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ORIGINAL ARTICLE

Factors Having an Impact on Relapse and Survival in Transplant Recipients With Alcohol-Induced Liver Disease

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Abstract

Objective: To assess the impact of standardized pretransplant alcohol abstinence and treatment guidelines on liver transplant outcomes.

Methods: This study assessed the posttransplant relapse and survival associated with a pretransplant guideline mandating alcohol abstinence, addiction treatment, and Alcoholics Anonymous (AA) attendance. This retrospective cohort study included liver recipients with alcohol-induced liver disease transplanted between January 1, 2000, and December 31, 2012, at a Midwest transplant center. Cox regression models tested for associations between pretransplant treatment, demographic and clinical characteristics, and outcome measures.

Results: Of 236 liver recipients (188 [79.7%] male; 210 [89%] white; mean follow-up, 88.6±55.0 months), 212 (90.2%) completed pretransplant treatment and 135 (57.2%) attended AA weekly. At 5 years, 16.3% and 8.2% had relapsed to any alcohol use and to high-dose drinking, respectively. Smoking during the 6 months before transplant was associated with any relapse (P=.0002) and high-dose relapse (P<.0001), and smoking at transplant was associated with death (P=.001). High-dose relapse was associated with death (hazard ratio, 3.5; P<.0001).

Conclusion: A transplant center with a guideline requiring abstinence, treatment, and AA participation experienced lower posttransplant relapse rates from those previously reported in comparable large US transplant programs. Smoking cessation may further improve posttransplant outcomes.

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Alcohol-induced liver disease (ALD) is the most common indication for liver transplant in the United States. Liver recipients with ALD who remain abstinent after transplant have been found to survive on average just as long as if not longer than recipients with other causes of liver disease. However, relapse rates during the first 5 years after transplant in the United States have been documented in the range of 30% to 50%,[1-4] and return to alcohol use is associated with worse outcomes including graft injury and death.[5-9] Given a US organ shortage, resulting in daily deaths of those on the liver transplant waitlists, the allocation of organs to candidates with higher risk of posttransplant alcohol relapse presents an ongoing clinical and ethical concern.

Multiple previous studies have investigated associations between demographic and clinical factors and posttransplant relapse. These studies have found that age, social support, family history of alcohol use disorders, history of previous treatment for an alcohol use disorder, length of pretransplant abstinence, smoking, comorbid substance use and psychiatric disorders, and noncompliance with clinic visits all have an impact on posttransplant relapse risk.[1,2,8] In 2016, the International Liver Transplant Society endorsed recommendations that candidates with ALD undergo assessment by mental health specialists,

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regardless of specific length of sobriety, and engage in addiction treatment if indicated.[10] However, the recommendations did not characterize appropriate candidates or type and duration of interventions, deferring to local addiction experts. Moreover, few studies have examined the efficacy of psychosocial treatment interventions, which are the primary evidence-based approaches for treatment of alcohol use disorders, specifically for populations of liver transplant recipients.

More than 2 decades ago, Wagner et al[11] called for empirical studies into modified relapse prevention therapies for patients with ALD. Subsequently, 4 European groups evaluated alcohol treatment interventions specific for their populations of liver candidates.[12-15] Two of the groups had impressive findings. Björnsson et al[13] implemented "structured management," which included psychosocial assessment by an addictions expert and addiction treatment. Their relapse outcomes proved superior to those from prior studies and their comparison group; they noted decline in the relapse rate from 48% to 22%. Addolorato et al[12] found significantly improved rates of posttransplant abstinence after implementing a psychosocial treatment program embedded in their liver transplant center.

In the United States, Weinrieb et al[16] pursued the first randomized, controlled study of motivational enhancement therapy for alcohol use disorders in patients with ALD awaiting transplant. Motivational enhancement therapy provided no significant benefit over standard community treatments in relapse to drinking, mood, general health outcomes, or survival. Rodrigue et al[17] reviewed an ALD cohort for associations between substance abuse treatment/Alcoholics Anonymous (AA) and posttransplant sobriety. Attendance at AA meetings was included in the definition of treatment. Thirty-four percent of the total group relapsed to any alcohol use. Only recipients pursuing both pretransplant and posttransplant treatment had significantly lower rates of alcohol relapse.

Transplant centers in the United States do not have uniform guidelines regarding candidate involvement in treatment programs for alcohol use disorders and AA meetings as prerequisites to listing, although they are competing for a shared organ supply.[18] This study examined the impact of application of a specific treatment guideline, which included pretransplant addiction treatment and AA attendance, on liver recipients with ALD at a major US transplant center. It also explored the role of other demographic, psychosocial, and medical factors, including smoking, on the outcome measures of posttransplant relapse and survival in liver recipients with ALD.

METHODS

Study Setting

This retrospective cohort study was approved by the Institutional Review Board of Mayo Clinic and conducted in compliance with established ethical standards. It included all patients with a primary or secondary diagnosis of ALD receiving liver transplant at the William J. von Liebig Transplant Center, Mayo Clinic, Rochester, Minnesota, from January 1, 2000, through December 31, 2012, who survived surgery. Study participants were 18 years of age or older. Multiorgan transplants were excluded from the study. For individuals who underwent more than 1 liver transplant, the study included the clinical data pertinent to the first transplant.

Participants and Assessments

Each patient in the cohort was diagnosed with cirrhosis by a transplant hepatologist and with *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* alcohol use disorder (or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* alcohol abuse or alcohol dependence) by an addiction psychiatrist. After initial pretransplant assessments by a social worker, addiction counselor, and addiction psychiatrist, the candidates followed up with the addiction psychiatrist or addiction counselor during subsequent quarterly or biannual pretransplant visits with the hepatologist. Psychiatrists have been embedded in the transplant center since 2000 and work with a multidisciplinary team including alcohol and drug counselors and social workers. The hepatologists and psychiatrists assessed candidates through clinical interviews and examinations and with biomarkers (urine or serum alcohol and drug levels, urine ethyl glucuronide, mean corpuscular volume, aspartate

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aminotransferase, alanine aminotransferase, and γ-glutamyltransferase).

All recipients received weekly follow-up care at the transplant center for 1 to 2 months after transplant. Follow-up care routinely included meetings with the addiction psychiatrist or counselor and laboratory testing to monitor liver function. After discharge to home from the transplant center, recipients returned for a 4-month posttransplant evaluation, a 1-year posttransplant reassessment, and annual evaluations thereafter. Whereas some patients followed up routinely with the psychiatrist or counselor, most returned for follow-up substance use care only if they reported slips or relapse to drinking, had positive urine screens, or had laboratory findings suggestive of return to drinking.

Data included demographic variables of age, sex, marital status, and race. The medical variables of interest were cause of liver disease, liver cancer diagnoses, use of medications for hepatic encephalopathy before transplant, presence of steatohepatitis in the explant, and body mass index. Psychiatric variables included abstinence dates for alcohol and other substances of abuse, type and completion of an addiction treatment intervention after diagnosis of liver disease and establishment of abstinence (counseling, outpatient, or residential treatment), attendance of AA (or alternative weekly self-help meetings), AA sponsorship, family history of alcohol or drug problems in first- and second-degree relatives, number of prior addiction treatments, smoking status, and depression.

Guideline Criteria

The transplant center initiated the guideline with the goals of standardizing practice and reducing risk of posttransplant relapse. The guideline was based on evidence within the addiction psychiatry/medicine literature, which has reported benefits from multiple psychosocial treatment interventions and AA.[19-21] The guideline included abstinence from alcohol, cannabis, illicit substances, benzodiazepines, and opioids unless approved by the transplant center staff; completion of an outpatient addiction treatment program (some patients were referred for individual counseling or residential treatment on the basis of substance use disorder severity and local treatment resources); and attendance of AA or other self-help addiction recovery meetings once weekly with sponsorship. The AA sponsors are individuals with prolonged alcohol abstinence who regularly attend the same meeting and provide support, accountability, and recovery guidance to their "sponsees."

The treatment component of the guideline was mandated for most candidates with less than 1.5 years of abstinence as a pragmatic cutoff. Many of the patients presenting for assessment already had 6 to 12 months of abstinence, although much of the time was spent ill or in hospital settings, and the patients still had little insight into their alcohol use disorder and skills for maintaining long-term abstinence. After 1.5 years, most patients struggled to obtain insurance coverage for a treatment program. The AA (or other self-help meeting) component was mandated for most candidates until they reached 3 years of abstinence. Although the treatment team encouraged indefinite involvement in AA for sober support, the team chose 3 years as a cutoff for mandated weekly attendance because most patients had achieved stable sober support systems by the time they had reached 3 years of abstinence. The guideline encourages tobacco product cessation, although it does not mandate it. Transplant listing was deferred for patients until completion of the guideline requirements, except in cases of urgent need for listing.

Exceptions to the guideline included the diagnosis of hepatocellular carcinoma, where immediate transplant listing may decrease waitlist time and improve outcome. Patients with ALD and hepatocellular carcinoma were advised that their eventual transplant would be contingent on completion of the alcohol use disorder guideline. Other guideline exceptions included select patients too encephalopathic or debilitated to complete the guidelines before transplant. If patients were deemed to have highly favorable prognostic factors for posttransplant abstinence and treatment adherence by the transplant selection committee, they were offered transplant listing contingent on agreement to complete posttransplant addiction treatment, generally in the transplant center's outpatient addiction program, during early posttransplant recovery.

TABLE 1. Demographic and Clinical Variables[a,b]

Demographic variables		Treatment and substance use variables				Medical and psychiatric variables	
Variables	Total (N=236)	Variables	Total (N=236)	Variables	Total (N=236)	Variables	Total (N=236)
Male sex		Any before treatment		Years sober, before transplant[c]		HCC	
Yes	188 (79.7)	Yes	212 (90.2)	Mean (SD)	4.54 (5.82)	Yes	77 (32.6)
		Counseling before transplant		Median	2.2	HCV	
Age at transplant (y)							
Mean (SD)	55.10 (7.30)	Yes	130 (55.3)	Range	0.0-30.2	Yes	89 (37.7)
Median	55.6	Outpatient, before transplant		Smoking at time of transplant		Steatohepatitis	
Q1, Q3	50.2, 60.4	No	65 (27.7)	No	190 (80.5)	No	211 (90.2)
Range	(33.4-72.0)	Yes	170 (72.3)	Yes	46 (19.5)	Yes	23 (9.8)
White		Residential treatment, before transplant		Smoking 6 months before transplant		Encephalopathy medication before transplant	
No	26 (11.0)	No	214 (91.1)	No	175 (74.2)	No	62 (26.4)
Yes	210 (89.0)	Yes	21 (8.9)	Yes	61 (25.8)	Yes	173 (73.6)
Married		AA, weekly before transplant		Family history of alcoholism		MELD score at first liver transplant	
Yes	177 (75.0)	Yes	135 (57.2)	Yes	109 (46.2)	Mean (SD)	16.70 (6.73)
Partner		Any before treatment or AA		Sponsor, before transplant		Depression at liver transplant	
No	45 (19.1)	No	22 (9.4)	No	114 (48.3)	No	194 (82.2)
Yes	191 (80.9)	Yes	213 (90.6)	Yes	122 (51.7)	Yes	42 (17.8)

[a]AA, Alcoholics Anonymous; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.
[b]Categorical variables are presented as number (percentage).
[c]Number (standard deviation).

Outcome Measures

Outcome data of this cohort were collected through December 31, 2016. Members of the research team (J.P.A. and T.D.S.) abstracted data from the electronic medical record.

Resumption (relapse) of alcohol use after transplant was divided into 4 categories:

1. *limited* (rare or infrequent drinking at daily and weekly doses within recommended standards of the National Institute on Alcohol Abuse and Alcoholism [NIAAA]: 4 or fewer drinks per day for men; 3 or fewer drinks per day for women; 14 or fewer drinks per week for men; and 7 or fewer drinks per week for women);
2. *low-dose* (regular use at doses within recommended standards of the NIAAA);
3. *high-dose without morbidity or mortality* (regular use above recommended standards of the NIAAA without morbidity or mortality);
4. *high-dose with morbidity or mortality* (regular use above recommended standards of the NIAAA with associated morbidity or mortality, which included elevated transaminases, fatty liver, pancreatitis, acute alcohol-induced hepatitis, and other medical problems directly associated with return to drinking per physician assessment).

Categories 1 and 2 were grouped as low-dose drinking. They were grouped together, given the unlikely negative impact of this degree of alcohol use on liver function, other organ systems, and medication adherence. Groups 3 and 4 were combined as the high-dose drinking group.[22]

Statistical Analyses

Baseline demographic and risk factor variables were characterized using percentage (categorical), mean (standard deviation), and median (continuous). Comparisons between those sober for less than 3 years and those sober for 3 years or more were evaluated using χ^2 test and *t*-test, respectively.

Survival (to death), time to any relapse, and time to high-dose relapse after transplant were evaluated using the Kaplan-Meier estimator and Cox proportional hazards regression. Time zero was date of initial liver

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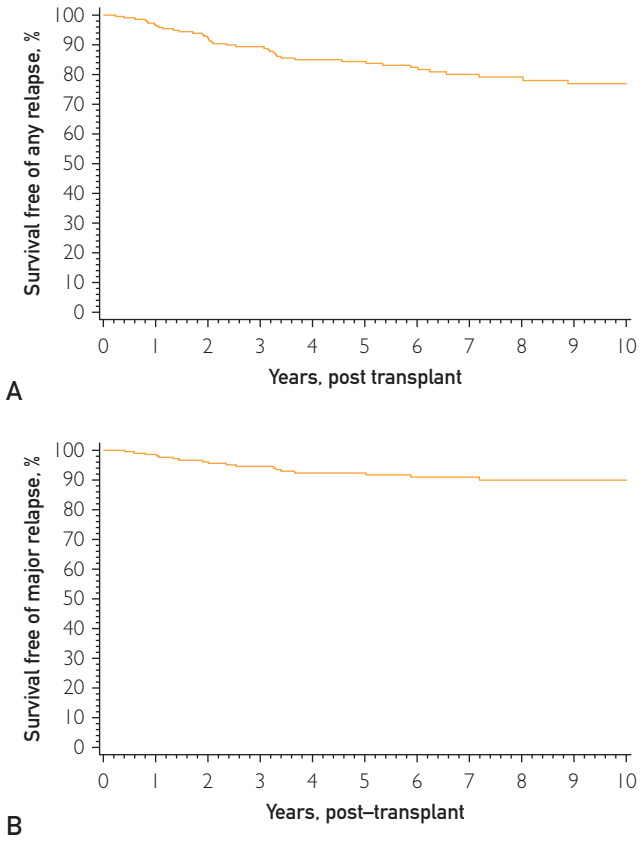

FIGURE 1. A, Yearly posttransplant survival rates free of any relapse. B, Yearly posttransplant survival rates free of major relapse.

transplant; censoring occurred on loss to follow-up or on December 31, 2017, whichever came first. For all landmark analysis, conditional on surviving and remaining in contact for 1 year, date of last contact was used as the censoring date. Anyone who experienced the end point during the first year was not eligible to be in the landmark analysis. Martingale residuals were used to assess the functional form of continuous baseline variables; Schoenfeld residuals were used to assess the proportional hazards assumption. For each of the 3 end points, stepwise Cox proportional hazards models were run with criteria to enter and to stay of α=.05.

Separately, the end points of any relapse and high-dose relapse were assessed as potential risk factors for death by treating them as time-dependent variables using start/stop methodology.[23] Here, a variable indicating relapse (or high-dose relapse) occurring before last follow-up or before death was set to 1 on the date of the first relapse (or high-dose relapse).

Yearly rates of each end point were assessed by enumerating the number of events (death, any relapse, or any high-dose relapse) and the person-years in each interval and dividing the number of events by the person-years. We assumed the events followed a Poisson distribution when calculating the 95% CIs (using the exact method).

RESULTS

Demographics and Medical Comorbidities

A total of 242 individuals with ALD received liver transplants between 2000 and 2012; of these, 6 individuals died the day of transplant, leaving 236 individuals available for follow-up. Of the 236 liver recipients, 188 (79.7%) were men, 210 (89%) were white, 177

TABLE 2. Yearly Rates of Any Relapse and High-Dose Relapse

	Any relapse				High-dose relapse			
Time (interval)	No.	PY	Rate, %	95% CI, %	No.	PY	Rate, %	95% CI, %
0-1 years	7	219.7	3.2	1.3-6.6	3	220.8	1.4	0.3-4.0
1-2 years	9	194.2	4.6	2.1- 8.8	5	198.2	2.5	0.8-5.9
2-3 years	6	173.2	3.5	1.3-7.5	3	181.7	1.6	0.3-4.8
3-4 years	8	155.2	5.2	2.2-10.2	4	165.8	2.4	0.6-6.2
4-5 years	1	144.1	0.7	0.0-3.9	0	153.6	0.0	0.0-2.4
5-6 years	3	123.7	2.4	0.5-7.1	2	133.6	1.5	0.2-5.4
6-7 years	3	100.5	3.0	0.6-8.7	0	111.4	0.0	0.0-3.3
7-8 years	1	79.4	1.3	0.0-7.0	1	90.4	1.1	0.0-6.2
8-9 years	2	68.9	2.9	0.4-10.5	0	79.9	0.0	0.0-4.6
9-10 years	0	60.7	0.0	0.0-6.1	0	71.7	0.0	0.0-5.1
10+ years	1	155.6	0.6	0.0-3.6	1	198.5	0.5	0.0-2.8

PY, person-years in interval.

(75%) were married, and 191 (80.9%) were partnered; median age at transplant was 55.6 years (Table 1). Mean (standard deviation) follow-up time was 88.6 (55.0) months. There were 140 (59%) who had been sober for 3 years or less before transplant. Sobriety for 3 years or less was associated with hepatocellular carcinoma (P=.001), treatment of encephalopathy with lactulose or rifaximin (P=.0013), and higher Model for End-Stage Liver Disease score at first transplant evaluation (P=.0011; Supplemental Table 1, available online at http://www.mcpiqojournal.org).

Substance Use Clinical Characteristics

Of the 236 transplant recipients, 212 (90.2%) participated in some type of pretransplant addiction treatment after establishing abstinence: 8.9% completed a residential treatment program, 72.3% an outpatient program, and 55.3% individual counseling. Also, 135 (57.2%) engaged in once-weekly pretransplant AA meetings (or other self-help meetings) before transplant, and 122 (51.7%) had an AA sponsor. The median duration of AA meeting attendance was 3 months. Posttransplant abstinence was not associated with number of pretransplant months abstinent or duration of pretransplant abstinence of more than 3 years (compared with those with abstinence of 3 years or less). Other noteworthy substance use clinical characteristics included family history of alcoholism in 109 (46.2%) and active smoking in 46 (19.5%; Table 1).

Posttransplant Relapse

Among the 236 patients with ALD, 41 returned to various degrees of alcohol use during follow-up after transplant. Of those, 22 of 41 experienced limited or low-dose use, and 19 of 41 relapsers returned to high-dose drinking. Of 93 deaths during the course of the study, 6 (6%) were secondary to alcohol-related causes. Therefore, 6 of 236 (3%) of the total cohort had alcohol-related death. During the first 5 years after transplant, 16.3% relapsed (any alcohol use), and after 10 years, 22.0% had relapsed (Figure 1A). Rate of relapse (any) was 3.2% (95% CI, 1.3%-6.6%) in the first year. Yearly relapse rates are tabulated (Table 2). In univariate analysis, a diagnosis of co-occurring hepatitis C virus was not associated with relapse. However, co-occurring hepatocellular carcinoma was associated with any relapse and high-dose relapse (P=.05 for both). Univariate analysis also found smoking within the 6 months before and at the time of transplant associated with any relapse and high-dose relapse (Table 3). Smoking within the 6 months preceding transplant, age (protective), and steatohepatitis (in the explant) came into the multivariable model and were associated with any relapse (Table 4).

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TABLE 3. Univariate Cox Proportional Hazards Modeling of Time to Any Relapse (r=41) and of Time to High-Dose Relapse (r=19)[a]

Variable	Any relapse			High-dose relapse		
	HR	95% CI	*P*	HR	95% CI	*P*
Male	1.50	0.63-3.57	.36	1.34	0.39-4.59	.64
Age at transplant (10-year increase)	0.59	0.39-0.88	.01	0.76	0.42-1.37	.37
White race	0.78	0.30-1.98	.60	0.92	0.21-3.97	.91
Sobriety evaluated before 2000	1.90	0.88-4.12	.10	1.31	0.38-4.54	.67
Any ALD treatment before transplant[b]	1.38	0.42-4.47	.59	—	—	.14[c]
Weekly AA meetings before transplant	1.38	0.73-2.60	.32	2.28	0.82-6.33	.11
Having a sponsor before transplant	1.77	0.94-3.34	.08	2.87	1.03-7.98	.04
Any partner or married	0.82	0.38-1.78	.62	1.04	0.30-3.59	.94
Married/long-term partner	0.74	0.37-1.47	.39	1.46	0.43-5.02	.55
Smoking at time of transplant	3.39	1.79-6.43	<.001	6.87	2.74-17.24	<.001
Smoking 6 months before transplant	3.76	2.02-6.97	<.001	9.71	3.47-27.16	<.001
Depression at transplant	1.78	0.89-3.55	.10	2.78	1.09-7.07	.03
HCV	1.22	0.65-2.27	.54	0.97	0.38-2.47	.95
HCC	0.47	0.22-1.01	.05	0.23	0.05-1.01	.05
Steatohepatitis	3.19	1.56-6.52	.002	1.64	0.48-5.65	.43
Family history of alcoholism	2.23	1.18-4.22	.01	2.18	0.86-5.53	.10
Pretransplant medications for encephalopathy	1.47	0.70-3.08	.31	1.13	0.41-3.15	.81
No. of months in AA before transplant	0.99	0.97-1.01	.54	1.00	1.00-1.02	.75
Less than 3 years of abstinence	1.09	0.58-2.06	.79	1.35	0.51-3.56	.54
Years sober before transplant	0.96	0.89-1.02	.18	0.95	0.85-1.05	.31
Per 1-unit increase in MELD score at first liver evaluation[d]	1.00	0.95-1.04	.91	0.96	0.89-1.04	.31

[a]AA, Alcoholics Anonymous; ALD, alcohol-induced liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MELD, Model for End-Stage Liver Disease.
[b]Counseling, outpatient, or residential treatment.
[c]Log-rank test *P* value; all 19 major relapsers had at least 1 before treatment.
[d]MELD score ≥40, set to 40.

Relapse to Any Alcohol Use More Than 1 Year After Transplant

Of the 205 patients without relapse at 1 year, 34 relapsed after 1 year. In univariate models, smoking at time of transplant and 6 months before transplant remained associated with an increased hazard of relapse, as did steatohepatitis in the explant. In univariate analysis, family history of alcoholism continued as a risk factor for relapse (hazard ratio [HR], 2.7; 95% CI, 1.3-5.6; P=.006), and older age was also significantly associated with a reduced hazard of relapse. Conditional on surviving 1 year, new depression and any (persistent) depression after transplant were associated with relapse (P<.001 for both). In the final model, smoking at the time of transplant, new depression, steatohepatitis, and having a sponsor before transplant all increased the hazard of any relapse by more than 2-fold (Supplemental Table 2, available online at http://www.mcpiqojournal.org).

Relapse to High-Dose Drinking

Among the 236 patients with ALD, 19 had a high-dose relapse after transplant. At 5 years after transplant, 8.2% had experienced a high-dose relapse (Figure 1B). The rate of high-dose relapse was 1.4% in the first year. Yearly rates of high-dose relapse are tabulated (Table 2). In univariate analysis, smoking within the 6 months before transplant, smoking at the time of transplant, depression at the time of transplant, and having a sponsor before transplant were associated with an increased hazard of high-dose relapse; those smoking 6 months before transplant had 9.7 times (95% CI, 3.5-27.2; P<.0001) and those

TABLE 4. Multivariable Cox Proportional Hazards Modeling of Time to Any Relapse (r=41) or Time to High-Dose Relapse (r=19)

Variable	Any relapse			High-dose relapse		
	HR	95% CI	*P*	HR	95% CI	*P*
Smoking during 6 months before transplant	3.76	2.02-7.02	<.001	10.24	3.66-28.63	<.001
Steatohepatitis	3.59	1.74-7.40	<.001			
Age per 10-year increase	0.60	0.39-0.92	.02			
Having a sponsor before transplant				2.78	1.00-7.74	.05
Depression at transplant				3.12	1.22-7.99	.02

HR, hazard ratio.

smoking at time of transplant had 6.9 times (95% CI, 2.7-17.2; P<.0001) the hazard of high-dose relapse compared with those not smoking (Table 3). Depression at transplant was associated with a nearly 3-fold increase in high-dose relapse (P=.03). Those who had a sponsor before transplant had 2.9 times the hazard of high-dose relapse as those without a sponsor (95% CI, 1.03-8.0; P=.04). Smoking within the 6 months before transplant, having a sponsor before transplant, and depression at transplant came into the stepwise multivariable modeling (Table 4). Smoking during the 6 months before transplant was associated with a 9.7-fold increase in the hazard of high-dose relapse in the joint model compared with no smoking (P<.0001).

Relapse to High-Dose Drinking More Than 1 Year After Transplant

Of the 209 patients who survived free of a high-dose relapse at 1 year, 16 had a high-dose relapse after 1 year. In univariate models, smoking at time of transplant and smoking 6 months before transplant were associated with an increased hazard of high-dose relapse (HR, 8.7 and 10.8, respectively; Supplemental Table 3, available online at http://www.mcpiqojournal.org). For those smoking within the year after transplant, the hazard of subsequent high-dose relapse was 4.4-fold higher than for those not smoking (P=.003). Having a family history of alcoholism was associated with a 3.8-fold increased hazard of high-dose relapse compared with those without such a history (P=.02); any new depression was associated with a 3-fold increased hazard of high-dose relapse as well (P=.02). In multivariable modeling, smoking during the 6 months before transplant (HR, 9.9; P<.0001) and a family history of alcoholism (HR, 3.3; P=.04) were associated with an increased risk of high-dose relapse (Supplemental Table 3).

Mortality After Transplant

Among the 236 liver recipients, 89 people died by date of last follow-up (21% died within 5 years); median survival was 13.4 years (Figure 2). Death rate was 7.6% (95% CI, 4.4%-12.1%) in the first year (for yearly death rates, see Supplemental Table 4, available online at http://www.mcpiqojournal.org). Univariate analysis found smoking at the time of transplant and use of medications for pretransplant encephalopathy associated with death; those smoking at the time of transplant had 1.9 times (95% CI, 1.2-3.0) the hazard of death (P=.01), and those using encephalopathy medications had 2.2 times (95% CI, 1.2-3.9) the hazard of death (P=.01). Marriage/long-term partnership was protective against death (HR, 0.61; P=.03). Neither comorbid hepatitis C virus nor hepatocellular carcinoma was associated with death. In stepwise multivariable modeling without time-dependent variables, both smoking at the time of transplant and use of encephalopathy medications before transplant were associated with a 2-fold increase in the hazard of death compared with those who did not smoke or did not use such

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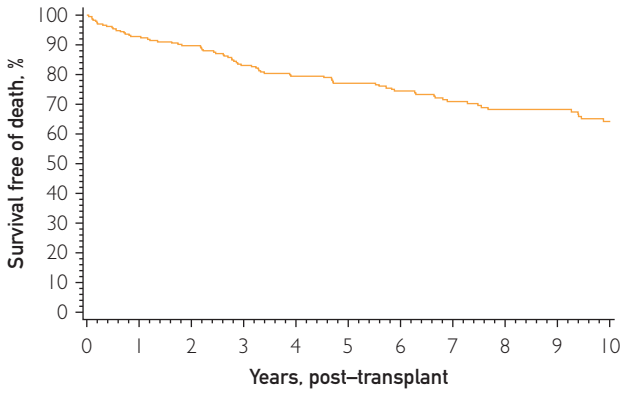

FIGURE 2. Yearly posttransplant survival rates free of death.

medications ($P<.004$ for both). In addition, having a sponsor before transplant was marginally associated with an increased hazard of death ($P=.02$). The time-dependent variable of high-dose relapse was associated with a more than 3-fold increase in the hazard of death compared with never having a high-dose relapse (no relapse and low-dose relapse) in univariate analysis (HR, 3.5; 95% CI, 1.9-6.5; $P<.0001$). In the stepwise modeling, when the 2 time-dependent variables (any relapse or high-dose relapse) were allowed to compete, only high-dose relapse came into the model (Supplemental Table 5, available online at http://www.mcpiqojournal.org).

Mortality More Than 1 Year After Transplant

Of the 211 recipients not lost to follow-up and surviving 1 year, 67 died during subsequent monitoring. Smoking during the 6 months before transplant and smoking at the time of transplant were associated with an increased hazard of death; hazards were 1.8 and 2.3 times higher ($P=.03$ and $P=.002$, respectively; Supplemental Table 6, available online at http://www.mcpiqojournal.org). In multivariate analysis, smoking at time of transplant was most strongly associated of the 2 with an increased risk of death; use of encephalopathy medications increased the hazard of subsequent death (HR, 2.5; 95% CI, 1.3-5.0), and an increase in Model for End-Stage Liver Disease score reduced the risk of death (HR, 0.94; 95% CI, 0.89-0.98). Neither relapse (any) nor high-dose relapse in the first year was associated with death subsequently (after that year; $P\geq.58$ for both).

DISCUSSION

Previous US studies during the past 2 decades have reported 5-year posttransplant alcohol relapse rates in the range of 30% to 50% among liver recipients with ALD. Among posttransplant relapsers, some resume high-dose drinking with worsened outcomes, including death. Since 2000, our institution has applied guidelines for candidates with ALD that mandate abstinence from alcohol and other substances of abuse, addiction treatment (or counseling) for those with less than 1.5 years of abstinence, and weekly AA attendance with sponsorship for the first 3 years of abstinence. Among this cohort of liver recipients with ALD, in which 90.2% completed some form of pretransplant alcohol use disorder treatment intervention and 57.2% attended AA weekly, only 16.3% resumed drinking during the first 5 years after transplant and 22.0% at 10 years. Of those, less than half resumed high-dose drinking, and 6% of the recorded deaths were associated with alcohol-related causes. These findings suggest the benefits of abstinence and treatment interventions, developed with the purpose of strengthening relapse prevention skills and development of sober support systems, for improvement of recipient outcomes and responsible stewardship of organ donations

compared with other historical models of care for these patients.

There were no direct associations between relapse and pretransplant alcoholism treatment (any type) or weekly AA attendance. Given the generally uniform application of the guideline, these findings were not surprising. Those who did not undergo treatment or attend AA were most often candidates with prolonged abstinence and strong sober support at the time of presentation to the transplant center. Therefore, those not mandated to attend treatment were deemed to be at low risk of relapse at time of presentation. Fewer recipients participated in AA (57.2%) than attended treatment (72.3% completed outpatient treatment and 55.3% attended individual counseling). This finding probably reflects the urgency for transplant in some recipients, who completed treatment without engaging in AA before transplant, and those who sought individual long-term counseling as an alternative to AA. More surprising was the absence of association between pretransplant months abstinent and long-term abstinence, which has been repeatedly found in previous research.[2,9] This finding may suggest that along with community sober support through AA, insight into addiction and relapse triggers eclipses the role of months abstinent as a factor in supporting long-term abstinence, when these are present. Also unexpected was the absence of difference between the group with abstinence of 3 years or less and the group with abstinence of more than 3 years in any relapse or high-dose relapse. Again, the finding may indicate that the interventions of treatment and AA are the critical factors for those with shorter duration of abstinence and that abstinence longer than 3 years predicts low risk of relapse in liver transplant recipients in general.

These relapse results compare favorably with those found by DiMartini et al[2] in their carefully monitored prospective study of 167 liver recipients with ALD at the University of Pittsburgh Medical Center. In their cohort, 42% had taken at least 1 drink by the end of 4.5 years and 26% had engaged in binge drinking (comparable to the high-dose drinking category). They also compare favorably with those of Rodrigue et al[17]; among their cohort of 118 recipients, 34% relapsed to some degree of alcohol use, and their mean post–liver transplant follow-up duration was only 55 months compared with 89 months for this study.

Prior studies with some of the lowest posttransplant relapse rates come from Europe. In their 2005 controlled study providing 5-year follow-up data, Björnsson et al[13] substantially reduced relapse in a cohort of patients with ALD from 48% to 22% through "structured management." Their pretransplant process included an interview by a psychiatrist and 12-step–based alcohol use disorder treatment. Pfitzmann et al[9] published similarly impressive results of a 19% relapse rate in a cohort of 300 patients with ALD with a mean follow-up time of 7.4 years. Six months of pretransplant abstinence was mandated for listing, although the study did not otherwise specify candidate involvement in alcohol use disorder treatment interventions or AA. Our findings build on those of Björnsson et al, which suggest that psychiatric assessment and alcohol use disorder treatment may be factors in lowering the posttransplant relapse rate.

The 5-year survival of 79% in our total cohort compares favorably with the national 5-year survival rate in liver recipients of 75%.[24] This survival rate is likely to be due to many positive factors, including surgical technique and medical skills of the multidisciplinary transplant team, in addition to selection of patients. Of note, those who had a high-dose relapse had an increased hazard of death of more than 3-fold ($P<.0001$). Thus, in the context of consistent guidelines, where the high-dose relapse rate was low, the guidelines may have been a factor in high cohort survival.

Rogal et al[25] associated untreated and undertreated posttransplant depression with mortality. Our findings did not associate posttransplant depression with death (Supplemental Table 6); however, on univariate analysis, an association with persistent and new depression with high-dose relapse was suggested. Also, a pretransplant AA sponsor was associated with a high-dose relapse. This counterintuitive finding may imply that those deemed at greatest risk for relapse were more often mandated to engage in AA before transplant. Only 51.7% of the total cohort had an

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AA sponsor before transplant; thus, nearly 50% were allowed to move forward without AA sponsorship despite the guideline. Those not mandated by the treatment team to obtain sponsorship were more likely to have other strong sober support or absence of available sponsors in more remote areas.

Our findings strikingly associate smoking with relapse and with death. Cox modeling identified smoking during the 6 months before transplant as significantly associated with both time to any relapse and time to high-dose relapse at a level of $P<.0001$. This finding, consistent with previous studies associating smoking and relapse,[26-29] has implications for transplant program expectations and guidelines regarding pretransplant smoking cessation. Moreover, smoking at time of transplant was associated with time to death, conditional on surviving 1 year. Thus, the effect of persistent smoking before transplant had a long-term negative impact on survival. Given the association between persistent smoking and relapse and the direct associations between both relapse and persistent smoking and survival, mandated pretransplant smoking cessation in liver candidates is a reasonable consideration to improve recipients' outcomes.

This study had several limitations. First, it was retrospective and without control or randomization. Nonetheless, it demonstrated a "real-world" consistent application of a treatment guideline during 12 years in a clinical setting, where level of care (residential vs outpatient treatment vs counseling interventions) is often dictated by insurance coverage. As a retrospective study, the cohort did not consistently receive psychiatric/addiction follow-up care on annual return visits to the transplant center. This limitation was offset by lifelong annual posttransplant hepatology follow-up care at our transplant center, which consistently included inquiry about alcohol use, urine screening for alcohol and drug use, laboratory testing, liver biopsies, and ultrasound examinations for evidence of recurrent disease. Although rare or low-dose drinking was likely to be underreported, relapse with negative impact on liver function would have been detected by the hepatology team. Second, this liver transplant cohort was predominantly male, white, and married/partnered, thus potentially limiting application of the findings to other demographic groups. Third, treatment programs and AA meetings vary considerably across communities and states in their quality and helpfulness to recovering alcoholics. Whereas absence of intervention standardization may diminish the extent to which one can draw conclusions about their efficacy, any retrospective study that incorporates community-based treatment programs and AA attendance will include heterogeneity of patient experience. As a cohort receiving treatment interventions and AA engagement, comparable to standard recommendations for nontransplant alcoholic populations, it appeared to benefit from these guidelines with less return to drinking.[19,21,30] Last, we have outcome data only for candidates who completed the guidelines and survived until transplantation, making the recipients a select and motivated cohort compared with those unwilling to follow guidelines, who may have undergone transplantation at another institution.

CONCLUSION

With a limited organ supply and daily deaths on transplant waitlists, the transplant community has an ethical imperative to serve as a wise steward of solid organs. This stewardship involves minimizing risk of graft loss and recipient death from preventable posttransplant negative outcomes, such as relapse to alcohol use. This study affirms in a large cohort during more than a decade several previous findings of predictive factors for posttransplant relapse and death, particularly persistent smoking before transplant. It also suggests the efficacy of a guideline for candidates with ALD, which included abstinence, treatment, and AA meeting involvement, in reducing posttransplant relapse and death. These findings warrant future prospective studies in liver transplant cohorts with ALD, and they behoove transplant programs to incorporate consistent guidelines into the care and pretransplant management of the candidate with alcohol-related liver disease.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AA**, Alcoholics Anonymous; **ALD**, alcoholic liver disease; **NIAAA**, National Institute on Alcohol Abuse and Alcoholism

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