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LIVER TRANSPLANTATION FOR ALCOHOLIC CIRRHOSIS: LONG TERM FOLLOW-UP AND IMPACT OF DISEASE RECURRENCE[1]

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Background. Alcoholic liver disease has emerged as a leading indication for hepatic transplantation, although it is a controversial use of resources. We aimed to examine all aspects of liver transplantation associated with alcohol abuse.

Methods. Retrospective cohort analysis of 123 alcoholic patients with a median of 7 years follow-up at one center.

Results. In addition to alcohol, 43 (35%) patients had another possible factor contributing to cirrhosis. Actuarial patient and graft survival rates were, respectively, 84% and 81% (1 year); 72% and 66% (5 years); and 63% and 59% (7 years). After transplantation, 18 patients (15%) manifested 21 noncutaneous de novo malignancies, which is significantly more than controls ($P=0.0001$); upper aerodigestive squamous carcinomas were overrepresented ($P=0.03$). Thirteen patients had definitely relapsed and three others were suspected to have relapsed. Relapse was predicted by daily ethanol consumption ($P=0.0314$), but not by duration of pretransplant sobriety or explant histology. No patient had alcoholic hepatitis after transplantation and neither late onset acute nor chronic rejection was significantly increased. Multiple regression analyses for predictors of graft failure identified major biliary/vascular complications ($P=0.01$), chronic bile duct injury on biopsy ($P=0.002$), and pericellular fibrosis on biopsy ($P=0.05$); graft viral hepatitis was marginally significant ($P=0.07$) on univariate analysis.

Conclusions. Alcoholic liver disease is an excellent indication for liver transplantation in those without coexistent conditions. Recurrent alcoholic liver disease alone is not an important cause of graft pathology or failure. Potential recipients should be heavily screened before transplantation for coexistent conditions (e.g., hepatitis C, metabolic diseases) and other target-organ damage, especially aerodigestive malignancy, which are greater causes of morbidity and mortality than is recurrent alcohol liver disease.

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INTRODUCTION

Hepatic transplantation is an accepted standard of care for end-stage liver disease. One-year survival rates approach

80% to 85% and late graft loss from chronic rejection is uncommon (*1*). Unfortunately, recurrence of the original disease is emerging as a major problem, affecting most viral hepatitis patients and 15% to 25% of those with autoimmune liver diseases within 5 years (*2, 3*). End-stage alcoholic liver disease may be an excellent indication for transplantation, because short-term survival rates are comparable with other indications (*4–6*), and drinking relapse can potentially be controlled.

Indeed, alcoholic liver disease has emerged as a leading indication for transplantation (*7*), although it is a controversial use of resources (*8*) because the original disease and recurrence require "deliberate" patient activity. Studies of alcoholic liver transplant recipients have therefore justifiably focused on alcohol relapse, hoping to provide support for stringent pretransplant selection criteria that are intended to minimize disease recurrence. This approach, however, has deflected attention away from the impact of coexistent diseases such as viral hepatitis and aerodigestive cancers. A holistic approach that addresses these issues is required.

We undertook this retrospective cohort analysis (123 alcoholic patients, median 7 years follow-up at one center) to examine all aspects of liver transplantation associated with alcohol abuse. We aimed to better define the impact of past alcohol use, associated diseases, and drinking relapse on survival and graft disease.

METHODS

Data Collection

Between January 1991 and December 1992, 123/513 (24%) primary liver allograft recipients at the University of Pittsburgh had a diagnosis of alcoholic liver disease. The diagnosis was determined from a consensus of surgical, hepatological, and psychiatric evaluations; patients had a history of sustained excessive alcohol use (normally ≥20 g ethanol/day, women; ≥60 g ethanol/day, men) with a diagnosis of alcohol abuse or dependence after psychiatric evaluation in conjunction with laboratory data. Before abstinence, most patients drank on a daily basis; for others, the average weekly alcohol usage was converted into average daily drinks for comparison. Daily alcohol consumption, by patient report, was converted to grams of ethanol. For lifetime ethanol exposure, the average daily amount was multiplied by the duration of drinking. The criteria for transplant eligibility that related to alcohol use were relatively liberal: 6 months pretransplant sobriety, or rehabilitation, with exceptions in select cases.

Pretransplant serology for hepatitis B and C (EIA-2) virus infection was available in 119 patients, the others were missing serology for hepatitis B (n=1), hepatitis C (n=2), and both hepatitis B and hepatitis C (n=1). Coexistent disease(s) were discovered primarily during examination of the native hepatectomy specimens and serologic studies for viral hepatitis infection. A diagnosis of hemachromatosis was based on the presence of at least 3+ iron deposited primarily in biliary epithelial cells and hepatocytes, a pattern indicative of hemachromatosis. Cases with significant iron overload in nonparenchymal cells and periseptal hepatocytes were not included. A diagnosis of alpha-1-anti-trypsin deficiency was based on the presence of large (>4 microns) periodic acid-Schiff positive globules, after diastase digestion, which has been previously shown to correlate with α_1-antitrypsin abnormalities (*9*).

The histology slides from all native livers and allograft biopsies were reviewed, without knowledge of the clinical findings, and then correlated with clinical and radiological data to generate a record of patient follow-up. The necro-inflammatory activity and fibrosis staging were carried out according to the modified hepatitis activity index of Ishak et al. (*10*) Allograft biopsies were performed for investigation of graft dysfunction. Three patients had no allograft biopsy. Fifty-two patients had allograft biopsies more than 6 months after transplant (including failed allografts).

Alcohol relapse was defined as any alcohol use revealed by the patient after transplant, or ad hoc blood alcohol assays. All patients with abnormal monthly liver biochemistry were questioned about relapse, but there were no protocol prospective interviews or alcohol assays. Latest follow-up was taken to be date of death, graft failure, or the latest laboratory test. Where patients were retransplanted, data pertinent to the first graft was used for statistical analysis. A comparison group was generated from the other 390 patients receiving primary liver transplants during the same period. These studies were approved by the local institutional review board approval (protocol #2105PUHnew).

Statistical Analyses

Statistical analyses included basic descriptive statistics, chi-square and non-parametric tests, and modeling techniques including logistic and Cox proportional hazards regression. All models comparing those who underwent transplantation for alcoholic liver disease with the nonalcoholic group were fit adjusted for age, sex, and severity of illness (UNOS status) at the time of transplantation. Survival rates were obtained using the Kaplan Meier method. Time-dependent covariates were used when appropriate. Analyses were performed using Statistical Analysis System for Windows (version 6.12).

RESULTS

Pretransplantation Characteristics

The study cohort contained 91 men and 32 women, of median age 53 years (range 28–75). All but one patient had cirrhosis. Alcohol was the only identified factor in 80 (65%), whereas 43 (35%) had another possible contributing factor; these included hepatitis C (20/120 tested, 17%), hepatitis B and acute acetaminophen toxicity without cirrhosis (1/121, 0.8%), hemochromatosis (9[including one with α_1-anti-trypsin deficiency]/123, 8%), α_1-anti-trypsin deficiency alone (4/123, 3%), sarcoidosis (1/123, 0.8%), epithelioid granulomas of unknown cause (2/123, 1.6%), and explant hepatitis in seronegative patients (see below, 6/123 5%). Twelve patients (10%) had hepatocellular carcinoma (T2–T4), and one had an unsuspected peripheral cholangiocarcinoma.

Complete pretransplant alcohol histories, including nature, quantity, frequency, and duration of alcohol intake, were available for 110 patients (29 women, 81 men); the remainder had less complete but adequate documentation of excessive intake. Women reported alcohol consumption before transplant of median 93 g/day (range 23–675 g/day), and men reported a median 140 g/day (range 23–955 g/day). The median estimated lifetime intake of alcohol was 408 kg (range 85–3572 kg) for women, and 638 kg (range 51–8038 kg) for men. Men had a longer median duration of drinking than women (15 years vs. 12 years), whereas women had a longer median duration of pretransplant sobriety (26 months vs. 12 months).

Native Liver Pathology Review

Fifty-six of 123 native livers (45%) had features suggestive of alcoholic liver disease, including livers from 9 hepatitis C–infected patients (Table 1). These features included micronodular cirrhosis, perivenular pericellular fibrosis, central-nodular Mallory's bodies (41 cases), and steatohepatitis

TABLE 1. **Histologic determinations of prevalent injuries in 123 explanted native livers, relative to assessment of alcohol injury**

Histopathologic evidence for alcohol-related liver injury	Number of patients	Histopathology suspicious for HCV/HCV seropositive cases	Histopathology of coexistent conditions (n)
None/minimal	67 (54%)	9/11 (82%)	hemochromatosis (3) α_1-antitrypsin deficiency (2) epithelioid granulomas, unknown cause (2) HBV + acute acetaminophen toxicity (1) ? viral hepatitis, but seronegative (6)
Mild	25 (20%)	0/3	hemochromatosis (4[a]) α_1-antitrypsin deficiency (2) sarcoid (1)
Moderate/strong	31 (25%)	1/6 (17 %)	hemochromatosis (2) α_1-antitrypsin deficiency (1)

[a] One patient had evidence of both hemochromatosis and α_1-antitrypsin deficiency.
HCV, hepatitis C.

(4 cases; always focal) *(11)*. Twenty-three (34%) of the other 67 livers without evidence of alcohol injury showed some other insult on histology (Table 1). Six native livers without alcohol injury showed chronic hepatitis, but were from patients with negative pretransplant viral serology. Nevertheless, four of the six patients went on to develop allograft viral hepatitis B or C after transplantation, suggesting that the pretransplant serology was false negative. If that assumption is made, then the explant histology did not indicate a cause of the cirrhosis in 44/123 (36%) patients.

Mallory's bodies ($P=0.0044$) and steatosis ($P=0.0201$) were more frequent in patients with shorter pretransplant sobriety (Table 2). Steatohepatitis (4 cases) was too infrequent for correlation.

Graft and Patient Survival after Transplantation

Follow-up was available for all patients (median 2543 days). Tables 3 and 4 detail causes of graft failure and death. Actuarial patient and graft survival rates were, respectively, 84% and 81% (1 year), 83% and 80% (2 years), 72% and 66% (5 years), and 63% and 59% (7 years). Graft and patient survival did not differ significantly from controls transplanted during the same period (data not shown). Seventy-one (57%) patients had functioning first allografts at latest follow-up (median 2647 days, range 1513–2931). Hepatocellular carcinoma recurred in 3 of 12 patients (170, 260, 720 days) and caused death.

Extrahepatic Malignancy after Transplantation

Excluding posttransplant lymphoproliferative disorders (PTLD), 27 patients developed 33 new malignancies after transplantation. This is significantly more than in nonalcoholic controls (Table 5; $P=0.0001$). Eighteen patients (15%) manifested 21 noncutaneous malignancies, which is also significantly more than controls ($P=0.0001$); in 7 patients the malignancy was fatal. The most common primary sites were upper aerodigestive, urogenital, lung, and colonic (Table 5). Upper aerodigestive squamous carcinomas were overrepresented compared with controls ($P=0.03$). Twelve patients (10%) (including three with noncutaneous malignancies) developed cutaneous malignancy—none fatal. Three patients (2.5%) (including one with colonic adenocarcinoma) developed PTLD; it was fatal in two.

TABLE 2. **Correlation of duration of sobriety before transplantation with steatosis and Mallory's bodies in the explanted native liver**

Sobriety (months)	Mallory's bodies[a]	Steatosis[b]
1–6	18/32 (56%)	21/32 (66%)
7–24	9/41 (22%)	14/41 (34%)
>24	11/46 (24%)	19/46 (41%)

Sobriety duration was known in 119 patients. Mallory's bodies: central nodular location required to eliminate examples due to cholatestasis ([a] $P=0.0044$; [b] $P=0.0201$). The analysis was done using two different logistic regression models. Mallory bodies and steatosis were the two dichotomous outcomes and pretransplant sobriety was the independent variable. Thus, the one univariate model indicated that pretransplant sobriety does affect Mallory bodies, and the other univariate model indicated that pretransplant sobriety affects steatosis.

TABLE 3. **Causes of death or graft failure in the first 6 months after transplantation (first graft only)**

	Number of patients	Time range (days)
Cause of death		
Cardiovascular	2	1–2
Infection	9	21–159
Graft failure without death		
Primary nonfunction	4	0
Hepatic artery thrombosis	2	6–15

Alcohol Relapse: Incidence and Impact

Thirteen patients had definite relapse, confirmed in eight by positive blood alcohol tests (on multiple occasions in four, and >100 mg/dl in six), and admitted by five others. Three patients relapsed within 6 months after transplantation. Three additional patients had histology suspicious for relapse, but without other evidence, and denied alcohol use. Logistic regression using variables of the alcohol history (length of sobriety, duration of drinking, lifetime ethanol consumption, average drinks per day), native liver histology, and posttransplant liver injury tests was used to identify markers of relapse after transplantation. Daily ethanol consumption was significant when all 16 patients were considered ($P=0.03$), and marginally significant when only the 13

TABLE 4. Causes of death or graft failure after 6 months (first graft only) (n=35)

Cause of death	Graft disease	Patient number (%)	Time range (days)	Comments
Cardiovascular		3 (9)	1805–2351	
Suicide		1 (3)	370	
PTLD		2 (6)	783, 1841	
Recurrent HCC		3 (9)	265–1316	
New malignancy (invasive carcinomas)		7 (20)	577–2169	upper aerodigestive (5) lung (1) uncertain primary (1)
Infection	HCV+cr+strictures (1) HCV (1) chronic bile duct injury (1)	5 (14)	236–2100	lung (3) abdomen (1) infected thrombus (1)
Hepatic encephalopathy	HCV+cr	1 (3)	1602	post-TIPSS encephalopathy
Unknown	No evidence	7 (20)	198–2636	transitional cell carcinoma (2)
Graft failure without death				
	Hepatic artery thrombosis	3 (9)	1126–1339	
	Biliary strictures	2 (6)	291, 1731	
	HCV	1 (3)	1604	

HCC, hepatocellular carcinoma; HCV, hepatitis C infection; cr, chronic rejection; strictures, bile duct strictures; PTLD, posttransplant lymphoproliferative disorder; TIPSS, transjugular intrahepatic portosystemic shunt.

TABLE 5. New extrahepatic malignancies after transplantation

Primary	Histology	Number of tumors in alcohol cohort	Histology	Number of tumors in control cohort
Upper aerodigestive	Squamous	8	Squamous	2
Genitourinary	Transitional cell (4), Prostate adenocarcinoma (2)	6	Prostate adenocarcinoma	3
Lung	Squamous (2), Small cell (1)	3	Adenocarcinoma	2
Colorectal	Adenocarcinoma	2	Adenocarcinoma	3
Hematological (not PTLD)	Follicle centre cell lymphoma	1	Acute myeloid leukaemia	1
Unknown	Clear cell carcinoma	1	Adenocarcinoma	1
Other		0	Breast adenocarcinoma (1), Thyroid papillary (1), Duodenal Kaposi sarcoma	3
Skin	Squamous (10), Basal cell (1), Melanoma (1)	12	Squamous (2), Basal cell (5), Melanoma (1), Kaposi (1)	9
Total		33 (27/123pts)		24 (24/390pts)

relapse-confirmed patients were considered (P=0.09). At relapse, the serum GGTP:ALP ratio was elevated compared with nonrelapsers, whether the 13 known or the 16 known/suspected group was analyzed (relapsers vs. nonrelapsers: 1.13 vs. 0.63, median; P=0.017). Other factors analyzed, including steatosis and Mallory bodies in the native liver, duration of pretransplant sobriety, and estimated lifetime ethanol consumption, were not significant.

Allograft biopsies before relapse (12 patients) were not suspicious for alcohol injury. Seven of 13 patients had liver biopsies after relapse (1–10 biopsies, 2 weeks–4 years), of which only four had histology (mildly) suspicious for alcohol injury (Table 6). No patient had clear-cut alcoholic hepatitis. Only one patient had evidence of progressive fibrosis due to alcohol injury—moderate centrilobular pericellular fibrosis, 4.5 years after relapse. However, interpretation of the cause of fibrosis was complicated by concurrent hepatitis C infection and rejection-related central venulitis during this interval.

Although progressive alcohol injury was generally not seen in biopsies from relapse patients, they had other progressive liver disease; all five patients who were anti-hepatitis C–positive before transplant developed recurrent viral hepatitis, with four showing progressive fibrosis (maximum modified Chronic Hepatitis Fibrosis scores (*10*): 3/6 in two and 5/6 in

the other two), and the 5th showing de novo hepatitis B on latest biopsy (2543 days after transplant).

Four of the 13 confirmed relapse patients required hospital admission for noninfectious complications related to drinking, including acute alcohol toxicity, acute rejection after noncompliance, alcohol-related polyneuropathy, and recurrent acute pancreatitis. Poor compliance with immunosuppressive therapy was noted for three severely relapsing patients, two of whom developed chronic rejection in addition to recurrent hepatitis C with fibrosis. Four confirmed relapse patients died (321–2273 days after transplant): three from infection and one from a ruptured intracranial aneurysm. Follow-up of the surviving nine confirmed relapse patients ranged from 2265 to 2931 days. Of the three patients suspicious for relapse based on histology alone, one died (sepsis, 2019 days), and two survived (at 2711 and 2737 days follow-up).

Other Causes of Allograft Dysfunction

One hundred nineteen allografts (97%) had primary function. Twenty-six (22%) patients developed major biliary or vascular complications. These included 3 (2%) with biliary anastomotic leaks and 16 (13%) with bile duct strictures, of which 4 were associated with hepatic artery stenosis or

TABLE 6. Histopathological findings in allograft biopsies obtained after alcohol relapse

Patient	Days after transplant	Features suspicious for alcohol injury	Coexistent graft disease	Alcohol injury on later biopsies
1	210	None	HCV; cr	No (autopsy liver: 321 days)
2	465	Steatosis, rare Mallory	HCV	No (771, 946, 2300 days)
3	443	Marginal steatohepatitis	HCV; cr	Moderate pericellular fibrosis (1812 days)
4	1115	Mild steatofibrosis	None	No (1521, 1581 days)
5	1364	Steatosis	HCV	Marginal steatohepatitis (2543 days)
6	2288	None	None	N/A
7	2805	None	HCV	N/A

Allograft biopsies suspicious for alcohol injury, from patients without other evidence for relapse

1	1098	Steatosis	None	No (1393, 1544 days)
2	1193	Mild steatofibrosis	None	N/A
3	1281	Steatosis, rare Mallory	None	Marginal steatohepatitis (1968 days)

Steatosis, centrilobular steatosis; Mallory, centrilobular Mallory's bodies; Marginal steatohepatitis, steatosis with minimal acute inflammation, borderline for low grade steatohepatitis; Steatofibrosis, steatosis with perivenular and pericellular fibrosis, suggestive of inactive steatohepatitis; cr, chronic rejection.

thrombosis. Eleven patients (9%) developed allograft artery stenosis or thrombosis, and one developed portal vein thrombosis related to a chronic inflammatory pancreatic mass. We sought pretransplant factors that predicted these major biliary/vascular complications: univariate analyses identified high estimated lifetime ($P=0.0001$) and daily ($P=0.0008$) ethanol consumption. In addition, donor age ($P=0.03$; younger donor = fewer complications) and lifetime ethanol consumption were only marginally significant in a bivariate model ($P=0.11$ without an influential outlier). The duration of sobriety pretransplant, hepatitis C serology, and various native liver histological parameters were not predictive.

Biopsy-proven acute rejection affected 71 (60%) functioning allografts and was of moderate or severe intensity in 19 (16%). Forty-five (38%) patients had only a single acute rejection episode (range 1–5 episodes). The first rejection episode occurred later in patients with longer pretransplant sobriety ($P<0.02$). Chronic rejection affected three patients (2%) (321–1135 days), all of whom had poor compliance with the recommended immunosuppression. However, there was no significant difference in the rate of late-onset (>6 months) acute or chronic rejection between alcoholic patients that relapsed and those that did not or between the alcoholic cohort and the nonalcoholic controls (data not shown).

Sixteen (13%) patients showed chronic bile duct injury on biopsy. Proportional hazards regression using time-dependent covariates was used to evaluate the maximum and minimum liver biochemistry values during serial 6-month intervals after transplantation. Patients with chronic bile duct injury on liver biopsy had higher maximum and minimum GGTP ($P<0.001$ and 0.0001, respectively), SGOT ($P<0.04$ and 0.01, respectively), and higher minimum SGPT ($P<0.05$), compared with other transplanted alcoholics without chronic bile duct injury. The predictors of chronic bile duct injury were hepatitis C infection ($P<0.04$), and pericellular fibrosis on biopsy ($P<0.01$). Four (3%) patients had Cytomegalovirus graft infection (38–169 days).

Twenty patients showed hepatitis B or hepatitis C infection after transplant (Table 7). Hepatitis C recurred in 14 of 19 patients seropositive before transplant and was diagnosed on biopsy with positive serology—with confirmatory RT-PCR or branched chain DNA assays in 9 of 14 cases. Nine of 14

patients with recurrent hepatitis C developed fibrosis stage 3 (of 6) or worse on biopsy, including two stage 5 and one cirrhosis. Two additional patients developed hepatitis C antibodies after transplantation and showed hepatitis without fibrosis on biopsy (679, 1859 days; donor serology was negative). Fibrosis in hepatitis C infection progressed faster in relapsers compared with nonrelapsers, but numbers were small and the difference was not significant.

Patients who underwent transplantation for alcoholic liver disease alone had fewer graft biopsies than nonalcoholic controls transplanted for hepatitis C disease (median 4 vs. 6 per patient, $P=0.009$). Moreover, hepatitis C–seropositive alcoholics had more graft biopsies than hepatitis C seronegative alcoholics (median eight vs. four per patient, $P=0.0107$). Hepatitis B recurred in the patient with hepatitis B surface antigen pretransplant and affected five patients who were seronegative pretransplant (donor serology was negative). Since liver allograft biopsies in our population are carried out largely because of liver allograft dysfunction, the above results are at least one way of showing that recurrent hepatitis C disease has a greater impact on allograft dysfunction than recurrent alcohol abuse.

In a univariate model, viral hepatitis in the allograft was a marginally significant predictor of allograft failure, although numbers were small (hepatitis C alone: $P=0.07$; hepatitis C or hepatitis B: $P=0.073$). Multiple regression analyses for independent predictors of graft failure identified development of "mechanical" biliary or vascular complications ($P=0.01$); chronic bile duct injury on biopsy ($P=0.002$), and pericellular fibrosis on biopsy ($P<0.05$). When analyses of outcomes were repeated comparing those with lifetime etha-

TABLE 7. Viral hepatitis after transplant (20 patients)

Infection	Number of patients	Diagnosis (days after transplant)	Maximum modified HAI fibrosis score on biopsy
HBV, recurrent	1	1163	3
HBV, new onset	5	169–2543	0–6
HCV, recurrent	14	45–1364	0–6
HCV, new onset	2	679, 1859	0

(note: 2 patients developed both HBV and HCV graft infection)
HAI, hepatitis activity index; HBV, hepatitis B; HCV, hepatitis C.

nol consumption ≥600 kg vs. <600 kg (men) or ≥150 kg vs. <150 kg (women) with those with daily ethanol consumption ≥60 g vs. <60 g (men) or ≥20 g vs. <20 g (women) there were no significant differences.

DISCUSSION

Patients with cirrhosis and a history of excessive alcohol use are labeled as having alcoholic liver disease, a term that may inappropriately combine a social/psychiatric designation with a statement of etiology for liver disease. Two main reasons explain the difficulties in estimating the contribution of alcohol to cirrhosis. First, micronodular cirrhosis may evolve toward a macronodular pattern (12). In such cases, which are often without earlier biopsy, the final histology might be indeterminate for cause. Second, at least 31% of the patients in this and other studies had coexistent conditions that alone could have been the indication for liver transplantation (7, 13–18). Indeed, native livers from hepatitis C–infected patients here and in other studies often showed morphology of chronic hepatitis rather than alcohol injury (Table 1), suggesting that alcohol had exacerbated viral damage rather than the other way around (19, 20). In alcoholics, the presence and severity of clinical liver disease correlate with hepatitis C seropositivity (17, 21); alcohol may increase hepatitis C replication and liver injury (22) and accelerate fibrosis (23). Hence, such cases might be better regarded as a subgroup of the coexistent diagnosis (hepatitis C) rather than alcohol liver disease, especially when considering the impact of pretransplant diagnosis on graft outcome.

Alcoholic liver disease is cured by transplantation, but a legacy of social and systemic injury remains. The most serious medical predisposition is to malignancy (24), which was common—particularly aerodigestive carcinomas—and caused death in this and other studies (25–28). This is likely attributable to heavy smoking in addition to alcohol problems; however, we were unable to obtain smoking histories in both the study subjects and controls. Regardless, thorough otorhinolaryngology screening should be carried out before listing alcoholic patients for transplantation (27).

In contrast to some reports (27, 29) and its frequent use as a screening criterion (30, 31), pretransplant sobriety shorter than 6 months did not predict relapse in this or in previous studies at our center (34) and elsewhere (32–36). In our cohort, daily ethanol consumption better predicted relapse, perhaps because it better indicates the severity of addiction (37). No explant histological feature in this or another (38) study predicted relapse, unlike with Conjeevaram et al., who correlated Mallory bodies with relapse (16). The finding of many Mallory bodies in 16% of explants in the Conjeevaram study (16), compared with small foci in 33% explants here, suggest different pretransplant drinking behaviors.

The contribution of relapse to morbidity after transplantation has proved difficult to define (14, 39). Prospective studies show relapse in 34% to 95% of selected patients (14, 32, 40), and we have started a prospective study of alcohol use after transplant for alcoholic liver disease. Here we probably underidentified relapse; we relied largely on liver injury test abnormalities, patient reports of alcohol use, blood alcohol tests, and clinical suspicion through drinking patterns that could not be concealed. For less severe consumption, covert drinking may be difficult to detect.

Hepatic manifestations of relapse might include alcoholic liver disease, alcohol exacerbation of coexistent conditions such as hepatitis C, or late-onset acute or chronic rejection because of noncompliance (41). Here, recurrent alcohol liver disease was limited to steatosis (42) and was not responsible for progressive fibrosis. These results compare favorably with others: allograft alcoholic hepatitis and cirrhosis after relapse are well described (5, 16, 43, 44), but are uncommon and rarely cited as a significant cause of graft failure (6, 27, 30). Steatosis affected fewer than 10% of patients after 7 years follow-up, compared with much higher recurrence rates for autoimmune liver diseases or viral hepatitis (15–25% and >50%, respectively), with a proportion of the latter developing cirrhosis by that time. The possibility that alcohol relapse might accelerate hepatitis C–related fibrosis in allografts needs further study. Such studies should evaluate both alcoholic and nonalcoholic hepatitis C–infected patients (7, 42, 45–47), because nonalcoholic recipients report alcohol use after transplant as frequently as alcoholic ones (48). Late onset acute and chronic rejection attributable to poor compliance was a manifestation of heavy relapse, as reported (30), but was uncommon in this and other studies of those transplanted for alcoholic liver disease (5, 30, 49). Indeed, late-onset acute and chronic rejection were not significantly more common in relapsers than in nonrelapsers or in alcoholics versus nonalcoholic controls.

The infrequency of alcoholic liver disease after transplantation could be due to effective recipient screening, alcohol abuse short of the threshold needed for liver disease, short follow-up (50), factors that render the new liver alcohol-resistant, or any combination of these. Determinants of the alcohol threshold for liver disease probably include liver-intrinsic properties, because only about 20% of alcohol abusers develop clinical liver disease (21, 51, 52). There is a genetic predisposition to alcohol-related cirrhosis (53), perhaps involving polymorphic genes that also influence drinking behavior (54, 55), such as mitochondrial aldehyde dehydrogenase (56, 57). Study of relapsing alcoholic patients who do and do not develop alcoholic liver disease in the allograft might facilitate identification/understanding of allelic regulators of progressive alcohol-related liver injury.

Although recurrent alcohol liver disease was not a problem, heavy relapse clearly imposed health problems, reflected by admissions for noninfective complications and deaths from systemic infections (15, 27, 30, 39, 49, 58). Even so, our results are similar to other studies in which only 10% to 13% of patients had alcohol relapse that caused physical morbidity or mortality (59, 60). More importantly, this study reaffirms the good graft and patient survival of those transplanted for alcoholic liver disease, comparable with results in other liver diseases (7), and support our continuing relatively "liberal" selection policy.

We were able to identify clinical and histological factors predictive of graft failure. Major biliary and vascular complications are not surprising, while biopsy evidence of pericellular fibrosis or focal chronic bile duct injury is more subtle, but nonspecific, evidence of significant graft injury. Focal chronic bile duct injury has also been associated with hepatitis C infection before (61, 62), as we found here.

Past studies have found a lower acute rejection incidence in transplanted alcoholics, compared with other disease indications (63, 64), but more detailed correlations within the alcohol

group have not been reported. The present suggestion that long pretransplant sobriety is associated with freedom from early acute rejection is nevertheless difficult to rationalize.

In conclusion, alcoholism is a brain-centered addictive disorder in which people submit themselves to an alcohol-rich environment that can damage many tissues. Those presenting for liver transplantation might seem to be preselected for proclivity to alcohol-induced liver disease, but this study shows that up to 30% have coexistent diseases that alone could have necessitated liver transplantation. We found recurrent alcohol liver disease to be a relatively benign disorder by comparison with recurrent viral and autoimmune liver disease and not an important cause of graft failure. Nevertheless, heavy relapse in a minority of patients can shorten survival, primarily through infectious complications, and may accelerate progression of recurrent viral hepatitis.

Thus, in those without coexistent conditions, alcoholic liver disease is an excellent indication for liver transplantation. A new liver introduces a new genetic variable, which could potentially delay recurrent liver disease, even in severe relapse. Our data are insufficient to determine whether this is true, but consistent with the hypothesis. However, chronic alcohol-induced and other addictive behavior-induced injury (e.g. smoking) of other target continues to evolve, of which carcinogenesis may be accelerated by immunosuppression (65). Hence, patients should be heavily screened for other target organ damage, which is a greater cause of morbidity and mortality than recurrent alcohol liver disease.

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