis abuse. No particular pattern was identified for recidivism.

Survival

Ten of the 27 patients died after transplant. The range in times between transplant and death was 2.07 to 60.05 months. Of the 8 patients who relapsed, 2 died at 15.4 and 23.5 months after transplant due to sepsis and HCV recurrence, respectively, both patients were compliant with their medication. Of the 19 patients who did not relapse, 8 patients died at 2.1, 3.8, 7.5, 12.3, 12.5,

Table 5. Retransplant and deaths

	Number of patients
Cause of retransplant (n=5)	
Hepatic artery thrombosis	2
Recurrent hepatitis C viral infection	3
Cause of death (n=10)	
Sepsis	6
Recurrent hepatitis C viral infection	2
Recurrent hepatocellular carcinoma	1
Myocardial ischemia	1

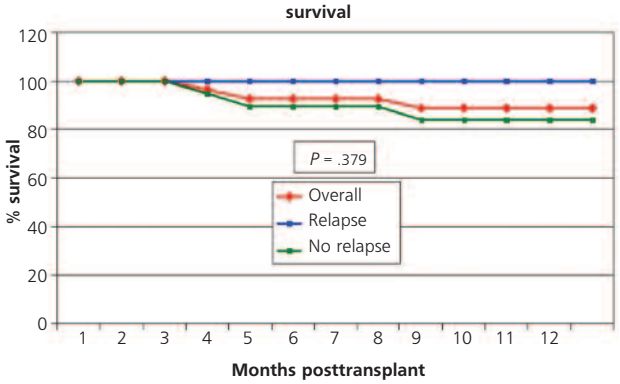

Figure 1. Kaplan-Meier survival curve for patients who relapsed and those who did not relapse.

12.8, 24.4, and 60.0 months after transplant due to sepsis (n=5), recurrent HCV (n=1), recurrent hepatocellular carcinoma (n=1), and myocardial ischemia (n=1) (Table 5). Overall actuarial 1-year survival rates in the relapse and no-relapse groups were 100% and 83.9%, respectively (Figure 1).

Retransplant

Five patients in the study required retransplant. The time between the first and second transplants ranged from 0.5 to 41 months, with a mean of 13.2 months. Of the 5 patients with a second transplant, 2 relapsed and 3 did not. There was no statistically significant difference regarding relapse (P = .574). The retransplants in patients in the relapse group were performed at 8 days and 13.21 months owing to hepatic artery thrombosis and recurrent HCV, respectively. The retransplants in patients in the nonrelapse group were performed at 12 days, 11.37 months, and 40.95 months owing to hepatic artery thromboses and recurrent HCV in the remaining 2 patients (Table 5).

Discussion

Liver transplant programs in the United States widely accept patients with histories of opioid dependence (19), and it is likely that there is wide acceptance of patients with histories of abuse of other substances. Koch and Banys report generally favorable outcomes following transplant in opioid-dependent patients (19); Kanchana and associates (21) and Liu and associates (22) report no apparent differences in outcomes in methadone-dependent patients who undergo liver transplant. Further, renal transplant outcomes may be no worse in heroin addicts than in patients without heroin addiction (23, 24). This study broadens existing research by examining liver transplant outcomes in patients that abuse a variety of substances.

In this, the first study of posttransplant survival outcomes in patients with histories of nonalcoholic substance abuse or polysubstance abuse, there were no differences regarding survival between patients in the group that relapsed and patients in the group that did not relapse (P = .379). As such, pretransplant assessment of relapse potential, even if better known in this population, may not necessarily be a pertinent factor when determining transplant candidacy. These results support the concept that patients with nonalcoholic substance abuse or polysubstance abuse issues should not be categorically denied access to transplant based on substance use history alone.

Rates of relapse with alcohol over 5 years after liver transplant range from 30% to 50% (25, 26). The rate of relapse found in this study (29.6%) of nonalcoholic substance abuse and polysubstance abuse compares with the rate for relapse on alcohol after transplant. There were no clear predictors of relapse in this study of patients with pretransplant histories of nonalcohol substance abuse. In patients with alcoholic liver disease, reported predictors of posttransplant alcohol relapse include having a first-degree relative with alcohol problems and having a history of prior alcohol rehabilitation (8). The same variables were examined in this study; however, we found no statistically significant results. No significant differences were noted between patients who relapsed and patients who did not relapse regarding age, race, sex, specific substance abuse diagnoses, number of substances abused, psychiatric diagnoses, history of psychiatric hospitalizations, legal convictions, or having a first-degree relative with a history of alcohol or substance abuse. While it seems logical that there would be relapse predictors, none was found in this study.

The absence of predictive factors for posttransplant relapse does not help clarify selection criteria of such patients that present for liver transplant. However, the fact that survival outcomes were no different in those who relapsed

versus those who did not suggests that posttransplant survival outcomes in this population might be affected by factors other than the substance abuse.

A possible limitation in this study is the case selection method. Cases were culled from those referred to the transplant psychiatrist by personnel on the transplant team. At that time in the program, some patients also were referred by personnel on the transplant team to substance abuse counselors or programs; therefore, patients were missed in this study potentially skewing both survival data and predictors of relapse. An additional limitation in this study is the method of relapse identification. It has been suggested that the best method of doing such is through clinical interview and assessment (8). Perhaps, by using that additional method, different rates of relapse might have been found. In addition, in this study population, it is not clear that all posttransplant patients received routine urine toxicology screens, potentially missing some patients who relapsed. Finally, this study did not assess length of abstinence prior to transplant, a factor variably reported to affect posttransplant alcohol relapse rates in patients with alcoholic liver disease.

Future studies of this nature should consider studying compliance and health behaviors after transplant, including possible links with substance abuse, as these variables may affect graft and patient survival after transplant.

Conclusions

In this study of patients with histories of alcoholism, nonalcoholic substance abuse, and polysubstance abuse, we found no difference in posttransplant survival rates between those patients who relapsed and those who did not. This supports the argument that patients with alcoholic and nonalcohol substance abuse issues with end-stage liver disease should not categorically be denied a liver transplant based solely on substance abuse history. In addition, no clear predictors of relapse for any substance abuse or dependence were identified. This suggests that the potential for relapse alone might not be a pertinent factor when assessing these patients for liver transplant. Further studies in this population are necessary to continue exploring the factors that might affect posttransplant survival and predict posttransplant relapse.

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