Six strategies for successful liver transplant in ALD that aren't the "6-month rule"

Sara Zachman, MD, MPH
Department of Psychiatry – Addiction Division

UNMC Transplant Symposium
March 8, 2024

University of Nebraska Medical Center Nebraska Medicine

1

(Representative) Case

39-year-old male with history of alcohol-associated cirrhosis, alcohol use disorder, and unspecified anxiety, presenting with his wife for LT evaluation.

Multiple prior quit attempts with longest period of abstinence being 2 months, followed by returns to use. Previous admissions for alcohol withdrawal management and pancreatitis. First admission for liver disease 3 months ago when presented with jaundice.

Denies alcohol use since prior to recent admission and PEth pending.

2

(Representative) Case

39-year-old male with history of **alcohol-associated** cirrhosis, **alcohol use disorder**, and unspecified anxiety, presenting with his wife for LT evaluation.

Multiple prior quit attempts with longest period of **abstinence** being 2 months, followed by **returns to use**. Previous admissions for **alcohol withdrawal management** and pancreatitis. First admission for liver disease 3 months ago when presented with jaundice.

Denies alcohol use since prior to recent admission and PEth pending.

3

Alcohol Use Disorder (AUD)

- In 2022, 28.8 million **(11.2%) of adults** (18+) in the US had an AUD
  - Only **1 in 4** who needed SUD treatment received it in the past year
- For many, **chronic, relapsing-remitting biopsychosocial disease**
- Only see robust abstinence after **5 years**

4

Alcohol-associated Liver Disease (ALD)

- Includes *acute alcohol-associated hepatitis* and *alcohol-associated cirrhosis*
- ALD = Now **#1 indication** for LT in US
- Trends in age, women, minority populations, since COVID

5

AUD & ALD Intersection

- **Evolution** from alcohol use as absolute contraindication → routine reason for LT
- Wide range of "relapse rates" from **4 to 95%**
- Drinking patterns among patients with ALD post-LT
  - Most commonly, **complete abstinence** (~54%), then **"low-level fluctuating use"** (~26%)
  - Initial drinking in *months* post-LT vs. heavy drinking in *years* post-LT
- Alcohol use a/w **increased complication rates** of post-LT liver fibrosis, graft injury, rejection
- **Comparable survival rates** as compared to other indications for LT

6

Group # (%)	Onset of use post-LT	Average pattern of use (SD = standard drink)	Timing of heaviest use
#1 (~54%)	N/A	Complete abstinence	N/A
#2 (~26%)	2.8 mos	Fluctuating low-level use (0.5 SD/week)	N/A
#3 (~6%)	3.5 mos	Early-onset, rapidly accelerating moderate use (3.5 SD/week)	1.7 years
#4 (~7%)	2.8 mos	Steady increase to moderate use after 3 years post-LT (2 SD/day)	6 years
#5 (~6%)	42 days	Early-onset, continuously increasing heavy use (3.7 SD/day)	3 years

7

"6-month rule"

Advantages

- Time to allow for **hepatic recovery** in absence of alcohol
- **Standardized**, clearly defined, & equitable (among patients with ALD)
- *Some* studies show association with increased rates of long-term abstinence

Disadvantages

- **Mixed evidence** and often *not* correlated with risk of return to alcohol use
- Practically **may not be time** to accomplish

8

So, what's the alternative?

1) Standardized pre-LT assessment
2) Standardized use of biomarkers
3) Rating scales
4) Robust pre-LT monitoring and support
5) Robust post-LT monitoring and support
6) Team education

9

1) Standardized pre-LT assessment

- **Alcohol use history**
  - Younger age at onset of drinking
  - >10 drinks per day at time of transplant consideration
  - Multiple unsuccessful treatment attempts
  - History of legal problems due to alcohol use
  - Shorter pre-transplant abstinence
  - Lack of insight into alcohol use problems
  - Lack of acceptance of alcohol use as a problem
  - Lack of candor and/or deceptive behavior with respect to transplant team
  - Severe AUD
- **Other substance use history**
  - Active, untreated polysubstance use (except cannabis)
  - Comorbid tobacco use
- **Mental health history**
  - Active, untreated mental health diagnosis
  - Recent suicide attempt
- **Treatment adherence history**
  - History of extensive nonadherence to treatment
- **Social criteria**
  - Lack of network supportive of recovery
  - Only 1 support person w/o alcohol u

10

1) Standardized pre-LT assessment

Table 5 Pooled risk factors of alcohol relapse

Factors	N	OR	95%CI	Pooling method	I^2	Egger test (P-value)
Demographic factors						
Age < 50 years	6	1.16	0.43 - 3.15	Random effect	75.2	0.55
Sex (male)	23	0.89	0.69 - 1.11	Fixed effect	21.7	0.43
Unmarried	14	1.84	1.39 - 2.43	Fixed effect	14.6	0.57
Lack of social support	5	1.78	0.72 - 4.38	Random effect	49.5	0.18
Low SES	3	0.99	0.15 - 6.50	Random effect	86.3	0.28
Unemployed	10	1.33	0.93 - 1.89	Fixed effect	7.7	0.74
Family history of alcohol use	7	1.49	0.94 - 2.36	Fixed effect	23.0	0.50
Risk behavior factors						
Smoking	9	1.72	1.21 - 2.46	Fixed effect	0	0.69
Substance use	8	1.06	0.48 - 2.34	Random effect	58.5	0.71
Alcohol dependence	4	1.22	0.43 - 3.40	Random effect	61.8	0.15
High HRAR	4	2.93	0.30 - 28.64	Random effect	79.6	0.18
Social factors						
Abstinence < 6 months	20	2.76	2.10 - 3.61	Fixed effect	18.1	0.02
Rehabilitation program	11	1.10	0.59 - 2.04	Random effect	67	0.71
Comorbidity						
Psychiatric disease	9	3.46	1.87 - 6.39	Random effect	40.6	0.02
Depression	3	2.13	0.49 - 9.25	Random effect	54.4	0.60

N Number, *OR* Odds ratio, *CI* Confidence interval, I^2 I^2 statistics, *SES* Socioeconomic status, *HRAR* High-risk alcohol relapse scale

11

1) Standardized pre-LT assessment

TABLE 3.

Univariate and multivariate logistic regression analyses to examine risk factors associated with post-LT relapse

Variable	Univariate, OR (95% CI)	*P*	Multivariate, OR (95% CI)	*P*
Psychiatric illness	6.08 (2.29-16.2)	<0.001	5.22 (1.78-15.4)	0.003
Addiction evaluation before LT	2.63 (1.07-6.4)	0.034	–	
Continued alcohol use after first advice	5.0 (1.75-14.3)	0.003	3.80 (1.28-11.3)	0.016
Family history of AUD	2.35 (0.97-5.59)	0.059	–	
Enrollment in inpatient rehabilitation pre-LT	4.55 (1.78-11.7)	0.002	–	
SIPAT subdomain score: psychological suitability and psychopathology	1.15 (1.04-1.3)	0.007	–	

AUD, alcohol use disorder; CI, confidence interval; LT, liver transplant; OR, odds ratio; SIPAT, Stanford Integrated Psychosocial Assessment for Transplantation.

12

1) Standardized pre-LT assessment

- Per SIPAT, **ABSOLUTE CONTRAINDICATIONS**
  - Inadequate social support system
  - Active illicit substance use
  - Active alcohol dependence/"abuse"
  - Active nicotine "abuse"
  - Active manic or psychotic symptoms that may impair adherence with treatment
  - Current suicidal ideation (in a patient with a history of multiple suicidal attempts)
  - Dementia
  - *Non-adherence with treatment
  - *History of "recidivism" of substance "abuse" after previous organ transplantation
  - * = in the case of a re-transplant candidate

13

1) Standardized pre-LT assessment

- Per SIPAT, **RELATIVE CONTRAINDICATIONS**
  - *High Risk*
    - Active alcohol use (suspected to be directly causative/exacerbating medical problem)
    - Active "abuse" of prescribed substances
    - Limited adherence with treatment (e.g., self-management with interference with care)
    - Deceptive behavior
    - Current SI (with no prior h/o of SAs of multiple suicidal attempts)
    - High degree of denial or ambivalence regarding transplantation
    - Personality disorders
  - *Moderate Risk*
    - Alcohol use (not directly causative of medical problem)
    - Prescribed ("medical") cannabis use
    - Inability to understand relevant information and poor receptiveness to education
    - Reluctance to relocate near care center
    - Absence of adequate living environment –OR– Reluctance to relocate to a more appropriate housing environment
    - Limited or restricted access to resources
    - Controlled major psychiatric disorder
  - *Low Risk*
    - Obesity (BMI > 30-40)
    - Limited literacy
    - Cognitive disorders

14

2) Standardized use of biomarkers

Table 1 Diagnostic performance of biomarkers for alcohol relapse detection after liver transplantation

Markers	Sample	Detection window	Cohort size	Cutoff	Sensitivity (%)	Specificity (%)	Reference
CDT	Serum	Up to 4 weeks	112	>2.6%	21	100	33
			141	>2.6%	25	98.6	34
			121	>2.1%	29.7	96.4	35
EtG	Urine	Up to 80 h	141	≥0.5 mg/L	89.3	98.9	34
			112	≥0.5 mg/L	71	98	33
			121	>0.5 mg/L	89.2	98.8	35
	Hair	3–6 months	112	≥7 pg/mg	84	92	33
PEth	Blood	2–4 weeks	112	>20 ng/mL	100	96	33
			151	≥8 ng/mL	61.5[1]	73.9[1]	36
Ethanol	Serum	10–12 h	141	≥0.1 g/kg	—	—	34
			112	≥0.1 g/kg	25	100	33
			121	—	10.8	100	35
	Urine	Up to 24 h	121	—	10.8	100	35
Methanol	Serum	2 days	141	≥5 mg/L	22.2	99.3	34
			112	≥5 mg/L	25	100	33

CDT, carbohydrate-deficient transferrin; EtG, ethyl glucuronide; PEth, phosphatidylethanol.
[1]Calculated from raw data extracted from the study.

15

3) Rating scales

Rating scale	Components	Scoring
SALT (Sustained-Alcohol use post-LT score)	• >10 drinks/day at initial hospitalization • Multiple prior alcohol tx attempts • Prior alcohol-related legal issues • Prior illicit substance "abuse"	Total = 0-11 • Score ≥ 5 a/w high risk for return to alcohol use
HRAR (High-Risk Alcoholism Relapse scale)	• Duration of heavy drinking • No. of drinks/day • No. of prior inpatient alcohol tx attempts	Total = 0-6 • Score ≥ 4 a/w high risk for return to alcohol use
SIPAT (Stanford Integrated Psychosocial Assessment for Transplant)	• Patient readiness level • Effect of substance use • Psychological suitability • Social support system	Total = 0-119 • Higher scores a/w worse post-LT outcomes and adverse psychiatric/psychosocial outcome • Score > 21 (vs. ≥ 30) a/w high risk for return to alcohol use

16

3) Rating scales

TABLE 5.

Comparing the predictive validity of relapse of the 3 scoring systems

	Sensitivity	Specificity	PPV	NPV
HRAR cutoff ≥4	0.13	0.87	0.11	0.90
SALT cutoff ≥5	0.27	0.89	0.21	0.91
SIPAT cutoff ≥21	0.96	0.19	0.12	0.97
SIPAT cutoff ≥30	0.78	0.51	0.16	0.95

HRAR, high-risk alcoholism relapse; PPV, positive predictive value; NPV, negative predictive value; SALT, sustained alcohol use post–liver transplantation; SIPAT, Stanford Integrated Psychosocial Assessment for Transplantation.

17

3) Rating scales: *Honorable mentions*

- **HALT**: Harmful Alcohol use after LT score
- **PACT**: Psychosocial Assessment of Candidates for Transplantation
- **ARRA**: Alcohol Relapse Risk Assessment
- **S-DAT**: Social Determinant Acuity Tool

18

4) Robust pre-LT monitoring and support

- Continued **biomarker testing** for select patients
- Connection with **addiction specialist and/or other appropriate medical professionals**
  - Some programs offer integrated, co-located specialists
- **Individual therapy**
  - Ontario program: Mandatory relapse prevention sessions pre- and post-LT
- **Mutual support groups** (AA / AA alternatives)
- **Peer support**
- Involvement of **family**/supportive relationships

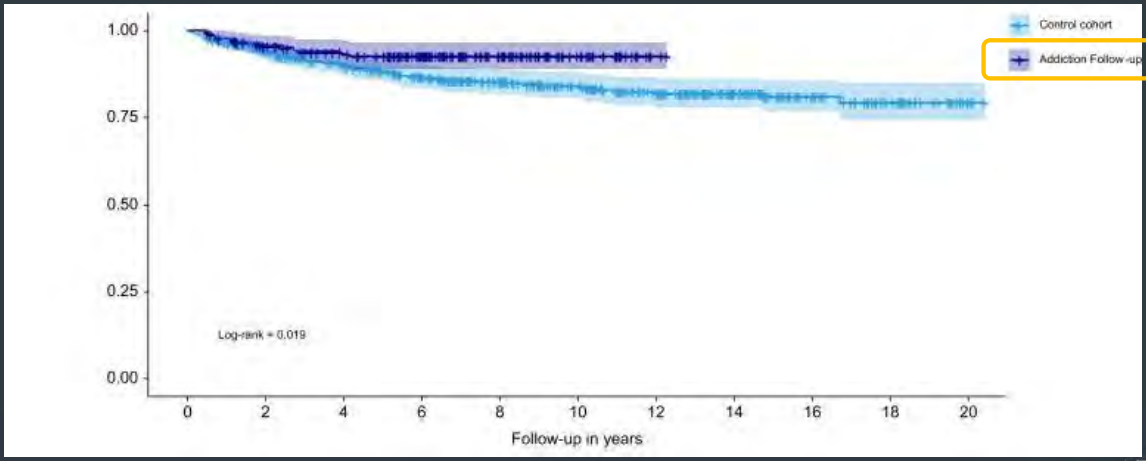
19

5) Robust post-LT monitoring and support

- **Keep going!**
  - All the same pre-LT monitoring and support, dialed up/down on individualized basis
- Routine **assessment of alcohol use** and supports at hepatology follow-up visits
- Multidisciplinary **communication** and connections
- Consider **timeline** of average vulnerability for return to use

20

5) Robust post-LT monitoring and support



21

6) Team education

- Any efforts to foster a **supportive, non-judgmental environment** for patients
  - → Increased chance for open communication, honest disclosure, early detection
- Includes **all** clinic staff & multidisciplinary team members
- **Priorities:**
  - Latest non-stigmatizing language
  - Nature of AUD
  - Motivational interviewing
  - Available resources for additional support

22

Case Summary

1) *Standardized pre-LT assessment*
   - Routine evaluation with addiction psychiatry with assessment of risk/protective factors
   - → Suitable candidate with specific recommendations
2) *Standardized use of biomarkers*
   - At evaluation: EtG/ethanol and PEth both negative
   - Pre- and post-LT testing (as below)
3) *Rating scales*
   - SIPAT: 25
   - SALT: 4
4) *Robust pre-LT monitoring and support*
   - Monthly PEth testing
   - Meeting with peer support specialist at time of evaluation and periodically as needed
   - Established with addiction psychiatrist, individual therapist, weekly SMART Recovery meetings
     - Started on acamprosate for AUD and sertraline for GAD
   - Patient and wife attended a few sessions of support group for liver transplant patients

23

Case Summary

5) *Robust post-LT monitoring and support*
   - Monthly PEth testing at least 1st year (ideally 2 years), followed by random PEth testing
   - Occasional moderate alcohol use self-reported during hepatology follow up and corroborated with +PEth (38) around 2 years post-LT
   - Meeting with peer support at time of hepatology visit for check-in, support, and re-connection with resources
   - Increased frequency of appointments with addiction psychiatrist and individual therapist, as well as SMART Recovery meetings
6) *Team education*
   - Regular trainings, grand rounds, other educational opportunities for transplant team on language, AUD, MI concepts, community resources
   - All multidisciplinary staff members grow in confidence to discuss substance use, encourage disclosure, and connect patients with resources

24

References

Asrani, S. K., Trotter, J., Lake, J., Ahmed, A., Bonagura, A., Cameron, A., … Klintmalm, G. (2019). Meeting Report: The Dallas Consensus Conference on Liver Transplantation for Alcohol Associated Hepatitis. *Liver Transplantation*, *26*(1), 127–140. https://doi.org/10.1002/lt.25681

Carrique, L., Quance, J., Tan, A., Abbey, S., Sales, I., Lilly, L., … Selzner, N. (2021). Results of Early Transplantation for Alcohol-Related Cirrhosis: Integrated Addiction Treatment With Low Rate of Relapse. *Gastroenterology*, *161*(6), 1896-1906.e2. https://doi.org/10.1053/j.gastro.2021.08.004

Chuncharunee, L., Yamashiki, N., Thakkinstian, A., & Sobhonslidsuk, A. (2019). Alcohol relapse and its predictors after liver transplantation for alcoholic liver disease: a systematic review and meta-analysis. *BMC Gastroenterology*, *19*(1). https://doi.org/10.1186/s12876-019-1050-9

Daniel, J., Dumortier, J., Del Bello, A., Gamon, L., Molinari, N., Faure, S., … Donnadieu-Rigole, H. (2023). Integrating an addiction team into the management of patients transplanted for alcohol-associated liver disease reduces the risk of severe relapse. *JHEP Reports*, *5*(10), 100832. doi:10.1016/j.jhepr.2023.100832

DiMartini, A., Dew, M. A., Day, N., Fitzgerald, M. G., Jones, B. L., DeVera, M. E., & Fontes, P. (2010). Trajectories of Alcohol Consumption Following Liver Transplantation. *American Journal of Transplantation*, *10*(10), 2305–2312. https://doi.org/10.1111/j.1600-6143.2010.03232.x

Kwong, A. J., Ebel, N. H., Kim, W. R., Lake, J. R., Smith, J. M., Schladt, D. P., … Kasiske, B. L. (2022). OPTN/SRTR 2020 Annual data report: Liver. *American Journal of Transplantation*, *22*, 204–309. doi:10.1111/ajt.16978

Lim, N., Leventhal, T. M., Thomson, M. J., Hassan, M., Thompson, J., Adams, A., … Lake, J. (2023). Protocolized screening and detection of occult alcohol use before and after liver transplant: Lessons learned from a quality improvement initiative. *PubMed*. https://doi.org/10.1111/ctr.15036

Liu, J., & Man, K. (2023). Biomarkers for monitoring alcohol sobriety after liver transplantation for alcoholic liver disease. *Journal of Gastroenterology and Hepatology*, *38*(8), 1227–1232. doi:10.1111/jgh.16269

Rice, B. A., Mehta, N., Grab, J., Dodge, J. L., & Sherman, C. B. (2023). Patient survey augments detection of harmful alcohol relapse after liver transplant for alcohol-associated cirrhosis. *Hepatology Communications*, *7*(5). https://doi.org/10.1097/hc9.0000000000000126

Rice, J. P., & Lucey, M. R. (2013). Should length of sobriety be a major determinant in liver transplant selection? *Current Opinion in Organ Transplantation*, *18*(3), 259–264. https://doi.org/10.1097/mot.0b013e32835fb94b

Schroeder, M., Pedersen, M., Petrasek, J., & Grant, L. (2023). Outcomes following liver transplant for alcohol-associated liver disease: comparing alcohol-associated hepatitis and cirrhosis. *Hepatology Communications*, *7*(5). https://doi.org/10.1097/hc9.0000000000000132

Sedki, M., Kwong, A., Bhargava, M., Ahmed, A., Daugherty, T., Kwo, P., … Goel, A. (2023). Alcohol use in liver transplant recipients with alcohol-related liver disease: A comparative assessment of relapse prediction models. *Transplantation*. doi:10.1097/tp.0000000000004800

Singal, A. K., Bataller, R., Ahn, J., Kamath, P. S., & Shah, V. H. (2018). ACG Clinical Guideline: Alcoholic Liver Disease. *The American Journal of Gastroenterology*, *113*(2), 175–194. https://doi.org/10.1038/ajg.2017.469

Sue Hyon Kim, Jang, Y., & Kim, H. (2023). Concept and risk factors of alcohol relapse in liver transplant recipients with alcohol-related aetiologies: A scoping review. *International Journal of Mental Health Nursing*, *32*(6), 1583–1597. https://doi.org/10.1111/inm.13196

25

Thank you! & Questions?

- Sara Zachman, MD, MPH
  - szachman@unmc.edu

26