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Heterogeneity in Center Practices in Liver Transplantation for Alcohol-Associated Liver Disease in the United States

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INTRODUCTION: **Alcohol-related liver disease (ALD) is now the leading indication for liver transplantation (LT) in the United States (US). It remains unclear how centers are managing the medical and psychosocial issues associated with these patients.**

METHODS: **We conducted a web-based survey of LT centers in the United States to identify center-level details on peri-LT management of ALD and related issues.**

RESULTS: **Of the 117 adult LT centers, 100 responses (85.5%) were collected, representing all Organ Procurement and Transplantation Network regions. For alcohol-associated cirrhosis, 70.0% of the centers reported no minimum sobriety requirement while 21.0% required 6 months of sobriety. LT for severe alcohol-associated hepatitis was performed at 85.0% of the centers. Monitoring protocols for pre-LT and post-LT alcohol use varied among centers.**

DISCUSSION: **Our findings highlight a change in center attitudes toward LT for ALD, particularly for severe alcohol-associated hepatitis.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C547, http://links.lww.com/AJG/C548

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INTRODUCTION

Alcohol-associated liver disease (ALD) is now the leading indication for liver transplantation (LT) in the United States (US) because of an increase in the prevalence of alcohol use disorder (AUD), particularly among younger people and women (1–3). Furthermore, demonstration of LT as a lifesaving therapy for select candidates with alcohol-associated hepatitis (AAH) has forced centers to re-evaluate previous attitudes and practices that have restricted LT in this patient population (3–6). After LT, relapse in alcohol use can have significant long-term effects on both graft and patient survival (7, 8). Successful management of AUD pre-LT and post-LT requires a multidisciplinary approach including hepatologists, addiction specialists, social workers, and psychiatrists (9).

With the increase in LT for ALD, it is not clear how centers are managing the new burden of accompanying complex medical and psychosocial issues to optimize clinical outcomes in their patients. We conducted a national survey of LT centers to define current center resources, practices, and protocols in the management of ALD before and after LT.

METHODS

We developed a survey (see Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/AJG/C547) using case-based and logic-based questions and disseminated this survey using a national list of 117 adult LT medical directors from January 05, 2021, to March 08, 2021. No incentives were provided for completion of the survey. The survey was deemed exempt by the Institutional Review Board at the University of Minnesota. Further methods are described in the supplemental material, Supplementary Digital Content 1, http://links.lww.com/AJG/C547.

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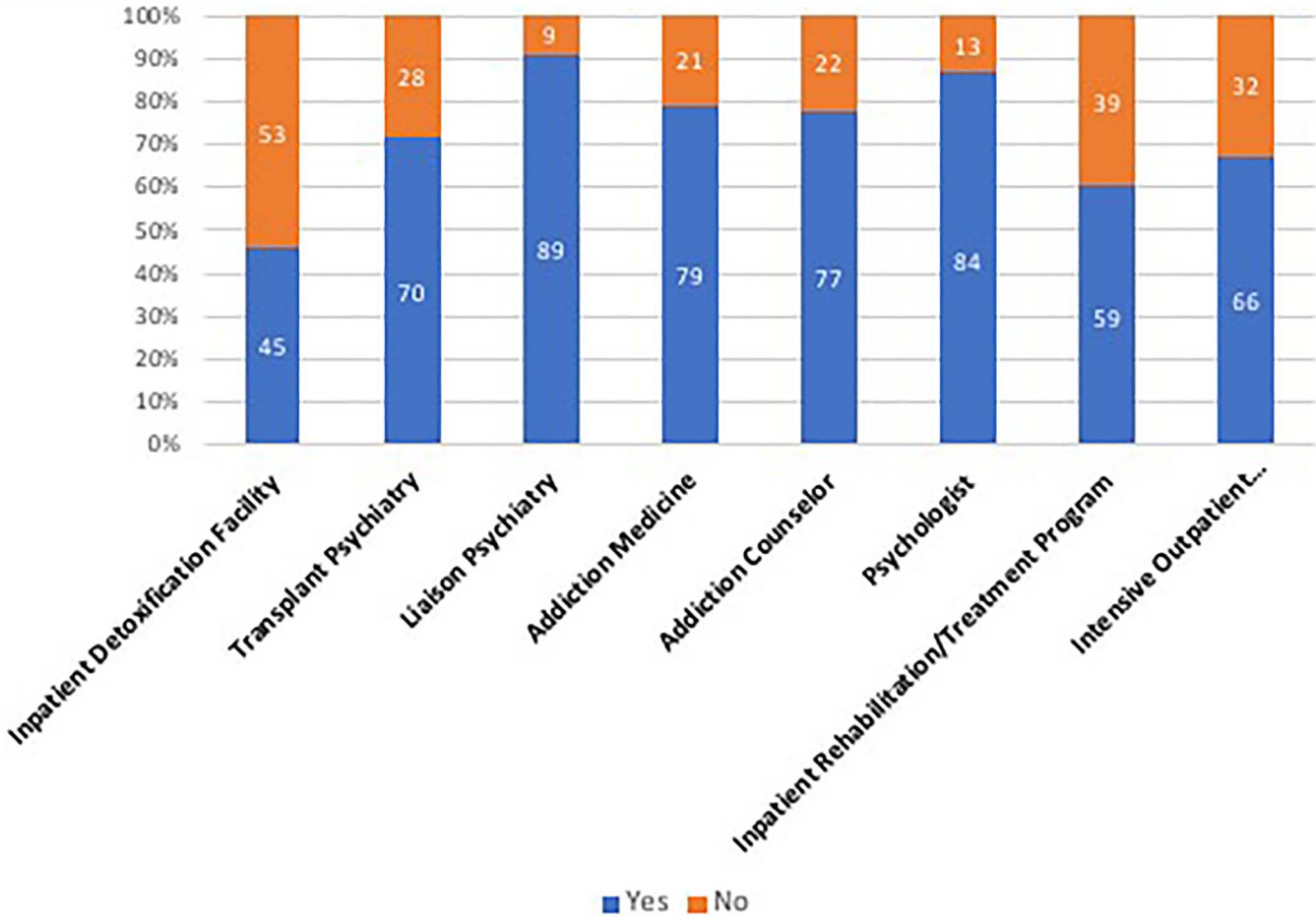

Figure 1. Center resources for the management of alcohol use disorder.

RESULTS

Center characteristics and resources

There were 100 unique responses (85.5%) representing all 11 of the Organ Procurement and Transplantation Network regions. Responding center characteristics are presented in Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C548. The availability of resources for the management of AUD is described in Figure 1.

LT for alcohol-associated cirrhosis

Most of the responding centers (70.0%) reported no minimum sobriety requirement for consideration of LT for alcohol-associated cirrhosis (AAC). Of the remaining 30 centers, 21 centers (70.0%) required a minimum sobriety time of 6 months and 9 (30.0%) required a minimum of 3 months (Table 1).

Monitoring for alcohol use in patients with AAC

During the evaluation and listing periods, all centers used alcohol biomarkers to monitor sobriety in patients with AAC: 95.0% of the centers used serum phosphatidylethanol (PETH). In the event of reported alcohol use or a positive alcohol biomarker, 74.0% of the centers used a protocol. In the post-LT period, biomarkers were used by 79.0% of the centers to monitor sobriety while PETH remained the most commonly used assay. In the event of reported alcohol use or positive biomarkers in the post-LT period, 46 centers (46.5%) reported that they had a protocol. A visit with a transplant provider (87%) and social worker (84.8%) was the most common component.

LT for severe AAH

Regarding severe AAH, 85 centers (85.0%) reported performing LT, most of whom (75.3%) started this practice within the past 5 years. Seventy-four centers (87.1%) reported using an institution-specific protocol with a high degree of similarity in protocol components between centers (Figure 2).

For relapse risk stratification, the Stanford Integrated Psychosocial Assessment for Transplant score was used in 45 centers (60.8%) (Table 2). Approximately 70% of the centers reported inclusion of a patient contract or agreement, and 62 centers (83.8%) scheduled or arranged a treatment plan for AUD before LT. Defined metrics for success in patients undergoing LT for severe AAH were used in 29 centers (39.2%). In the post-LT period, 74 centers (87.1%) reported using alcohol biomarkers to monitor sobriety from alcohol, again with a near uniform use of serum PETH (95.9%). Forty-three of the 74 centers (58.1%) had a specific protocol for monitoring alcohol use, the majority on a monthly basis. Forty of the 85 centers (47.1%) performing LT for severe AAH reported having a protocol in the event of reported alcohol use or positive alcohol biomarkers.

Table 1. LT for alcohol-associated cirrhosis

Does your center have a minimum sobriety requirement for alcohol-associated cirrhosis?	%
Yes	30.0
Does your center have a minimum sobriety requirement before evaluation/listing for LT?	N (%)
Yes	30 (30.0)
What is the duration of minimum sobriety required at your center?	N (%)
3 mo	9 (30.0)
6 mo	21 (70.0)
Pre-LT monitoring for sobriety	N (%)
Self-report	90 (90.0)
Direct interviewing	91 (91.0)
External report	85 (85.0)
Alcohol biomarkers	100 (100.0)
Serum phosphatidylethanol	95 (95.0)
Urine ethyl glucuronide	61 (61.0)
Serum carbohydrate-deficient transferrin	3 (3.0)
Serum gamma-glutamyltransferase	19 (19.0)
Monthly	46 (46.9)
3-Monthly	21 (21.4)
6-Monthly	1 (1.0)
Not checked routinely	24 (24.5)
Does your center have a protocol in the event of alcohol use?	N (%)
Yes	73 (73.7)
Protocol components	N (%)
Evaluation or listing placed on hold	59 (80.8)
Patient is delisted	33 (45.2)
Chemical dependency evaluation	33 (45.2)
Transplant provider visit	51 (69.9)
Mental health/Addiction medicine provider visit	43 (58.9)
Social work visit	57 (78.1)
Post-LT monitoring for sobriety	N (%)
Self-report	86 (86.0)
Direct interviewing	82 (82.0)
External report	70 (70.0)
Alcohol biomarkers	79 (79.0)
Serum phosphatidylethanol	74 (93.7)
Urine ethyl glucuronide	39 (49.4)
Serum carbohydrate-deficient transferrin	1 (1.3)
Serum gamma-glutamyltransferase	11 (13.9)
Frequency	
Monthly	27 (34.2)
Every 3 mo	20 (25.3)
Every 6 mo	2 (2.5)
Other	6 (7.6)
Not checked routinely	24 (30.4)
Does your center have a protocol in the event of alcohol use?	N (%)
Yes	46 (46.5)
Protocol components	N (%)
Chemical dependency evaluation	30 (65.2)
Transplant provider visit	40 (86.9)
Mental health/addiction medicine provider visit	35 (76.1)
Social work visit	39 (84.8)

LT, liver transplantation.

Subgroup analysis by practice type, center volume, and MMaT

No differences were observed when subgroup analyses were performed according to center type (university-based versus non-university-based), center volume (1–50, 51–100, and >100), and center MMaT (≤26, 27–29, and ≥30). (see Supplemental Tables 2 to 4, Supplementary Digital Content 2, http://links.lww.com/AJG/C548).

DISCUSSION

We report the findings from a national survey of LT centers on practices and the use of protocols in patients who undergo LT for ALD. Notably, most of the centers are now engaging in LT for severe AAH. Furthermore, our results underscore the heterogeneity across centers when considering resources and practices in the care of patients with ALD.

In response to the clinical scenario involving AAC, our results show that most of the LT programs no longer impose a mandatory sobriety requirement in the evaluation process for patients with ALD. A recent study showed no difference in clinical outcomes between patients undergoing LT with less than 6 months of sobriety from alcohol and those with at least 6 months sobriety (10). LT centers seem to have embraced both the complexity of AUD as a disease entity and the fact that the risk of alcohol relapse after LT cannot be distilled into a simple time frame.

Similarly, most US LT programs are offering LT for severe AAH today in contrast with 47 in 2019 (11). This is likely because of the growing body of evidence describing excellent short-term outcomes in patients undergoing early LT for severe AAH (4–6). Most of the centers reported using a protocol: Adequate caregiver support and insight into diagnosis of AUD were the most frequent components of these protocols, aligning with recommendations from the recent Dallas Consensus Conference on LT for AAH (12). Despite such protocols, most centers did not have a defined metric of success for LT in AAH and for those who did, there was a lack of consensus indicating that guidance on the metrics of success after LT for ALD is much needed and will likely need to incorporate program and patient priorities (13).

Our results also show the prominent role of alcohol biomarkers in both pre-LT and post-LT monitoring for alcohol use

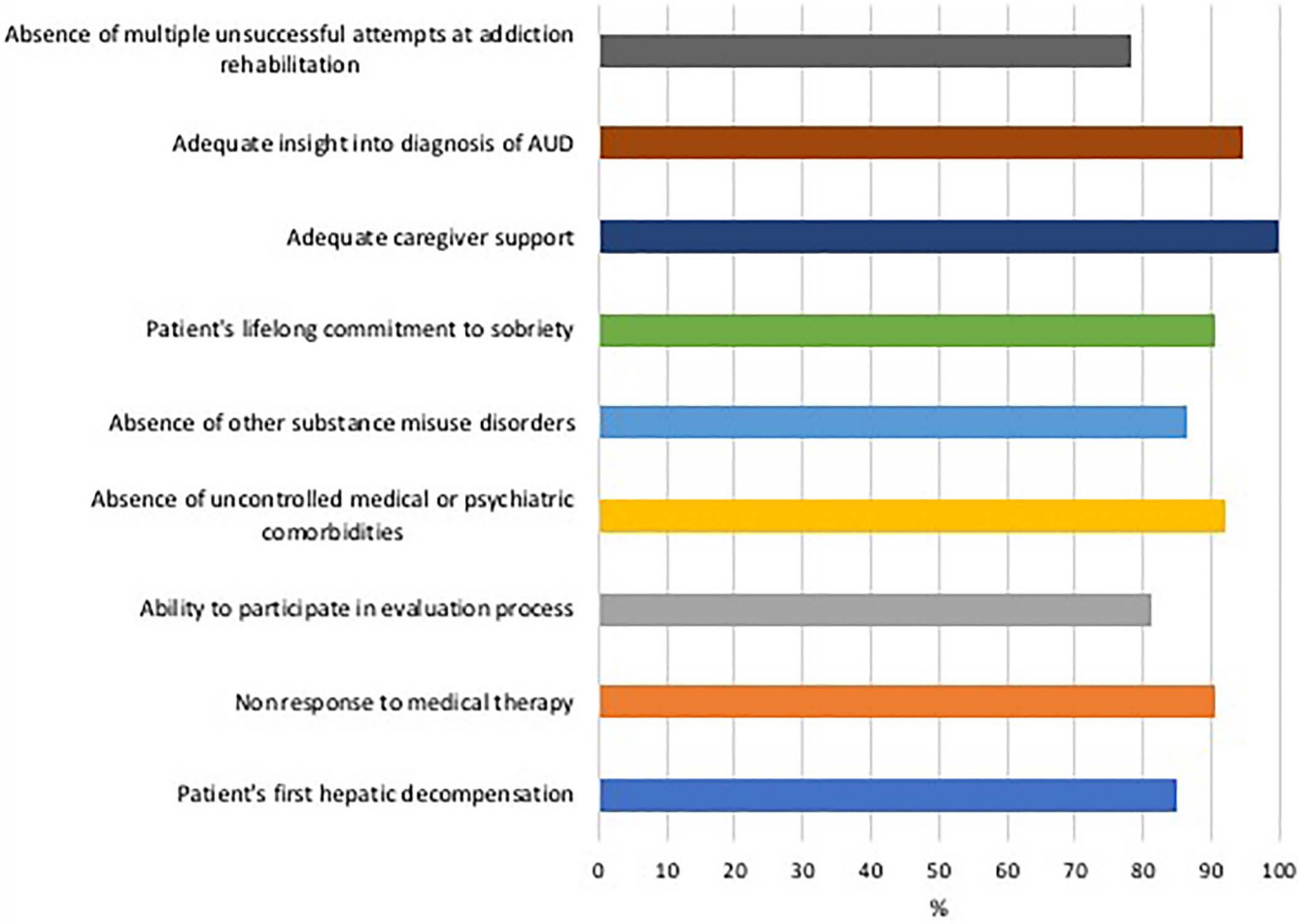

Figure 2. Center protocols for the evaluation and listing of patients with severe alcohol-associated hepatitis. AUD, alcohol use disorder.

in patients with ALD. Serum PETH, a highly specific and sensitive marker of alcohol use, was almost ubiquitous for monitoring for alcohol use before and after LT for all types of ALD (14, 15). A protocolized use of alcohol biomarkers can facilitate the detection of slips in alcohol use to provide a critical opportunity for intervention before they develop into full relapses and affect clinical outcomes (7, 8).

We observed a concerning drop-off in protocol-based routine monitoring between the pre-LT and post-LT settings. In addition, visits with transplant providers were featured prominently in protocols for the management of recurrent alcohol use in our survey. With a recent survey reporting that gastroenterology and hepatology providers often do not feel comfortable prescribing medications for the management of AUD, our data raise questions of whether transplant providers are adequately trained to manage the needs of this growing patient population (16).

There was significant heterogeneity across LT centers regarding access to resources for the management of AUD. Many centers did not have access to a transplant psychiatrist or addiction medicine specialist as part of their LT program. Integration of psychiatry and addiction services into LT clinics has been shown to reduce costs and improve clinical outcomes (17–20). Because the incidence of ALD continues to increase, LT centers will need to ensure that they are adequately resourced to care for the lifelong needs of these patients.

The strengths of this survey include the high response rate of 85.5%, which ensures that our findings are representative of the US LT community. We chose to evaluate practices and protocols at a center level to minimize any biases and variability that may arise from sampling individual providers. The survey design did not allow us to explore possible reasons for the heterogeneity in resources and protocols for ALD management, which needs further study.

In summary, as the burden of ALD increases across the United States, most LT centers no longer require a minimum sobriety requirement before pursuing LT, and most centers are now performing LT for severe AAH. The results of our survey underscore the need for greater standardization of care to improve clinical outcomes in patients with ALD. Further work should explore the quality of currently used ALD protocols and interview-based studies to investigate sources of heterogeneity in LT practices.

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Table 2. LT for severe AAH

Does your center perform LT for severe AAH?	%
Yes	85.0
No. of years performing LT for severe AAH	%
0–5 yr	75.3
5+ yr	24.7
No. of patients evaluated for LT for severe AAH per year	n (%)
0–5 patients	3.5
6–10 patients	24.7
11–20 patients	31.8
20+ patients	40.0
No. of patients transplanted for LT for severe AAH per year	n (%)
0–5 patients	51 (60.0)
6–10 patients	15 (17.7)
11+ patients	19 (22.4)
Does your center have a protocol for evaluation and transplantation of patients with severe AAH?	n (%)
Yes	74 (87.1)
How long has your center been using a protocol?	n (%)
0–1 yr	16 (21.6)
2-4 yr	42 (56.8)
5+ yr	16 (21.7)
Which scoring systems are incorporated into your center protocol?	n (%)
SALT	26 (35.1)
SIPAT	45 (60.8)
Other	18 (24.4)
None	12 (16.2)
Does your center protocol include a patient contract/ agreement?	n (%)
Yes	52 (70.3)
Is a treatment plan for AUD arranged before LT?	n (%)
Yes	62 (83.8)
Does your center's protocol have a defined metric for "success" in patients undergoing LT for severe AAH?	n (%)
Yes	29 (39.2)
What metric does your center define as "success" in these patients?	n (%)
Absolute sobriety	20 (68.9)
Starting treatment for AUD	16 (55.2)
Graft survival	22 (75.9)
Patient survival	22 (75.9)
Does your center audit your protocol for LT for patients with severe AAH?	n (%)
Yes	52 (70.3)
How often does your center audit this protocol?	n (%)
Monthly	2 (3.9)
Every 3 mo	9 (17.3)
Every 6 mo	12 (23.1)
Annually	22 (42.3)
Other	7 (13.5)
Post-LT monitoring for sobriety	n (%)
Self-report	75 (88.2)
Direct interviewing	73 (85.9)
External report	66 (77.6)
Alcohol biomarkers	74 (87.1)
Serum phosphatidylethanol	71 (95.9)
Urine ethyl glucuronide	41 (55.4)
Serum carbohydrate-deficient transferrin	1 (1.4)
Serum gamma-glutamyltransferase	13 (17.6)
Does your center check alcohol biomarkers routinely after LT for severe AAH?	n (%)
Yes	43 (58.1)
Frequency	
Monthly	25 (58.1)
Every 3 mo	10 (23.3)
Every 6 mo	1 (2.3)
Annually	1 (2.3)
Other	6 (13.9)
Does your center have a protocol in the event of alcohol use?	n (%)
Yes	40 (47.1)
Protocol components	n (%)
Chemical dependency evaluation	24 (60.0)
Transplant provider visit	36 (90.0)
Mental health/Addiction medicine provider visit	31 (77.5)
Social work visit	35 (87.5)

AAH, alcohol-associated hepatitis; AUD, alcohol use disorder; LT, liver transplantation; SALT, Sustained Alcohol use post-Liver Transplant; SIPAT, Stanford Integrated Psychosocial Assessment for Transplant.

CONFLICTS OF INTEREST

Guarantor of the article: Nicholas Lim, MD.

Specific author contributions: N.L.-study concept, study design, data collection, data analysis, article writing, and article revision; A.J.K.-study design, data collection, data analysis, and article revision; S.M.J.-study design, data collection, data analysis, and article revision; M.T.J.-study design, data collection, data analysis, and article revision; M.K.-study design, data collection, data analysis, and article revision; K.N.-study design, data collection, data analysis, and article revision; A.P.-study design, data collection, data analysis, and article revision; A.S.-study design, data collection, data analysis, and article revision; Q.T.-data analysis and article revision; A.P.-study design, data collection, data analysis, and article revision. All authors have approved the final version of the article.

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Potential competing interests: S.M.J. is on the medical advisory board for Eisai and Takeda and is on the speakers' bureau for AbbVie, Gilead, and Takeda. A.P. is on the medical advisory board for Eisai, Exelixis, AstraZeneca, and Genetech; on the data safety monitoring board for Replimune; and on the speakers' bureau for Simply Speaking Hepatitis (CME). All other authors have no disclosures to report.

Data transparency statement: Data can be made available on request to the corresponding author.

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