



# Identification of Quantifiable Predictors of Relapse in Patients with Alcohol-Associated Liver Disease

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Abstinence in patients with alcohol-associated liver disease (ALD) reduces mortality. Most predictors of relapse are not quantifiable, preventing objective analysis of relapse risk and targeted intervention to improve clinical outcomes. We prospectively enrolled patients with ALD from November 2016 to December 2019 and administered a survey with two previously published scales to assess insight into alcohol-use disorder (Hanil Alcohol Insight Scale [HAIS]) and social support (Community Assessment Inventory Scale [CAIS]). Relapse was assessed using surveys and metabolite testing. Unadjusted and prespecified adjusted regression analyses identified predictors of relapse. We enrolled 81% of eligible patients (n = 136), of whom 58 had follow-up data available at the time of analysis. Over a median follow-up of 1 year (interquartile range: 0.5-1.4), 10 patients relapsed (17%). Patients who relapsed were more likely to continue drinking despite either a diagnosis of liver disease or a decompensating event, and were less likely to have been transplanted (all  $P < 0.05$ ). In unadjusted regression, the HAIS and the “support inside the home” subcategory of the CAIS were predictive of relapse, with odds ratio (OR) = 0.84 (95% confidence interval 0.72-0.97) and 0.85 (0.74-0.97). In adjusted regression, the HAIS was no longer significant, with adjusted OR = 0.70 (0.49-1.00,  $P = 0.05$ ), whereas the “support inside the home” subcategory of CAIS remained significant, with adjusted OR = 0.69 (0.51-0.92,  $P = 0.01$ ). **Conclusions:** Risk factors for relapse in patients with ALD were identified and quantified prospectively, suggesting opportunities to objectively identify patients at risk for relapse as well as to intervene to prevent relapse. (*Hepatology Communications* 2021;5:1156-1164).

**A**lcohol-associated liver disease (ALD) is the leading cause of gastrointestinal-related death among women and men, with a crude mortality rate of 6.8 per 100,000.<sup>(1)</sup> ALD can be defined clinically as evidence of liver damage that occurs in the setting of high-risk drinking. The NIAAA has defined high-risk drinking to include the consumption of four or more drinks on any day

or eight or more drinks per week for women (five or more drinks on any day or 15 or more drinks per week for men),<sup>(2,3)</sup> but these thresholds are not particular to ALD. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) defines alcohol addiction by the diagnosis of alcohol use disorder (AUD), which is often co-morbid with ALD and predicts high-risk drinking.<sup>(4,5)</sup> Clinically defined

*Abbreviations:* ALD, alcohol-associated liver disease; aOR, adjusted odds ratio; AUD, alcohol use disorder; CAIS, Community Assessment Inventory Scale; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAIS, Hanil Alcohol Insight Scale; IQR, interquartile range; LT, liver transplant; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

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ALD presents on a histologic spectrum, ranging from simple steatosis to significant fibrosis that can be further complicated by features of liver decompensation (ascites, hepatic encephalopathy, or variceal bleeding).<sup>(4)</sup> Regardless of where patients with ALD are on the histologic spectrum, complete abstinence has been shown to only occur in a minority of patients (< 50%) over follow-up periods of 4-5 years. This minority of abstinent patients, however, experience significantly improved survival.<sup>(6,7)</sup> Thus, identifying predictors of any alcohol relapse in the setting of ALD is critical in order to develop interventions to prevent it from occurring and to improve survival.

Current predictors of alcohol relapse identified in patients with ALD are mostly non-modifiable and have been studied primarily in post-liver transplant (LT) cohorts, which represent a minority of patients with ALD.<sup>(8,9)</sup> Some of these variables include family history, demographics, socioeconomic, community support, alcohol history, psychiatric history, and medical factors.<sup>(8)</sup> In the few studies conducted in the pretransplant population, younger age, female gender, and prior alcohol rehabilitation attendance predicted future relapse.<sup>(6,10)</sup> Prior relapse risk-prediction models that were validated in post-LT populations remain limited, as they included factors that were either subjectively assessed by the clinician researcher or scored using retrospective data.<sup>(8,11)</sup>

Therefore, an unmet research need involves identifying quantifiable and more objective predictors of alcohol relapse in patients with liver disease, especially in those who are pretransplant. In prior addiction populations, use of the Hanil Alcohol Insight Scale (HAIS)<sup>(12)</sup> and Community Assessment Inventory Scale (CAIS)<sup>(13)</sup> proved to be predictive of alcohol relapse<sup>(14)</sup> and of attendance in treatment programs

for opioid addiction, respectively.<sup>(15)</sup> These scores have not been assessed in the liver disease population, and research has been limited to those who chose to participate in alcohol relapse prevention programs and/or research. Our aim was to study the ability of these patient-reported scales to forecast relapse even in the presence of already identified predictors in a prospective cohort of patients with ALD. If found to be predictive of relapse, these scales would offer a more objective assessment to stratify relapse risk in the pretransplant evaluation that could potentially be intervened upon, ultimately improving survival.

## Methods

### PARTICIPANT SELECTION AND STUDY SETTING

From November 2016 to December 2019, English-literate patients with clinically diagnosed ALD (evidence of liver damage in the context of either high-risk drinking or AUD) aged 18-80 years old were enrolled from the inpatient and outpatient setting of a single quaternary liver transplant center in New York City. Exclusion criteria included unclear or mixed etiology of liver disease, as evidenced by abnormal iron studies, positive viral hepatitis serologies, or other testing. Patients who were actively drinking were also excluded, given concerns about ability to provide consent. Eligible patients were identified through electronic health record screening and physician referral. Potentially eligible participants were approached for enrollment and, if enrolled, were asked to complete an initial as well as follow-up surveys. Patients had the option of

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completing the initial surveys in person using a tablet or a computer provided to them or using their own devices from home. All patients were sent follow-up surveys through e-mail and were given the option of completing them in person during clinic visits if their follow-up survey date coincided with scheduled appointments. Survey responses were recorded using REDCap electronic data capture tools hosted at Weill Cornell Medicine.<sup>(16,17)</sup> Our institutional review board approved the study (protocol #1601016922), and all participants provided written, informed consent. Our study was registered at ClinicalTrials.gov protocol NCT03267069.

## SURVEY DETAILS

Patients completed a comprehensive survey that included patient demographics (survey location, age, sex, race, and smoking status), socioeconomic factors (education, employment, and household income), psychiatric factors (psychiatric disorders and history of other substance abuse), and alcohol use history (AUD within the year prior to enrollment as well as historical patterns of alcohol use, presentations to the emergency room for withdrawal, attendance of rehabilitation for alcohol use, arrests for alcohol use, relapse after being diagnosed with liver disease or after a decompensating event, and presurvey abstinence duration). It is important to note that while most questions related to alcohol use history asked in relation to the patient's lifetime, the questions specific to AUD were asked over the past 12 months, as is standard per DSM-5 criteria for AUD. To assess quantifiable relapse risk factors investigating insight into AUD and social support, the following surveys were used with permission: the CAIS<sup>(13)</sup> and the HAIS.<sup>(12)</sup>

## DATA COLLECTION

Data were extracted from chart review and included details not captured in the survey and that were previously proposed to be essential in this population. This included laboratory values, liver disease-related complications (e.g., ascites, varices, hepatic encephalopathy, hepatocellular carcinoma), and transplant status at the time of survey.<sup>(4)</sup> A minimum of two co-authors extracted each data point to ensure accuracy and reproducibility.

## IDENTIFICATION AND CATEGORIZATION OF RELAPSE

Relapse was defined as any alcohol consumption in the follow-up period. This definition was chosen given that it is the most commonly used definition in the literature on relapse in post-LT patients.<sup>(18-24)</sup> Patients were identified as having relapsed via scheduled follow-up surveys (quarterly for the first year and every 6 months for the second year) in conjunction with metabolite or urine ethyl glucuronide testing performed at the provider's discretion during follow-up clinic visits, with a standard practice of every 3-6 months with Model for End-Stage Liver Disease (MELD) labs. Patients positive for relapse were then categorized as having either a sustained relapse (alcohol use occurring over a minimum of 100 days) or unsustained relapse (alcohol use occurring less than 100 days with a return to abstinence).<sup>(25)</sup>

## OBJECTIVES

Our primary aim focused on prospectively identifying quantifiable risk factors for alcohol relapse in patients with ALD by evaluating the ability of the HAIS and CAIS to predict alcohol relapse. The secondary aim of the study involved identifying additional relapse risk factors.

## SURVEY ANALYSIS

Validated survey composite scores were generated as originally published with the exception of the HAIS.<sup>(12)</sup>

As indicated in Supporting Table S1, the HAIS uses 20 questions to assess insight into the importance of alcohol abstinence with response options of "agree," "not sure," and "disagree." Based on published recommendations, each question scored received -1, 0, or 1 points, with higher scores suggesting increased insight.

The CAIS uses 37 questions to assess social support overall and in the following four areas: family within the home (6 items), family living outside the home (10 items), friends (8 items), and the community (13 items) (Supporting Table S1).<sup>(13)</sup> Response options involved a four-point Likert scale ("disagree strongly," "disagree," "agree," and "agree strongly"), with each question receiving 1 to 4 points. Questions were scored overall and within the four areas, with higher scores indicating more support.

## STATISTICAL ANALYSIS

Where appropriate, continuous variables were compared using Student *t* tests or rank-sum tests, and categorical variables were assessed using chi-square or Fisher's exact tests. The ability of the scales to predict relapse was assessed first in unadjusted regression, with relapse being the dependent variable and either the HAIS or the CAIS as the independent variables. These scales were then assessed in *a priori* specified adjusted logistic regression, controlling for variables predictive of relapse in pretransplant ALD populations (age, sex, and history of attending alcohol rehabilitation), as well as variables identified to be statistically significantly different between the studied cohorts. A supplemental adjusted regression analysis was conducted that excluded all posttransplant patients, given the potential for this population to differ greatly from pretransplant patients with regard to predictors of relapse.

## Results

### STUDY POPULATION AND RELAPSE EVENTS

We enrolled 81% (136 of 168) of eligible patients, of whom 70% (95 of 136) started the survey, and 60% (82 of 136) completed the survey, with follow-up data available on 43% of these patients (58 of 136) (Figure 1). A total of 35 of 58 (60.3%) of patients had metabolite testing over the study period. Over a median follow-up of 1 year (interquartile range [IQR] 0.5-1.4), 10 of 58 patients (17%) relapsed, of whom 5 were sustained (8.6%) and 5 were unsustainable (8.6%). Most relapses were identified by self-reported follow-up surveys ( $n = 7$ , 70%), while the remaining were identified by metabolite testing ( $n = 3$ , 30%).

### COHORT DEMOGRAPHICS, SOCIOECONOMICS, AND PSYCHIATRIC FACTORS

Most of the study cohort involved recruitment from the outpatient location (72%, 42 of 58), and most patients were men (74%, 43 of 58), non-Hispanic White (74%, 43 of 58), and middle aged

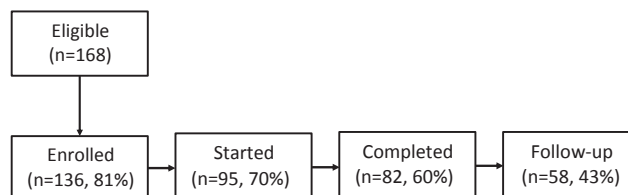


FIG. 1. Study cohort.

(median age 55 years, IQR 47-62). Demographics of patients who relapsed in comparison to those who remained abstinent were not significantly different (Table 1). Most patients were college educated (55%, 32 of 58) and reported an income > \$35,000 (67%, 39 of 58).

### LIVER DISEASE HISTORY

Laboratory values were not significantly different between the cohorts (Table 2). The median MELD score was 11 with an IQR of 8-18, and most patients had portal hypertension: ascites (86%, 50 of 58), hepatic encephalopathy (66%, 38 of 58), and varices (64%, 37 of 58). Patients who relapsed in comparison to those who abstained were less often transplanted at the time of survey and more often declined for transplant or were found to have no acute indication for transplant evaluation ( $P < 0.01$ ).

### ALCOHOL USE HISTORY

Of the patients who relapsed, 90% ( $n = 9$ ) met the criteria for AUD within the year of survey completion, in comparison to 44% ( $n = 21$ ) of those who abstained ( $P = 0.01$ ) (Table 3). All of the patients who relapsed reported a history of drinking after being diagnosed with ALD, in comparison to 67% of those who abstained ( $P = 0.03$ ).

### IDENTIFYING QUANTIFIABLE AND MODIFIABLE SOCIAL SUPPORT AND ALCOHOL INSIGHT DIFFERENCES

Patients who relapsed reported less social support than abstinent patients: The mean respective total CAIS scores were 108 (SD = 15) and 120 (SD =

**TABLE 1. PATIENT DEMOGRAPHICS, SOCIOECONOMICS, AND PSYCHOSOCIAL FACTORS**

Characteristic	Relapse (n = 10)	Abstinent (n = 48)	P
<b>Demographics</b>			
Outpatient location, n (%)	8 (80)	34 (81)	0.71
Age, mean (range)	52 (44-61)	55 (52-58)	0.55
Women, n (%)	2 (20)	13 (27)	0.49
Race/ethnicity, n (%)			0.15
Non-Hispanic White	5 (50)	38 (79)	
Hispanic White	2 (20)	4 (8)	
Black	1 (10)	2 (4)	
Asian	1 (10)	2 (4)	
Other	1 (10)	2 (4)	
Active smoker, n (%)	1 (10)	4 (9)	0.63
<b>Socioeconomics</b>			
College-educated, n (%)	7 (70)	25 (52)	0.49
Employed, n (%)	6 (60)	15 (31)	0.09
Household income >\$35,000, n (%)	5 (50)	34 (71)	0.27
<b>Psychiatric factors</b>			
Psychiatric disorders self-reported at time of survey			
Depression	0 (0)	8 (17)	0.20
Bipolar	0 (0)	2 (4)	0.68
Anxiety	0 (0)	9 (19)	0.16
Other mood disorder	1 (10)	1 (2)	0.32
History of nonmarijuana illicit drugs, n (%)	0 (0)	17 (35)	0.03

15) ( $P = 0.02$ ). Within the CAIS, 9 of the 37 CAIS questions were significantly different between the cohorts (Supporting Table S2). Analysis of the four categories comprising the CAIS (support within the home, support outside the home, support from friends, and support from community) suggested that six questions assessing social support within the home (Supporting Table S1) most significantly affected the findings. The mean score for social support within the home of patients who relapsed, 16 (SD = 7), was significantly lower than the score for patients who abstained, 21 (SD = 4) ( $P < 0.01$ ), whereas the other three categories were not significantly different between the cohorts (Table 4 and Supporting Table S2). Additionally, patients who relapsed had less insight into their AUD. The median HAIS score was significantly lower in

**TABLE 2. LIVER DISEASE HISTORY**

	Relapse (n = 10)	Abstinent (n = 48)	P
<b>Laboratory values at time of survey*</b>			
Sodium, median (IQR)	138 (136-139)	137 (134-140)	0.97
Creatinine, median (IQR)	0.83 (0.77-0.94)	0.90 (0.75-1.08)	0.46
AST, median (IQR)	52.0 (38.0-77.0)	44.0 (25.0-56.0)	0.34
ALT, median (IQR)	34.5 (22.0-44.0)	29.0 (21.0-50.0)	0.81
Bilirubin, median (IQR)	1.6 (1.0-3.3)	2.2 (0.9-4.7)	0.61
Albumin, median (IQR)	3.2 (2.8-3.9)	3.2 (2.9-4.0)	0.84
INR, median (IQR)	1.2 (1.1-1.4)	1.2 (1.2-1.7)	0.39
MELD score, median (IQR)	16 (9-21)	11 (10-18)	0.37
Maddrey score, median (IQR)	11.3 (-2.2-26.3)	15.4 (9.2-44.9)	0.34
<b>Liver disease–related complications, n (%)</b>			
Ascites	8 (80)	42 (88)	0.62
Varices	7 (70)	30 (63)	0.73
Hepatic encephalopathy	4 (40)	34 (71)	0.07
Hepatocellular carcinoma	1 (10)	7 (15)	0.58
Liver-related complications per patient, median (IQR)	2 (1-3)	3 (2-3)	0.37
<b>Clinical status at time of survey</b>			
Transplanted	1 (10)	15 (31)	0.01
Wait-listed	0 (0)	17 (35)	
Center declined	4 (40)	7 (15)	
No acute indication for evaluation	5 (50)	9 (19)	

\*Laboratory values reported removed patients with a history of transplant at the time of the survey (n = 16).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

patients who relapsed, 2.0 (IQR -2.5 to 7.0), compared to those who abstained, 8.0 (IQR 5.0-11.0) ( $P = 0.03$ ) (Table 4). Of the 16 questions comprising the scale, 8 questions were significantly different between the cohorts (Supporting Table S2).

## PREDICTING RELAPSE

In unadjusted logistic regression, the HAIS and CAIS surveys were predictive of relapse with respective odds ratios (ORs) of 0.84 (95% confidence interval [CI] 0.72-0.97,  $P = 0.02$ ) and 0.95 (95% CI 0.90-1.00,  $P = 0.05$ ) (Table 5). Assessment of the subcategories comprising the CAIS suggested that support within the home was independently predictive of relapse in unadjusted regression, 0.85 (95% CI 0.74-0.97,  $P = 0.02$ ), whereas the other CAIS subcategories were not predictive of relapse (Table 5). In adjusted regression controlling for age, sex, history of attending alcohol

**TABLE 3. ALCOHOL USE HISTORY AND INSIGHT INTO AUD**

	Relapse (n = 10)	Abstinent (n = 48)	<i>P</i>
Alcohol use history			
AUD,* n (%)	9 (90)	21 (44)	0.01
Monthly engagements with alcohol present, median (IQR)	1 (0-4.5)	1 (0-3)	0.92
Significant other consumes alcohol, n (%)	3 (30)	16 (33)	0.26
Family history of alcohol abuse, n (%)	7 (70)	21 (44)	0.12
Heavy alcohol consumption			
Age started, median (IQR)	28 (20-37)	28 (18-39)	0.71
Daily drinks, <sup>†</sup> median (IQR)	6 (2-10)	5 (4-11)	0.74
Years drank heavily, median (IQR)	13 (7-24)	15 (8-30)	0.67
Drink preference(s), n (%)			
Spirits	5 (50)	30 (63)	0.35
Wine	4 (40)	24 (50)	0.41
Beer	3 (30)	24 (50)	0.21
ER presentations for withdrawal, n (%)	4 (40)	7 (15)	0.11
Attended rehabilitation facility, n (%)	3 (30)	18 (38)	0.48
Arrested for alcohol use, n (%)	1 (10)	13 (27)	0.24
Drinking after liver-disease diagnosis, n (%)	10 (100)	32 (67)	0.03
Drinking after a decompensating event, <sup>‡</sup> n (%)	8 (80)	15 (33)	0.01
Presurvey abstinence (in years)	0.6 (0.1-1.0)	1.0 (0.3-3.5)	0.18

\*AUD as defined by the DSM-5.<sup>(5)</sup>

<sup>†</sup>Daily drinks were defined as 12 oz of beer, 8-9 oz of malt liquor, 5 oz of wine, or 1.5 oz of liquor.

<sup>‡</sup>Decompensating events included the occurrence of one or more of the following features: ascites, variceal bleeding, encephalopathy, hepatocellular carcinoma, or hepatorenal syndrome. Abbreviation: ER, emergency room.

rehabilitation, drinking after being diagnosed with decompensated liver disease, presence of AUD in the year before survey completion, and LT status, the CAIS remained statistically significant with an adjusted OR (aOR) of 0.92 (95% CI 0.85-0.99, *P* = 0.04), whereas the HAIS trended toward significance with an aOR of 0.70 (95% CI 0.49-1.00, *P* = 0.05). The CAIS subcategory of support within the home remained independently predictive in adjusted regression (aOR = 0.69 [0.51-0.92], *P* = 0.01). When excluding posttransplant patients from analysis, results of adjusted regression remained unchanged (Supporting Table S3).

**TABLE 4. USE OF SCALES IN PATIENTS WITH ALD**

	Relapse (n = 10)	Abstinent (n = 48)	<i>P</i>
CAIS, <sup>(1,3)</sup> mean (SD)	108 (15)	120 (15)	0.02
Support within the home	16 (7)	21 (4)	<0.01
Support outside the home	31 (7)	34 (5)	0.08
Support from friends	24 (4)	26 (4)	0.14
Support from the community	39 (5)	40 (6)	0.40
HAIS, <sup>(1,2)</sup> median (IQR)	2.0 (-2.5-7.0)	8.0 (5.0-11.0)	0.03

**TABLE 5. VARIABLES PREDICTIVE OF RELAPSE**

	Unadjusted		Adjusted*	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
CAIS <sup>(1,3)</sup>	0.95 (0.90-1.00)	0.05	0.92 (0.85-0.99)	0.04
Support within the home	0.85 (0.74-0.97)	0.02	0.69 (0.51-0.92)	0.01
Support outside the home	0.91 (0.79-1.04)	0.16	0.91 (0.77-1.07)	0.25
Support from friends	0.89 (0.73-1.10)	0.28	0.83 (0.63-1.09)	0.19
Support from community	0.98 (0.87-1.11)	0.80	0.89 (0.72-1.10)	0.28
HAIS <sup>(1,2)</sup>	0.84 (0.72-0.97)	0.02	0.70 (0.49-1.00)	0.05

\*Adjusted for age, sex, history of attending alcohol rehabilitation, history of drinking after being diagnosed with decompensated liver disease, presence of AUD, and LT status.

## Discussion

In our cohort of patients with ALD, we prospectively identified and quantified predictors of alcohol relapse using the HAIS and CAIS (Tables 4 and 5).<sup>(12,13)</sup> Patients who relapsed in comparison to those who successfully abstained reported decreased social support and decreased insight into their AUD, identified using the CAIS and HAIS, respectively (Table 4). Multivariate adjusted regression confirmed the predictive ability of the CAIS (aOR = 0.92, 95% CI 0.85-0.99, *P* = 0.04) and the potential predictive value of the HAIS (aOR = 0.70, 95% CI 0.49-1.00, *P* = 0.05), thereby suggesting the efficacy of using these scores to more objectively quantify risk of relapse.

Although no comparison of these findings exists within the ALD population, administration of the

HAIS to 117 Korean men discharged from an alcohol treatment center found that patients with worse insight into their AUD (lower HAIS scores) were more likely to have relapsed at 1-year follow-up in comparison to patients with increased insight (higher HAIS scores).<sup>(14)</sup> Additionally, study of the CAIS in 196 opioid-dependent adults identified that those not enrolled in treatment programs had significantly lower CAIS scores in comparison to those in treatment programs, suggesting the importance of social support in obtaining treatment for drug addiction.<sup>(15)</sup> Our findings, in the context of the previously published literature, further emphasize the important roles of insight into AUD and of social support in identifying patients at risk of relapse.

Most of our cohort involved relapse events occurring in nontransplanted patients ( $n = 9$ , 90%), which has become an increasingly important population to study. Although much of the prior literature in ALD studied predictors of relapse in highly prescreened, post-LT populations,<sup>(8)</sup> given the increasing incidence in the United States of high-risk drinking,<sup>(3,26)</sup> identifying predictors of relapse in pretransplant patients with ALD has become crucial to prevent the need for future transplantation and to reduce mortality.<sup>(6,7)</sup> In the studies that were previously conducted in nontransplanted patients, several of the identified predictors of relapse were not predictive of relapse in our cohort, likely because of fundamental differences in the populations studied and study length.<sup>(6,10)</sup> Iasi et al., for example, found women to be at increased risk for relapse in a small retrospective study of 73 patients including only 5 women.<sup>(10)</sup> This finding, however, was not observed in our study nor Altamirano et al.'s larger study, which included 142 patients.<sup>(6)</sup> Altamirano et al.'s study also found that younger patients or those with a history of prior alcohol rehabilitation attendance were at increased risk for relapse, which was not found in our cohort.<sup>(6)</sup> Lucey et al.'s study found higher rates of relapse, with about 32% of the ALD cohort returning to drinking.<sup>(27)</sup> The differences between the findings of our study and of these previously conducted studies points to differences in study design. Iasi et al.'s study was retrospectively conducted, whereas ours and Altamirano et al.'s were prospective. Additionally, Altamirano et al.'s study focused on patients with biopsy-proven alcohol-associated hepatitis and followed patients for much longer (median follow-up = 4.58 years), whereas our

study clinically defined ALD, incorporating patients on the spectrum of disease with a shorter follow-up time. Lucey et al.'s study had much longer follow-up of 49 months, at which point we too may have captured a greater percentage of relapse in our pretransplant cohort.<sup>(27)</sup> Importantly, even within the shorter period of follow-up in our study, risk factors for relapse were identified.

Risk factors for relapse identified in our cohort included the presence of AUD in the year before enrollment, increased drinking after liver disease diagnosis, and increased drinking after a decompensating liver event. The presence of AUD has consistently been found to be a risk factor for relapse.<sup>(28)</sup> More recently, alcohol use after the liver disease diagnosis has also been found to be a predictor of post-LT relapse.<sup>(29)</sup> These new additional characteristics that were identified suggest important variables for clinicians to consider when classifying patients as low-risk and high-risk for relapse.

Despite our small sample size, the observed overall relapse event rate of 17% (10 of 58) in our cohort over a median follow-up of 1 year (IQR 0.5-1.4) is consistent with previously published literature. Earlier research studying nontransplanted populations with ALD reported relapse event rates ranging from 13.7% (10 of 73) with less than 3 months of follow-up to over 50% with more than 4 years of follow-up.<sup>(6,7,10)</sup> A recent multicenter retrospective study by Lee et al., investigating posttransplant alcohol use, found a cumulative probability of sustained alcohol use of 10% at 1 year,<sup>(25)</sup> which was consistent with the 8.6% (5 of 58) observed in our cohort. Early intervention to prevent sustained relapse in nontransplanted patients with ALD with risk factors for relapse may be of particular benefit.

Study limitations included being a single-center site of small sample size with modest diversity. Follow-up data were not available in most of the enrolled subjects, creating a potential selection bias, and the follow-up period was short. Our follow-up rate, however, is similar to prior studies in patients with AUD, which is characterized by high rates of attrition.<sup>(30,31,32)</sup> An additional limitation is that the online nature of this study has the potential to bias the types of patients who are able or willing to participate. This was mitigated to an extent by offering patients the option to complete surveys in person. Although only modestly diverse, our cohort was more diverse than that

previously studied in multicenter studies.<sup>(25)</sup> This diversity, with inclusion of both pretransplant and posttransplant patients, is important to note, as posttransplant patients likely have very different drinking behaviors, risks for relapse, and lower relapse rates. We mitigated this possibility by excluding the posttransplant patients in multivariable adjusted analysis and found that HAIS or CAIS were still significantly predictive of relapse risk. Finally, although the study was prospective, data were not collected on behavioral or pharmacologic AUD interventions occurring after enrollment. Presumably, interventions would alter relapse rates and should be taken into account in future work. The findings reported here should be validated in additional, more diverse prospective cohorts with longer follow-up to determine the generalizability of the findings.

Study strengths include the comprehensive prospective study design, the assessment of new quantifiable relapse risk factors, and that much of the included cohort was before transplant. Although prior studies suggested the roles of insight into AUD and of social support in preventing relapse,<sup>(8,21)</sup> the lack of quantification challenged providers in trying to objectively incorporate these findings into patient care. Our findings add to this literature, suggesting use of the HAIS and CAIS to objectively assess insight into AUD and social support. We have begun to incorporate these surveys into our transplant evaluation. Additionally, our findings add to the small amount of literature reporting predictors of relapse in non-transplanted patients, a much-needed area of focus in future studies, given the increased national prevalence of high-risk drinking, AUD and ALD, as well as the strong survival benefit abstinence offers.

In conclusion, we identified quantifiable predictors of relapse in patients with ALD—the HAIS and CAIS—as well as additional risk factors to consider in patients with ALD when assessing relapse risk. Our findings further emphasize the important roles that insight into AUD and social support have in identifying patients at risk for relapse. If confirmed in larger samples with longer follow-up, these findings suggest opportunities for the HAIS and CAIS, which are both quantifiable and objective measures, to identify those at risk for relapse. As the burden of ALD increases, continued identification and quantification of risk factors will become increasingly imperative, to

potentially change a patient's disease course, improve survival, and decrease the need for transplantation.

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## REFERENCES

- 1) Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology* 2019;156:254-272.e211.
- 2) National Institute on Alcohol Abuse and Alcoholism (NIAAA). Drinking Levels Defined. Available at <https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking>. Accessed April 24, 2020.
- 3) U.S. Department of Health and Human Services; Office of Disease Prevention and Health Promotion. 2015-2020 Dietary Guidelines. Available at <https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/appendix-9/>. Accessed December 28, 2020.
- 4) Shen NT, Salajegheh A, Brown RS Jr. A call to standardize definitions, data collection & outcome assessment to improve care in alcohol-related liver disease. *Hepatology* 2019;70:1038-1044.
- 5) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Association; 2013.
- 6) Altamirano J, López-Pelayo H, Michelena J, Jones PD, Ortega L, Ginés P, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival. *Hepatology* 2017;66:1842-1853.
- 7) Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. *J Hepatol* 2017;66:610-618.
- 8) Shenoy A, Salajegheh A, Shen NT. Multimodal multidisciplinary management of alcohol use disorder in liver transplant candidates and recipients. *Transl Gastroenterol Hepatol* 2020. 10.21037/tgh.2020.02.22.
- 9) Ventura-Cots M, Ballester-Ferre MP, Ravi S, Bataller R. Public health policies and alcohol-related liver disease. *JHEP Rep* 2019;1:403-413.
- 10) Iasi M, Vieira A, Añez CI, Trindade R, Codovani N, Favero S, et al. Recurrence of alcohol ingestion in liver transplantation candidates. *Transplant Proc* 2003;35:1123-1124.
- 11) Shen NT, Shenoy A, Brown RS Jr, Verna EC. Identifying risk of alcohol relapse after liver transplantation: what tools do we need? *Liver Transpl* 2019;25:1133-1135.
- 12) Kim JS, Kim GJ, Lee JM, Lee CS, Oh JK. HAIS (Hanil Alcohol Insight Scale): validation of an insight-evaluation instrument for practical use in alcoholism. *J Stud Alcohol* 1998;59:52-55.
- 13) Brown BS, O'Grady KE, Battjes RJ, Katz EC. The Community Assessment Inventory—client views of supports to drug abuse treatment. *J Subst Abuse Treat* 2004;27:241-251.



- 14) Kim JS, Park BK, Kim GJ, Kim SS, Jung JG, Oh MK, et al. The role of alcoholics' insight in abstinence from alcohol in male Korean alcohol dependents. *J Korean Med Sci* 2007;22:132-137.
- 15) Kelly SM, O'Grady KE, Schwartz RP, Peterson JA, Wilson ME, Brown BS. The relationship of social support to treatment entry and engagement: the Community Assessment Inventory. *Subst Abuse* 2010;31:43-52.
- 16) Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-381.
- 17) Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- 18) Lucey MR, Carr K, Beresford TP, Fisher LR, Shieck V, Brown KA, et al. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. *Hepatology* 1997;25:1223-1227.
- 19) Coffman KL, Hoffman A, Sher L, Rojter S, Vierling J, Makowka L. Treatment of the postoperative alcoholic liver transplant recipient with other addictions. *Liver Transpl Surg* 1997;3:322-327.
- 20) DiMartini A, Magill J, Fitzgerald MG, Jain A, Irish W, Khera G, et al. Use of a high-risk alcohol relapse scale in evaluating liver transplant candidates. *Alcohol Clin Exp Res* 2000;24:1198-1201.
- 21) Rodrigue JR, Hanto DW, Curry MP. The alcohol relapse risk assessment: a scoring system to predict the risk of relapse to any alcohol use after liver transplant. *Prog Transplant* 2013;23:310-318.
- 22) Egawa H, Nishimura K, Teramukai S, Yamamoto M, Umeshita K, Furukawa H, et al. Risk factors for alcohol relapse after liver transplantation for alcoholic cirrhosis in Japan. *Liver Transpl* 2014;20:298-310.
- 23) Lombardo-Quezada J, Colmenero J, Lopez-Pelayo H, Gavotti C, Lopez A, Crespo G, et al. Prediction of alcohol relapse among liver transplant candidates with less than 6 months of abstinence using the high-risk alcoholism relapse score. *Liver Transpl* 2019;25:1142-1154.
- 24) Weeks SR, Sun Z, McCaul ME, Zhu H, Anders RA, Philosophie B, et al. Liver transplantation for severe alcoholic hepatitis, updated lessons from the world's largest series. *J Am Coll Surg* 2018;226:549-557.
- 25) Lee BP, Mehta N, Platt L, Gurakar A, Rice JP, Lucey MR, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. *Gastroenterology* 2018;155:422-430.e421.
- 26) Mellinger JL, Shedden K, Winder GS, Tapper E, Adams M, Fontana RJ, et al. The high burden of alcoholic cirrhosis in privately insured persons in the United States. *Hepatology* 2018;68:872-882.
- 27) Lucey MR, Connor JT, Boyer TD, Henderson JM, Rikkens LF, Group DS. Alcohol consumption by cirrhotic subjects: patterns of use and effects on liver function. *Am J Gastroenterol* 2008;103:1698-1706.
- 28) Rustad JK, Stern TA, Prabhakar M, Musselman D. Risk factors for alcohol relapse following orthotopic liver transplantation: a systematic review. *Psychosomatics* 2015;56:21-35.
- 29) Deutsch-Link S, Weinrieb RM, Jones LS, Solga SF, Weinberg EM, Serper M. Prior relapse, ongoing alcohol consumption, and failure to engage in treatment predict alcohol relapse after liver transplantation. *Dig Dis Sci* 2020;65:2089-2103.
- 30) Zemore SE, Lui C, Mericle A, Hemberg J, Kaskutas LA. A longitudinal study of the comparative efficacy of Women for Sobriety, LifeRing, SMART Recovery, and 12-step groups for those with AUD. *J Subst Abuse Treat* 2018;88:18-26.
- 31) Loveland D, Driscoll H. Examining attrition rates at one specialty addiction treatment provider in the United States: a case study using a retrospective chart review. *Subst Abuse Treat Prevention Policy* 2014;9:41.
- 32) Radtke T, Ostergaard M, Cooke R, Scholz U. Web-based alcohol intervention: study of systematic attrition of heavy drinkers. *J Med Internet Res* 2017;19:e217.

## Supporting Information

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep4.1704/suppinfo](https://onlinelibrary.wiley.com/doi/10.1002/hep4.1704/suppinfo).