JAMA Internal Medicine | Original Investigation

National Trends and Long-term Outcomes of Liver Transplant for Alcohol-Associated Liver Disease in the United States

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IMPORTANCE Alcohol-associated liver disease (ALD) has emerged as the most common indication for liver transplant in the United States, but data on the reasons for this increase and long-term post-liver transplant outcomes among liver transplant recipients are sparse.

OBJECTIVE To characterize trends and long-term outcomes of liver transplant for ALD in the United States between 2002 and 2016.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective, national cohort study used data from the United Network for Organ Sharing database to evaluate all liver transplants performed in the United States between January 1, 2002, and December 31, 2016.

MAIN OUTCOMES AND MEASURES National and regional trends in liver transplant for ALD, with a sensitivity analysis with hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC) included, and early (≤90 days after liver transplant) and late (>90 days after liver transplant) patient and graft survival.

RESULTS The cohort consisted of 32 913 patients, including 9438 with ALD and 23 475 without ALD (patients who had HCV infection and HCC indications were excluded). Median age of patients with ALD was 54 years (interquartile range, 47-60 years) and of patients without ALD was 54 years (interquartile range, 44-61 years). Patients with ALD (vs non-ALD) were more frequently male (7197 of 9438 [76.2%] vs 11 767 of 23 475 [50.1%]; $P < .001$) and white (7544 [80.0%] vs 17 251 [73.5%]; $P < .001$). The proportion of liver transplants for ALD increased from 24.2% (433 of 1791) in 2002 to 27.2% (556 of 2044) in 2010 and 36.7% (1253 of 3419) in 2016. With HCV infection included, the proportions of liver transplant for ALD were 15.3% in 2002, 18.6% in 2010, and 30.6% in 2016, representing a 100% increase in liver transplant for ALD, of which 48% was associated with a decrease in HCV infection as an indication for liver transplant. The magnitude of increase in ALD was regionally heterogeneous and associated with changes in patient characteristics suggestive of alcoholic hepatitis: decreasing age ($\chi^2 = 36.5$; $P = .005$) and increasing model for end-stage liver disease score ($\chi^2 = 69.1$; $P < .001$). Cumulative unadjusted 5-year posttransplant survival was 79% (95% CI, 78%-80%) for ALD vs 80% (95% CI, 79%-80%) for non-ALD; cumulative unadjusted 10-year posttransplant survival was 63% (95% CI, 61%-64%) for ALD vs 68% (95% CI, 67%-69%) for non-ALD ($P = .006$). In multivariable analysis, ALD was associated with increased risk of late death after liver transplant (adjusted hazard ratio, 1.11; 95% CI, 1.03-1.20; $P = .006$).

CONCLUSIONS AND RELEVANCE The findings suggest that early liver transplant for alcoholic hepatitis may be leading to broader acceptance of ALD for liver transplant. Late survival among liver transplant recipients with ALD was inferior to that among recipients with non-ALD indications, suggesting a need for future studies to identify patient profiles associated with best outcomes. Regional differences suggest heterogeneity in policies toward liver transplant for ALD.

JAMA Intern Med. doi:10.1001/jamainternmed.2018.6536
Published online January 22, 2019.

Invited Commentary
Supplemental content

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Alcohol-associated liver disease (ALD) has recently emerged as the most common indication for liver transplant in the United States.[1] This increase has been ascribed to the decline in hepatitis C virus (HCV) infection as an indication for liver transplant owing to direct-acting antiviral therapy.[2] However, there have been other recent changes in the management of ALD, including a shift in attitudes toward mandated periods of alcohol abstinence before liver transplant, frequently referred to as the "6-month rule."[3] Shortening the mandated period of alcohol abstinence would be anticipated to allow more patients with ALD to survive until liver transplant. In addition, recent studies[4-6] have shown increasing prevalence of harmful drinking among Americans that is most pronounced among women and persons of disadvantaged socioeconomic populations, highlighting the changing demographic features of ALD. An improved understanding of the factors influencing rates of transplant for ALD may help inform policy regarding liver transplant for this indication.

We hypothesized that a key factor associated with liver transplant for ALD was the landmark Franco-Belgian trial of early liver transplant for severe alcoholic hepatitis published in 2011.[7] In that pilot study of 26 patients, there was no mandated sobriety period before liver transplant (ie, early liver transplant).[7] The study revealed a survival benefit; however, liver transplant was only undertaken in a carefully selected subpopulation of patients with ALD with key inclusion criteria being severe alcoholic hepatitis as the first liver-decompensating event (ie, no prior episode of alcoholic hepatitis or liver disease), nonresponse to medical therapy, presence of close supportive family members, absence of severe comorbid disorders, agreement to adhere to lifelong abstinence from alcohol, and consensus about liver transplant selection among a multidisciplinary group of medical professionals who assessed each candidate.[7] These results prompted extensive discussion within the US transplant community regarding the need for mandated sobriety periods for ALD.[7-11] Recently, a multicenter US study[12] of early liver transplant for acute alcoholic hepatitis reported excellent short-term outcomes, with 84% 3-year survival among carefully selected patients. Whether this collective experience with early liver transplant for acute alcoholic hepatitis has encouraged a broader acceptance of ALD as an indication for liver transplant is the subject of our study. In addition, because early liver transplant for ALD is not uniformly accepted across US health care centers,[3] we evaluated the national and regional distribution of liver grafts for ALD.

Finally, because ALD is a leading indication for liver transplant, there appeared to be a need to reappraise post-liver transplant outcomes. Earlier studies[13,14] on posttransplant outcomes for ALD were conducted nearly a decade ago. The present study used a contemporary cohort from the United Network for Organ Sharing (UNOS) database to address the long-term outcomes after liver transplant for ALD and factors associated with early and late graft and patient survival.

Key Points

Questions Why has liver transplant for alcohol-associated liver disease doubled in recent years, and what is the long-term survival among recipients of a liver transplant for alcohol-associated liver disease?

Findings In this multicenter, prospective, national cohort study, 48% of the increase in liver transplant for alcohol-associated liver disease was associated with a decrease in liver transplant for hepatitis C virus infection. Five-year posttransplant survival was 11% lower in patients with alcohol-associated liver disease.

Meaning The findings suggest that changing attitudes regarding liver transplant for acute alcoholic hepatitis may influence use of liver transplant for alcohol-associated liver disease, with disproportionate changes across United Network for Organ Sharing regions; national policy may help address this disparity.

Methods

The study analyzed prospectively collected UNOS registry data from patients who underwent liver transplant between January 1, 2002, and December 31, 2016, reflecting the institution of the model for end-stage liver disease (MELD)–based allocation system and available UNOS follow-up time at analysis. The MELD score is a scoring system that incorporates values for serum bilirubin, creatinine, and international normalized ratio to predict 90-day mortality in patients with end-stage liver disease; possible scores range from 6 to 40, with higher scores indicating higher probability of short-term mortality. The University of California San Francisco Institutional Review Board deemed this study to be exempt from review because it used publicly available registry data containing only deidentified data.

Study Population

Adult liver transplant recipients were included to compare ALD vs non-ALD. Patients who were younger than 18 years or who had HIV, acute hepatic failure, MELD exception criteria (criteria that can be used to award increased priority to patients on the liver transplant list), or prior liver transplant were excluded. Patients with ALD included those with a primary listing diagnosis of alcoholic cirrhosis or alcoholic hepatitis. Patients with non-ALD included those with a primary listing diagnosis of nonalcoholic steatohepatitis, hepatitis B, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and cryptogenic and other liver diseases. The proportion of patients with non-ALD with a secondary listing diagnosis of ALD was determined. Categorization into ALD vs non-ALD was based on primary diagnosis for UNOS listing only. To evaluate trends in liver transplant for ALD associated with variables beyond the decline in HCV infection as an indication, the primary analyses excluded all patients with a primary or secondary listing diagnosis of HCV. Further, to evaluate the outcomes of early liver transplant for alcoholic hepatitis, patients with a listing or transplant diagnosis of hepatocellular carcinoma (HCC) were excluded because HCC is typically

an exclusion criterion in policies concerning early liver transplant.[3,12,15,16] We then performed sensitivity analyses with HCV infection and HCC included. In the sensitivity analysis involving HCC, patients with a secondary listing diagnosis of alcoholic cirrhosis or alcoholic hepatitis were categorized as having ALD if the primary listing diagnosis was HCC.

Recipient and Donor Characteristics

Baseline and clinical characteristics were captured at the time of liver transplant. Donor characteristics were those used to calculate the donor risk index.[17] Adjustment for era-effect and time-trend bias analyses (to reflect advances in surgical and medical management in liver transplant) was conducted by dividing the study period into 3 equal time intervals: liver transplant performed from 2002 through 2006, 2007 through 2011, and 2012 through 2016. These 5-year periods were chosen for ease of interpretation given that the cumulative survival results are summarized at 5- and 10 years after liver transplant. Sensitivity analyses of final multivariable survival models were performed by individual transplant year as a categorical variable to test the robustness of these era cut points.

Regional and National Trends in Liver Transplant for ALD

We assessed national and regional trends of liver transplants performed for ALD vs non-ALD by UNOS region (1 through 11) and by year of transplant. We assessed differences among the years of liver transplant in the proportion of liver transplants for ALD vs non-ALD by sex, Medicaid insurance status, age, and MELD at liver transplant.

To evaluate the potential association of the Franco-Belgian trial[7] with early liver transplant for alcoholic hepatitis we specifically compared the proportion of liver transplants for ALD with the proportion of liver transplants for non-ALD indications in 2002, 2010, and 2016. Although the Franco-Belgian trial was published in 2011, the data were first presented in 2009, and there is evidence that changes regarding liver transplant for alcoholic hepatitis were occurring in US centers by 2010, thus the rationale for the 2010 cut point. The cut points of 2002 and 2016 were selected to reflect the institution of the MELD-based allocation system and available UNOS follow-up time at analysis, respectively. We also assessed the proportion of liver transplant recipients with a primary listing diagnosis of alcoholic hepatitis.

Because there is no national policy regarding early liver transplant, we hypothesized that changes may vary regionally as liver transplant programs shifted their attitudes toward increased acceptance of early liver transplant for alcoholic hepatitis and ALD. To assess this hypothesis, we assessed regional changes in the proportion of liver transplants for ALD from 2010 through 2016 compared with changes from 2002 through 2010. In addition, to account for misclassification of alcoholic hepatitis as ALD in UNOS,[18] we evaluated other surrogates associated with alcoholic hepatitis (eg, higher MELD score, younger age).[18,19] We assessed trends in mean age and median MELD score at the time of liver transplant among patients with ALD and whether these factors correlated with the increase in the proportion of liver transplant for ALD overall or with regional variations from 2010 through 2016.

Posttransplant Patient and Graft Survival

Patient mortality was defined as death from any cause. Graft failure was defined as retransplantation or death. Results of earlier studies[12] have suggested high early mortality among patients with alcoholic hepatitis. Early (≤90 days after liver transplant) mortality reflects perioperative associations, whereas late (>90 days after liver transplant) graft and patient survival reflect nonperioperative associations. Among late events, cumulative probability of 1-, 5-, and 10-year graft failure and death were determined.

Statistical Analysis

Categorical variables were compared using the χ^2 test. Continuous variables were first assessed for normality; then comparisons were made using the 2-sample *t* test for variables with parametric distributions and the Wilcoxon rank sum test for variables with nonparametric distributions. Attributable increase was calculated from the absolute difference in percentage increase, comparing the cohort including and excluding HCV.

Trends in the proportion of liver transplant for ALD from 2002 through 2010 and 2010 through 2016 were estimated using a logit-binomial model for the annual number of liver transplants for ALD in each year with the total number of liver transplants as the number of trials. The model included main effects for region and year and the interaction between them. The effect of year was modeled as piecewise linear regression with a change point in 2010, defined so that the coefficient for year in the second period captured the change in trend. To evaluate regional variability in changes in trend, we tested the interaction between region and the coefficient for year in the second period. Goodness of fit was checked using scatter plots of the observed and fitted year-specific proportions of liver transplants for ALD.

With a focus on 2010 through 2016, trends in mean age and median MELD score among ALD and non-ALD liver transplant recipients were examined using linear and quantile regression, which respectively minimize the sum of the squared and absolute deviations between the observations and fitted values; quantile regression was used for MELD to address skewness. To estimate and compare trends in the ALD and non-ALD groups, the models included main effects for year and ALD and the interaction between them.

Associations of national trends from 2010 through 2016 in the proportion of liver transplant for ALD were estimated using logistic models; these models included main effects for region, year, and age or MELD scores and the 2-way interactions between year and age or MELD.

The association of age and MELD score with regional variation in 2010 through 2016 trends in ALD proportions was examined using logistic models for ALD among liver transplant recipients. These models included main effects for region, year, and age or MELD score as well as the 3-way interaction between them; 2-way interactions were not statistically significant, and thus were excluded from the model. The association of age or MELD score with between-region variability in trend was assessed using a test for the 3-way interaction. For alcoholic hepatitis, which varied by region but not year, we used

a simpler model including main effects for region, year, and alcoholic hepatitis and the 2-way interactions between year, region, and alcoholic hepatitis. We assessed the association of alcoholic hepatitis with regional variability by testing the interaction of alcoholic hepatitis and year.

To estimate the increase in the proportion of liver transplants for ALD associated with the decrease in HCV infection, we calculated the percentage increase in the ALD proportions from 2002 to 2016, with and without liver transplants for HCV infection. The proportion of liver transplants associated with HCV infection was estimated by the absolute difference between these proportions. To estimate any change in the proportion of liver transplants for ALD associated with changes in allocation policy for HCC, we calculated the percentage increase in the ALD proportions from 2002 to 2016 with and without liver transplants for HCC. The proportion of liver transplants associated with HCC was then estimated by the absolute difference between these proportions.

Posttransplant graft and patient survival were estimated by transplant indication using Kaplan-Meier plots and compared using a log-rank test. The assumption of proportionality was tested for all variables in the multivariable Cox proportional hazards regression models and separately for overall death and graft failure. Hazards were reasonably proportional with the exception of that for ALD, which was addressed by performing stratified analysis by early and late graft and patient survival. Follow-up time for graft survival was defined as the interval of time between the date of transplant and the date of second liver transplant if necessary, death, or last follow-up. Follow-up time for patient survival was defined as the interval between the date of transplant and the date of death or last follow-up. Patients remaining alive at last follow-up were censored. Kaplan-Meier estimates of 1-, 5-, and 10-year graft failure and death were separately determined. To evaluate factors associated with post–liver transplant graft loss and patient mortality, separate Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs, with robust SEs to account for center clustering. To differentiate between perioperative and nonperioperative graft loss and deaths, separate Cox proportional hazards regression models were estimated for early (≤90 days after liver transplant) and late (>90 days after liver transplant) graft and patient survival. For both early graft and patient survival, events within 90 days after liver transplant were evaluated, and follow-up was censored at 90 days after liver transplant. For both late graft and patient survival, events occurring more than 90 days after liver transplant were evaluated; patients experiencing early events or censoring at fewer than 90 days after liver transplant were excluded. Factors with univariate $P < .10$ were included in initial multivariable models, with final models selected using backward elimination ($P > .05$ for removal). Hospitalization status was not included in final multivariable models because this variable was collinear with mechanical ventilation status. Variables with greater than 20% missing data were excluded. All statistical analyses were performed using Stata IC, version 13.1 (Stata Corp). Two-sided P values less than.05 were considered to be statistically significant.

Results

Of 32 913 patients who received liver transplant, 9438 had a diagnosis of ALD and 23 475 had a non-ALD diagnosis (eFigure 1 in the Supplement). The median age of patients with ALD was 54 years (interquartile range [IQR], 47-60 years) and of patients without ALD was 54 years (IQR, 44-61 years). Patients with ALD (vs non-ALD) were more frequently male (7197 of 9438 [76.2%] vs 11 767 of 23 475 [50.1%]; $P < .001$) and white (7544 [80.0%] vs 17251 [73.5%]; $P < .001$) and had Medicaid insurance (ALD, 1645 of 9438 [17%] vs non-ALD, 2736 of 23 475 [12%]; $P < .001$). Patients with ALD had higher median MELD scores (26 [IQR, 20-34] vs 24 [IQR, 18-33]; $P < .001$) and more often required renal replacement therapy at liver transplant (1924 [20.3%] vs 3569 [15.2%]; $P < .001$). Baseline characteristics are summarized in **Table 1**. Of 9438 ALD recipients, 147 (1.6%) had a secondary listing diagnosis of nonalcoholic steatohepatitis. In the non-ALD group, 365 of 23 475 (1.6%) had a secondary listing diagnosis of ALD.

Among patients with ALD, 153 had a primary diagnosis of alcoholic hepatitis and 9285 did not. Those with a primary diagnosis of alcoholic hepatitis (vs alcohol-associated cirrhosis), were younger (median age, 47 years [IQR, 37-56 years] vs 54 years [IQR, 47-60 years]; $P < .001$) and more likely to be female (48 [31.4%] vs 2193 [23.7%]; $P < .001$). They also had characteristics suggestive of more severe disease, including higher median MELD score (36 [IQR, 28-40] vs 26 [IQR, 20-33]; $P < .001$) and hospitalization at the time of liver transplant (114 [74.5%] vs 3851 [41.5%]; $P < .001$). These characteristics are summarized in eTable 1 in the Supplement.

National Trends in Liver Transplants for ALD

The proportion of liver transplants for ALD increased from 24.2% (433 of 1791) in 2002 to 27.2% (556 of 2044) in 2010 and 36.7% (1253 of 3419) in 2016 (**Figure 1**A). The proportion of liver transplants with a listing diagnosis of alcoholic hepatitis increased from 0% (0 of 1791) in 2002 to 0.59% (12 of 2032) in 2010 and 1.05% (36 of 3419) in 2016 (Figure 1B). Mean age decreased 1.5 years (95% CI, 0.5-2.4 years; $P = .003$) among patients with ALD but increased by 1.3 years (95% CI, 0.7-2.0 years; $P < .001$) among patients without ALD ($P < .001$) (eFigure 2A in the Supplement), and the median MELD score increased 4.5 points (95% CI, 3.5-5.5 points; $P < .001$) for ALD but was unchanged (95% CI, -0.7 to 0.7 point; $P = >.99$) for non-ALD ($P < .001$) (eFigure 2B in the Supplement) after 2010. In the unadjusted analysis, both factors were associated with ALD as an indication for liver transplant (odds ratio [OR], 0.94 SD increase in age; 95% CI, 0.89-0.99; $P = .01$; OR, 1.24 per SD increase in MELD score; 95% CI, 1.17-1.31; $P < .001$). Demographic data are represented in eFigure 2 in the Supplement.

Among liver transplant recipients from 2002 through 2010, 5211 of 13 779 (37.9%) recipients without ALD vs 1580 of 4765 (33.2%) with ALD were hospitalized at the time of liver transplant ($P < .001$). In contrast, among liver transplant recipients from 2010 through 2016, the inverse was true: 5368 of 11 184 (48.0%) recipients with non-ALD vs 2622 of 5229 (50.1%) with ALD were hospitalized at the time of liver transplant

Table 1. Recipient and Donor Characteristics at the Time of Liver Transplant[a]

Characteristic	Patients With ALD (n = 9438)	Patients Without ALD (n = 23 475)	*P* Value
Recipients			
Age, median (IQR), y	54 (47-60)	54 (44-61)	.52
Male	7197 (76.2)	11 767 (50.1)	<.001
Race/ethnicity			<.001
White	7544 (80.0)	17 251 (73.5)	
Black	356 (3.8)	2339 (10.0)	
Hispanic	1301 (13.8)	2584 (11.0)	
Asian	131 (1.4)	998 (4.3)	
Other	106 (1.1)	303 (1.3)	
Highest educational level			<.001
High school or below	3950 (41.8)	8905 (37.9)	
College or above	4212 (44.6)	10 435 (44.4)	
Unknown	1276 (13.5)	4120 (17.5)	
Medical insurance			<.001
Private	5621 (60.0)	14 635 (61.2)	
Medicare, Medicaid, or other	3817 (40.4)	8840 (37.8)	
Body mass index, median (IQR)[b]	27.8 (24.4-31.8)	28.2 (24.3-32.9)	<.001
Diabetes[c]	1761 (18.7)	6102 (26.0)	<.001
Mechanical ventilation	571 (6.0)	2260 (9.6)	<.001
Renal replacement therapy	1924 (20.3)	3569 (15.2)	<.001
Portal vein thrombosis at liver transplant[d]	752 (8.0)	2078 (8.8)	.01
Serum sodium level, median (IQR)[e]	135 (131-138)	136 (133-139)	<.001
Total bilirubin level, median (IQR)[e]	6.4 (3.1-13.8)	6.7 (3.0-18.1)	<.001
INR, median (IQR)[e]	1.9 (1.5-2.5)	1.8 (1.4-2.4)	<.001
Serum creatinine level, median (IQR)[e]	1.3 (0.9-2.2)	1.2 (0.8-2.0)	<.001
MELD score, median (IQR)[e]	26 (20-34)	24 (18-33)	<.001
SLK recipient	995 (10.5)	1778 (7.6)	<.001
Days on wait list, median (IQR)	32 (9-124)	49 (8-215)	<.001
Years of follow-up, median (IQR)	3.9 (1.3-7.8)	4.7 (1.6-8.8)	<.001
Donors			
Age, median (IQR), y	43 (27-55)	41 (25-54)	<.001
Male	5774 (61.1)	13 496 (57.5)	<.001
Race/ethnicity			.02
White	6369 (67.5)	16 110 (68.6)	
Black	1515 (16.0)	3713 (15.8)	
Hispanic	1235 (13.1)	2778 (11.8)	
Asian	183 (1.9)	497 (2.0)	
Other	136 (1.4)	368 (1.6)	
Height, median (IQR), cm	173 (165-180)	170 (164-178)	<.001
Nonbeating heart donor[f]	507 (4.2)	924 (3.9)	<.001
HCV positive	13 (0.1)	45 (0.2)	.24
Anti-HBc positive	339 (3.6)	889 (3.8)	.33
Donor infection[g,h]	4892 (55.0)	10 621 (49.9)	<.001
Warm ischemia time, median (IQR), min[i]	16 (10-23)	15 (9-21)	.04
Cold ischemia time, median (IQR), h	6.2 (4.9-8.0)	6.2 (4.8-8.0)	.06
Donor risk index, median (IQR)	1.5 (1.2-1.8)	1.5 (1.2-1.8)	.39

Abbreviations:
ALD, alcohol-associated liver disease;
HBc, hepatitis B core antigen,
HCV, hepatitis C virus;
INR, international normalized ratio;
IQR, interquartile range;
MELD, model for end-stage liver disease; SLK, simultaneous liver-kidney transplant.

[a] Data are presented as number (percentage) or patients unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] For diabetes status, there were 118 missing values (1%) in the group with ALD and 463 (2%) in the group without ALD.

[d] For portal vein thrombosis at liver transplant, there were 162 missing values (2%) in the group with ALD and 576 (2%) in the group without ALD.

[e] Laboratory values at time of liver transplant.

[f] Denominator 9152 for ALD, owing to 1607 patients with missing data and 21 868 for non-ALD, owing to 286 patients with missing data.

[g] Deceased donor clinical infection documented in United Network for Organ Sharing database.

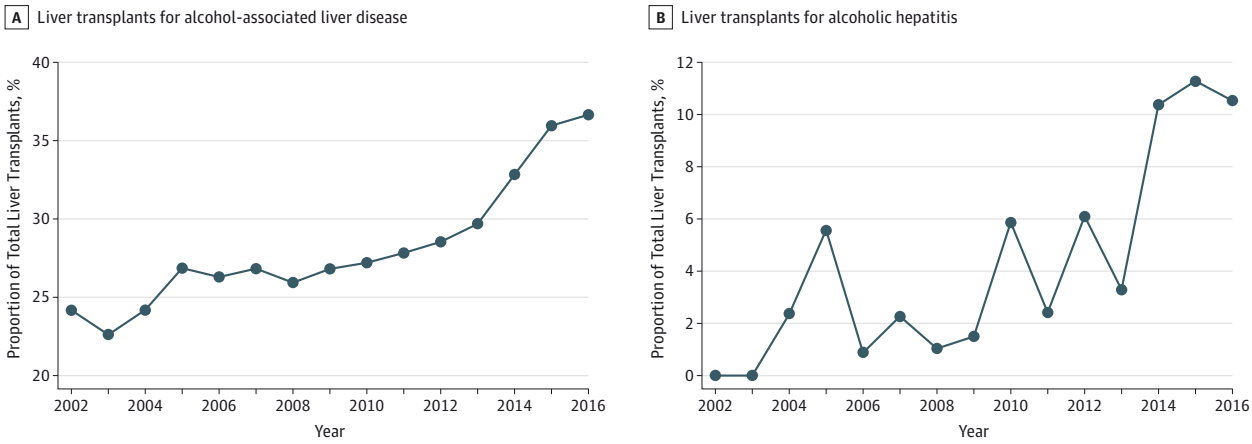
[h] Denominator 8893 for ALD owing to 545 patients with missing data, and 21 289 for non-ALD owing to 2186 patients with missing data.

[i] Among donors who died of circulatory causes only, the denominator was 360 for ALD owing to 147 with missing data and 705 for non-ALD owing to 219 with missing data.

(*P* = .01). Among patients with ALD, those with alcoholic hepatitis were more likely than those without alcoholic hepatitis to be hospitalized at the time of liver transplant (114 of 153 [74.5%] vs 3851 of 9285 [41.5%]; *P* < .001).

We performed sensitivity analyses comparing ALD liver transplant trends including and excluding liver transplant for HCV infection and HCC (**Table 2**). The proportion of patients with ALD as the primary indication for liver transplant with those with HCC and HCV infection excluded increased 51.6% from 2002 (433 of 1791 [24.2%]) to 2016 (1253 of 3419 [36.7%]). When including patients with HCV infection, the relative increase was 100%, from 481 of 3154 (15.3%) in 2002 to 1286 of

Figure 1. Proportion of Liver Transplants for Alcohol-Associated Liver Disease and Alcoholic Hepatitis in the United States, 2002-2016



Alcoholic hepatitis diagnosis was derived from United Network for Organ Sharing listing code for liver transplant.

Table 2. Proportion of Liver Transplants Performed for ALD in 2002 and 2016, With HCV Sensitivity Analysis

	Proportion of Liver Transplants Performed for ALD, %			
Primary Analysis	2002	2016	Relative Increase	Associated Increase[a]
ALD (n = 32 913)[b]	24.2	36.7	51.6	[Reference]
ALD and HCV infection (n = 50 211)[b]	15.3	30.6	100	48.4
ALD and HCC (n = 42 064)[b]	24.0	34.7	44.6	−7.0

Abbreviations: ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease.

[a] To estimate the increase in the proportion of liver transplants for ALD associated with the decrease in HCV infections, we calculated the percentage increase in the ALD proportions from 2002 to 2016, with and without liver transplants for HCV. The proportion associated was estimated by the absolute difference between these proportions. To estimate any change in the proportion of liver transplants for ALD associated with changes in allocation policy for HCC, we calculated the percentage increase in the ALD proportions from 2002 to 2016, with and without liver transplants for HCC. The proportion associated was then estimated by the absolute difference between these proportions.

[b] Primary analysis included all adult liver transplant recipients from 2002 to 2016 except those with HCV infection, HCC, HIV infection, acute or fulminant hepatic failure, MELD exception criteria, and prior liver transplant.

4202 (30.6%) in 2016, suggesting that a 48.4% absolute increase in the proportion of liver transplants performed for ALD may be associated with the decline in HCV infection (Table 2).

Regional Trends in Liver Transplants for ALD

All 11 UNOS regions had an increase in the proportion of liver transplants for ALD between 2010 and 2016, whereas 9 regions had an increase between 2002 and 2010 (**Figure 2**). There was significant heterogeneity across regions between 2010 and 2016 (χ^2 = 28.2; P = .002), with the largest increases in regions 2 (24.2%; 51 of 213 transplants [23.9%] in 2010; 188 of 391 [48.1%] in 2016) and 4 (14.0%; 47 of 157 transplants [29.9%] in 2010; 135 of 307 [44.0%] in 2016) and the smallest increases in regions 3 (2.8%; 117 of 392 transplants [29.8%] in 2010; 214 of 655 [32.7%] in 2016) and 10 (4.6%; 54 of 199 transplants [27.1%] in 2010; 110 of 346 [31.8%] in 2016). Regional changes in the proportion of liver transplants for ALD between 2010 and 2016 were not associated with regional changes between 2002 and 2010 (r = 0.11; P = .74). However, regional increases between 2010 and 2016 were independently associated with concurrent changes in younger age (χ^2 = 36.5; P = .005) and higher MELD score (χ^2 = 69.1; P < .001) but were not independently associated with the regional proportion of liver transplants with alcoholic hepatitis as listing diagnosis (P = .43).

Graft and Patient Survival

Median follow-up was 3.9 vs 4.7 years after liver transplant for ALD vs non-ALD (P < .001). Cumulative unadjusted 1-year post-liver transplant graft survival was 91% (95% CI, 91%-92%) for ALD vs 89% (95% CI, 89%-90%) for non-ALD; 5-year post-liver transplant graft survival was 79% (95% CI, 78%-80%) for ALD vs 80% (95% CI, 79%-80%) for non-ALD; and 10-year post-liver transplant graft survival was 60% (95% CI, 58%-61%) for ALD vs 63% (95% CI, 62%-64 for non-ALD (P = .01) (**Figure 3**A). Cumulative unadjusted 1-year post-liver transplant patient survival was 91% (95% CI, 91%-92%) for ALD vs 90% (95% CI, 89%-90%) for non-ALD; 5-year post-liver transplant patient survival was 79% (95% CI, 78%-80%) for ALD vs 80% (95% CI, 79%-80%) for non-ALD; and 10-year post-liver transplant patient survival was 63% (95% CI, 61%-64%) for ALD vs 68% (95% CI, 67%-69%) for non-ALD (P = .006) (Figure 3B). In multivariable analysis, ALD (vs non-ALD) as an indication for liver transplant had similar risk of overall graft failure (adjusted HR [aHR], 0.98; 95% CI, 0.93-1.03; P = .50) and death (aHR, 1.04; 95% CI, 0.98-1.11; P = .15). There were 8052 post-liver trans-

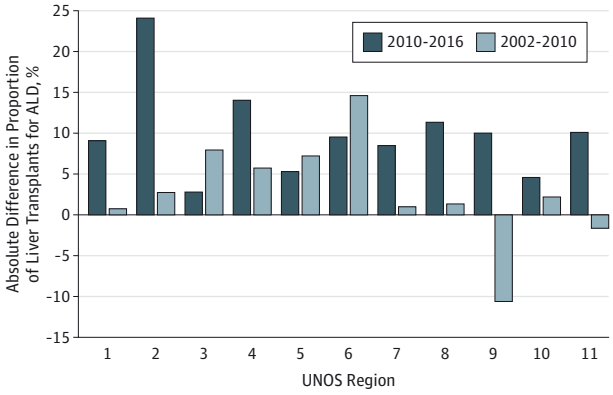
plant deaths (2321 of 9438 [24.6%] patients in the ALD group and 5731 of 23 475 [24.4%] in the non-ALD group; $P = .73$) (eTable 2 in the Supplement).

Alcohol-associated liver disease (vs non-ALD) as an indication for liver transplant was associated with decreased risk of early death (aHR, 0.83; 95% CI, 0.74-0.93; $P < .001$) but increased risk of late death (aHR, 1.11; 95% CI, 1.03-1.20; $P = .006$). However, ALD was not associated with increased risk of late graft failure (aHR, 1.02; 95% CI, 0.96-1.08; $P = .54$) but was associated with significantly lower likelihood of retransplantation (aHR, 0.79; 95% CI, 0.68-0.92; $P = .002$).

Factors Associated With Overall Survival After Liver Transplant Among Patients With ALD

Factors associated with posttransplant death in multivariable analyses for patients with ALD were donor risk index (aHR, 1.44; 95% CI, 1.26-1.63; $P < .001$), mechanical ventilation at liver transplant (aHR, 1.52; 95% CI, 1.18-1.95; $P < .001$), portal vein thrombosis at liver transplant (aHR, 1.26; 95% CI, 1.06-1.50; $P = .008$), white race/ethnicity (aHR, 1.24; 95% CI, 1.07-1.45; $P = .005$), higher MELD score (aHR, 1.01; 95% CI, 1.01-1.02; $P < .001$), and older age (aHR, 1.02; 95% CI, 1.02-1.03; $P < .001$) (eTable 3 in the Supplement). College education (aHR, 0.91; 95% CI, 0.83-1.00; $P = .04$) and private medical insurance (aHR, 0.84; 95% CI, 0.77-0.93; $P < .001$) were associated with decreased risk of posttransplant death among patients with ALD.

Figure 2. Absolute Changes in the Proportion of Liver Transplants for Alcohol-Associated Liver Disease (ALD) by United Network for Organ Sharing (UNOS) Region

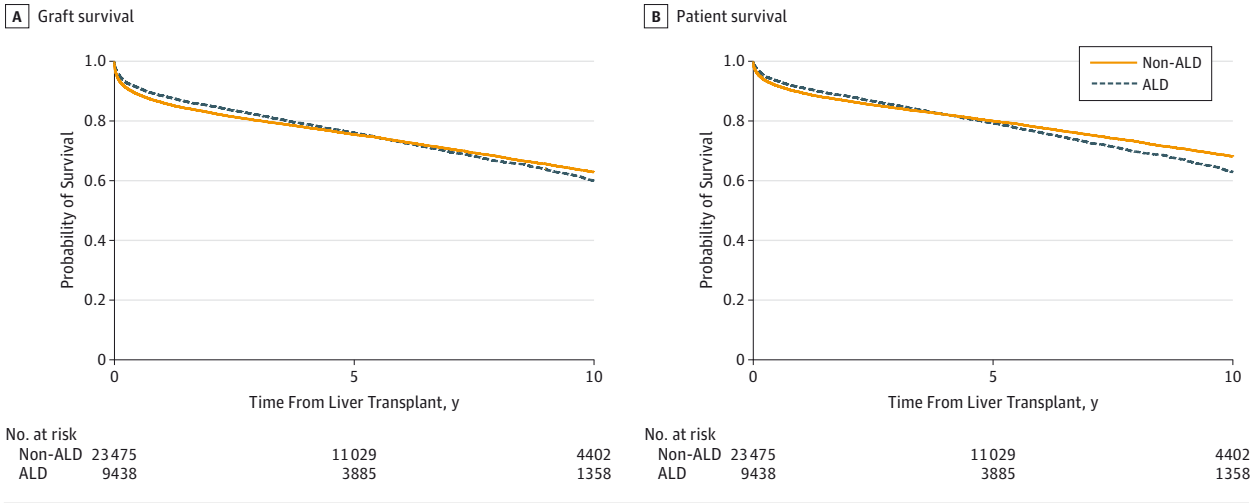


There was significant heterogeneity across regions from 2010 to 2016 ($P = .002$), with the largest increases in regions 2 and 4 and smallest increases in regions 3 and 10.

Discussion

The findings suggest that the increase in ALD to be the most common indication for liver transplant is not only associated with the decline in HCV infection. This study shows that the proportion of ALD diagnoses has increased 100% since 2002; 48% of the increase may be associated with a decline in HCV infection as an indication for liver transplant. Of note, the most significant increases occurred after 2010, coinciding with the landmark trial of early liver transplant for severe alcoholic hepatitis.[7] These increases do not appear to be directly associated with liver transplant for alcoholic hepatitis because alcoholic hepatitis as a listing diagnosis comprised less than 1% of liver transplants performed between 2010 and 2016; however, we acknowledge that alcoholic hepatitis is often misclassified[18] as alcoholic cirrhosis. Nonetheless, ALD as an indication for liver transplant has broadly increased, and our analyses suggest that this increase may be in part associated with shifting attitudes toward the need for 6 months of abstinence for liver transplant eligibility. Although the 6-month rule is widely applied, it is not an absolute policy; UNOS has never adopted this policy, and US transplant centers are allowed to set their own policies regarding abstinence requirements for liver transplant eligibility.[20] A notable increase in liver transplants for ALD, especially since 2014, coincides with the first

Figure 3. Cumulative Probability of Graft and Patient Survival After Liver Transplant for Alcohol-Associated Liver Disease (ALD) vs Non-ALD



Solid lines indicate non-ALD; dashed lines indicate ALD.

US reports of early liver transplant for alcoholic hepatitis at national meetings. These reports have been published recently[12,15,16] with generally favorable results, which we hypothesize may further increase the application of early liver transplant for ALD. We acknowledge, however, that these are temporal associations only and the increase of ALD as an indication for liver transplant may be associated with other unknown or unmeasured factors. Nevertheless, given the significant increase in liver transplants for ALD in the United States, it may be time for a national consensus on best practices for patients with ALD in need of liver transplant.

Although all UNOS regions experienced an increase in liver transplants for ALD in recent years, the increase was significantly heterogeneous. Regional increases from 2010 through 2016 had no correlation with prior regional ALD listing trajectories (ie, background demographics and regional trends) but were strongly correlated with changes suggestive of a region's increasing acceptance of early liver transplant for ALD, specifically, an increase in the region's median MELD score and decrease in the region's mean age among patients with ALD. These results suggest that there may be regional disparities in access to liver transplant for ALD; whether this is related to different attitudes toward ALD and requirements for sobriety is unknown. Again, this finding highlights the value of a national policy for liver transplant in ALD to abrogate any potential inequity in health care access for liver transplant related to the patient's geographical region and the liver transplant policy of the local center.

Other trends specific to liver transplant in ALD may be reflective of national trends in ALD.[4] Of note, the proportion of women undergoing liver transplant for ALD increased, which is in parallel with reports of a marked increase in harmful drinking patterns among women compared with men.[4] In addition, the proportion of patients insured by Medicaid increased among liver transplant recipients for ALD not in the non-ALD group, a trend that predates Medicaid expansion from the Patient Protection and Affordable Care Act. These changes appear to be specific to alcohol; there are no American Association for the Study of Liver Diseases or UNOS policies specific to other individual nontobacco and noncannabis substances, such as methamphetamine use, and there appears to be limited changes in attitudes toward such substances among liver transplant centers.[21] These findings highlight the changing landscape of liver transplant and the need to consider multiple factors when considering future trends and policy.

Although our era analysis indicated a 2-fold improvement in early patient survival within the past 10 years, likely reflecting improved operative and perioperative management, improvement in late survival has been more modest. Our analysis provides insight into areas to target for further study. Mechanical ventilation and donor risk index were the strongest risk factors, both independently associated with increased risk of overall death among patients with ALD by greater than 40%, whereas other variables had more modest associations, which suggests the importance of both recipient and donor selection. We identified risk factors associated with death by cancer (older age, male, and white race/ethnicity) and infection (age, donor risk index), which were the 2 most common causes of late death after liver transplant for ALD. Although older age was independently associated with both outcomes, registry data do not capture other risk factors that would be informative, including immunosuppression, smoking, and alcohol use after liver transplant. Although studies have reported cancer and infection to be the most common causes of death among abstinent recipients of liver transplants for ALD, the most significant risk factor for graft failure beyond 5 years after liver transplant for ALD was the return to harmful alcohol consumption after liver transplant.[22,23] The lower retransplantation rate observed among patients with ALD vs those without ALD may be associated with alcohol consumption because recurrent alcohol use is likely to preclude consideration of retransplantation. However, confirmation is not possible with our study design; there is no dedicated UNOS code for either alcohol use or death from alcohol use, and the establishment of these codes would aid future research on outcomes after liver transplant. Nevertheless, our findings align with earlier studies that reported a significant proportion of deaths due to graft failure associated with recurrent alcohol use, cancer, and infection.

Strengths and Limitations

This study has numerous strengths. Use of national registry data provides a comprehensive overview of the liver transplantation landscape, with updated trends and 10-year outcomes for liver transplant for ALD, a disease that has seen recent changes in epidemiology, and changes in liver transplant practices. Examination by era, UNOS region, and exclusion of HCV infection and HCC allowed investigation into potential factors associated with the increase in ALD as an indication for liver transplant other than the decrease in HCV infection. Stratification of outcomes into early vs late highlighted the importance of infections and cancer and the need for targeted studies into contributing factors and interventions that can improve graft and patient survival.

Our study has limitations. First, we used registry data, and conclusions are by association and not causal. However, the timing of observed trends, differential increases in MELD score, and decreasing age among the group with ALD, which were independently associated with the heterogeneous regional increase in liver transplants for ALD, support our primary hypothesis that shifting attitudes toward mandated sobriety periods in ALD are important. The shifting attitudes may continue to shape the liver transplantation landscape in future years because many centers still adhere to mandated sobriety periods.[3] These mandates may change with increasing data and acceptance of early liver transplant for ALD. Second, as with any registry study, inaccuracies in coding and missing data present challenges and would best be addressed by center-driven prospective studies.

Conclusions

In conclusion, the rapid emergence of ALD as the leading indication for liver transplant may be associated with the decrease in HCV infection and shifting attitudes toward the length of pre–liver transplant sobriety necessary to undertake liver transplant

for ALD; both of these factors may continue to be associated with an increase the proportion of liver transplants performed for ALD. Patient and graft survival among patients with ALD were comparable with those among patients without ALD but with an increase in late deaths, which may be clinically significant given the increased focus on long-term outcomes in liver transplant recipients. Future studies focused on improving disparities in access to liver transplant for ALD and optimizing short- and long-term survival among transplant recipients with ALD should be encouraged.

ARTICLE INFORMATION

Accepted for Publication: October 1 2018.

Published Online: January 22, 2019. doi:10.1001/jamainternmed.2018.6536

Author Contributions: Dr Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lee, Cullaro, Terrault.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lee, Terrault.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lee, Vittinghoff, Dodge, Cullaro.
Administrative, technical, or material support: Terrault.
Supervision: Cullaro, Terrault.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases UCSF Liver Center T32 DK060414 (Dr. Lee) and DK026743 (Dr Terrault).

Role of the Funder/Sponsor: The National Institute of Diabetes and Digestive and Kidney Diseases had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol*. 2018;16(8):1356-1358. doi:10.1016/j.cgh.2017.11.045

2. Cholankeril G, Liu A, Sandhu J, et al. Increasing acceptance of severe acute alcoholic hepatitis as an indication for liver transplantation with outcomes comparable to fulminant hepatic failure. *Hepatology*. 2017;66(suppl 1):17A.

3. Zhu J, Chen PY, Frankel M, Selby RR, Fong TL. Contemporary policies regarding alcohol and marijuana use among liver transplant programs in the United States. *Transplantation*. 2018;102(3):433-439.

4. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(9):911-923. doi:10.1001/jamapsychiatry.2017.2161

5. Dawson DA, Goldstein RB, Saha TD, Grant BF. Changes in alcohol consumption: United States, 2001–2002 to 2012–2013. *Drug Alcohol Depend*. 2015;(148):56-61.

6. Kerr WC, Mulia N, Zemore SE. U.S. trends in light, moderate, and heavy drinking episodes from 2000 to 2010. *Alcohol Clin Exp Res*. 2014;38(9):2496-2501. doi:10.1111/acer.12521

7. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365(19):1790-1800. doi:10.1056/NEJMoa1105703

8. Donckier V, Lucidi V, Gustot T, Moreno C. Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. *J Hepatol*. 2014;60(4):866-871. doi:10.1016/j.jhep.2013.11.015

9. Lucey MR. Liver transplantation for severe alcoholic hepatitis- The PRO view. *Liver Int*. 2017;37(3):343-344. doi:10.1111/liv.13343

10. Fung JYY. Liver transplantation for severe alcoholic hepatitis-The CON view. *Liver Int*. 2017;37(3):340-342. doi:10.1111/liv.13286

11. Lucey MR. Liver transplantation for alcoholic liver disease. *Nat Rev Gastroenterol Hepatol*. 2014;11(5):300-307. doi:10.1038/nrgastro.2013.247

12. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. *Gastroenterology*. 2018;155(2):422-430.e1. doi:10.1053/j.gastro.2018.04.009

13. Lucey MR, Schaubel DE, Guidinger MK, Tome S, Merion RM. Effect of alcoholic liver disease and hepatitis C infection on waiting list and posttransplant mortality and transplant survival benefit. *Hepatology*. 2009;50(2):400-406. doi:10.1002/hep.23007

14. Burra P, Senzolo M, Adam R, et al; ELITA; ELTR Liver Transplant Centers. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant*. 2010;10(1):138-148. doi:10.1111/j.1600-6143.2009.02869.x

15. Lee BP, Chen P-H, Haugen C, et al. Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. *Ann Surg*. 2017;265(1):20-29. doi:10.1097/SLA.0000000000001831

16. Im GY, Kim-Schluger L, Shenoy A, et al. Early liver transplantation for severe alcoholic hepatitis in the United States—a single-center experience. *Am J Transplant*. 2016;16(3):841-849. doi:10.1111/ajt.13586

17. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant*. 2006;6(4):783-790. doi:10.1111/j.1600-6143.2006.01242.x

18. Lee BP, Im GY, Dodge JL, et al. Higher early post-liver transplant mortality in recipients with severe alcoholic hepatitis vs alcoholic cirrhosis. *J Hepatol*. 2018;68(suppl 1):S808. doi:10.1016/S0168-8278(18)31887-7

19. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009;360(26):2758-2769. doi:10.1056/NEJMra0805786

20. Beresford TP, Everson GT. Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule, and relapse–but where are the data? *Liver Transpl*. 2000;6(6):777-778. doi:10.1053/jlts.2000.19027

21. Parker R, Armstrong MJ, Corbett C, Day EJ, Neuberger JM. Alcohol and substance abuse in solid-organ transplant recipients. *Transplantation*. 2013;96(12):1015-1024. doi:10.1097/TP.0b013e31829f7579

22. Dumortier J, Dharancy S, Cannesson A, et al. Recurrent alcoholic cirrhosis in severe alcoholic relapse after liver transplantation: a frequent and serious complication. *Am J Gastroenterol*. 2015;110(8):1160-1166. doi:10.1038/ajg.2015.204

23. Rice JP, Eickhoff J, Agni R, Ghufran A, Brahmbhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. *Liver Transpl*. 2013;19(12):1377-1386. doi:10.1002/lt.23762