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Increase in Alcoholic Hepatitis as an Etiology for Liver Transplantation in the United States: A 2004–2018 Analysis

Nabil Nouredin, MD,¹ Ju Dong Yang, MD,^{2,3} Naim Alkhouri, MD,⁴ Samantha M. Noreen, PhD,⁵ Alice E. Toll, MS,⁵ Tsuyoshi Todo, MD,⁶ Walid Ayoub, MD,^{2,3} Alexander Kuo, MD,^{2,3} Georgios Voidonikolas, MD,⁶ Honore G. Kotler, RN, PhD-c, ACNP, CCTC,⁶ Michalyn D. Pelphrey, MSN,³ Brenda J. Durand, RN, BSN,³ Kambiz Kosari, MD,⁶ Todd V. Brennan, MD,⁶ Irene Kim, MD,⁶ Andrew S. Klein, MD,⁶ Ekihiro Seki, MD, PhD,² Nicholas N. Nissen, MD,⁶ Shelly C. Lu, MD,² Vinay Sundaram, MD,^{2,3} and Mazen Nouredin, MD, MHSc^{2,3}

Background. Changing opinions on the alcohol abstinence requirement have led to increased liver transplantation (LT) for alcoholic hepatitis (AH). We aimed to determine the trend in LT for AH in the United States and overall and graft survival rates. **Methods.** Adult liver-alone and liver-kidney registrations added to the Organ Procurement and Transplantation Network waiting list between 2004 and 2018 were divided into 3 periods (2004–2009, 2010–2013, 2014–2018). Kaplan-Meier survival models illustrated patient and graft survival. **Results.** Between 2004 and 2018, 529 AH patients were registered for and 254 received LT. By periods, 116, 73, and 340 patients were registered for and 49, 17, and 188 patients received LT, respectively, indicating an increase in LT for AH from 2014 to 2018. Yearly registrants from 2014 to 2018 were 32, 47, 51, 70, and 140, and recipients were 16, 24, 24, 38, and 88, respectively, indicating increases of 338% and 450% in registrants and recipients, respectively, since 2014. AH patients had the highest 1- and 3-year posttransplant survival (93.2% and 87.3%, respectively) and graft survival (90.4% and 84.8%, respectively) comparing to other LT recipients. **Conclusions.** LT for AH in the United States is at an all-time high with an increased overall patient and graft survival.

(*Transplantation Direct* 2020;6: e612; doi: 10.1097/TXD.0000000000001051. Published online 8 October, 2020.)

INTRODUCTION

Alcoholic hepatitis (AH), a serious condition associated with excessive alcohol intake, can lead to jaundice, ascites, and worsening of liver function that may ultimately result in death.¹ Severe AH, defined as presenting a Maddrey's score ≥ 32 , is associated with significant mortality, especially since

treatment is limited to corticosteroids, which often fails.¹ Consequently, this has led to the search for alternatives to improve patient outcomes. Liver transplantation (LT) has been proposed as a treatment for severe AH,² with growing support since a 2011 European study suggested that in selected cases, LT leads to improved survival and might be an acceptable approach in patients who are carefully

Received 1 July 2020.

Accepted 20 July 2020.

¹ School of Medicine, Department of Internal Medicine, University of Nevada, Las Vegas, Las Vegas, NV.

² Division of Digestive and Liver Diseases, Cedars-Sinai Medical Center, Los Angeles, CA.

³ Department of Medicine, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA.

⁴ Arizona Liver Health, Chandler, AZ.

⁵ Research Department, United Network for Organ Sharing, Richmond, VA.

⁶ Department of Surgery, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA.

M.N. was involved in most of the roles including conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resourcing, supervision, validation, visualization, etc. N.N., J.D.Y., N.A., and S.M.N. were involved with methodology. Formal analyses were carried out by S.M.N. and A.E.T. Software handling was done by N.A. and S.M.N. N.N. and M.N. were involved in writing the original draft. All authors were involved in validation, reviewing, and editing the article.

M.N. has been on the advisory board for Gilead, Intercept, Pfizer, Novartis, Blade, EchoSens North America, OWL, and Abbott. M.N. has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Novartis, Shire, and Zydus. M.N. is a minor shareholder or has stocks in Anaetos and Viking. N.A. has received research support from Genfit, Galmed, Madrigal, Allergan, and Gilead. N.A. has been on the advisory board for Gilead and Allergan. N.A. is on the speaker bureau for Intercept and Gilead.

The authors declare no conflicts of interest.

Correspondence: Mazen Nouredin, MD, MHSc, Division of Digestive and Liver Diseases, Cedars-Sinai Fatty Liver Program, 8900 Beverly Blvd., Los Angeles, CA 90048. (Mazen.Nouredin@cshs.org).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001051

selected, that is, patients not responding to corticosteroids; with no prior episode of AH; having strong family support; with no severe comorbid conditions; and agreeing to a life-long abstinence from alcohol.³ The requirement for a 6-month abstinence period before LT has been challenged due to lack of data supporting it.⁴⁻⁷ The case for LT in severe AH is further strengthened by studies conducted by US consortium; these studies have reiterated the improved survival following LT for AH, with a score created to predict the likelihood of relapse post LT.⁸⁻¹¹

With the decline of chronic hepatitis C virus (HCV) infection as an indication for LT since 2014, there has been a shift in the indications for LT in the United States. According to recent reports, alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH) are the 2 leading indications for LT overall,^{12,13} while NASH is the leading indication in women.¹⁴

Subsequent to their analysis of data from the Organ Procurement and Transplantation Network (OPTN), Lee et al¹⁵ reported a slight increase in LT for AH in 2016. The authors also examined the overall and graft survival rates at 1, 5, and 10 years posttransplant. However, these assessments were made for ALD overall,¹⁵ and there is a knowledge gap in specific data on the recent national trend in LT for AH and patient or graft survival posttransplantation. We hypothesized that due to the shift in attitude on LT for AH, there would be an increase in the incidence of LT in the United States for patients presenting with AH, and that LT for AH may result in better overall and graft survival compared with other causes. We investigated this by analyzing OPTN data on LT collected over a 15-year period.

MATERIALS AND METHODS

Patient Cohort

This study analyzed entries made into the OPTN registry, which includes data on all donors, waitlisted candidates, and transplant recipients in the United States, as described elsewhere (<https://optn.transplant.hrsa.gov/data/about-data/>). Patients on the waiting list for LT, including adult liver-alone and liver-kidney registrations from January 1, 2004, through December 31, 2018, were considered. Adult deceased-donor liver-alone and liver-kidney transplant recipients during the same time period were used to analyze trends in liver transplants. For posttransplant survival rates, the cohort of liver-alone and liver-kidney transplant recipients was examined from 2004 to 2017 and 2004 to 2015 to assess 1- and 3-year survival, respectively. Candidates awaiting multiorgan transplants other than liver-kidney, previous liver transplant recipients, recipients of multiorgan transplants, and candidates aged <18 years old at listing were excluded.

The causes compared for both waitlisted patients and recipients of LT included NASH, ALD, HCV, HCV+ALD, HCV+hepatocellular carcinoma (HCC), NASH+HCC, and ALD+HCC. We did not include OPTN data from patients with hepatitis B virus or cholestatic liver disease in our analysis since advances made in the last 2 decades in the medical management of these liver diseases have resulted in improved outcomes and a decrease in the need for LT. We further confirmed this by retrieving OPTN data on LT in patients with these indications (data not shown).

The periods in this study were defined based on recently reported studies that investigated other etiologies for LT during

3 different periods (2004–2009, 2010–2013, 2014–2018).^{13,14} These periods are also consistent with milestone changes in the management of AH that are described in the literature and recent research. Although the European study on AH was published in 2011, the first presentation was in 2009, which consequently highlights 2010 as a potentially important timepoint for assessing the change in trends in performing LT for AH.^{3,16} Similarly, 2014 was chosen by other studies as a watershed moment because of the introduction of direct-acting antivirals against HCV infection, which led to the decline of HCV as an indication for LT.¹⁷ Additionally, national presentations in the United States on AH and LT increased around that time.¹⁵

The Institutional Review Board determined that this study is exempt from review because it used deidentified, publicly available registry data.

Statistical Analysis

The number of registrations for LT added to the waiting list, and patients who received LTs by etiology were summarized by year of listing, as well as percentages within each era. Characteristics of patients registered on the waiting list and LT recipients by etiology were provided by counts and percentages or median with lower and upper quartiles, as appropriate. Comparisons of characteristics across etiologies were performed using Pearson chi-square and Kruskal-Wallis tests, with adjustments for multiple comparisons using the Benjamini-Hochberg procedure.¹⁸ Chi-square tests were used to assess changes in the proportion of AH patients waitlisted relative to other etiologies, and were adjusted for multiple comparisons by the Benjamini-Hochberg procedure.

Competing risk models were used to estimate the probability of deceased-donor transplant, live-donor transplant, death/too ill, or another removal at 90, 180, and 365 days for waitlisted patients by etiology. Point estimates as well as 95% confidence intervals (95% CI) are provided. Mortality and graft failure data were censored at 1 and 3 years for respective Kaplan-Meier survival models. Additionally, an analysis of AH patients alone was performed by period. These periods were defined as 2004–2009, 2010–2013, and 2014–2017 for the 1-year Kaplan-Meier survival models, and 2004–2009, 2010–2013, and 2014–2015 for the 3-year survival models. Pairwise log-rank tests were used to assess differences by period. Each set of pairwise tests was adjusted using the Benjamini-Hochberg procedure. These analyses are based on OPTN waitlist data as of May 24, 2019, and OPTN transplant data as of July 5, 2019. Data are subject to change based on future data submission or correction.

RESULTS

Patient Characteristics

Between 2004 and 2018, 529 patients with AH were registered for LT and 254 received LT. Registered patients had a median (quartile 1 [Q1], quartile 3 [Q3]) age of 46 (37, 55) years, were mostly male (66%), and Caucasian (80%). The median (Q1, Q3) body mass index (BMI) was 28.3 kg/m² (24.6, 31.9), and the median (Q1, Q3) model for end-stage liver disease (MELD) score was 34 (19, 40). AH patients who received LT had a median (Q1, Q3) age of 42 (34, 52) years, were mostly male (67%), and Caucasian (80%) (Table 1). The median (Q1, Q3) BMI in recipients was 30.1 kg/m² (25.3, 33.2), and the median MELD score at the time of LT was

TABLE 1.**Summary of characteristics of liver recipients for AH by period, 2004–2018**

LT recipients for AH					
Characteristics	2004–2009 N = 49	2010–2013 N = 17	2014–2018 N = 188	Combined N = 254	P
Age in y, median (Q1, Q3)	54 (48, 58)	40 (31, 42)	39 (33, 50)	42 (34, 52)	<0.001 ^b
Gender					0.590 ^a
Male (%)	36 (73)	11 (65)	123 (65)	170 (67)	
Female (%)	13 (27)	6 (35)	65 (35)	84 (33)	
Race/ethnicity					0.439 ^a
Black (%)	1 (2)	2 (12)	4 (2)	7 (3)	
Hispanic (%)	7 (14)	2 (12)	22 (12)	31 (12)	
Asian (%)	0 (0)	0 (0)	6 (3)	6 (2)	
White (%)	40 (82)	12 (70)	150 (80)	202 (80)	
Other (%)	1 (2)	1 (6)	6 (3)	8 (3)	
Laboratory MELD score at transplant ^c , median (Q1, Q3)	23 (17, 30)	36 (30, 40)	39 (35, 42)	38 (30, 41)	<0.001 ^b
Allocation MELD score at transplant, median (Q1, Q3)	23 (16, 30)	37 (31, 40)	40 (36, 40)	38 (30, 40)	<0.001 ^b
Ascites					0.025 ^a
Absent (%)	6 (12)	4 (24)	33 (18)	43 (17)	
Slight (%)	32 (65)	7 (41)	71 (38)	110 (43)	
Moderate (%)	11 (23)	6 (35)	84 (44)	101 (40)	
Hepatic encephalopathy					0.041 ^a
None (%)	10 (21)	4 (23)	44 (23)	58 (23)	
Grades 1–2 (%)	34 (69)	10 (59)	86 (46)	130 (51)	
Grades 3–4 (%)	5 (10)	3 (18)	58 (31)	66 (26)	
BMI in kg/m ² , median (Q1, Q3)	28.3 (24.0, 31.9)	31.5 (26.9, 33.1)	30.3 (25.6, 33.7)	30.1 (25.3, 33.2)	0.282 ^b
Transplanted with kidney					0.004 ^a
No (%)	44 (90)	12 (71)	178 (95)	234 (92)	
Yes (%)	5 (10)	5 (29)	10 (5)	20 (8)	
Type II diabetes mellitus					0.926 ^a
No (%)	44 (90)	16 (94)	174 (92)	234 (92)	
Yes (%)	4 (8)	1 (6)	13 (7)	18 (7)	
Missing (%)	1 (2)	0 (0)	1 (1)	2 (1)	

^aPearson test.^bKruskal-Wallis test. Statistical tests were adjusted for multiple comparisons using the Benjamini-Hochberg procedure.^cLaboratory MELD score is only capped at 40 for purposes of allocation.

AH, alcoholic hepatitis; BMI, body mass index; LT, liver transplantation; MELD, model for end-stage liver disease.

38 (30, 41). Only 8% of recipients had diabetes—the lowest prevalence among other etiologies (Table S1, SDC, <http://links.lww.com/TXD/A286>).

For the overall period 2004–2018, the number of registrants for both liver and kidney transplant (liver-kidney transplant) as per cause were as follows: AH—10%, ALD—10%, HCV—10%, and NASH—13% ($P < 0.001$ for NASH versus AH or ALD or HCV). Additionally, the corresponding number of recipients of liver-kidney transplant as per etiology were AH—8%, ALD—10%, HCV—9%, and NASH—12%, with a similar trend for NASH versus AH or ALD or HCV ($P < 0.001$).

Trends in Implementation of LT for the Management of AH in the 3 Time Periods

Over the 3 periods, 116, 73, and 340 patients with AH were registered for LT, and 49, 17, and 188 registered patients received LT, respectively. This indicates a sharp increase in LT for AH in the most recent period (Figure 1). Table 1 provides summaries of recipients among the AH patients across the time periods of interest. Median (Q1, Q3) ages of registrants for the periods were 53 (46, 57) years, 50 (42, 57) years, and 42 (34, 52) years, respectively ($P < 0.001$). While the proportion of male registrants with AH dropped from 78% in

2004–2009 to 66% in 2010–2013 and to 62% in 2014–2018, indicating an increase in female registrants with AH in the most recent period ($P = 0.017$), there was no significant difference in the percentage of females with AH receiving LT across periods ($P = 0.592$). For the 3 periods, median laboratory MELD scores at registration increased from 20 to 27 and 37, respectively ($P < 0.001$). In parallel, the median laboratory MELD scores at transplant for these periods increased from 23 to 36 and 39, respectively ($P < 0.001$), indicating an increased severity in disease in AH patients who were registered and received LT in the most recent period. Additionally, during the period of 2014–2018, registrants with AH had the highest probability of receiving a deceased-donor LT at 1 year (67%; 95% CI, 63–71), while registrants with HCV had the lowest (40%; 95% CI, 40–41) (Figure S1, SDC, <http://links.lww.com/TXD/A286>).

Trends in Implementation of LT for the Management of AH in the Period 2014 to 2018

As more data on LT for the management of AH has emerged in the United States over the last 5 years, we investigated the trends in the most recent period. Between 2014 and 2018, the yearly number of LT registrants with AH were 32, 47, 51, 70, and 140, respectively, and LT recipients were 16, 24,

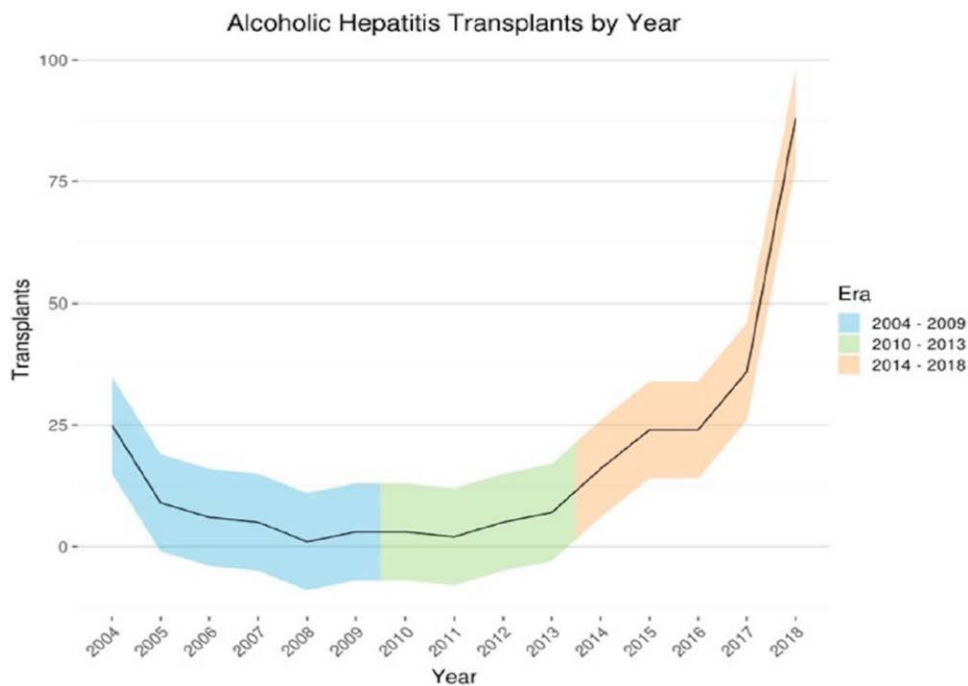


FIGURE 1. Alcoholic hepatitis liver recipients by year illustrating the increase trend of AH for LT between 2004 and 2018. AH, alcoholic hepatitis; LT, liver transplantation.

24, 36, and 88, respectively (Table S2, SDC, <http://links.lww.com/TXD/A286>). This translates as a 3.4-fold increase in the number of LT registrants with AH, and a 4.5-fold increase in the number of LT recipients for AH since 2014. Interestingly, the most striking increase was from 2017 to 2018, with a doubling in the number of LT registrants with AH and more than doubling in the number of LT recipients for AH.

Overall and Graft Survival Rates Following LT for the Management of AH

Following LT, patients with AH had the highest 1- and 3-year survival rates in comparison to patients with other causes, at 93.2% and 87.3%, respectively (Table 2; Figure 2). By time periods, AH patients who had received LT during 2004–2009 had the highest 1-year patient survival. However, interestingly, at 3 years posttransplant, the survival estimates for all 3 periods were within 2% of each other. There were no statistically significant differences by period in the 1- or 3-year survival rates posttransplant for AH patients (Figures S2 and S3, SDC, <http://links.lww.com/TXD/A286>). Despite lower survival within the first 6 months following LT, AH patients had the highest 1- and 3-year graft survival rates posttransplant (Table 3, Figure 3). However, there were no statistically significant differences by period in 1- and 3-year graft survival rates posttransplant for AH patients (Figures S4 and S5, SDC, <http://links.lww.com/TXD/A286>). The overall and graft survival rates following LT in AH patients were much higher than those seen in patients with NASH and NASH+HCC, both of which were previously shown to be the most rapidly increasing indications for LT (Tables 2 and 3).^{13,14} It is worth noting that survival data for AH patients receiving LT are limited by the low number of transplants. Finally, the proportion of transplant recipients with AH who were reregistered or retransplanted was negligible—<3.5% and <3%—respectively (data not shown).

DISCUSSION

Results published by Mathurin et al³ and subsequent studies conducted by the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH)^{8-11,15} have paved the way for considering LT for AH patients. Investigators with ACCELERATE-AH, a multicenter observational study describing outcomes of early LT in patients with severe AH, noted a slight increase in frequency of LTs for the management of AH in the United States in 2016.¹⁵ They further postulated that since their presentations occurred first in 2014, the reported increase in the number of LTs in 2016 could be partially due to their data.¹⁹ We hypothesized that ACCELERATE-AH's efforts may finally have shifted attitudes toward LT for management of AH in the United States²⁰ and discovered an increase in the number of registrants and LT recipients in AH patients in the period 2014–2018 in the OPTN registry.

In our comprehensive analysis, we discovered that during 2014–2018, the number of LT registrants with AH almost doubled, and the number of LT recipients more than doubled in comparison to those for the periods 2004–2009 and 2010–2013 combined. The most striking increase was in 2018 when the number of registrants and recipients doubled compared with 2017. AH patients were not only more likely to receive LT than those with other causes but also had the best overall and graft survival. To our knowledge, this is the first report that describes these findings. We also discovered an increase in the proportion of females with AH who were registered for LTs in our defined period. These findings are juxtaposed with our previous report that NASH is the leading cause of LTs in women in the United States, while ALD is the leading cause for men.¹⁴ Our present analysis highlights the continual change in gender disparity in etiologies requiring LT. We also note that in the most recent period (2014–2018), the LT registrants with AH were younger and had higher MELD scores

TABLE 2.**Posttransplant patient survival by pathogenesis**

Pathogenesis	One-year patient survival, LT recipients during 2004–2017				Three-year patient survival, LT recipients during 2004–2015			
	N	N events	Survival estimate (%)	95% CI	N	N events	Survival estimate (%)	95% CI
Alcoholic hepatitis	166	11	93.2	(89.4–97.2)	106	13	87.3	(81.1%, 94.0%)
ALD	11 182	889	91.9	(91.4–92.4)	8363	1185	85.3	(84.6–86.1)
HCC + ALD	682	57	91.5	(89.4–93.7)	488	77	83.8	(80.5–87.2)
HCC + HCV	3569	298	91.5	(90.5–92.4)	3003	586	79.7	(78.3–81.2)
HCC + NASH	772	92	87.8	(85.5–90.2)	527	98	80.8	(77.5–84.3)
HCV	16 275	1867	88.2	(87.7–88.7)	14 630	2969	78.8	(78.2–79.5)
HCV/ALD	3841	383	89.8	(88.8–90.8)	3416	647	80.2	(78.8–81.6)
NASH	8997	906	89.7	(89.1–90.4)	6621	1079	83.2	(82.3–84.1)

The significance of bold refers to alcoholic hepatitis group which is the patient population of interest in the paper.

ALD, alcoholic liver disease; CI, confidence intervals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; NASH, nonalcoholic steatohepatitis.

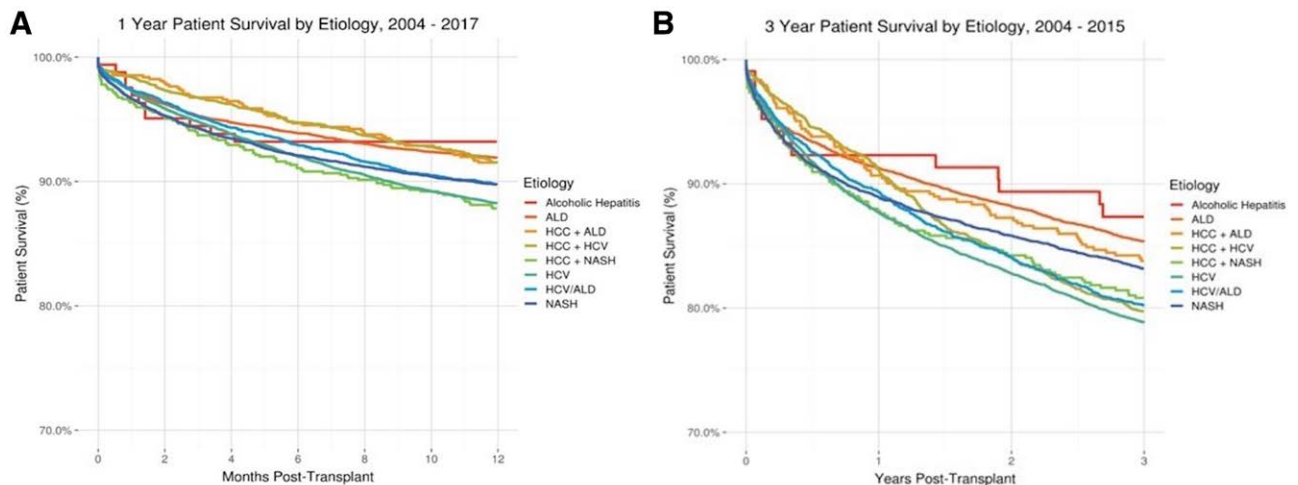


FIGURE 2. Overall, 1- and 3-year patient survival: (A) overall patient 1-year survival (between 2004 and 2017) divided by most common etiologies including AH, ALD, HCC + ALD, HCC + HCV, HCC + NASH, HCV, HCV/ALD, NASH; (B) overall 3-year survival (between 2004 and 2015) for the same causes. AH, alcoholic hepatitis; ALD, alcoholic liver disease; CI, confidence intervals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

indicating that LTs are now being performed in younger patients with a more severe disease.

A central issue is identifying when LT is justified in patients with AH. A recent study reported a notable survival benefit with early LT for AH in comparison to late LT.¹⁰ Such data are of utmost importance and may continue to shift the attitude toward early LT for AH patients. In our analysis, we noticed that the median time from registration on the OPTN waiting list to receiving an LT decreased dramatically from 58 days in the 2004–2009 period to 5 days in the 2014–2018 period (Table S3, SDC, <http://links.lww.com/TXD/A286>). While a detailed analysis of any relationship is a subject for future studies, we can speculate that this reduction in waiting time could be one of the factors that have led to improved survival rates in AH patients receiving LT. The higher overall and graft survival rates for AH compared with NASH and NASH+HCC could be the result of the younger age, lower BMI, and lower occurrence of diabetes in patients with AH. In addition, the higher post-LT survival rate in patients with AH could be attributed to careful selection at the time that the patients at their sickest point and quicker listing in the OPTN registry in comparison to other etiologies where many patients could have been listed while they are less sick and

were not suitable for transplant when they got sicker. Also, since not all patients with acute AH had progressed to cirrhosis at the time of LT, this could have a favorable impact on outcomes in these patients. Finally, the decrease in HCV and HCV+HCC as indications for LT could have contributed to this shift in attitude as more organs would be available for transplant.^{14,17}

While LT is gaining more acceptance as a treatment for AH, future studies are needed to identify the patient population as well as the ideal timeframe to maximize beneficial outcomes. To date, the exact reason for low survival in the first 6 months following transplant in AH patients compared with other etiologies are unknown. Although we noticed a lower short-term survival (2–6 months posttransplant) following LT in AH for the period 2014–2018 in comparison to previous periods, our analysis did not find these differences to be statistically significant. As for a possible reason for this, we speculate that the upward trend in LT for AH in recent years could be in part due to even severe AH cases with poorer prognosis being considered for LT. The majority of deaths following LT, regardless of etiology, happen early (<1 y) and are usually attributable to pulmonary infections, sepsis, multiorgan failure, and early allograft dysfunction.^{21,22} These infections might be possibly

TABLE 3.
Posttransplant graft survival by pathogenesis

Pathogenesis	One-year graft survival, LT recipients during 2004–2017				Three-year graft survival, LT recipients during 2004–2015			
	N	N events	Survival estimate (%)	95% CI	N	N events	Survival estimate (%)	95% CI
Alcoholic hepatitis	166	16	90.4	(86.0-95.0)	106	16	84.8	(78.2-92.0)
ALD	11 182	1164	89.5	(89.0-90.1)	8363	1440	82.6	(81.8-83.4)
HCC+ALD	682	65	90.4	(88.2-92.7)	488	85	82.3	(79.0-85.8)
HCC+HCV	3569	384	89.2	(88.2-90.2)	3003	671	77.3	(75.8-78.8)
HCC+NASH	772	107	86.0	(83.6-88.5)	527	113	78.3	(74.9-82.0)
HCV	16 275	2354	85.5	(84.9-86.0)	14 630	3553	75.3	(74.6-76.1)
HCV/ALD	3841	495	87.0	(86.0-88.1)	3416	792	76.5	(75.0-77.9)
NASH	8997	1124	87.5	(86.8-88.1)	6621	1290	80.3	(79.4-81.3)

The significance of bold refers to alcoholic hepatitis group which is the patient population of interest in the paper.

ALD, alcoholic liver disease; CI, confidence intervals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; NASH, nonalcoholic steatohepatitis.

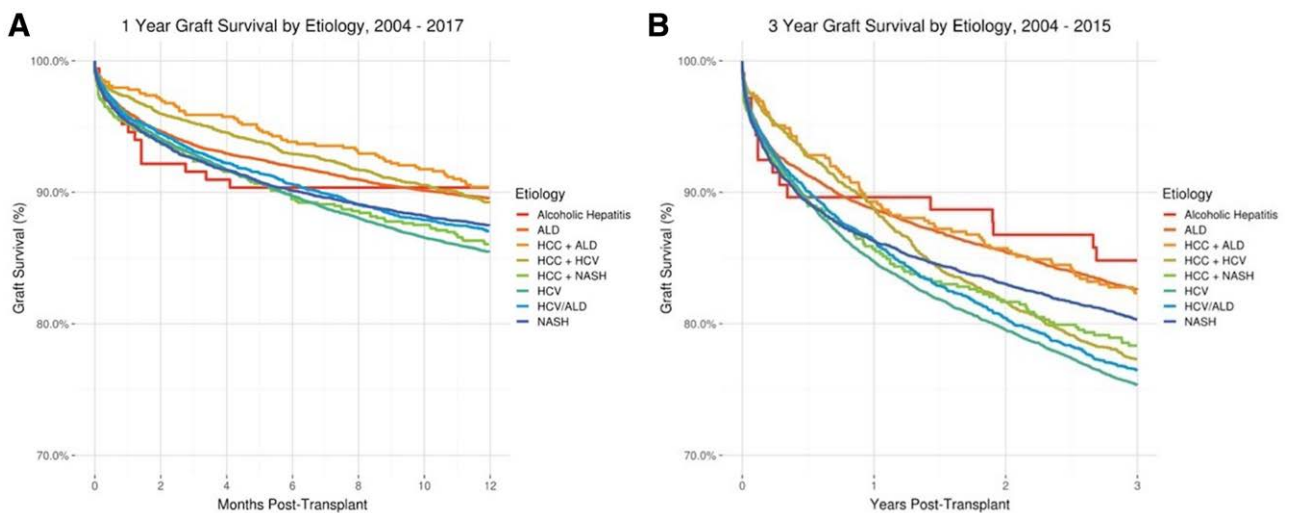


FIGURE 3. 1- and 3-year graft survival: (A) 1-year graft survival (between 2004 and 2017) divided by most common etiologies including AH, ALD, HCC+ALD, HCC+HCV, HCC+NASH, HCV, HCV/ALD, NASH; (B) 3-year graft survival (between 2004 and 2015) for the same pathogenesis. AH, alcoholic hepatitis; ALD, alcoholic liver disease; CI, confidence intervals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

increased in the first 6 months in patients transplanted due to AH. This was evident in the Mathurin study³ as 5 of 6 deaths in their cohort were related to infection within 2 weeks post LT, with a trend of longer duration of pre-LT corticosteroids in patients who are deceased.

Although it could be argued that AH patients have the highest MELD scores at the time of transplant ($P < 0.001$),²³ thereby rendering them prone to poorer outcomes, it is also evident that LT recipients with AH have the best 1- and 3-year survival rates. A recent review by Wu et al has reported an improved posttransplant survival of 77%–100% at 6 months in AH patients receiving LT in comparison to those receiving supportive care.²⁴ Further research is needed to improve survival at 6 months of AH patients receiving LT. Of note, we discovered that AH patients comprised 10% and 8% of all patients, respectively, in the OPTN registry for the described period who were registered for and received liver-kidney transplant. In general, these proportions were comparable for all pathogenesis except NASH, which was slightly higher (13% and 12%, respectively). Hence, in our opinion, the increase in LT in AH patients should not have a negative impact on the availability of kidneys for patients awaiting kidney transplants.

Since the main aim of our analysis was to ascertain the trends in LT as well as 1- and 3-year survival in AH patients, we have focused our discussion on our findings. However, there are other key issues that need to be taken into consideration while qualifying AH patients for LT. Alcohol recidivism has a substantial and negative impact on patient and graft survival outcomes in AH patients who have undergone LT. Although it would have been insightful to compare the outcomes of LT with or without the 6-month abstinence rule, sobriety data were not available as part of the OPTN registry and this precluded further analysis. We recommend that the agency should collect this information pre- and posttransplant, especially for AH. Robust prediction models have been recently investigated,^{11,25} despite this AH patients will need to be screened for the risk of relapse and offered psychosocial support both before and after LT. This, in turn, further adds to the already high burden of medical resource utilization in LT. Transplant programs will also need to bear in mind the impact that the increase in LT in AH will have on LT for other etiologies, especially considering the perennial problem of shortage of donor organs, and take a holistic approach while considering LT in AH patients.

One of the limitations in our analysis is the inability to exclude entries in the OPTN database that could possibly be incorrect diagnosis. In a recent study, among 124 recipients with a chart-review diagnosis of AH, only 35% had AH as the listing diagnosis in OPTN data.⁸ Therefore, an underestimation of the number of AH patients reported is likely. It could even be argued that the sharp increase in LTs for AH in 2018 is due to increased awareness and more accurate coding for AH. Although this is a possibility, it is unlikely because awareness and related publications have increased steadily since 2014. This is supported by our finding that the period 2014–2018 had more LTs for AH than the entire 10 years prior. Another limitation is the possibility of erroneous coding for other etiologies; the need for updated codes in OPTN data is a well-recognized challenge. Finally, the notable differences in age and MELD scores for the 3 time periods we assessed underscores the lack of robust uniformity across these periods for the sake of comparison. The use of more precise definitions for AH patients qualifying for LT, perhaps using explant histology or the National Institute on Alcohol Abuse and Alcoholism consensus criteria,²⁶ could provide a more accurate estimate on LT in AH.

The main strength of our study is that it represents the most up-to-date dynamic epidemiology of registrants and transplanted patients in the United States, with the focus on AH as the cause for LT and its comparison to other pathogenesis. Moreover, ours is also the first study to look at the overall patient and graft survival for AH patients receiving LT using OPTN data.

There has been a recent increase for AH as an indication for listing and receiving LT with the most striking increase in 2018, reflecting the shift in attitude toward performing LT in patients with AH. These patients had fewer comorbidities and were more likely to receive LT with favorable graft and survival outcomes. We believe that early LT for AH should be performed after careful selection. We also recommend that this selection process needs to be revised and harmonized among LT centers in the United States. To do this, we will require more data such as pre- and posttransplant sobriety records, etc, and further research. Moreover, policymakers, insurers, and LT centers that still mandate a 6-month sobriety rule need to reconsider such a requirement. Even though the 6-month sobriety rule is widely adopted, it is not an unconditional policy, and the United Network of Organ Sharing has never stipulated such a rule. Indeed, the American Association for the Study of Liver Diseases recently published a new guidance that supports considering selected patients with severe AH for LT.²³ However, with the overall shortage of organs, if AH patients are more likely than in the past to receive LT, this will affect other indications and possibly mortality overall. Future studies need to estimate the effect on other pathogenesis.³

REFERENCES

1. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009;360:2758–2769.
2. Lucey MR. Is liver transplantation an appropriate treatment for acute alcoholic hepatitis? *J Hepatol*. 2002;36:829–831.
3. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1790–1800.
4. Beresford TP, Everson GT. Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule, and relapse—but where are the data? *Liver Transpl*. 2000;6:777–778.
5. Im GY, Cameron AM, Lucey MR. Liver transplantation for alcoholic hepatitis. *J Hepatol*. 2019;70:328–334.
6. Im GY, Lucey MR. Practical concerns and controversies in the management of alcoholic hepatitis. *Gastroenterol Hepatol (N Y)*. 2016;12:478–489.
7. McCallum S, Masterton G. Liver transplantation for alcoholic liver disease: a systematic review of psychosocial selection criteria. *Alcohol Alcohol*. 2006;41:358–363.
8. Lee BP, Im GY, Rice JP, et al. Underestimation of liver transplantation for alcoholic hepatitis in the national transplant database. *Liver Transpl*. 2019;25:706–711.
9. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. *Gastroenterology*. 2018;155:422–430.e1.
10. Lee BP, Samur S, Dalgic OO, et al. Model to calculate harms and benefits of early vs delayed liver transplantation for patients with alcohol-associated hepatitis. *Gastroenterology*. 2019;157:472–480.e5.
11. Lee BP, Vittinghoff E, Hsu C, et al. Predicting low risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: the sustained alcohol use post-liver transplant score. *Hepatology*. 2019;69:1477–1487.
12. Cholankeril G, Gonzalez HC, Satapathy SK, et al. Increased wait-list mortality and lower rate for liver transplantation in Hispanic patients with primary biliary cholangitis. *Clin Gastroenterol Hepatol*. 2018;16:965–973.e2.
13. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547–555.
14. Noureddin M, Vipani A, Bresee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol*. 2018;113:1649–1659.
15. Lee BP, Vittinghoff E, Dodge JL, et al. National trends and long-term outcomes of liver transplant for alcohol-associated liver disease in the United States. *JAMA Intern Med*. 2019;179:340–348.
16. Dureja P, Lucey MR. The place of liver transplantation in the treatment of severe alcoholic hepatitis. *J Hepatol*. 2010;52:759–764.
17. Flemming JA, Kim WR, Brosgart CL, et al. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology*. 2017;65:804–812.
18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Stat Soc: Series B (Methodological)*. 1995;57:289–300.
19. Zhu J, Chen PY, Frankel M, et al. Contemporary policies regarding alcohol and marijuana use among liver transplant programs in the United States. *Transplantation*. 2018;102:433–439.
20. Sharma P, Arora A. Is the M probe really necessary to measure liver stiffness by FibroScan? *Hepatology*. 2012;55:2043–4; author reply 199.
21. Adam R, Karam V, Delvart V, et al; All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol*. 2012;57:675–688.
22. Lee DD, Croome KP, Shalev JA, et al. Early allograft dysfunction after liver transplantation: an intermediate outcome measure for targeted improvements. *Ann Hepatol*. 2016;15:53–60.
23. Crabb DW, Im GY, Szabo G, et al. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;71:306–333.
24. Wu T, Morgan TR, Klein AS, et al. Controversies in early liver transplantation for severe alcoholic hepatitis. *Ann Hepatol*. 2018;17:759–768.
25. Lombardo-Quezada J, Colmenero J, López-Pelayo H, 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.
26. Crabb DW, Batailler R, Chalasani NP, et al; NIAAA Alcoholic Hepatitis Consortia. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA alcoholic hepatitis consortia. *Gastroenterology*. 2016;150:785–790.