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Patient survey augments detection of harmful alcohol relapse after liver transplant for alcohol-associated cirrhosis

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Abstract

Background: Predicting the risk of alcohol relapse after a liver transplant for alcohol-associated liver disease is critical to guide candidate selection and optimize alcohol use disorder management. We aimed to use patient survey to augment the detection of alcohol relapse and its risk factors and to understand patient perceptions of the importance of alcohol abstinence.

Methods: In this retrospective cohort study, we used a telephone survey and chart review to assess the incidence of post-transplant harmful alcohol relapse, risk factors, and long-term outcomes for patients transplanted for alcohol-associated cirrhosis at our center from 2002 to 2016.

Results: Over the median follow-up of 5.9 years, 20.4% relapsed, with 9.3% harmful relapse after median of 4.0 years. The survey response rate was 44.0% (n = 110). Of survey responders, 44.3% did not recall discussing alcohol in post-transplant clinics, and 17.6% of relapses were identified by the survey alone. In univariate analysis, shorter pretransplant sobriety (OR: 0.96 per month, $p = 0.02$) and history of pretransplant relapse (OR: 2.99, $p = 0.02$) were associated with post-transplant harmful relapse. After adjusting for these factors, High-risk Alcoholism Relapse score ≥ 4 predicted harmful relapse (OR: 3.43, $p = 0.049$). A total of 27.3% of patients with both pretransplant relapse and High-risk Alcoholism Relapse score ≥ 4 relapsed to harmful use compared with 5.2% of those with 1 or neither risk factor ($p < 0.001$). Harmful relapse was associated with increased graft loss (30.4% vs. 17.4%) and inferior 10-year post–liver transplant survival (61.5% vs. 80.7%).

Conclusions: Incorporating patient survey data allowed the detection of relapses otherwise unreported to clinicians, highlighting the need for novel

Abbreviations: AC1, chance-corrected agreement coefficient; ALD, alcohol-associated liver disease; AR, alcohol relapse; AUD, alcohol use disorder; HRAR, High-risk Alcoholism Relapse; IQR, interquartile range; LT, liver transplant; MELD, Model for End-stage Liver Disease.

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strategies to detect relapse. Utilizing this augmented data, we identified pretransplant sobriety length, pretransplant relapse, and High-risk Alcoholism Relapse score ≥ 4 as risk factors that should be evaluated pretransplant to guide candidate selection and peritransplant alcohol use disorder management.

INTRODUCTION

With the rise of alcohol-associated liver disease (ALD) as the most common indication for liver transplant (LT) in the US,[1,2] understanding the incidence and long-term effects of alcohol relapse (AR) after LT is more important than ever. Predicting the risk of post-LT relapse before LT is critical for LT candidate selection and for determining which patients will require more intensive alcohol use disorder (AUD) treatment both pre-LT and post-LT to prevent AR. AUD is a chronic, relapsing disease that can be difficult to treat[3] and warrants dedicated management before and after LT. Post-LT AR seems to be common, though reported rates and definitions of AR vary widely.[4]

Longer durations of pre-LT abstinence have been associated with lower risk of AR,[5–10] previously leading many transplant centers to adopt the "6-month rule" for abstinence pre-LT. However, carefully selected patients with no proscribed period of pre-LT abstinence have now been shown to have post-LT AR rates and outcomes similar to those of the patients transplanted after >6 months' abstinence.[11–14] This suggests the importance of risk factors other than a specific duration of pre-LT sobriety. As many centers and national guidelines move toward early LT for ALD without specified pre-LT abstinence,[11,12,14–17] identifying these other risk factors is imperative. Several tools have been proposed to predict post-LT AR, but no single tool is reliably predictive. For example, the High-risk Alcoholism Relapse (HRAR) score was initially developed and validated in US veterans to predict AR in patients hospitalized for AUD treatment.[18] Two large studies investigating this score in patients transplanted for ALD found that a higher HRAR score was significantly associated with heavy AR,[7,19] though one smaller study did not.[20]

The effects of post-LT AR on graft outcomes and mortality are also incompletely understood. Although some studies investigating post-LT AR have not linked relapse with poorer outcomes,[7,8] many studies have found that relapse to harmful alcohol use is associated with significantly increased morbidity and mortality.[9,18,20–23] As such, an attempt to predict which patients are at the highest risk for harmful AR is vital to improve post-LT outcomes. United Network for Organ Sharing data found that the recipient and allograft survival after LT for ALD are comparable to other indications at 5 years after LT,[2] but 10-year survival remains inferior.[13] These analyses did not include AR data but suggest that studies without long-term follow-up may not capture significant mortality differences that seem to occur later in patients transplanted for ALD. Some discrepancies in results may also be explained by difficulty diagnosing post-LT AR, as research frequently relies on retrospective chart review in which formal assessments of alcohol use may not be completed or documented.[24,25] Patients may also be less likely to disclose AR to their established providers due to concerns about provider judgment or the negative repercussions of documenting substance use in their medical record.[26–28]

In this study, we aimed to overcome some of these barriers by performing a telephone survey of patients in addition to retrospective chart review to assess the incidence of AR post-LT, characterize associated risk factors, and evaluate long-term outcomes after LT.

METHODS

Through retrospective chart review, we identified all 269 consecutive patients who underwent LT for ALD at the University of California, San Francisco, from May 2002 to January 2016. All patients included had a primary diagnosis of ALD. After excluding 5 patients who died in the immediate post-transplant period and 14 patients who were lost to follow-up or followed up at other centers, the final study cohort included 250 patients (Figure 1). The University of California, San Francisco Institutional Review Board approved all study protocols (approval number 15-18523).

Before listing for LT, all patients underwent psychosocial evaluation by social workers with expertise in liver transplant evaluations. According to the institution's policy, during the study period, all patients were required to maintain at least 6 months of pre-LT abstinence. Through chart review, including the review of clinical notes, social work evaluations, and alcohol biomarkers, we gathered data on sociodemographic variables and the following pre-LT risk factors: duration of drinking, number of daily drinks, length of pre-LT sobriety, rehabilitation program attendance, history of AR after

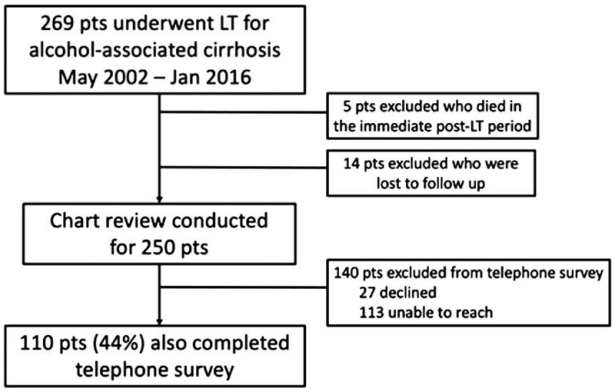

FIGURE 1 Flow diagram of study patients. Abbreviations: pts, patients; LT, liver transplant.

initial sobriety was achieved, hospital admission for alcohol-associated issues, alcohol-associated legal complications, other mental health disorder diagnoses (including depression, anxiety, bipolar disorder, and post-traumatic stress disorder), illicit drug use (excluding cannabis), tobacco use, opioid prescription, family history of AUD, and relationship status at the time of LT. When characterizing the number of daily drinks, the duration of drinking, and prior alcohol inpatient rehabilitation, we used cutoff values from the HRAR score[18] and then calculated the HRAR score for each patient with the available data. The total score ranges from 0 to 6 points and contains 3 variables: duration of heavy drinking (0–2 points), number of daily drinks (0–2 points), and number of prior inpatient treatments for AUD (0–2 points).[18] We also reviewed clinical notes, social work notes, and alcohol biomarkers to assess for post-LT alcohol use, alcohol-associated admission, rehabilitation program attendance, new mental health disorder diagnosis, graft loss, and mortality.

To augment the data obtained from chart review, we conducted a telephone survey of transplant recipients to assess the AR incidence and risk factors. Interviewers were not involved in patient care, and patients were assured that individual responses would not be disclosed to their care team. We excluded 140 patients from the telephone survey, as 27 declined and 113 could not be reached (Figure 1). Patients were asked about the same pre-LT risk factors as assessed by chart review, as well as post-LT variables, including alcohol use, alcohol-associated admissions, rehabilitation program attendance, and new mental health disorder diagnoses (see Supplement for the full text of survey, http://links.lww.com/HC9/A233). We investigated pre-LT relapse with the question, “After you quit drinking, did you ever relapse with alcohol?” and specified the definition of relapse as “even a single sip of alcohol.” To evaluate patient insight, we asked whether patients thought their liver disease was caused by or related to alcohol. We inquired whether patients recalled being asked about alcohol use in their clinic visits after LT. In cases where information was discrepant between chart review and survey answers for the score components, we selected the higher value (eg, longer duration of drinking).

We defined post-LT AR as any alcohol use after LT, identified by chart review and/or survey. AR was considered harmful if there was any report of sustained, heavy, or binge drinking or any alcohol-associated emergency room visit or hospital admission. Other relapses were classified as “slips” or nonsustained.

The primary outcome was post-LT harmful AR, with post-LT survival as a secondary outcome. Patient characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. The characteristics were stratified by post-LT harmful AR and compared with Kruskal-Wallis and Pearson chi-squared tests, as appropriate. The association of post-LT harmful AR and explanatory variables known before the transplant was explored using univariate and multivariable OR and 95% CI estimated by logistic regression. To determine the incidence of post-LT harmful AR and post-LT patient survival, outcomes were assessed for the overall cohort and stratified by pre-LT AR. Observed post-LT AR and patient survival probabilities and 95% CI were estimated at 5 years using the Kaplan-Meier method, with stratified analyses compared using the log-rank test. For post-LT survival, patient follow-up was measured from the date of LT to death (event), with patients remaining alive censored at the date of retransplant or last follow-up. For post-LT AR, patient follow-up was measured from the date of LT to post-LT AR, with patients censored at the date of death or last follow-up. Agreement between chart review and survey responses was assessed through the Gwet Chance-Corrected Agreement Coefficient (AC1). All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Patient characteristics are shown in Table 1. Patients were predominantly male (78.8%) and White (58.0%) or Hispanic (32.8%), with a median age of 56.2 years at the time of LT (IQR: 50–62). One third had public insurance (Medicare or Medicaid). A total of 46.0% had comorbid Hepatitis C, and 35.2% had HCC. The Median Model for End-stage Liver Disease scores were 19 at listing (IQR: 13–27) and 33 at the time of match (IQR: 25–38).

Patients were abstinent from alcohol for a median of 31.1 months (IQR: 16–74) pre-LT. Most patients drank heavily for >25 years (52.1%) or 11–25 years (39.5%), with most drinking <9 drinks per day (60.9%). Before LT, 33.6% relapsed with alcohol at least once, 82.6% attended alcoholics anonymous or other outpatient

TABLE 1 Baseline characteristics stratified by any alcohol relapse versus no relapse

	Total (n = 250), n (%)	Any alcohol relapse post-LT		
		No (n = 199), n (%)	Yes (n = 51), n (%)	*p*
Demographics				
Male sex	197 (79)	162 (81)	35 (69)	0.06
Age at time of LT	56.2 (50–62)	56.6 (51–63)	53.9 (47–59)	0.02
Race	—	—	—	0.02
White	145 (58)	108 (54)	37 (73)	—
Hispanic	82 (33)	73 (37)	9 (18)	—
Asian	14 (6)	9 (5)	5 (10)	—
Black	7 (3)	7 (4)	0	—
Other	2 (1)	2 (1)	0	—
Chronic Hepatitis C[a]	115 (46)	97 (49)	18 (36)	0.12
Hepatocellular carcinoma	88 (35)	77 (39)	11 (22)	0.02
MELD at listing[b]	19 (13–27)	18 (13–24)	23 (16–30)	0.01
MELD at match[c]	33 (25–38)	33 (26–38)	33 (20–39)	0.77
Months from listing to LT	7.5 (3–16)	8 (3–17)	7 (2–16)	0.26
Months from sobriety to LT[d]	31.1 (16–74)	36.5 (17–103)	22.5 (12–35)	< 0.001
Psychosocial variables				
Family history of alcohol use disorder[e]	100 (43)	80 (43)	20 (42)	1.00
Long-term relationship at time of LT[f]	200 (81)	159 (80)	41 (82)	0.79
Illicit drug use[d]	126 (51)	104 (53)	22 (43)	0.21
Tobacco use[g]	176 (72)	146 (75)	30 (59)	0.02
Opioid prescription[h]	56 (25)	40 (23)	16 (36)	0.09
Pre-LT mental health disorder diagnosis[i]	87 (36)	65 (34)	22 (45)	0.18
Post-LT mental health disorder diagnosis[j]	58 (25)	42 (23)	16 (32)	0.20
Alcohol-associated factors				
Duration of drinking (years)[k]	—	—	—	0.80
> 25	87 (52)	70 (53)	17 (50)	—
11–25	66 (40)	51 (38)	15 (44)	—
< 11	14 (8)	12 (9)	2 (6)	—
Drinks per day[l]	—	—	—	0.04
< 9	114 (61)	93 (65)	21 (49)	—
9–17	46 (25)	29 (20)	17 (40)	—
> 17	27 (14)	22 (15)	5 (12)	—
Inpatient rehabilitation programs attended[m]	—	—	—	0.40
≥ 2	2 (1)	1 (1)	1 (2)	—
1	29 (15)	22 (14)	7 (17)	—
0	164 (84)	130 (85)	34 (81)	—
HRAR score[n]	2 (2–3)	2 (2–3)	2 (2–3)	0.43
HRAR score ≥ 4[n]	38 (21)	29 (21)	9 (23)	0.77
Alcohol relapse pre-LT[o]	71 (34)	50 (30)	21 (47)	0.05
Alcohol-associated legal complication[p]	79 (48)	67 (52)	12 (33)	0.06
Admissions for alcohol withdrawal[q]	17 (22)	15 (25)	2 (11)	0.33
Outpatient rehabilitation program (including alcoholics Anonymous)[r]	180 (83)	139 (81)	41 (89)	0.19

Note: Data are expressed as median (interquartile range) or number (percentage). The following superscripts indicate number of missing data points for each category:
[a]1.
[b]15.
[c]101.
[d]4.
[e]16.
[f]2.
[g]5.
[h]29.
[i]8.
[j]13.
[k]83.
[l]63.
[m]55.
[n]72.
[o]39.
[p]86.
[q]173.
[r]32.

Abbreviations: LT, liver transplant; MELD, Model for End-stage Liver Disease; HRAR, High-risk Alcoholism Relapse.

rehabilitation program, 15.9% underwent inpatient rehabilitation, 22.1% were admitted for alcohol withdrawal, and 48.2% had alcohol-associated legal complications. Before LT, 36.0% of patients had been diagnosed with a mental health disorder. Of the 178 patients (71.2%) who had sufficient data to calculate the HRAR score, the median HRAR score was 2 (IQR: 2–3), and 21.3% (n = 38) had a score of HRAR $\geq$ 4.

AR and associated risk factors

Over median follow-up of 5.9 years (IQR 3.4–9.6), 20.4% of patients (n = 51) relapsed to any alcohol use, as identified by chart review (82.4%) or survey (17.6%). Post-LT AR occurred after a median of 4.0 years (IQR: 2.1–7.2). Harmful AR was demonstrated in 9.3% of all patients (n = 23), also after a median of 4.0 years (IQR: 2.1–7.3).

Characteristics of participants who relapsed to harmful alcohol use are shown in Supplementary Table 1 (http://links.lww.com/HC9/A232). Compared with all others, those with harmful AR were younger at the time of LT (50.1 vs. 56.6 y, $p = 0.003$), had a shorter length of pre-LT sobriety (14.9 vs. 34.6 mo, $p < 0.001$), and were more likely to have relapsed after initial sobriety attempts pre-LT (57.1% vs. 30.9%, $p = 0.015$). Pre-LT mental health disorders were numerically more common in patients with harmful AR (52.4% vs. 33.9%, $p = 0.09$). Patients with comorbid HCC or hepatitis C had less harmful AR than those without (3.5% vs. 12.4%, $p = 0.02$ and 5.3% vs. 12.5%, $p = 0.05$, respectively). Those who harmfully relapsed were less likely to have a history of alcohol-associated legal complications (6.3% vs. 52.1%, $p < 0.001$) or pre-LT tobacco use (52.2% vs. 74.0%, $p = 0.027$).

On univariate analysis, pre-LT relapse (OR: 2.99, 95% CI, 1.19–7.48, $p = 0.02$) was associated with post-LT harmful relapse, and HRAR score $\geq$4 trended toward significance (OR: 2.69, 95% CI, 0.89–8.10, $p = 0.08$) with post-LT harmful AR (Table 2). Duration of pre-LT sobriety (OR: 0.96 per month, 95% CI, 0.94–0.99, $p = 0.02$), age at transplant (OR: 0.92 per year, 95% CI, 0.88–0.97, $p = 0.002$), pre-LT legal complications (OR: 0.06, 95% CI, 0.01–0.48, $p = 0.01$), pre-LT tobacco (OR: 0.38, 95% CI, 0.16–0.92, $p = 0.03$), and comorbid HCC or hepatitis C were associated with less post-LT relapse.

The cumulative incidence of harmful relapse at 5 years post-LT was 17.0% for those with a history of pre-LT AR compared with only 7.0% for those without ($p = 0.016$, Figure 2A). A total of 40.0% of those who harmfully relapsed had HRAR $\geq$4 compared with 19.9% of all others ($p = 0.10$). After adjusting for pre-LT AR and pre-LT sobriety length, HRAR $\geq$4 independently predicted harmful relapse (OR: 3.43, 95% CI, 1.00–11.75, $p = 0.049$, Table 3). In bivariate models adjusting for HRAR $\geq$4, both pre-LT AR (OR: 3.37, 95% CI, 1.05–10.82, $p = 0.04$, Table 3) and pre-LT sobriety length (OR: 0.96 per month, 95% CI, 0.93–1.00, $p = 0.05$, Table 3) independently predicted post-LT harmful relapse. When considering these objective pre-LT risk factors of pre-LT AR and HRAR $\geq$4, we found that patients with both risk factors were significantly more likely to have harmful relapse after LT than patients with 1 or neither risk factor (27.3% vs. 5.2%, $p < 0.001$, Figure 2B).

Telephone survey results and comparison with chart review

The survey response rate was 44.0% (n = 110). Of all relapses, 17.6% were identified by survey alone. When surveyed, 33% of patients whose relapse was identified by chart review denied post-LT alcohol use.

Only 54.5% of those surveyed believed alcohol was the primary cause of their liver disease, and 21.1% thought that alcohol was not involved at all. Of the 26.1% of participants with harmful relapse who completed the telephone survey, 50.0% reported alcohol as the primary cause of their liver disease, and the remaining 50.0% acknowledged that alcohol was involved but did not think it was the primary cause. Of all survey responders, 44.3% did not recall being asked about alcohol use in post-LT clinic visits. Participants who relapsed were more likely to report a new diagnosis of mental health disorder after LT when surveyed (33.3% vs. 12.8%, $p = 0.03$).

The results for agreement between variables obtained through chart review versus survey are shown in Table 4. Agreement for post-LT AR was high (AC1: 0.80). The agreement was fair for the duration of alcohol use (AC1: 0.37), moderate for pre-LT AR (AC1: 0.48) and pre-LT mental health disorder (AC1: 0.60), and substantial for post-LT mental health disorder (AC1: 0.67). The agreement was highest for relationship status at the time of LT (AC1: 0.90), post-LT alcohol-associated hospitalization (AC1: 1.0), and post-LT rehabilitation (AC1: 0.81).

Graft and patient outcomes

Graft loss, including death, occurred in 18.8% of patients (n = 47). Compared with all others, participants who harmfully relapsed had numerically more graft loss (30.4% vs. 17.4%, $p = 0.16$), as well as inferior 5- and 10-year post-LT survival (81.2% vs. 89.9% and 61.5% vs. 80.7%, respectively, Figure 3) though $p > 0.05$ for these numerical differences. Fifty percent of deaths in participants who relapsed to harmful alcohol use were related to substance use (including alcohol and/or illicit drugs).

TABLE 2 Univariate logistic regression for the association between various pre-LT risk factors and harmful alcohol relapse[a]

	OR (95% CI)	p
Demographics		
Female sex	2.12 (0.85, 5.31)	0.11
Age at transplant	0.92 (0.88, 0.97)	0.002
Race	—	0.96
Hispanic	0.87 (0.34, 2.24)	0.77
Other	0.98 (0.21, 4.64)	0.98
White	Reference	
Chronic hepatitis C	0.38 (0.15, 1.01)	0.05
HCC	0.26 (0.07, 0.88)	0.03
MELD at listing	1.04 (0.996, 1.09)	0.070
MELD at match	0.99 (0.94, 1.05)	0.68
Months from listing to LT	0.99 (0.96, 1.02)	0.68
Months from sobriety to LT	0.96 (0.94, 0.99)	0.02
Psychosocial variables		
Family history of alcohol use disorder	1.52 (0.64, 3.6)	0.34
Long-term relationship at time of LT	0.87 (0.3, 2.46)	0.79
Illicit drug use	0.47 (0.19, 1.15)	0.10
Tobacco use	0.38 (0.16, 0.92)	0.03
Opioid prescription	1.86 (0.74, 4.72)	0.19
Pre-LT mental health disorder diagnosis	2.14 (0.87, 5.27)	0.10
Post-LT mental health disorder diagnosis	1.81 (0.72, 4.53)	0.20
Alcohol use patterns		
Duration of heavy drinking (y)	—	0.49
>25	0.96 (0.11, 8.66)	0.97
11–25	1.86 (0.21, 16.18)	0.58
<11	Reference	
Drinks per day	—	0.02
>17	2.63 (0.71, 9.75)	0.15
9–17	4.33 (1.53, 12.23)	0.01
<9	Reference	
HRAR score	1.26 (0.85, 1.85)	0.25
HRAR score ≥4	2.69 (0.89, 8.10)	0.08
Alcohol relapse pre-LT	2.99 (1.19, 7.48)	0.02
Alcohol-associated legal complication	0.06 (0.01, 0.48)	0.01
Admissions for alcohol withdrawal	0.85 (0.16, 4.44)	0.85
Outpatient rehabilitation program (including Alcoholics Anonymous)	4.42 (0.57, 34.09)	0.15
Inpatient rehabilitation programs attended	—	0.31
≥2	0 (0–1)	0.99
1	2.39 (0.78, 7.3)	0.13
0	Reference	

[a]Three patients who had post-LT AR of unknown severity (slip or harmful drinking) are excluded from this analysis.
Abbreviations: HRAR, High-risk Alcoholism Relapse; LT, liver transplant; MELD, Model for End-stage Liver Disease.

DISCUSSION

With ALD now the leading indication for LT in the US, understanding how to appropriately assess the risk of post-LT AR and its effect on outcomes is imperative to guide candidate selection and inform peri-LT management of AUD. In our large, diverse cohort at a high-volume center with long-term follow-up, we found that nearly 1 in 10 patients relapsed to harmful drinking after a prolonged post-LT period (median 4 y). We demonstrated that post-LT relapse was commonly under-reported to clinicians. Use of a telephone survey allowed for the identification of a significant proportion of relapses that would otherwise have been missed by chart review alone. By incorporating data from both survey and chart review, we identified 3 variables that can be evaluated pre-LT to assess the risk of post-LT harmful relapse: length of pre-LT sobriety, history of AR pre-LT, and HRAR score ≥4, suggesting that patients with these risk factors may need enhanced monitoring and treatment for AUD pre- and post-LT.

Our study has several unique strengths. The utilization of a telephone survey to identify relapse and assess risk factors in this population is novel. This facilitated the identification of relapses that were not detected by chart review alone. Finding nearly 20% of relapses through the survey alone highlights the potential for missed opportunities in standard clinical care and the need to use specific strategies to encourage alcohol use disclosure. Telephone surveys also provided a unique opportunity to understand patient perceptions regarding their AUD. Investigators who conducted surveys were not involved in patient care; this lack of relationship and the anonymity of telephone communication may have improved patient comfort with disclosing alcohol use behaviors without the fear of repercussion or provider judgment.[26–28] In addition, we report long-term outcomes to 10 years after LT, which enabled us to characterize clinical outcomes multiple years after relapse and is particularly important in light of our finding that AR typically presented years after LT. Prior research has also shown that poorer outcomes occur later for patients transplanted for ALD compared with other LT indications.[13,29]

Risk factors for harmful AR after transplant

Although longer periods of sobriety pre-LT consistently associate with less relapse, many centers are moving away from requiring a minimum length of sobriety pre-LT, and national society guidelines are discouraging the use of pre-LT abstinence duration as an absolute criterion for LT candidacy.[16,17] In addition, the requirements of prolonged abstinence may not be feasible in the context of hepatic decompensation and the need for a more urgent life-saving liver transplant. Our finding that harmful relapse occurred even after an extended period of pre-LT sobriety (median 15 mo) emphasizes the importance of considering other variables, and we identified pre-LT AR and HRAR score ≥4 as key risk factors to consider.

History of AR pre-LT strongly associated with increased harmful AR after LT (OR: 3, $p = 0.015$). This finding is supported by a recent study of 155 patients transplanted for ALD, which also demonstrated that relapse after an initial sobriety attempt was a strong risk factor for post-LT AR.[10] Prior AR may be a marker of inadequate AUD

TABLE 3 Regression models for the association between various pre-LT risk factors and harmful relapse

Model A. Regression model for the association between harmful relapse and HRAR score ≥4, pre-LT relapse, pre-LT length of sobriety.	**OR (95% CI)**	***p***
HRAR score ≥4	3.43 (1.00, 11.75)	0.049
Relapse pre-LT	2.82 (0.84, 9.41)	0.093
Length of sobriety pre-LT	0.96 (0.93, 1.002)	0.064
Model B. Regression model for the association between harmful relapse and HRAR score ≥4, pre-LT relapse.	**OR (95% CI)**	***p***
HRAR score ≥4	2.61 (0.81, 8.41)	0.107
Relapse pre-LT	3.37 (1.05, 10.82)	0.042
Model C. Regression model for the association between harmful relapse and HRAR score ≥4, pre-LT length of sobriety.	**OR (95% CI)**	***p***
HRAR score ≥4	4.27 (1.29, 14.09)	0.017
Length of sobriety pre-LT	0.96 (0.927, 1.00)	0.051

Abbreviations: HRAR, High-risk Alcoholism Relapse score; LT, liver transplant.

management and thus more severe AUD that requires more robust treatment. We also found significant disagreement on the prevalence of pre-LT AR between chart review and survey, indicating that patients may be underreporting to providers pre-LT. This highlights an opportunity to change practices in pre-LT evaluation and develop strategies to better identify pre-LT AR, such as implementing standardized alcohol screening protocols in pre-LT clinics, augmenting the use of alcohol biomarkers pre-LT, and investing in provider education on motivational interviewing and other approaches to encourage patient disclosure of substance use.

After adjusting for pre-LT sobriety length and pre-LT AR, HRAR ≥4 independently predicted post-LT harmful relapse (OR: 3.4, $p < 0.05$). These results confirm those of 2 other large studies investigating the HRAR score as a tool to predict post-LT AR, which found that HRAR ≥3 or HRAR ≥4 were strongly associated with heavy drinking.[7,19] Although one smaller study did not find HRAR to be predictive of post-LT AR, this disparate

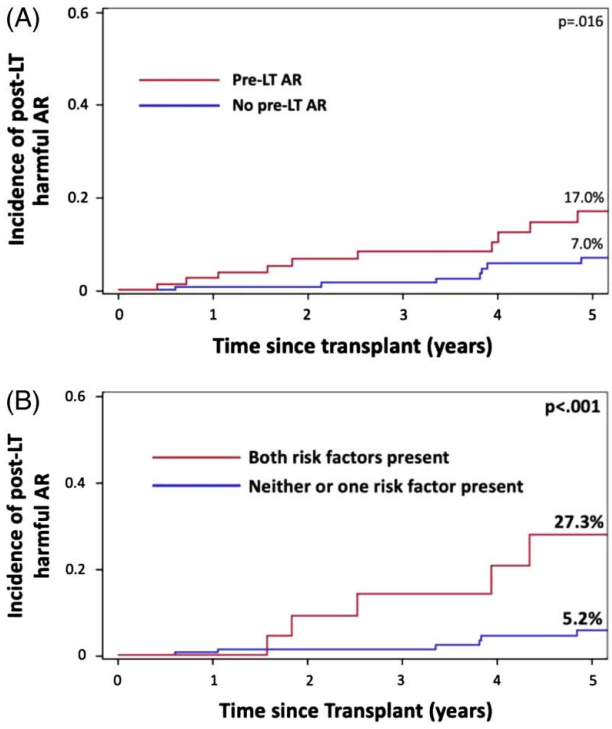

FIGURE 2 (A) Kaplan-Meier probability of post-transplant harmful alcohol relapse in patients with or without pretransplant alcohol relapse. (B) Kaplan-Meier probability of post-transplant harmful alcohol relapse in patients with both risk factors of pretransplant alcohol relapse and High-risk Alcoholism Relapse score ≥4 compared with those with neither or one of these risk factors. Abbreviations: LT, liver transplant; AR, alcohol relapse.

TABLE 4 Gwet chance-corrected agreement coefficient (AC1)[a] comparing results of chart review and telephone survey

Variable	**AC1**
Pre-LT duration of heavy drinking	0.37
Family history of alcohol use disorder	0.42
Pre-LT alcohol relapse	0.48
Pre-LT mental health diagnosis	0.60
Pre-LT drinks per day	0.64
Post-LT new mental health diagnosis	0.67
Pre-LT outpatient rehabilitation	0.68
Pre-LT illicit drug use	0.73
Pre-LT admissions for alcohol withdrawal	0.76
Pre-LT tobacco use	0.76
Pre-LT inpatient rehabilitation	0.77
Post-LT alcohol relapse	0.80
Post-LT rehabilitation	0.81
Long-term relationship at time of LT	0.90
Post-LT alcohol-associated hospitalization	1.00

[a]This coefficient measures the agreement between data from survey responses and data gathered from chart review. The coefficient scale ranges from −1 to 1. A value of 1 would represent perfect agreement, whereas a value between −1 and 0.2 is generally considered poor agreement (the worst possible level of agreement).
Abbreviation: LT, liver transplant.

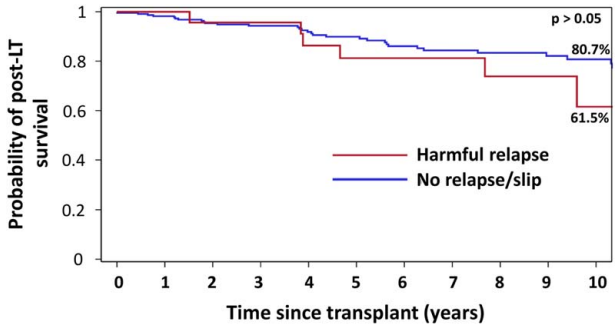

FIGURE 3 Kaplan-Meier probability of post-transplant survival in patients with harmful alcohol relapse compared with those with no alcohol relapse or slip relapse. Abbreviations: LT, liver transplant.

result may be explained by the small sample size with few participants characterized as high risk by HRAR and few known relapses.[20]

When considering the combination of pre-LT AR and HRAR ≥ 4, we found that patients with both risk factors were 5 times more likely to relapse to harmful drinking than those with 1 or neither of these risk factors ($p < 0.001$). Although these are not modifiable pre-LT, using this combination may enable LT providers to identify candidates with a higher risk of harmful relapse who will require additional resources for AUD management before and after LT. Given the rising number of candidates with ALD awaiting and undergoing LT,[2] it will be important to stratify candidates with regard to the risk of AR to appropriately triage and deploy AUD resources, which are often limited.

Although other published studies have found that a history of alcohol-associated legal issues and tobacco use are associated with post-LT relapse,[5,30] we did not confirm these findings. Some research suggests that legal sanctions and other mandated interventions after convictions for driving under the influence of alcohol lead to decreased heavy drinking and decreased rates of future alcohol-associated legal problems.[31,32] In addition, the American Psychiatric Association removed alcohol-associated legal problems as a criterion for diagnosing AUD in the fifth edition of the Diagnostic and Statistical Manual of Mental Health Disorders, citing poor fit with other criteria used for the diagnosis.[33] Furthermore, the growing body of evidence demonstrating significant racial bias in legal convictions, including enforcement of driving under the influence, highlights the limitations of studying alcohol-associated legal issues.[34]

Diagnosing AR after transplant

Our finding that a substantial proportion of ARs was detected by survey alone suggests that clinicians may be missing important opportunities to diagnose and treat post-LT relapse. Our analysis of agreement between chart review and survey responses found the best correlation for more objective variables (ie, relationship status at the time of LT) with more discrepancy for variables that patients may be less willing to report to providers, including pre-LT AR and duration of drinking. We also found that the importance of post-LT abstinence was not sufficiently emphasized to patients, as almost half of those surveyed did not recall a discussion of alcohol use during post-LT follow-up visits. These results suggest the need to improve protocols for monitoring alcohol use behaviors both pre- and post-LT, which may include more systematic screening for alcohol by utilizing structured, validated tools and/or regular use of objective measures, such as alcohol biomarkers, that have been shown to accurately detect alcohol use in the post-LT setting.[16] In addition, addiction specialists have been reported to detect recurrent alcohol use with greater sensitivity than hepatologists,[35] suggesting the need for addiction medicine collaboration across the continuum of LT care.

We found that new mental health disorders were common in post-LT and associated with AR, suggesting the importance of diagnosing and treating mental health disorders post-LT to potentially prevent AR. Depression is common in ALD and consistently correlates with negative post-LT outcomes, including survival.[36–41] One prospective study of ALD LT recipients found a 17% increase in mortality for each 1-point increase on the Beck Depression Inventory, with heightened mortality for those with new depression after LT (HR: 1.56 for mortality, $p = 0.004$).[41] Rogal et al[36] showed improved survival with depression treatment in this population. In addition, almost half of our patients who reported a new mental health diagnosis after LT did not have this documented in their chart. Because of the retrospective nature of chart review, one limitation of our study is the lack of more granular data on the specific nature or severity of mental health disorders in our cohort, especially as mental health disorders may be inaccurately documented in the medical record. This highlights the need for better long-term monitoring of mental health disorders, which may include more regular use of validated assessments, such as the Patient Health Questionnaire-9, in post-LT clinic visits.[42]

Relationship of harmful AR with long-term outcomes

Importantly, we found that harmful AR was associated with numerically greater graft loss and inferior post-LT survival, with half of the deaths in those with harmful relapse attributable to alcohol and/or illicit drug use. Several other large studies with long-term follow-up have found significant increases in mortality for recipients who relapse to harmful drinking.[6,9,29,43,44] Harmful AR has also been linked to graft cirrhosis, graft loss, and

medication nonadherence.[8,19] Given the prolonged time from LT to AR that we and others have demonstrated, longer follow-up periods may be necessary to fully realize the effects of harmful AR. Indeed, United Network for Organ Sharing data, including all LT in the US, between 2002 and 2016 found that ALD (vs. non-ALD indication) was associated with decreased risk of early death but an increased risk of late death.[13]

Our study has several limitations. Our data are derived from a single center. LT protocol at the time of data collection required 6 months of pre-LT sobriety, which may limit the generalizability of our results to candidates being evaluated for LT with <6 months of abstinence. Retrospective data collection may have led to underestimation or misreporting of alcohol-associated factors, including relapse. Furthermore, because of the heterogeneity of documentation of granular details of AR in the medical record, we were unable to use standardized criteria (ie, National Institute on Alcohol Abuse and Alcoholism definitions) to differentiate harmful AR from nonharmful AR, which introduced subjectivity into our categorization of AR. In addition, a significant number of patients included in the study could not be reached or declined to complete the telephone survey. Although some relapses were identified objectively because of clinically recognized consequences of relapse, identification of other relapses was dependent on accurate patient reporting, either to clinicians or through our survey; toxicology data were not routinely collected unless clinicians determined that it was indicated. As is highlighted by our finding that many relapses were under-reported to clinicians, reliance on the patient report to detect relapse is flawed and subject to multiple biases, including recall bias and social desirability response bias, which may have led recipients to over-report behaviors perceived as "good" while under-reporting those perceived as "bad."

In conclusion, our study shows that post-transplant alcohol use is common and that relapse to harmful drinking is associated with inferior post-transplant outcomes. By incorporating patient surveys into our data collection, we found that almost 20% of AR was missed during post-LT follow-up, highlighting the need for improved strategies to detect a return to alcohol use during post-LT care. We report 3 easily obtained pre-LT variables that can help predict the risk of post-LT harmful AR: length of pre-LT sobriety, history of AR before LT, and HRAR score ≥ 4, with significantly increased risk of harmful AR in candidates with both AR before LT and HRAR ≥ 4. Assessing these variables can assist in pre-LT candidate risk stratification and identification of patients needing augmented AUD therapy across the spectrum of pre- and post-LT care. In addition, given the potentially long duration from LT to AR and its harmful effects, patients would benefit from dedicated prolonged AUD monitoring and treatment. Future research is needed to investigate the potential for novel multimodal strategies, including biomarker surveillance and integrated care models, to better detect and prepare for post-LT relapse.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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