ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2026; 31: e952998
DOI: 10.12659/AOT.952998

Received: 2026.01.31
Accepted: 2026.06.17
Available online: 2026.11.13
Published: 2026.XX.XX

Return to Alcohol Use After Liver Transplant: Who Is at Risk?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Sienna D. Lila
BC 2 Kelly C. Hsu
AB 3 Katherine C. Specht
AB 4 Maria P. Diaz Soto
AB 5 Eric M. Przybyszewski
ABCD 6 Ana Ivkovic
ABCD 6 Mladen Nisavic
ABCDE 5 Wei Zhang
ABCDE 7 Leigh Anne Dageforde
AB 8 Sofia G. Baptista
ABCDE 8 Heidi Yeh
ABCDEF 5 Emily Bethea

1 Department of Medicine, University of Washington, Seattle, WA, USA
2 School of Medicine, Tufts University, Boston, MA, USA
3 Chan Medical School, University of Massachusetts, Worcester, MA, USA
4 Department of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA, USA
5 Department of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA
6 Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
7 Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
8 Department of Surgery, Massachusetts General Hospital, Boston, MA, USA

Corresponding Author: Sienna D. Lila, 1959 NE Pacific Street, Box 356421, Seattle, WA 98195, USA
Phone: 503-956-2627, e-mail: slila@uw.edu

Financial support: None declared
Conflict of interest: None declared

Background: Alcohol-associated liver disease remains the leading indication for liver transplant (LT), yet there has been limited analysis of what psychosocial factors correlate with biomarker-confirmed return to alcohol use in the post-LT setting.

Material/Methods: We conducted a single-center, retrospective, cohort study of all adult patients with alcohol-associated liver disease who received a liver transplant (LT) between 2016 and 2022. Medical records were queried for demographics, psychosocial variables, pre-LT sobriety duration, and 1-year post-LT mortality. Logistic regression and time-to-event analysis was used to correlate these factors with post-LT biomarker-confirmed return to alcohol use, defined as at least 1 positive urine ethyl glucuronide, urine ethyl sulfate, or serum phosphatidylethanol.

Results: Of 194 LT recipients, 52 (27% of all patients, 42% of those tested) tested positive for 1 or more alcohol biomarkers at least once. Female sex and younger age, but not pre-LT sobriety duration, were identified as independent risk factors for biomarker-confirmed post-LT return to alcohol use. Survival analysis identified a shorter time to biomarker confirmed return to alcohol use for patients with < 6 months ($P < 0.0001$) and 6-12 months ($P < 0.0001$) of pre-LT sobriety, compared with those with ≥ 12 months sobriety. However, patients with shorter pre-LT sobriety duration underwent biomarker testing significantly earlier following LT ($P < 0.0001$). There was no difference in 1-year post-LT mortality between patients with <6 months and those with > 6-month pre-LT sobriety.

Conclusions: In this retrospective cohort study, we observed that 1-year mortality and biomarker-confirmed return to alcohol use outcomes were not affected by pre-LT sobriety duration, supporting evolving standards that favor individualized risk assessment over fixed abstinence periods.

Keywords: Alcohol Abstinence • Alcohol Drinking • Alcohol-Related Disorders • Biomarkers • Liver • Mortality • Transplantation

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/952998

3075 3 3 39

APPROVED GALLEY PROOF

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

APPROVED GALLEY PROOF

Introduction

Alcohol-related liver disease (ALD) includes a spectrum of disease states, including alcohol-related steatosis, steatohepatitis, acute hepatitis, fibrosis, and cirrhosis. In the United States, ALD is the most common indication for liver transplant (LT), accounting for over 40% of new waitlist registrants [1]. A 5-fold increase in transplants for ALD over the past decade has been driven by a change in eligibility criteria, with over 85% of LT centers offering transplantation without a prespecified duration of abstinence [1,2].

Available data (with post-LT follow-up < 5 years) suggests LT outcomes for patients with ALD are comparable to those for other indications [3,4]. Cumulative rates of any alcohol use in the 5 years following LT are estimated to be between 30% and 40% and approaches 50% with long-term follow-up [5,6]. For 12% to 33% of patients transplanted for ALD, this return to alcohol use (RAU) is at harmful levels after transplantation [5,7-9]. Despite widespread acceptance of alcohol biomarker testing as a reliable indicator of alcohol use, there has been limited analysis of which psychosocial factors correlate with biomarker-confirmed RAU in the post-LT setting.

Biomarker testing detects recent alcohol consumption more reliably than patient self-reporting alone [10-14] and can affect clinical decision-making, including transplant candidate selection [11,15]. Three different types of biomarkers to detect alcohol use have been used in LT. Ethyl sulfate (EtS) and ethyl glucuronide (EtG) are urine biomarkers that have been used to monitor for alcohol consumption and typically remain detectable up to 48 hours after light drinking and up to 4 to 10 days after heavy consumption [16]. Phosphatidylethanol (PEth), a serum phospholipid that develops in the presence of ethanol, is correlated with the volume of alcohol consumption in the preceding 3 to 4 weeks [16] and has become broadly utilized to assess amount of alcohol use. PEth has high sensitivity (95%-99%) and specificity (100%) for high levels of alcohol consumption [17,18] and good sensitivity for lower levels of consumption (81.8%) [19]. Using a PEth cutoff value of 20 ng/mL optimizes sensitivity and specificity for detecting heavy alcohol use (ie, more than 7 drinks per week or more than 3 drinks on any day for women, and more than 14 drinks per week or more than 4 drinks on any day for men) [20]. Existing work on post-LT alcohol use has focused on PEth testing alone, with a median follow-up time of 18 months [21].hile the use of biomarkers to detect alcohol use after LT has been reported, little is known regarding specific psychiatric comorbidities that correlate with RAU after LT as indicated by positive biomarker testing. We aim to investigate psychosocial predictors of RAU after LT, based on alcohol biomarker testing.

Material and Methods

Study Design and Population

This was a single-center retrospective cohort study conducted at the major urban transplant center of Massachusetts General Hospital (MGH) in Boston, Massachusetts. The study population consisted of adult patients (age > 18 years) who received a LT for ALD (including alcohol-associated hepatitis and decompensated alcohol-associated cirrhosis) from January 1, 2016, to December 31, 2022. All urine EtG/EtS and serum PEth values obtained after LT were included, up until the point of data retrieval (November 2, 2023). Biomarker-confirmed RAU was defined as at least 1 positive PEth (> 20 ng/mL) or EtG/EtS (> 100 ng/mL) result during follow-up. In the primary regression analysis, all transplanted patients were included, and patients without a documented positive biomarker result—including those who never underwent biomarker testing—were classified as outcome-negative. Because alcohol biomarker testing was not performed uniformly across the cohort, a sensitivity analysis was performed restricting the analysis to patients who underwent at least 1 biomarker test to assess the potential effect of surveillance bias. Time to biomarker-confirmed RAU was defined as the interval from LT to the first positive alcohol biomarker test. One-year post-LT mortality, defined as all-cause death occurring within 365 days of liver transplantation, was obtained through UNOS reporting and manual chart review of electronic medical records. Patients were classified as deceased or alive at 1 year, and mortality rates were compared between patients with less than 6 months vs 6 or more months of pre-LT sobriety using Fisher's exact test. Patients without documented death at 1-year after LT were assumed to be alive. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul and approved by the Mass General Brigham Institutional Review Board (protocol #2022P002229).

Psychosocial Predictors of RAU

Demographic and psychosocial variables were obtained by chart review of transplant center electronic medical records. Transplant hepatology, psychiatry, and social work evaluations were reviewed for age, sex, pre-LT sobriety duration, comorbid psychiatric and non-alcohol use disorder (AUD) substance use disorders, and use of medication for alcohol use disorder (MAUD). Psychiatric disorders recorded included major depressive disorder (MDD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD) or trauma, and the presence of an active grief process. A composite variable for psychiatric comorbidities included the aforementioned disorders with the addition of bipolar disorder. Non-AUD substance use disorders were aggregated into a single composite variable, including cannabis, nicotine, opioid, and cocaine use disorders.

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Annual Biomarker Testing Rates

For longitudinal assessment of testing practices, the total number of alcohol biomarker tests (PEth and EtG/EtS separately and combined, both negative and positive results included) was calculated for each calendar year and expressed both as absolute counts and as tests per eligible post-LT patient. Trends in annual testing rates (PEth and EtG/EtS combined) over time were evaluated using simple linear regression, with calendar year treated as a continuous variable.

Statistical Analysis

Baseline patient characteristics were stratified by patients who underwent alcohol biomarker testing ("Tested") and those who did not ("Untested). Categorical variables were reported as percentages and continuous variables were reported as means or medians with interquartile ranges. Univariate analysis was performed using chi-square test or Fischer's exact test, where appropriate. Multivariate analysis on all 194 transplanted patients was performed using logistic regression to assess for factors associated with biomarker-confirmed RAU. This analysis was adjusted for age (continuous), sex (male/female), pre-LT sobriety (in months, continuous), whether or not the patient was prescribed MAUD (binary yes/no), MDD, GAD, additional non-AUD substance use disorder, trauma/PTSD, presence of an active grief process, and psychiatric comorbidity (binary yes/no). Although sobriety duration was presented descriptively using clinically relevant categories (<6, 6-12, ≥ 12 months) for ease of comprehension, it was modeled as a continuous variable in the regression analyses to preserve information and avoid loss of statistical power. Regression models were fit using complete-case analysis, such that observations with missing data in any covariate included in a given model were excluded. Separate time-to-event analyses were conducted for (1) time to first biomarker test and (2) time to biomarker-confirmed RAU, with event-free probabilities estimated using the Kaplan-Meier method. Patients without the event of interest were censored at the administrative end of follow-up (November 2, 2023). Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) and Prism 10 version 10.3.1 (GraphPad Software, San Diego, CA, USA).

Results

In total, 194 patients were transplanted for ALD during the study period. The majority of study participants were middle-aged (median age 56 years), White (91%), male (72%), insured (97%), and spoke English as their preferred language (97%). Half (46%) of patients had less than a college education. Forty-one patients (21%) had less than 6 months of sobriety before transplant, 48 (25%) had 6 to 12 months, and 104 (52%) had 12 or more months (**Table 1**). Median follow-up time from date of transplant was 43 months (IQR 29-63), and maximum follow-up time was 93 months.

A total of 125 (64%) patients were tested for alcohol biomarkers during the post-LT period. In the primary analysis of the full cohort, 27% (52/194) of patients met criteria for biomarker-confirmed RAU. In the sensitivity analysis restricted to patients who underwent biomarker testing, 42% (52/125) of patients met criteria for biomarker-confirmed RAU. A total of 113 (58%) patients were tested via urine EtG/EtS, and 37% of those tested had a positive value (> 100 ng/mL), with a median value of 3372 ng/mL (IQR 889-10 000). Eighty-two (42%) patients were tested via serum PEth, and 41% of those tested had a positive value (> 20 ng/mL), with a median value of 115 (IQR 56-267). The median time to biomarker-confirmed RAU was 24 months by PEth (IQR 13-40), 7.5 months by EtG/EtS (IQR 3-17), and 9.5 months by either test (IQR 3-20). Median time to biomarker-confirmed RAU was 6 months (IQR 3-21) for patients with less than 6 months pre-LT sobriety, 12 months (IQR 4-19) for patients with 6 to 12 months pre-LT sobriety, and 10 months (IQR 3-35) for patients with 12 or more months pre-LT sobriety (**Table 2**).

Psychosocial Factors and RAU

Patients who underwent alcohol biomarker testing were younger (median age 53 vs 59 years, $P < 0.0001$) and more likely to be female (34% vs 17%, $P = 0.03$) than patients who did not undergo testing (**Table 1**). In a multivariate analysis of all transplanted patients, female sex was associated with biomarker-confirmed RAU by either urine or serum biomarkers (OR 2.92; 95% CI 1.23-6.91, $P = 0.01$). Older age was protective against biomarker-confirmed RAU (OR 0.95; 95% CI 0.91-0.99, $P = 0.01$). Being prescribed MAUD, history of MDD, GAD, additional substance use disorder other than AUD (cannabis use disorder, nicotine use disorder, opioid use disorder, and cocaine use disorder), PTSD or trauma, active grief process, or the presence of a psychiatric comorbidity was not associated with biomarker-confirmed RAU use after LT (**Table 3**).

Relationship Between Pre-LT Sobriety and Biomarker-Confirmed RAU, Testing Patterns, and Post-LT Mortality

By bivariate analysis, patients with shorter pre-LT sobriety were more likely to be tested for alcohol biomarkers ($\chi^2(2) = 18.21$, $P < 0.0001$) and more likely to have biomarker-confirmed RAU ($\chi^2(2) = 19.75$, $P = 0.0001$) in the post-LT setting. While a multivariate regression analysis showed no significant association between pre-LT sobriety duration and biomarker-confirmed RAU (OR 1.00; 95% CI 0.98-1.02, $P = 0.50$), this result is

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

APPROVED GALLEY PROOF

Table 1. Patient sociodemographic characteristics, by post-liver transplant (LT) biomarker testing status.

Characteristic	Total n = 194	Tested n = 125	Untested n = 69	*P* value
Age (years), median (IQR)	56 (46-62)	53 (42-60)	59 (53-64)	< 0.0001
Body mass index, mean	29	30	29	0.72
Sex, n(%)				0.03
Male	140 (72)	83 (66)	57 (83)	
Female	54 (28)	42 (34)	12 (17)	
Race, n(%)				0.21
White or Caucasian	176 (91)	116 (94)	60 (88)	
Black or African American	4 (2)	1 (0.8)	3 (4)	
Asian	2 (1)	2 (2)	--	
Native American or Alaska Native	2 (1)	1 (1)	1 (1)	
Biracial or other	6 (3)	4 (3)	2 (3)	
Not documented	4 (2)	1 (1)	3 (4)	
Ethnicity, n(%)				1.00
Hispanic/Latino	8 (4)	5 (4)	3 (4)	
Non-Hispanic/Latino	183 (94)	118 (94)	65 (94)	
Unknown	3 (2)	2 (2)	1 (1)	
Married, n(%)	112 (58)	66 (53)	46 (67)	0.11
Insured, n(%)	189 (97)	121 (97)	68 (99)	0.66
Highest education level, n(%)				0.93
Less than college	65 (46)	44 (79)	21 (75)	
College or more	58 (41)	38 (40)	20 (42)	
Other6	19 (13)	12 (13)	7 (15)	
Preferred language, n(%)				0.75
English	189 (97)	122 (98)	67 (97)	
Spanish	4 (2)	2 (2)	2 (3)	
Other	1 (0.5)	1 (1)	--	
Pre-LT sobriety duration, n (%)				< 0.001
< 6 months	41 (21)	37 (30)	4 (6)	
6-12 months	48 (25)	35 (28)	13 (19)	
> 12 months	104 (52)	52 (42)	52 (75)	

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2. Alcohol biomarker testing patterns and biomarker-confirmed return to alcohol use (RAU) after liver transplant (LT). Biomarker-confirmed RAU was defined as at least 1 PEth > 20 ng/mL or EtG/EtS > 100 ng/mL in the post-LT period.

	Biomarker testing n (%)	Biomarker-confirmed RAU n (% of tested)	Time to biomarker-confirmed RAU (months), median (IQR)
PEth or EtG/EtS	125 (64)	52 (42)	9.5 (3-20)
PEth	82 (42)	34 (41)	24 (13-40)
EtG/EtS	113 (58)	42 (37)	7.5 (3-17)
Pre-LT sobriety duration			
< 6 months	37 (90)	16 (43)	6 (3-21)
6-12 months	35 (73)	21 (60)	12 (4-19)
≥ 12 months	52 (50)	14 (27)	10 (3-35)

Total patients tested, by biomarker test: PEth only: 11; EtG/EtS only: 43; both: 71; neither: 69.
Abbreviations: PEth, phosphatidylethanol; EtG, ethyl glucuronide; EtS, ethyl sulfate.

Table 3. Psychosocial predictors of biomarker-confirmed return to alcohol use (RAU) after liver transplant (LT), multivariate logistic regression.

Variable	Full cohort (n = 194)		Tested-only cohort (n = 125)	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age	0.95 (0.91-0.99)	0.01	0.97 (0.10-13.43)	0.89
Female sex	2.92 (1.23-6.91)	0.01	2.43 (0.92-1.01)	0.17
Pre-LT sobriety (months)	1.00 (0.98-1.02)	0.50	0.99 (0.97-1.01)	0.44
Medication for alcohol use disorder	1.60 (0.84-3.06)	0.16	1.62 (0.71-3.73)	0.25
Major depressive disorder	1.52 (0.53-4.39)	0.43	1.22 (0.37-3.94)	0.74
Generalized anxiety disorder	0.80 (0.28-2.31)	0.68	0.90 (0.27-2.84)	0.86
Additional substance use disorder	0.73 (0.28-1.90)	0.51	0.56 (0.18-1.66)	0.30
Trauma/post-traumatic stress disorder	1.11 (0.45-2.72)	0.83	1.39 (0.46-4.17)	0.55
Grief	0.88 (0.33-2.34)	0.79	0.73 (0.23-2.18)	0.57
Psychiatric comorbidity (yes/no)	2.08 (0.55-7.87)	0.29	3.22 (0.77-14.47)	0.12

tempered by the observation that patients with shorter sobriety duration were more likely to be tested, and thus biomarker testing was not applied uniformly (**Table 3**). Nonetheless, in a sensitivity analysis restricted to patients who underwent post-LT biomarker testing, the association between pre-LT sobriety duration and biomarker-confirmed RAU remained non-significant (OR 0.99, 95% CI 0.97-1.01; $P = 0.44$). Survival analysis of the full transplanted cohort identified a shorter time to biomarker-confirmed RAU use for patients with less than 6 months ($P < 0.0001$) and 6 to 12 months ($P < 0.0001$) of pre-LT sobriety, compared with those with 12 or more months sobriety (**Figure 1**). However, patients with shorter pre-LT sobriety duration underwent biomarker testing significantly earlier following LT compared with those with longer periods of pre-LT sobriety (**Figure 2**, $P < 0.0001$). Thus, earlier detection of biomarker-confirmed RAU in patients with shorter sobriety may reflect earlier surveillance rather than earlier biological RAU. There was no difference in time to biomarker-confirmed RAU between patients with less than 6 months and 6 to 12 months of pre-LT sobriety. These relationships were consistent when analyzing EtG/EtS and PEth tests separately. There was no statistically significant difference in 1-year post-LT mortality between patients with less than 6 months and those with greater than 6 month pre-LT sobriety (4/41 vs 12/152 deaths; OR 1.26, 95% CI 0.28-4.48; $P = 0.75$).

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

APPROVED GALLEY PROOF

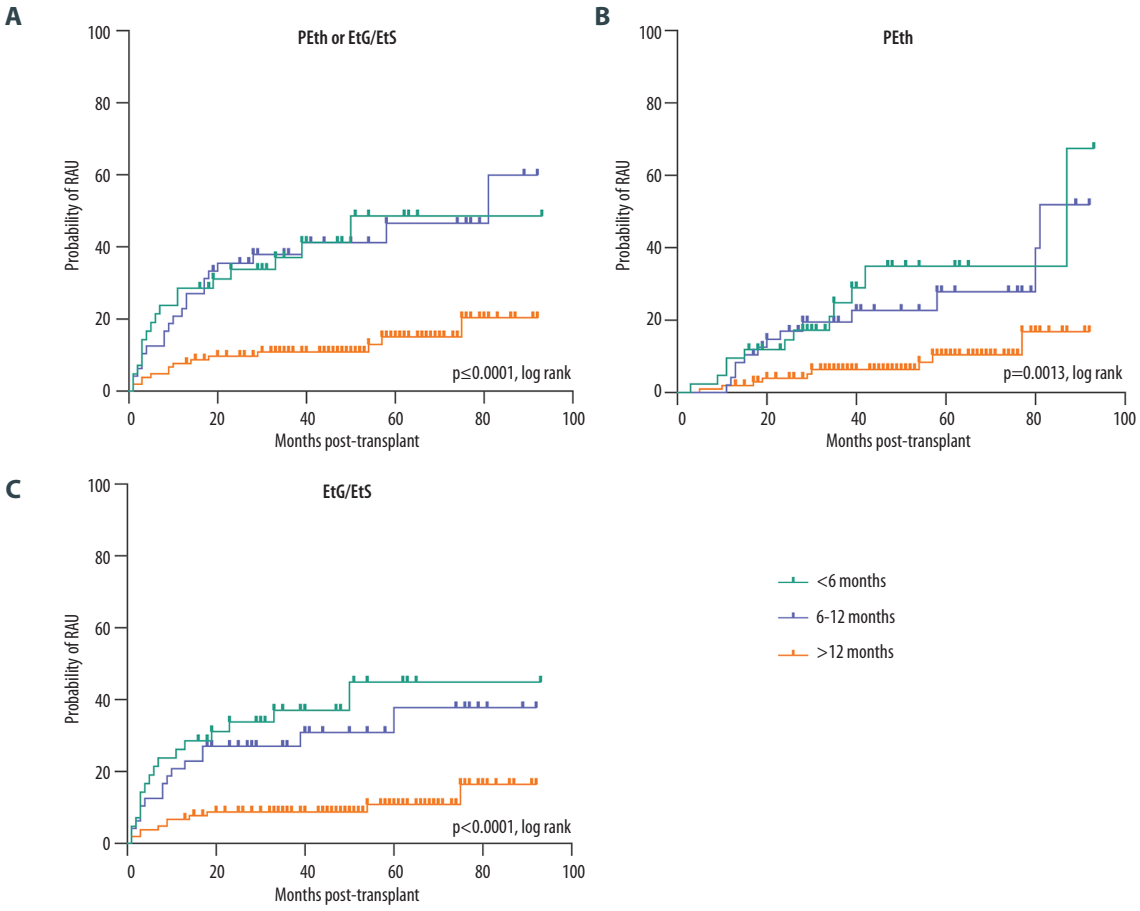


Figure 1. (A-C) **Probability of biomarker-confirmed return to alcohol use (RAU) by pre-liver transplant (LT) sobriety duration, Kaplan-Meier analysis.** Kaplan-Meier curves demonstrating time to first positive biomarker-confirmed RAU after LT, stratified by duration of pre-LT sobriety. Time zero was defined as the date of liver transplantation. Patients were censored at death or study administrative end date. Differences between groups were compared using the log-rank test. Biomarker-confirmed RAU was defined as at least 1 PEth > 20 ng/mL or EtG/EtS > 100 ng/mL in the post-LT period.
Abbreviations: PEth, phosphatidylethanol; EtG, ethyl glucuronide; EtS, ethyl sulfate.

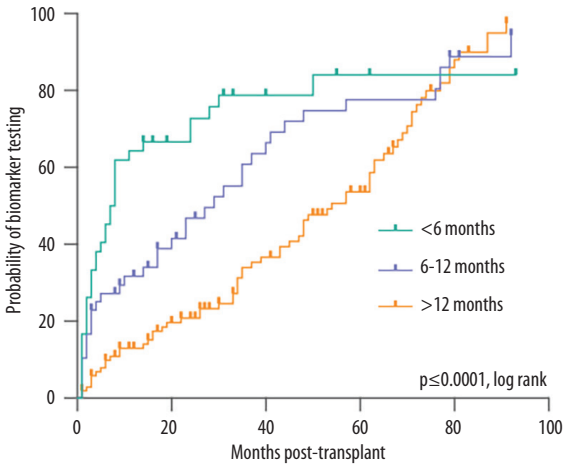


Figure 2. Probability of biomarker testing (PEth or EtG/EtS) by pre-liver transplant (LT) sobriety, Kaplan-Meier analysis. Kaplan-Meier curves demonstrating time to alcohol biomarker testing, stratified by duration of pre-LT sobriety. Time zero was defined as the date of liver transplantation. Patients were censored at death or study administrative end date. Differences between groups were compared using the log-rank test.
Abbreviations: PEth, phosphatidylethanol; EtG, ethyl glucuronide; EtS, ethyl sulfate.

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

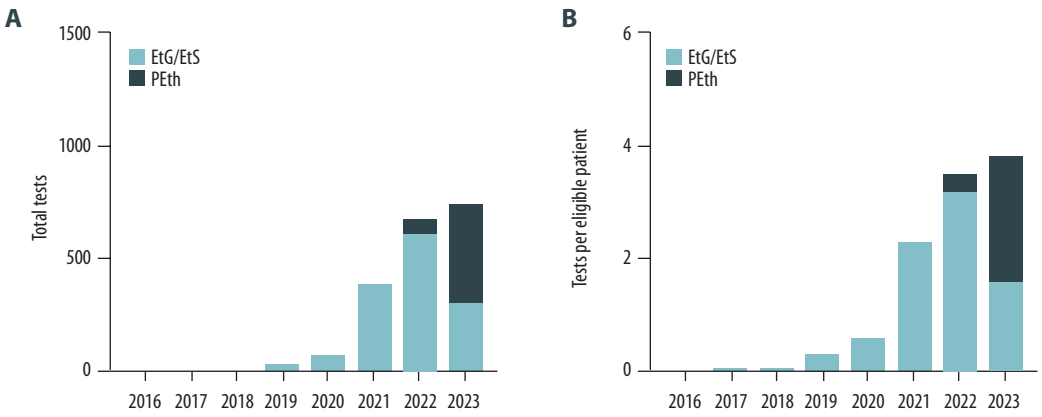


Figure 3. Biomarker testing rate by year. Bar graph demonstrating the total (**A**) and proportion (**B**) of study participants who underwent alcohol biomarker testing in each calendar year of the study period. Abbreviations: PEth, phosphatidylethanol; EtG, ethyl glucuronide; EtS, ethyl sulfate.

Testing Rates Over Time

There was a significant increase in the total tests per eligible patient (testing rate) with time ($P = 0.0014$), from 2016 to 2023. After the introduction of PEth testing in 2022 at the study center, the number of PEth tests per patient increased by 6.8-fold from 2022 to 2023, while testing with EtG/EtS decreased in the same time frame (**Figure 3**).

Discussion

In this retrospective cohort study, female sex and younger age were independently associated with a higher risk of biomarker-confirmed post-LT RAU in patients with ALD. However, these findings should be interpreted in the context of differential testing patterns, as women and younger patients were also more likely to undergo biomarker testing in the post-LT period. While several factors, such as hemoglobin, BMI, liver fibrosis, and HIV status, are associated with lower biomarker sensitivity, age and sex are generally not factors that falsely influence biomarker levels [16,19]. Historically, women have faced greater barriers to accessing AUD treatment than have men, for reasons including social stigma and economic- and time-related barriers [22-24]. In a study of patients with alcohol-related cirrhosis, women were less likely than men to have an in-person substance use visit or receive an FDA-approved relapse prevention medication [25]. With regards to behavioral therapy, a study of network-support treatment demonstrated that women were less likely to benefit from this type of program and had poorer drinking-related outcomes than men [26]. Female patients are also more often vulnerable to the harmful effects of alcohol than men, with a higher risk of progression to cirrhosis and development of associated complications [27]. These barriers, combined with our finding that female patients are at increased risk of biomarker-confirmed RAU after LT, underlines the critical need for additional resources dedicated toward supporting female patients with ALD undergoing evaluation for LT. Such resources may include female support groups for LT recipients, childcare assistance, and tailored behavioral treatments that incorporate and strengthen patients' existing support networks. Further work is needed to better understand risk factors and how to mitigate barriers in caring for female patients with AUD.

Our finding that younger patients may be at increased risk of biomarker-confirmed RAU is consistent with findings from previous literature [21,28-30]. Younger adults are at a higher risk for excessive alcohol intake and dangerous drinking patterns (binge drinking) [31,32]. Further investigation, potentially involving harm-reduction strategies for minimizing binge drinking, is required to identify ways of supporting younger patients through the post-LT period. Interestingly, we did not find an association between biomarker-confirmed RAU and any individual psychiatric comorbidity (ie, MDD, GAD, PTSD, grief), the presence or absence of a psychiatric comorbidity, or non-AUD substance use disorder. This deviates from previous literature, including a meta-analysis by Chuncharunee et al that found psychiatric comorbidities were the most significant risk factor for relapse after LT [7,28,33-35]. Given the present investigation was a single-center study, it is possible that it was not powered to identify a significant effect for individual psychiatric comorbidities. Identification, treatment, and support for patients with psychiatric comorbidities are likely crucial to the optimization of patient and graft outcomes after LT.

Pre-LT sobriety duration was a significant factor in biomarker testing patterns, with patients with shorter sobriety tested earlier and more often (**Figure 2**). This confounds the finding that shorter pre-LT sobriety (< 6 months) was associated with

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

APPROVED GALLEY PROOF

shorter time to biomarker-confirmed RAU. Providers may be more likely to initiate earlier post-LT surveillance for patients perceived to be at higher risk of RAU (ie, those with shorter pre-LT sobriety duration). Our finding that pre-LT sobriety duration is not an independent predictor of post-LT biomarker-confirmed alcohol use contradicts the findings of several studies [28,36-39]. However, given the differences in testing patterns across sobriety groups, we cannot draw definitive conclusions about the relationship between pre-LT sobriety duration and post-LT biomarker-confirmed RAU. Nonetheless, our observations contribute to the growing body of evidence supporting individualized risk assessment over fixed abstinence periods [21].

Long-term follow-up in this study (median of 43 months after LT) allowed for assessment of alcohol use in patients with longer pre-LT sobriety, in whom the first occurrence happened at a median of 12 months (for patients with 6-12 months sobriety) and 9.5 months (for patients with ≥ 12 months sobriety). This suggests that, while relapse can occur at any time after LT, the risk remains significant beyond the first year, and follow-up, as well as substance use treatment and monitoring, should extend accordingly.

This study had several limitations. The study cohort consisted of patients who successfully underwent LT and thus excluded patients with end-stage liver disease secondary to ALD that were either deemed not a candidate for transplant or died while on the waitlist, potentially introducing a selection bias. As previously discussed, patients with shorter pre-LT sobriety duration were more likely to be tested for alcohol use after LT, which may reflect provider bias surrounding risk of RAU and thus increased likelihood of identifying an episode of alcohol use, compared with patients who were tested less (or not at all). To mitigate this, our primary outcome was the presence of any positive test in the post-LT period, to avoid counting multiple positive tests that were recorded in the same drinking episode. The finding of a higher median time to biomarker-confirmed RAU by PEth testing vs EtG/EtS testing (24 vs 7.5 months, respectively) is potentially confounded by the fact that PEth testing was implemented later in the study period (2022) compared with EtG/EtS testing, which was in use from the beginning of the study period.

Conclusions

We found that female sex and younger age were independent risk factors for biomarker-confirmed post-LT RAU in our study cohort. Shorter pre-LT sobriety was not associated with an increased overall risk of biomarker-confirmed RAU or increase in 1-year post-LT mortality. Nonetheless, we observed that provider testing patterns varied by pre-LT sobriety duration, with patients with shorter sobriety being tested earlier. These findings highlight an opportunity for institutional quality improvement to promote consistent, evidence-based post-LT monitoring practices. Further studies using long-term biomarker data are warranted in order to distinguish between shorter and sustained relapses, evaluate their associations with short- and long-term graft function using biochemical and/or pathologic outcomes, and examine how AUD-focused and multidisciplinary interventions may improve post-LT patient-centered outcomes in the growing ALD population.

Acknowledgments

The authors would like to thank the Mass General Brigham Departments of Hepatology, Liver Transplantation, and Psychiatry for their support of this investigation. There are no funding sources to disclose for this study.

Department and Institution Where Work Was Done

Department of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA.

Patient Permission/Consent Declaration

This study was reviewed by the MGH Institutional Review Board and determined to be exempt from formal review due to its retrospective design and use of de-identified data. The requirement for informed consent was waived. All data were handled in compliance with institutional and federal privacy regulations.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2023 Annual Data Report: Liver. Am J Transplant. 2025;25(2S1):S193-287
2. Cholankeril G, Goli K, Rana A, et al. Impact of COVID-19 pandemic on liver transplantation and alcohol-associated liver disease in the USA. Hepatology. 2021;74(6):3316-29
3. Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: A study from the ELTR (European Liver Transplant Registry). Am J Transplant. 2010;10(1):138-48
4. 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):400-6

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

5. DiMartini A, Day N, Dew MA, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl. 2006;12(5):813-20
6. DiMartini A, Dew MA, Day N, et al. Trajectories of alcohol consumption following liver transplantation. Am J Transplant. 2010;10(10):2305-12
7. De Gottardi A, Spahr L, Gelez P, et al. A simple score for predicting alcohol relapse after liver transplantation: Results from 387 patients over 15 years. Arch Intern Med. 2007;167(11):1183-88
8. Lucey MR. Liver transplantation in patients with alcoholic liver disease. Liver Transplant. 2011;17(7):751-59
9. Rice JP, Eickhoff J, Agni R, et al. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. Liver Transplant. 2013;19(12):1377-86
10. Andresen-Streichert H, Beres Y, Weinmann W, et al. Improved detection of alcohol consumption using the novel marker phosphatidylethanol in the transplant setting: Results of a prospective study. Transpl Int. 2017;30(6):611-20
11. Fipps DC, Meyer R, Woods J, et al. Clinical utility and impact of phosphatidylethanol testing in liver transplantation evaluations. J Acad Consult Liaison Psychiatry. 2024;65(2):157-66
12. Scholten K, Twohig P, Samson K, et al. You can't handle the truth! Comparing serum phosphatidylethanol to self-reported alcohol intake in chronic liver disease patients. Dig Liver Dis. 2024;56(7):1215-19
13. Fleming MF, Smith MJ, Oslakovic E, et al. Phosphatidylethanol detects moderate-to-heavy alcohol use in liver transplant recipients. Alcohol Clin Exp Res. 2017;41(4):857-62
14. Segal A, Adkins E, Fatabhoy M, et al. Utility of phosphatidylethanol testing in liver transplant evaluation: Examining concordance to self-reported alcohol use. Liver Transplant. 2023;29(4):456-58
15. Selim R, Zhou Y, Rupp LB, et al. Availability of PEth testing is associated with reduced eligibility for liver transplant among patients with alcohol-related liver disease. Clin Transplant. 2022;36(5):e14595
16. Ulwelling W, Smith K. The PEth blood test in the security environment: What it is; why it is important; and interpretative guidelines. J Forensic Sci. 2018;63(6):1634-40
17. Hartmann S, Aradottir S, Graf M, et al. Phosphatidylethanol as a sensitive and specific biomarker: Comparison with gamma-glutamyl transpeptidase, mean corpuscular volume and carbohydrate-deficient transferrin. Addict Biol. 2007;12(1):81-84
18. Aradottir S, Asanovska G, Gjerss S, et al. PHosphatidylethanol (PEth) concentrations in blood are correlated to reported alcohol intake in alcohol-dependent patients. Alcohol Alcohol. 2006;41(4):431-37
19. Hahn JA, Murnane PM, Vittinghoff E, et al. Factors associated with phosphatidylethanol (PEth) sensitivity for detecting unhealthy alcohol use: An individual patient data meta-analysis. Alcohol Clin Exp Res. 2021;45(6):1166-87
20. Hahn JA, Fatch R, Barnett NP, Marcus GM. Phosphatidylethanol vs transdermal alcohol monitoring for detecting alcohol consumption among adults. JAMA Netw Open. 2023;6(9):e2333182
21. Torosian K, Shahrvini B, Johnson WM, et al. Psychosocial predictors of return to alcohol use after liver transplant: A multicenter cohort study. Alcohol Clin Exp Res. 2024;48(11):2137-44
22. Green BL, Rockhill A, Furrer C. Understanding patterns of substance abuse treatment for women involved with child welfare: The influence of the Adoption and Safe Families Act (ASFA). Am J Drug Alcohol Abuse. 2006;32(2):149-76
23. Khan S, Okuda M, Hasin DS, et al. Gender differences in lifetime alcohol dependence: results from the national epidemiologic survey on alcohol and related conditions. Alcohol Clin Exp Res. 2013;37(10):1696-705
24. Verissimo ADO, Grella CE. Influence of gender and race/ethnicity on perceived barriers to help-seeking for alcohol or drug problems. J Subst Abuse Treat. 2017;75:54-61
25. Mellinger JL, Fernandez A, Shedden K, et al. Gender disparities in alcohol use disorder treatment among privately insured patients with alcohol-associated cirrhosis. Alcohol Clin Exp Res. 2019;43(2):334-41
26. Litt MD, Kadden RM, Tennen H. Network Support treatment for alcohol dependence: Gender differences in treatment mechanisms and outcomes. Addict Behav. 2015;45:87-92
27. Bizzaro D, Becchetti C, Trapani S, et al. Influence of sex in alcohol-related liver disease: Pre-clinical and clinical settings. United Eur Gastroenterol J. 2023;11(2):218-27
28. Chuncharunee L, Yamashiki N, Thakkinstian A, Sobhonslidsuk A. Alcohol relapse and its predictors after liver transplantation for alcoholic liver disease: A systematic review and meta-analysis. BMC Gastroenterol. 2019;19:150
29. Rustad JK, Stern TA, Prabhakar M, Musselman D. Risk factors for alcohol relapse following orthotopic liver transplantation: A systematic review. Psychosomatics. 2015;56(1):21-35
30. Yu TW, Chen YM, Wang CC, et al. Incidence and risk factors of alcohol relapse after liver transplantation: Analysis of pre-transplant abstinence and psychosocial features. J Clin Med. 2020;9(11):3716
31. Quigley LA, Marlatt GA. Drinking among young adults: Prevalence, patterns, and consequences. Alcohol Health Res World. 1996;20(3):185-91
32. De Wever E, Quaglino V. [Risk factors and psychological vulnerabilities to binge-drinking in youth]. Encephale. 2017;43(5):486-90 [in French]
33. Egawa H, Nishimura K, Teramukai S, et al. Risk factors for alcohol relapse after liver transplantation for alcoholic cirrhosis in Japan. Liver Transplant. 2014;20(3):298-310
34. Kelly M, Chick J, Gribble R, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol. 2006;41(3):278-83
35. Karim Z, Intaraprasong P, Scudamore CH, et al. Predictors of relapse to significant alcohol drinking after liver transplantation. Can J Gastroenterol J Can Gastroenterol. 2010;24(4):245-50
36. Osorio RW, Ascher NL, Avery M, et al. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. Hepatology. 1994;20(1 Pt 1):105-10
37. Krom RA. Liver transplantation and alcohol: who should get transplants? Hepatology. 1994;20(1 Pt 2):28S-32S
38. Gish RG, Lee AH, Keeffe EB, et al. Liver transplantation for patients with alcoholism and end-stage liver disease. Am J Gastroenterol. 1993;88(9):1337-42
39. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: A report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Transplantation. 1998;66(7):956-62

APPROVED GALLEY PROOF

This work is licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]