Gastroenterology 2021;161:1896–1906

Results of Early Transplantation for Alcohol-Related Cirrhosis: Integrated Addiction Treatment With Low Rate of Relapse

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CLINICAL LIVER

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BACKGROUND & AIMS: In 2018, our team initiated a prospective pilot program to challenge the paradigm of the "6-month rule" of abstinence for patients with alcohol-related liver disease (ALD) requiring transplant. Our pilot involved an in-depth examination of patients' alcohol use, social support, and psychiatric comorbidity, as well as the provision of pre- and post-transplantation addiction treatment. **METHODS:** Patients with ALD were assessed for inclusion in the pilot by a multidisciplinary team. Relapse prevention therapy was provided directly to all patients deemed to meet the program's inclusion criteria. Random biomarker testing for alcohol was used pre and post transplantation. **RESULTS:** We received 703 referrals from May 1, 2018 to October 31, 2020. After fulfilling the program's criteria, 101 patients (14%) were listed for transplantation and 44 (6.2%) received transplants. There were no significant differences in survival rates between those receiving transplants through the pilot program compared with a control group with more than 6 months of abstinence ($P = .07$). Three patients returned to alcohol use during an average post-transplantation follow-up period of 339 days. In a multivariate analysis, younger age and lower Model for End-Stage Liver Disease scores at listing were associated with an increased likelihood of a return to alcohol use ($P < .05$); length of abstinence was not a predictor. **CONCLUSIONS:** Our prospective program provided direct monitoring and relapse prevention treatment for patients with ALD and with less than 6 months of abstinence and resulted in a reduction of post-transplantation return to drinking. This pilot study provides a framework for the future of more equitable transplant care.

Keywords: Alcohol-Related Liver Disease; Alcohol Use Disorder; Relapse Prevention Therapy; Biomarker Monitoring; 6 Months of Abstinence.

Most transplantation centers typically require 6 months of abstinence from alcohol for patients with alcohol-related liver disease (ALD) before liver transplantation (LT). This "6-month rule" intends to allow for the possibility of hepatic recovery in the absence of alcohol,[1,2] as well as increase the chances of maintained abstinence after transplantation.[2,3] However, enforcement of this rule has been associated with mortality rates as high as 70%.[4] There is also a paucity of support for this rule with respect to its effectiveness at preventing or predicting relapse,[5,6] with some studies often finding nonsignificant differences in relapse rates between those who were abstinent for 6 months vs those with more recent alcohol consumption.[7] Furthermore, overall outcomes of LT for ALD are similar or sometimes better than other well-accepted indications for transplantation, such as hepatitis C–related liver cirrhosis or hepatocellular carcinoma.[8,9]

It has become increasingly clear that the traditional 6-month rule is inadequate for predicting survival and relapse rates and requires re-evaluation to ensure equitable access to transplantation for patients with ALD. In response to such perceptual shifts, various procedural changes have been proposed by a number of centers and professional associations throughout the world.[10–12]

The Ontario ALD Pilot Program was launched in 2018 with the intention of providing access to transplantation for patients with ALD and less than 6 months of abstinence through in-depth medical and psychosocial assessment and intervention, both before and after LT. This involved the initiation of transplantation evaluation at any referral time point, a procedure not formerly practiced in Ontario, where referrals were only accepted once patients had reached 6 months of abstinence. This prospective study involved a specialized, multidisciplinary team approach consisting of transplant hepatologists, addiction and consultation-liaison psychiatrists, social workers, and a nurse practitioner, and was designed to assess the wide range of outcomes associated with patients receiving transplants within this pilot program. The study was designed based on criteria that have been reported to be associated with lower risk of relapse post LT, including the availability of social support,

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Abbreviations used in this paper: **ALD, alcohol-related liver disease; AUD, alcohol use disorder; EtG, ethyl glucuronide; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RPT, relapse prevention therapy; SAH, severe alcoholic hepatitis.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.08.004

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The "6-month rule" disadvantages patients with alcohol-related liver disease requiring transplantation, necessitating alternative methods of evaluation and the provision of appropriate addiction treatment.

NEW FINDINGS

Multidisciplinary assessment, engagement in relapse prevention therapy and ongoing biomarker monitoring contribute to low relapse and high survival rates for patients with less than 6 months of abstinence.

LIMITATIONS

Longer-term follow-up of these patients is required to help demonstrate whether the survival and abstinence rates persist with ongoing support.

IMPACT

Our assessment and intervention methods provide a framework for more equitable transplant care for all patients with alcohol-related liver disease.

absence of significant psychiatric comorbidity, and a confirmed willingness to abstain from alcohol on a lifelong basis.[13,14] Furthermore, we included more nuanced psychosocial criteria, such as unemployment and unstable housing, comorbid substance use disorders, and past failed attempts at addiction treatment, all of which have been associated with relapse to alcohol use.[2,15] In acknowledgement of the impact of these factors on the ability to remain abstinent from alcohol, our pilot program also included the direct provision of relapse prevention therapy (RPT) for all patients who proceeded with evaluation for transplantation. Finally, we broadened the inclusion for not only patients with severe alcoholic hepatitis (SAH), but also patients with decompensated chronic ALD with less than 6 months of abstinence.

The aims of our pilot were as follows: to determine patient suitability for transplantation and risk for relapse through the use of selective criteria, to operationalize a skilled team of clinicians to assess and mitigate this risk, and to monitor for alcohol use both pre and post LT and intervene when appropriate.

Our study challenges the paradigm of abstinence for the selection of patients with ALD for LT. Instead, we propose novel criteria to identify patients with ALD who will benefit from transplantation, based on in-depth examination of alcohol use and psychosocial risk assessment for recurrence of alcohol-related disease. Furthermore, our program is unique by providing RPT pre and post transplantation to reduce the risk of relapse. The Ontario ALD selection criteria aim to improve access to transplantation, reduce mortality on our waiting list, and provide better care for our patients after transplantation.

Methods

Alcohol-Related Liver Disease Pilot Program Development

In 2017, Trillium Gift of Life Network, Ontario's organ and tissue donation agency responsible for delivering and coordinating donation and transplant services, gathered a panel of experts in response to legal challenges regarding the equity and utility of the 6-month abstinence rule. The goal of this panel was to design a pilot program for transplantation for patients with ALD, regardless of their length of abstinence, by using specialized psychosocial criteria meant to assess risk for future relapse. The panel included experts in liver disease and transplantation, as well as addiction psychiatrists, addiction specialists, ethicists, social workers, and hospital administrators. The ALD Pilot Program was subsequently approved by all transplantation stakeholders and advisory committees within the province of Ontario and funded by the Ministry of Health. The prospective pilot program was launched in May 2018 at the Multi-Organ Transplant Program at Toronto General Hospital and was carried out by a multidisciplinary team consisting of transplant hepatologists, addiction and consultation-liaison psychiatrists, a nurse practitioner, a social worker, and an addiction therapist.

Referral Process

Patients with either SAH or chronic ALD with any length of abstinence were included in the pilot. Patients with comorbid nonalcohol etiologies (eg, hepatocellular carcinoma or hepatitis C) were also included. All referrals were triaged using the information included from the referring physicians and additional collateral information obtained from a provincial database (ConnectingOntario). When possible, further psychosocial information was obtained from the referral source, including information about alcohol use history, past treatment for alcohol use disorder (AUD), concurrent psychiatric diagnoses, social support, and housing.

Patient Selection and Inclusion Criteria

If no clear contraindications were identified, patients were scheduled for in-person assessment by the psychosocial and medical teams. Referrals for this pilot were accepted based on program-specific criteria and the patient's capacity to participate in psychosocial assessment. At the start of the pilot, a few patients who were unable to participate directly in assessment due to severity of hepatic encephalopathy were assessed through collateral sources of information. However, it was observed that this was an overall detriment to both the patient and the team, as patients had not had the opportunity to engage in critical conversations about transplantation, abstinence, and treatment.

Program-specific criteria included severity of AUD, willingness to commit to lifelong abstinence from alcohol, willingness to participate in RPT, no more than 1 previously failed treatment for AUD, no untreated or refractory severe psychiatric comorbidity likely to interfere with post-transplantation compliance, no comorbid active substance use disorder (excluding cannabis and tobacco), no history of recurrent problems with adherence to medical treatment (eg, medication, appointments, or laboratory requests), adequate social support, and stable housing (Supplementary Figure 2).

A diagnosis of severe AUD in itself did not automatically exclude patients from the pilot. Patients with severe AUD who were determined to pose an unacceptably high risk of return to problematic alcohol use fell within 2 categories. The first category consisted of those who continued to consume alcohol heavily despite decompensated liver disease and who understood that ongoing alcohol consumption would result in further

decompensation and/or possible death. The second group included those with severe AUD who exhibited a significant lack of insight into the association between their AUD and liver disease, to the point that they were highly unlikely to benefit from RPT. These challenging and nuanced cases required more extensive discussion by the committee, and the decision to accept or decline a patient was always reached by team consensus.

For the purpose of our pilot, we considered "prior treatment for AUD" to be significant engagement with evidence-based addiction treatment provided by licensed providers and/or treatment centers. Typically this included individual or group RPT, AUD psychopharmacological treatment with regular follow-up, and residential treatment programs. Engagement with Alcoholics Anonymous was not considered to be a treatment trial as, although it can be helpful to many, the quality of Alcoholics Anonymous groups varies widely and it is not staffed by licenced providers.

In addition to these criteria, patients referred with clinically suspected SAH were included in this category only if the diagnosis was biopsy-proven, refractory to steroid therapy, and the current presentation was the patient's first liver-decompensating event leading to a diagnosis of acute liver disease.

Initial Assessment

Each patient was assessed by one of the team's transplant hepatologists. Pretransplantation urine ethyl glucuronide (EtG) testing was performed at the time of the initial appointment and then randomly repeated until the patient received the transplant. Neither ethanol levels (which dissipate within a few hours of consumption) nor phospatidylethanol testing (which was not available in Ontario) were used. In addition to the initial medical evaluation, each patient was assessed by the various members of the ALD psychosocial team.

Addiction psychiatry assessment. Carrying a diagnosis of ALD does not guarantee that one will meet criteria for an AUD.[16] Moreover, the presence of an AUD distinguishes patients who will need addiction treatment to enhance their ability to achieve and maintain abstinence from alcohol and achieve long-term post-transplantation outcomes. To clarify these nuances, the addiction psychiatry evaluation consisted of a comprehensive history of the patient's past alcohol use, including duration of use, patterns of use, resulting negative consequences, periods of abstinence, previous access to treatment, and motivation for abstinence from alcohol. These factors contributed to varying diagnostic degrees of AUD, as per the *Diagnostic and Statistical Manual of Mental Disorders* 5th edition.[17] Other transplant-specific factors were also considered, including the patient's insight into the association between alcohol and their liver disease and the timeline between their diagnosis of decompensated liver disease and their ability to achieve abstinence from alcohol. The patient's willingness and ability to engage in treatment for alcohol use was assessed. Collateral information was gathered from family members as well as primary care providers, when available. Patients were asked to sign an abstinence contract combined with consent to grant permission for random biomarker testing pre and post transplantation. Finally, when appropriate, recommendations were made regarding various forms of pharmacotherapy found to be effective in helping patients manage alcohol cravings (ie, acamprosate, gabapentin, and baclofen) and patients were assisted with liaising with appropriate addiction treatment as needed.[18]

Social work assessment. Sociodemographic information (ie, age and income source) was recorded for each patient assessed by the social worker, as well as the length of self-reported abstinence. The social worker met with each patient and their support people to assess the availability of the emotional and instrumental support typically needed for transplantation and conducive to abstinence from alcohol. Corroboration and collaboration with patients' supporters have been described as an "absolute requirement" when assessing one's suitability for transplantation and the severity of past alcohol use.[16]

Relapse prevention therapy. Patients who met criteria for AUD were required to participate in RPT. The RPT provided within the transplantation program consisted of 6–10 individual sessions from a manual that was developed for the purposes of the pilot. The manual was created by the addiction therapist and the addiction psychiatrists on the team. It was subsequently reviewed and approved by the members of the pilot planning committee, which included addiction researchers who specialize in AUD treatment. There were 6 core sessions that were provided to all patients and covered the core components of RPT (eg, managing cravings and triggers and drink refusal skills) and an additional 4 elective sessions that could be selected by the patient (eg, managing emotional states and dealing with family and interpersonal problems). Booster sessions were available for patients who requested them and for those with severe AUD. The therapy provided was standardized as much as possible, while acknowledging variability in patient characteristic and need. Sessions were provided in-person, over the phone, and/or through other virtual means, depending on patient preference. Initiation of, and progression through, these sessions often depended on the patient's medical status, particularly for those who were critically ill before transplantation. Treatment was initiated as soon as possible to allow for patient engagement in the process before transplantation to improve treatment retention post transplantation. Considering this, the shortest course of pretransplantation treatment was 1 session with the addiction therapist for the purpose of introductions and to begin building rapport for future sessions. Patients were also directed to suitable resources in their geographical or linguistic community as needed. The ALD team monitored progress and completion of treatment throughout.

When patients accessed treatment at outside centers, the ALD addiction therapist (a registered social worker with specific experience and training in addiction therapy) would inquire preemptively about the type of treatment provided to ensure that it was evidenced-based and included the appropriate therapeutic modalities. Mutual support groups, such as Alcoholics Anonymous, were not discouraged, but were not considered to be solely adequate from a treatment perspective.

Alcohol-related liver disease team discussion. Once patients completed their evaluations, each case was discussed at a multidisciplinary meeting. If it was determined by the team that a patient met the program criteria, the patient then proceeded to the next step of the assessment, which included a complete medical workup before listing, as per our institution's standard of practice.

Post-Transplantation Outcomes

All post-transplantation patients were seen regularly in our clinics and assessed by a transplant hepatologist for evaluation of graft function. They were also followed by the addiction psychiatrist for ongoing treatment of AUD, monitoring of alcohol use, and screening for post-transplantation psychiatric disorders. The frequency of addiction psychiatry appointments was predetermined based on severity of AUD and the presence of psychiatric comorbidity. Those with mild to moderate AUD and absence of significant comorbid psychiatric illness were seen within 4 weeks of discharge from hospital post transplantation. If no active issues were identified, they were then seen at 4 months post discharge, and then at 1 year post transplantation. Patients with severe AUD and/or active psychiatric comorbidity were seen monthly for the first year post transplantation, with some variability dictated by patient need. Open communication was maintained with the post-transplantation coordinators so that new or worsening mental health concerns were identified early and follow-up with psychiatry was arranged promptly. Post-transplantation serum carbohydrate-deficient transferrin testing for alcohol was performed regularly at clinic appointments. Urine EtG and monitoring of liver enzymes (ie, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase) were also performed routinely in all recipients during the follow-up period.

Comparison group. To assess the survival outcomes of ALD patients receiving transplants within the pilot program, this group was compared to patients receiving transplants with more than 6 months of abstinence within our program in the 18 months before the institution of our pilot program.

Data collection and statistical analysis. Continuous variables were compared using Student t test. Categorical variables were compared using chi-square tests. Survival after LT was calculated using the Kaplan–Meier method and compared using the log-rank test. The independent association between relapse to alcohol post LT and clinical variables was assessed by multivariate logistic regression analysis with a backward elimination method. A $P < .5$ was considered as statistically significant. Statistical analysis was performed using STATA (Release 16, StataCorp, 2019).

Results

Patient Characteristics

From May 1, 2018 to October 31, 2020, 703 referrals were received through the pilot (Supplementary Figure 1) and reviewed by the multidisciplinary team. Among these 703 referrals, 111 (16%) had hepatocellular carcinoma on the background of ALD. A majority of these referrals (n = 482 [69%]) were outpatients and the remaining were for inpatients admitted in various hospitals across Ontario. The Model for End-Stage Liver Disease (MELD) scores for these patients ranged from 6 to 47, with a mean MELD score of 20 and mean MELD sodium score of 23.

Approximately one-fifth of referrals (n = 139 [19.7%]) were declined on initial review and discussion within our multidisciplinary team due to contraindications per the ALD criteria mentioned previously. Another 34 patients (4.8%) passed away before evaluation, and others were declined due to medical contraindications (n = 24 [3.4%]) or were better suited for the non-ALD pilot evaluation stream (n = 38 [5.4%]).

The remaining 439 referrals (62.5%) were accepted for initial assessment and were seen by 1 or several members of the ALD team. This included assessment by transplant hepatology (n = 421), addiction psychiatry (n = 332), and social work (n = 379). Twenty-five patients (6%) assessed in person had a positive EtG test at the time of their first encounter and, as a result, were excluded from further evaluation.

The psychosocial profiles of those assessed by social work and either accepted into the pilot (n = 159) or declined based on ALD criteria (n = 118) are presented in Table 1. Most of the patients were male, White, and actively employed. Those who were accepted into the pilot program were significantly older compared to their declined peers ($P < .01$). Accepted patients were more likely to be married ($P < .01$) and in receipt of active employment income ($P < .05$) or a retirement pension. Conversely, patients who were declined were more likely to be single ($P < .01$), unemployed ($P < .05$), or on government assistance ($P < .01$). There was no significant difference in sex or ethnicity between the 2 groups.

Psychosocial Profiles

Of the 332 patients assessed by addiction psychiatry, one-third (n = 146 [33%]) were declined for not meeting 1 or more of the ALD pilot criteria (Table 2). A majority of the declined patients were excluded on the basis of a severe AUD deemed likely to result in a return to problematic alcohol use in spite of RPT (n = 121 [84%]), and others were not willing to participate in RPT (n = 28 [19%]), had inadequate social support (n = 24 [16%]), or had significant psychiatric comorbidity likely to interfere with post-transplantation treatment adherence (n = 13 [11%]).

Half (n = 166) of patients assessed by addiction psychiatry met criteria for a severe AUD. Interestingly, a very similar number of patients met criteria for mild AUD (n = 50 [15%]) and moderate AUD (n = 51 [15%]), respectively, and another 48 patients (15%) did not meet diagnostic criteria for AUD. A small proportion (n = 15 [5%]) were not able to be assessed, typically due to medical reasons. Thirty-eight patients (11%) met criteria for a mood disorder and/or an anxiety disorder (n = 27 [8%]), although most did not meet *Diagnostic and Statistical Manual of Mental Disorders* 5th edition[17] criteria for a comorbid psychiatric diagnosis (n = 251 [76%]).

Forty-seven patients did not proceed with further evaluation due to their medical status, either becoming too unwell (n = 13 [3%]) or conversely experiencing clinical improvement to the point of losing their indications for transplantation (n = 34 [8%]). A small number of patients (n = 10 [2%]) passed away during initial ALD evaluation.

Table 1. Psychosocial Profiles of Patients Assessed[a] Through the Alcohol-Related Liver Disease Pilot Program

Characteristic	Proceed to medical evaluation (n = 159)	Decline (ALD criteria) (n = 118)	*P* value
Age, *y*, mean	55.0	51.5	.004[b]
Length of abstinence, mo, mean	4.7	3.1	
Sex, n (%)			.317
Male	107 (67)	86 (73)	
Female	52 (33)	32 (27)	
Marital status, n (%)			<.001[b]
Married	101 (63)	41 (35)	<.001[b]
Single	23 (14)	37 (31)	<.001[b]
Divorced	20 (13)	22 (19)	.164
In a relationship	11 (8)	13 (11)	.230
Widowed	4 (2)	5 (4)	.668
Income source, n (%)			<.001[b]
Active employment	46 (29)	21 (18)	.032[c]
Retirement	42 (26)	8 (7)	<.001[b]
Disability/sick leave	30 (19)	21 (18)	.820
Government assistance	19 (12)	38 (32)	<.001[b]
Unemployed	22 (14)	30 (25)	.015[c]
Ethnicity, n (%)			.397
White	134 (84)	93 (79)	.107
Asian-South	9 (6)	12 (10)	.161
Indigenous	6 (4)	3 (2)	.568
Latin American	2 (1)	1 (1)	.744
Black	1 (1)	2 (2)	.397
Indian-Caribbean	2 (1)	1 (1)	.744
Other (<1%)	5 (3)	6 (5)	.060

[a]Patients assessed by the social worker and were either accepted into the pilot or declined from further evaluation.
[b]$P < .01$.
[c]$P < .05$.

Medical Evaluation

After initial evaluation, 164 patients met the pilot criteria and proceeded to complete medical evaluation for transplantation (Table 3).

Seventeen patients (10%) improved during the assessment period to the point of no longer requiring LT and were discharged. These patients presented with an average length of abstinence of 5 months, ranging from no length of abstinence to more than 2 years. Fifteen patients passed away before completing the medical evaluation. The causes of death were comprised of the following diagnoses, which were not mutually exclusive: multi-organ system failure (n = 8), septic shock (n = 5), upper gastrointestinal bleed (n = 3), intracranial hemorrhage (n = 1), liver failure without further information (n = 3), spontaneous bacterial peritonitis (n = 3), pulmonary edema (n = 1), and pneumonia (n = 1). One autopsy report was obtained, which reported metastatic hepatoma as a postmortem finding.

During medical evaluation, another 4 patients were found to have a positive EtG test through random testing and were subsequently removed from the pilot with recommendations to access treatment for AUD to achieve remission before being reconsidered again. Another 5 patients were discharged due to a self-reported return to alcohol use.

Listing Outcomes

Approximately two-thirds (n = 101 [64%]) of the patients who underwent medical evaluation were subsequently listed for transplantation, with a mean MELD score of 26 and MELD sodium score of 28 at listing. This represented about 14% of all patients referred to the pilot program. While waiting for transplantation, 4 patients improved both clinically and biochemically and were subsequently removed from the waiting list, and 1 patient was removed due to medical deterioration. One patient was delisted after a positive EtG test, and later confirmed recent alcohol use through self-report. The mean waiting time between listing and transplantation was 75.2 days (range, 2–452 days. Fifteen patients (15%) passed away while on the waitlist.

Transplantation Outcomes

A total of 44 patients (23 outpatients and 21 inpatients) received transplants through the ALD Pilot Program, 4 of whom underwent live donor LT. The outpatient group had MELD scores ranging from 20 to 30 (n = 12), and the inpatient group had MELD scores >30 (n = 13). Only 2 outpatients had MELD scores >30, and no inpatients had scores <20. Finally, 9 outpatients were listed with a MELD

Table 2. Psychosocial Characteristics of Alcohol-Related Liver Disease Pilot Patients Who Were Declined in Phase 1 (n = 146)

Characteristic	n	%
Severe AUD likely to result in a return to problematic drinking in the post-transplantation period	121	82.6
Not committed to abstinence	28	19.1
Not willing to participate in AUD treatment	28	19.1
History of more than 1 failed AUD treatment attempt, as defined by a return to problem drinking that would meet criteria for an AUD	4	2.7
Comorbid substance use disorder, not including tobacco or cannabis	3	2.0
Untreated or refractory severe psychiatric comorbidity likely to interfere with treatment adherence[a]	13	8.9
Mood disorder	10	—
Anxiety disorder	6	—
Psychotic disorder	1	—
Eating disorder	1	—
History of nonadherence to medical advice	11	7.5
Inadequate social support	24	16.4
Unstable housing	3	2.0

[a]Not mutually exclusive.

Table 3. Outcomes of Alcohol-Related Liver Disease Pilot Patients Who Proceeded to Medical Evaluation/ Phase 2 (n = 164)

Outcome	n	%
Proceed to listing	105	64
Listed	101	—
Declined	3	—
Deferred	1	—
Clinical improvement/discharge	17	10
Deceased during evaluation	15	10
Currently in evaluation	15	9
Return to alcohol and discharged	5	3
Subsequent EtG and discharged	4	2
Decline (medical)	3	2

score <20, either for hepatocellular carcinoma or decompensated cirrhosis. ALD patients receiving transplants were significantly younger ($P < .01$), with significantly higher MELD scores at listing ($P < .01$) and at transplantation ($P < .01$) compared with patients receiving transplants with more than 6 months of abstinence (n = 111). ALD patients waited significantly less time on the waitlist than those with other indications for LT ($P < .05$). There were no significant differences in sex or length of post-transplantation hospital stay between the 2 groups (Table 4).

The psychosocial characteristics of patients receiving transplants through the pilot program are presented in Table 5. Although 86% of patients receiving transplants met criteria for AUD (with one-quarter falling within the severe range), 84% of this group had never accessed AUD treatment. Mood and anxiety disorders each occured in 9% of patients, and 2 patients (4.5%) had a diagnosis of opioid use disorder in sustained remission on methadone treatment. Survival rates between ALD Pilot Program patients and ALD patients with more than 6 months of abstinence were compared, with no significant differences between the 2 groups (Table 6, Figure 1).

Post-transplantation, 38 patients (86%) were discharged home after an average of 30 days in hospital. These patients were all alive with functioning grafts at an average follow-up of 339 days. Half of the patients who underwent transplantation (n = 22) were medically well enough to be able to engage in at least 1 or more sessions of RPT before transplantation. Post transplantation, all surviving patients received RPT and ongoing follow-up with addiction psychiatry. One patient remained admitted to hospital at the time this article was being written.

The remaining 5 patients (11%) passed away post transplantation at a mean of 29.6 days after transplantation (range, 34–79 days). Causes of death were not attributable to alcohol use. Two patients died from acute graft failure related to hepatic arterial occlusion; 1 died from peritonitis related to gastric perforation; 1 died from complications due to central pontine myelinolysis; and the last died from cardiac arrest.

Post-Transplantation Return to Alcohol Use

Of the 44 patients who underwent LT, 3 (6.8%) returned to alcohol use within an average of 260 days post transplantation (range, 33–453 days). Two patients were found to have positive biomarker tests by 3 months post transplantation and the third patient self-reported a slip to alcohol use around the 1-year post-transplantation mark. In all 3 cases, addiction psychiatry and the addiction therapist promptly connected with the patients to increase treatment intensity to prevent the short-term slips from becoming sustained relapses. Two of the patients remain engaged in regular follow-up with the transplant psychosocial team, and the first patient declined this support and has been nonadherent with medications and other medical advice. Interestingly, the rate of relapse was more than twice as high (16%) for transplanted patients with more than 6 months of abstinence in our program ($P = .21$).

Using binary logistic regression, the association between the presence of any relapse to alcohol (pre and post LT) and

Table 4. Characteristics of Patients Receiving Transplants in the Alcohol-Related Liver Disease Pilot Program Patients vs Patients With More Than 6 Months of Abstinence

Characteristic	Non-pilot patients with >6 mo abstinence (n = 111)	ALD pilot patients (n = 44)	*P* value
Age, *y*, mean	57.43	52.69	.003[a]
Sex, n (%)			.131
Male	84 (75.68)	28 (63.64)	—
Female	27 (24.32)	16 (36.36)	—
MELD at listing	19.22	26.02	<.001[b]
MELD at transplantation	20.33	27.11	<.001[b]
Time on waitlist, *d*	180.79	69.77	.025[a]
Length of stay (post transplantation), *d*	27.38	30.80	.485
Return to alcohol use, n (%)	18 (16.2)	3 (6.8)	.21

[a]$P < .05$.
[b]$P < .01$.

clinical parameters was determined. In multivariate analysis (Table 7), age at transplantation (odds ratio, 0.92; 95% confidence interval, 0.86–0.098; $P < .05$) and MELD score at listing (odds ratio, 0.90; 95% confidence interval, 0.93-0.99; $P < .05$) were found to be significantly associated with risk for relapse ($P < .05$) in that younger patients and those with lower MELD scores were more likely to relapse to alcohol use. Severe AUD was not significantly associated with risk for relapse in our program population.

Discussion

LT for patients with ALD is historically controversial due to the perceived self-inflicted nature of the disease and the relapsing nature of problematic alcohol use.[19] Patients with ALD may also be undertreated due to the stigma around their diagnosis, as well as the challenges around assembling teams to assess and treat them appropriately.[20] This was reflected in the Ontario context before our pilot, where evaluation of patients would be delayed until they reached the 6-month mark of abstinence. Our pilot program is the first in North America to accept patients with both acute and chronic decompensated liver disease regardless of the length of abstinence, while also providing integrated addiction treatment both before and after LT to reduce the risk of relapse to alcohol.

Our approach is unique compared to previous published data in several ways. First, we included patients with chronic ALD, and previous studies focused on those with SAH. Second, we used a multidisciplinary approach that consisted of a fully integrated, co-located team of medical and psychosocial clinicians. This format allowed for comprehensive and collaborative assessment and treatment of patients with ALD throughout their transplantation journey. Third, we were able to operationalize inclusive yet comprehensive criteria that allowed for patients with an acceptable risk for relapse to proceed with transplantation evaluation and surgery. In addition to the utilization of such criteria, we also directly provided the appropriate monitoring and RPT to mitigate the risk of relapse to alcohol. Our approach allowed an excellent result in the short term (339 days of follow-up), with a low rate of post-transplantation return to alcohol (6%) and ongoing patient engagement in RPT throughout the evaluation process.

Compared to previous studies that only included patients with SAH, our results confirm a similar survival benefit for early transplantation for patients with less than 6 months of abstinence,[13] even in the setting of decompensated cirrhosis, as well as lower relapse rates to alcohol[20] compared to ALD patients with longer periods of abstinence.[9] Although it is notable that some of the patients would have been more than 6 months abstinent at the time of transplantation, it is also true that many patients were urgently unwell with a very short duration of abstinence and likely would not have survived if they had not been able to be evaluated before the 6-month mark. One of the many benefits of our protocol was the ability to begin a patient's transplantation evaluation early, rather than having to wait until they reached 6 months of abstinence before assessment, as this was our previous practice before the pilot in Ontario and in Canada.

There were no post-transplantation deaths attributed to a return to alcohol use, although the follow-up time was of relatively short duration (mean, 339 days). These results suggest that the evaluation criteria used in this pilot are reliable indicators of survival benefit and relapse in the short term. We acknowledge that our mean MELD scores at time of listing (mean MELD score = 26) and at transplantation (mean MELD score = 27) were lower than previous published studies with SAH, allowing for a period of observation and intervention before transplantation.

Our statistical analyses demonstrate some significant results worth noting. Previous research has emphasized the importance of social support and resources in the context of transplantation suitability[13,14]; our results suggest that

Table 5. Psychosocial Characteristics of Patients Receiving Transplants Through the Alcohol-Related Liver Disease Pilot Program (n = 44)

Characteristics	Data
Age, *y*, mean	51.8
Length of abstinence (at referral), *mo*, mean	4.0
Sex, n (%)	
Male	28 (64)
Female	16 (36)
Marital status, n (%)	
Married	24 (55)
Single	11 (25)
Divorced	5 (11)
In a relationship	4 (9)
Income source, n (%)	
Active employment	13 (30)
Unemployed	9 (20)
Retirement	8 (18)
Disability/sick leave	8 (18)
Government assistance	6 (14)
Ethnicity, n (%)	
White	38 (86)
Asian-South	2 (5)
Other	4 (9)
Severity of AUD, n (%)	
Mild	18 (41)
Moderate	9 (20)
Severe	11 (25)
Does not meet criteria	6 (14)
Comorbid psychiatric illness, n (%)	
Mood disorder	4 (9)
Anxiety disorder	4 (9)
Opioid use disorder[a]	2 (4.5)
No. of standard drinks per day, n (%)	
<10	22 (50)
>10	22 (50)
Duration of alcohol use, n (%)	
<11 y	14 (32)
11–25 y	12 (27)
>25 y	18 (41)
Substance use, n (%)	
Tobacco	16 (36)
Cannabis	4 (9)
Legal history related to alcohol use, n (%)	
Yes	7 (16)
No	37 (84)
Family history of AUD, n (%)	
Yes	7 (16)
No	37 (84)
Past treatment history for AUD, n (%)	
Yes	7 (16)
No	37 (84)

[a]In remission, stable on methadone treatment.

those deemed suitable for our program were more often married and with a stable (and typically higher) income than patients who were declined. This further emphasizes the importance of a social worker providing psychosocial assessment and intervention to potentially mitigate factors that might make one unsuitable for transplantation, such as community referrals for professional support or financial assistance. Most of the patients assessed through our pilot were White (84%). There were no significant differences in race regarding patients being accepted or declined into the pilot program. The question remains as to what structural inequities might be barring racialized and marginalized populations from accessing a referral for transplantation evaluation in the first place, regardless of their indications for transplantation. This is further complicated when considering the intersection of race and addiction, in regard to the conceptualization of alcohol use, stigma, and access to culturally competent treatment. Our data collection and analysis are also limited by the lack of availability of race data for those referrals we declined before assessing in person.

Age was also an interesting factor to note. Older age was associated with an increased likelihood that one would be accepted into the program, and younger age was associated with an increased likelihood of relapse. The latter result is consistent with the literature[21,22] and may be partially explained by environmental factors, such as patients being in settings where alcohol is consumed more heavily, as well as a sense of invincibility at a younger age. Finally, length of abstinence was not associated with risk of relapse post-LT, supporting the practice of assessing risk and suitability using factors other than the "6-month rule."

Our pilot also provided unique and crucial psychosocial assessment and supports that are not routinely provided in other transplantation programs. A transplantation-specific addiction psychiatry assessment allowed for the diagnosis of AUD when applicable and for the initiation of appropriate treatment to support patients' abstinence in the long term. Most of the referred ALD patients met criteria for severe AUD, which highlights the complex nature of this patient population. Although our pilot did not use severe AUD as an absolute exclusion criteria, identifying those who belonged to this category early in the transplantation assessment process allowed for the provision of AUD treatment as soon as possible, and prompted frequent follow-up post transplantation. This approach has been identified previously as critically important when assessing complex cases of ALD and AUD,[23,24] albeit not in the setting of LT. The absence of a statistically significant relationship between severe AUD and return to drinking in this study may be partly due to the routine provision of AUD treatment within the transplantation program for all patients accepted into the pilot.

Integrated addiction psychiatry also allowed for closer follow-up of those with comorbid mental health concerns[13] and prompt access to mental health treatment post transplantation for those who experienced a worsening of their pre-existing mental health condition, or a de novo diagnosis. The direct on-site or virtual provision of RPT[14] improved access to treatment and also enhanced buy-in from the many patients who had never interacted with the addiction treatment context in the past. It is notable that all

Table 6. Kaplan-Meier Survival Curve for Alcohol-Related Liver Disease Pilot Program Patients vs Patients With More Than 6 Months of Abstinence[a]

Variable	Pilot program, n at risk (survival, %); 95% CI, % (n = 44)	Abstinent >6 mo, n at risk (survival, %); 95% CI, % (n = 111)
30-d survival	43 (95.45); 83.02–98.84	105 (97.25); 91.71–99.10
6-mo survival	34 (88.64); 74.83–95.11	98 (96.28); 90.4–98.59
1-y survival	25 (88.64); 74.83–95.11	91 (96.28); 90.4–98.59
2-y survival	6 (88.64); 74.83–95.11	82 (94.08); 87.26–97.31

NOTE. Likelihood ratio test for equality of survivor functions $P > \chi^2 = .0723$.
[a]See Figure 1.

transplanted patients connected with RPT after their transplantation. Our psychosocial team also helped to mitigate treatment barriers presented by distance and lack of resources through the use of telemedicine and collaboration with external organizations.[20,25]

Our pilot program highlights the importance of the multidisciplinary team in appropriately assessing this complex cohort of patients with ALD. The program received, on average, 26 new referrals per month. This represents an almost 3-fold increase from before the pilot, when an average of 9 referrals for patients with ALD were received per month. Each referred patient is given thorough consideration and is discussed at the multidisciplinary meeting before a team decision is reached. This is time- and labor-intensive and may not be readily apparent if only considering the number of patients listed (14% of total referrals) or receiving transplants (6% of total referrals). We believe that the multidisciplinary approach is essential to appropriately risk stratify these patients and it is essential that adequate resourcing and staffing be made available.

Biomarker testing proved to be an invaluable tool throughout the different phases of the pilot program. The stigma associated with a return to drinking can interfere with patients' willingness to disclose alcohol use and biomarkers provide objective data that can prevent a relapse from progressing to graft injury. The ability to detect a return to alcohol use is something that has been emphasized and valued in other studies,[10] as it allows for reinitiation or intensification of AUD treatment. For the few patients who returned to alcohol use, biomarker testing allowed for prompt involvement by the transplantation team in order to address the slip or relapse. This is similar to what was found in another pilot,[14] when most of those who returned to alcohol use were able to regain abstinence and did not experience a sustained relapse. Two of the 3 relapses were detected via biomarker testing only, and the third came to clinical attention through self-report. Beyond the timeframe of this pilot, such early intervention has the potential to prevent post-transplantation alcohol-related death.[26] Longer-term follow-up of these patients will help to inform whether this close monitoring will prevent poor graft outcomes in the future.

The value of our multidisciplinary approach is further emphasized when comparing the rates of post-transplantation return to alcohol between our pilot patients and those transplanted for ALD before the pilot. Although they met the criteria of having achieved more than 6 months of abstinence, approximately 16% (n = 18) of the latter group returned to drinking after transplantation. Although this difference is not significant ($P = .21$), this number is likely an underestimation, as biomarker testing was not used consistently before implementation of the ALD pilot and most detected relapses were identified via self-report or resulting medical complications. It is therefore likely that less severe alcohol use episodes went undetected.

An ongoing limitation in providing addiction assessment and RPT in the pretransplantion phase is the patient's medical status and ability to participate in such sessions. This limitation has also been highlighted by other centers,[27] and is something to consider when implementing relevant treatment and defining patients' adherence to them.

An important aspect of our study was inclusion of both patients with SAH and decompensated ALD without SAH. The distinction between both diagnoses is difficult, particularly in the absence of liver biopsy. Criteria such as those developed by the National Institute on Alcohol

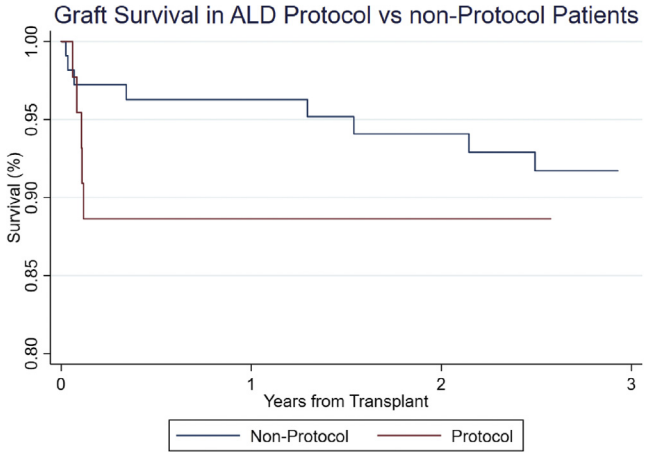

Figure 1. Graft survival in ALD protocol vs nonprotocol patients.

Table 7. Predictor Parameters of Likelihood of Relapse in Alcohol-Related Liver Disease Pilot Program Patients (n = 159)

Variable	Odds ratio	*P* value	95% Confidence interval
Age	0.919	.013	0.860–0.983
Married	3.759	.103	0.764–18.498
AUD severe	0.182	.115	0.022–15.14
MELD at listing	0.904	.027	0.826–0.989

NOTE. Likelihood ratio $\chi^2_4 = 15.70$. $P > \chi^2 = .0035$. Pseudo $R^2 = 0.1666$.

Abuse and Alcoholism Alcoholic Hepatitis Consortia have been proposed to help with diagnosis.[28] We retrospectively assigned the patients transplanted through our pilot as meeting definite or probable AH consensus criteria vs not. Based on the National Institute on Alcohol Abuse and Alcoholism Alcoholic criteria, 1 patient met definite AH diagnosis (met all criteria and had a pretransplantation biopsy). Eight others met probable AH diagnosis (patients without biopsy who otherwise met all other criteria). Finally, 35 did not meet AH criteria. However, explant examination of all patients in this study showed advanced fibrosis and cirrhosis, demonstrating the challenge of utilization of National Institute on Alcohol Abuse and Alcoholism Alcoholic criteria alone without biopsy for diagnosis of SAH.

We acknowledge that we did not follow those who were declined from the pilot and are unaware of their outcomes. Similarly, we do not know the profiles of patients who could have been referred before the initiation of the pilot, preventing us from conducting relevant comparative analyses. We also acknowledge that although we collected a number of different psychosocial factors to compare (ie, past treatment and psychiatric comorbidity), there are additional factors of interest that would have provided an additional level of depth to the profiles of these patients (ie, legal issues and smoking history).

Evidence to support the 6-month rule is mixed at best. Our pilot highlights the importance of considering a wide range of variables when assessing the risk for relapse for patients with ALD, rather than relying solely on the arbitrary passage of time. Although some risk for relapse to problematic alcohol use will inherently continue to exist in ALD patients, the results of our pilot show that this risk should not be enough to prevent patients from accessing transplantation, and that it can be realistically mitigated through appropriate measures. LT does not cure AUD,[23] but the implementation of our standardized selection criteria and evidence-based intervention provides a foundation for the provision of more equitable transplant care for those with ALD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.08.004.

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Received March 16, 2021. Accepted August 2, 2021.

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Acknowledgments
This work was supported by and in consultation with Trillium Gift of Life Network (https://www.giftoflife.on.ca/en/). The authors also acknowledge the contributions of Dr Bernard Le Foll and Dr Christian Hendershot in the development of this protocol. Lauren Carrique and Jill Quance contributed equally to this work.

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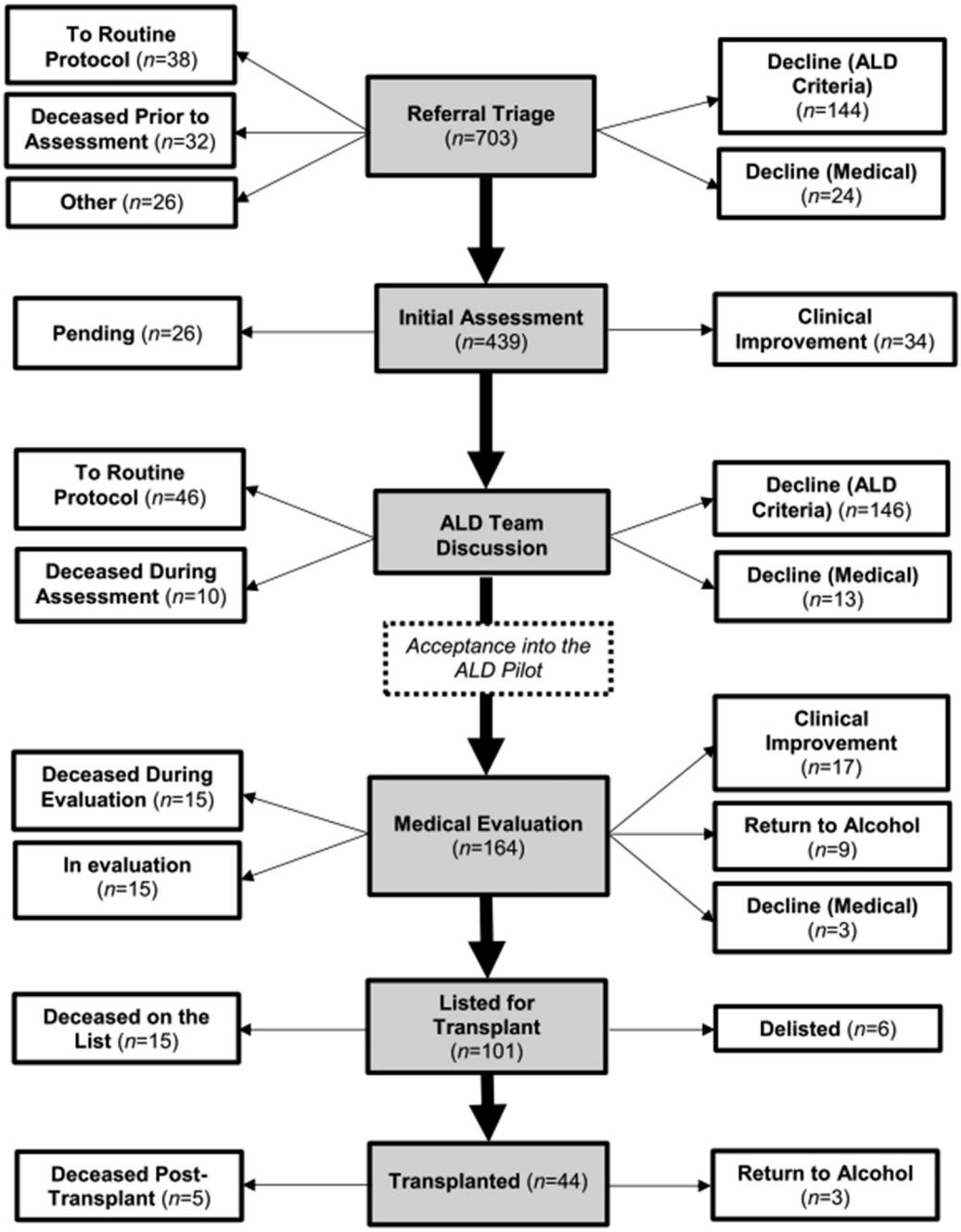
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Flow chart of all the patients referred to the ALD Pilot Program.

1. The patient does not meet criteria for moderate to severe AUD likely to result in a return to problematic drinking in the post-transplantation period.
2. The patient is willing to commit to abstinence from alcohol.
3. The patient is willing to commit to AUD treatment pre/post transplantation when recommended by transplant psychosocial team.
4. History of no more than 1 previously failed AUD treatment, where failure is defined as a return to problem drinking that would meet criteria for AUD.
5. Absence of comorbid active substance use disorder, excluding cannabis use and tobacco use disorder.
6. Absence of untreated and refractory severe psychiatric comorbidity (including personality disorder) likely to interfere with treatment adherence.
7. Other than in relation to alcohol use, no history of recurrent problems with adherence to medical treatment and repeated inability to follow-up. with/unable to contact patient.
8. The patient has a dedicated support person available to assist them throughout the process and stable housing.

Supplementary Figure 2. ALD Pilot Program suitability criteria.