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Liver Transplantation for Alcoholic Hepatitis is Likely Underestimated in the National Transplant Database

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Abstract

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Alcohol-associated liver disease can be coded in UNOS as either alcoholic cirrhosis or alcoholic hepatitis (AH), without specific criteria to assign either diagnosis. In this multi-center ACCELERATE-AH study, we sought to assess the concordance of clinician-diagnosis of AH at LT listing versus UNOS data-entry of AH as listing diagnosis. In a prior study, consecutive early LT recipients for AH between 2012–2017 were identified *by chart review* at 10 ACCELERATE-AH sites. In this current study, these same LT recipients were identified in the UNOS database; the primary UNOS diagnostic code was evaluated for concordance with the chart-review assignment of AH. In cases where the primary listing diagnosis in UNOS was not AH, we determined the reason for alternate classification. Among 124 ACCELERATE-AH LT recipients with a chart-review diagnosis of AH, only 43/124 (35%) had AH as listing diagnosis in UNOS; 80 (64%) were listed as alcoholic cirrhosis, and 1 (1%) as fulminant hepatic necrosis. Of the 81 patients missing AH as a UNOS listing diagnosis code, reasons for alternate classification identified were: 44 (54%) lack of awareness of a separate diagnosis code for AH; 13 (16%) concomitant clinical diagnosis of AH and alcoholic cirrhosis in the chart; 12 (15%) clinical uncertainty regarding the diagnosis of AH versus acutely decompensated alcoholic cirrhosis; and 12 (15%) data entry error.

Conclusion: In a large cohort of LT recipients with AH, only 35% were documented as such in UNOS. Increased education and awareness for those performing UNOS data entry, establishment of specific criteria to define AH in the UNOS database and ability to document dates of alcohol use would allow future research on alcohol-associated liver disease to be more informative.

Keywords

6-month rule; accelerate-ah; UNOS; alcohol; relapse

INTRODUCTION

Alcohol-associated liver disease (ALD) is implicated in 50% of liver-related deaths, and recently surpassed hepatitis C to become the most common indication for liver transplantation (LT) in the United States.[1] Alcoholic hepatitis (AH), a subset of ALD, characterized by acute onset of jaundice in the setting of excessive alcohol intake and associated with high short-term mortality, is increasingly being considered as indication for liver transplantation (LT) in highly select patients.[2] Early LT for severe AH is performed without a minimum sobriety period because 75–90% of these patients will not survive beyond two months from presentation.[2,3] However, this emerging indication for LT is controversial, particularly given the perceived risk of post-transplant alcohol relapse and the association of alcohol relapse with poor graft outcomes.[2,3]

Patients with ALD can be coded in the United Network for Organ Sharing (UNOS) database with a listing diagnosis of either alcoholic cirrhosis or alcoholic hepatitis. However, there are no specified criteria to assign patients to either one diagnosis versus the other. Precise coding of AH in this publically available national database is important, both for clinical care (i.e. patients and providers seeking centers that are performing LT for AH) and research. Given the increasing application of early LT for AH, accurate information on national trends for this new LT indication and post-transplant outcomes specific to AH are essential.

The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) is a multi-center consortium studying early LT for severe AH.[2] In a prior study,[2] we determined the listing diagnosis of AH among LT recipients by retrospective review of all clinical data by investigators at ACCELERATE-AH sites. In this current study, we sought to assess the concordance of AH as primary listing diagnosis for these same patients in the UNOS database.

METHODS

Study Population

Ten ACCELERATE-AH sites participated in this current study. In a prior study,[2] each site identified consecutive adult patients who presented with clinically diagnosed severe acute alcoholic hepatitis (jaundice, prolonged INR, chronic and recent alcohol use), without prior diagnosis of chronic liver disease or episodes of AH, and underwent LT without a minimum prescribed period of abstinence from alcohol. These AH patients had been retrospectively identified and confirmed to meet inclusion criteria by careful chart review by site investigators (authors of this manuscript) at each site. The identification of these study patients was performed prior to conception of this current study, and without *a priori* hypothesis or knowledge of UNOS listing diagnoses. These AH patients were linked to the UNOS database by center code, sex, age at LT, LT date, hospital discharge date, and days on the waitlist to ascertain the UNOS primary diagnostic code. In cases where the primary listing diagnosis in UNOS was not AH, the site investigator retrospectively reviewed the patient's chart, and discussed with their transplant coordinator (i.e. the individual responsible for data transfer to UNOS) to determine the reason for alternate classification – this was done systematically by asking the question "Why was this patient not coded as AH in UNOS?", and by allowing the following answers: 1=coordinator not aware there was a separate AH listing code in UNOS, 2=there was uncertainty at the time of listing about the diagnosis of AH vs. alcoholic cirrhosis, and coordinator chose alcoholic cirrhosis for UNOS entry 3=data entry error in UNOS, 4=given the controversy for this LT indication and heated atmosphere, a reluctance to publicly reveal LT for AH, 5=Other (please specify). For this current study, only patients who underwent LT between January 2012 – December 2017 were included.

Statistical Analysis

The study outcome, alternate classification of AH diagnosis, was defined as any ACCELERATE-AH patient who did not have AH as their primary listing diagnosis in UNOS (UNOS diagnosis code 4217). The study outcome (alternate classification of AH diagnosis) was coded as a categorical variable, and summarized by proportion. Patient demographics, alcohol-related and clinical characteristics in study patients classified with an AH diagnosis in the UNOS were compared to those with an alternate classification of AH diagnosis. Categorical variables were compared using the chi-square test. Continuous variables were first assessed for normality; then comparisons made using the two-sample t test for variables with parametric distributions, and Wilcoxon rank-sum test for variables with non-parametric distributions. We performed an additional calculation to quantify the potential impact of misclassification in underestimating the total number of LTs performed

for AH in the United States. First, we assessed the total number of LT recipients coded with a primary listing diagnosis of alcoholic hepatitis in the UNOS database (numerator), amongst adult LT recipients from January 2012 – December 2017 (denominator), excluding HIV transplants and re-transplants. Then, we estimated the proportion of LT for AH among total adult LTs during each year of the study period, accounting for misclassification under a scenario that assumed the same national misclassification rate as the rate calculated from ACCELERATE-AH. In this calculation to estimate the national number and proportion of LT recipients for AH accounting for alternate classification, the number of LT recipients with a UNOS listing diagnosis of AH in the entire national registry was multiplied by the alternate classification rate calculated from ACCELERATE-AH sites (i.e. the inverse of the proportion of LT recipients with a listing diagnosis of AH in the ACCELERATE-AH cohort). All analyses were performed using Stata IC version 13.1 (Stata Corp, College Station, Texas).

This study was approved by the Institutional Review Board at each participating center. University of California at San Francisco (UCSF) is the designated coordinating center for ACCELERATE-AH.

RESULTS

Of the 124 ACCELERATE-AH patients with a clinician confirmed diagnosis of AH for LT listing, only 43/124 (35%) had AH as the listing diagnosis in the UNOS database; 80 (64%) were listed as alcoholic cirrhosis, and 1 (1%) as fulminant hepatic necrosis. Employment at time of initial hospitalization was higher among those with AH as the listing diagnosis in UNOS versus not (29/43 [67%] vs. 36/81 [44%], p=0.02). Otherwise, patient demographics, alcohol-related and clinical characteristics were similar regardless of whether or not the patient had AH as the listing diagnosis in the UNOS database (Table 1).

Of the 81 patients missing AH as a UNOS listing diagnosis code, reasons for alternate classification of UNOS listing diagnosis were: 44 (54%) due to the transplant coordinator performing data entry being unaware of a separate diagnosis code for AH in UNOS. 13 (16%) due to concomitant clinical diagnosis of AH and alcoholic cirrhosis in the clinical chart, and alcoholic cirrhosis was chosen as the listing diagnosis in UNOS by the coordinator. 12 (15%) due to clinical uncertainty at the time of listing regarding the diagnosis of AH versus acutely decompensated alcoholic cirrhosis; and 12 (15%) due to data entry error. The reasons for lack of classification with AH as a UNOS diagnosis are summarized in Table 2. On retrospective review, 66 of 81 (81%) patients alternatively classified, including 12 of 12 (100%) patients with clinical uncertainty at the time of listing regarding the diagnosis of AH versus acute decompensated alcoholic cirrhosis, would have met would have met inclusion criteria[4] set forth by the NIAAA Alcoholic Hepatitis Consortia for the clinical diagnosis of AH.

In the UNOS database, there were 167 LT recipients with a primary listing diagnosis of AH from January 2012 to December 2017 – these LTs were performed among 49 LT centers and all 11 UNOS regions. The proportion of total LTs performed with a primary listing diagnosis of AH increased from 0.31% (17 / 5,414) in 2012 to 0.67% (48 / 7,125) in 2017. In a

sensitivity analysis assuming the same rate of alternate classification amongst all LT centers as ACCELERATE-AH sites (i.e. assuming only 35% of LT recipients for AH coded in UNOS with listing diagnosis of AH), the actual proportion of LT for AH among total U.S. LTs may be as high as 1.3% (482 / 37,112) between 2012–2017, and 1.9% (138 / 7,077) of the total LTs in 2017. These results are summarized in Table 3 and Figure 1.

Discussion

In the current era of increasing application and debate regarding the acceptability of LT for AH, accurate UNOS coding of AH is essential. In a large cohort of LT recipients with AH, only 35% were documented as such in UNOS. The majority of alternate classification was attributable to LT coordinators unaware of AH coding – a problem that can be rectified with increased awareness. These data also suggest that the recent emergence of ALD as the most common[1] indication for LT is not due solely to the decline in HCV with widespread availability of curative antiviral therapy (as suggested by others), but may also be related in part to an increase in LT for AH, which we show is likely underestimated in the UNOS database.

There exists a challenge to clinically distinguish severe AH from acute-on-chronic liver failure in patients with cirrhosis due to alcohol;[4,5] in the U.S., liver biopsy to diagnose AH is uncommon,[5,6] and studies have shown that a clinical diagnosis of acute AH is discordant with histology in approximately 25% of patients.[7] In this study, the majority of patients were coded as alcoholic cirrhosis in the UNOS database. Since over 90% of patients who present with severe AH have underlying cirrhosis,[8] the UNOS classification of “alcoholic cirrhosis” in LT recipients for AH is not necessarily wrong, but less precise. However, given the ongoing controversy regarding whether LT for AH is an acceptable indication for LT, ability to distinguish LT for AH in the national registry is important. Furthermore, there are only limited studies of LT for AH,[2,3,9] and it remains unclear whether long-term graft and patient survival, and rates of post-LT alcohol use are different in AH vs. alcohol-associated cirrhosis. For example, in the ACCELERATE-AH cohort, there were cases of rapid graft failure from recurrent alcohol-associated liver disease as early as 13 months post-LT, which has not been previously reported in large cohorts of alcohol-associated cirrhosis.[2,10,11] To aid clinical care and research in AH and cirrhosis due to ALD, in addition to increased education and awareness for those performing UNOS data entry, the establishment of specific criteria to define AH in the UNOS database (e.g. NIAAA criteria[4]), and ability to document dates of alcohol use (to quantify the period of pre-LT abstinence), would allow future research on alcohol-associated liver disease to be more informative. For example, diagnosis variables could be “alcohol-associated cirrhosis with alcoholic hepatitis”, “alcohol-associated cirrhosis without alcoholic hepatitis”, and “alcoholic hepatitis without cirrhosis”, and date of last pre-transplant alcohol use would be a new coding variable. We are not aware of any changes in UNOS coding of alcohol-associated liver disease during this study period. Indeed, in a shifting U.S. landscape in attitudes and ongoing debate regarding not only AH, but also pre-LT sobriety periods among the broader ALD population,[12] these initiatives would be a contemporary, and valuable update.

Our study had limitations. First, this was a retrospective study – data are thus limited to those provided by the UNOS registry and ACCELERATE-AH sites; in particular, the reasons for alternative classification are subject to recall bias by LT coordinators. However, given that the LT coordinators were not aware of the listing diagnosis of AH until queried during this current study, our results appear to be robust. Second, our sensitivity analysis assumes one-way alternative classification and that the national rate would be similar to that seen among ACCELERATE-AH sites, which needs to be interpreted with some caution. Nonetheless, no ACCELERATE-AH patient coded as AH in the UNOS database was found to have an alternate primary listing diagnosis in the actual patient chart during listing. Furthermore, this study included 10 LT programs in 7 UNOS regions, providing a comprehensive reflection of the national LT landscape for AH.

With ALD now the leading indication for LT in the United States, our results highlight the need for quality improvement in UNOS coding for this disease, in order to have national registry data that accurately depicts trends and outcomes specific to AH, and can better inform the debate regarding LT for this indication.

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List of Abbreviations

ACCELERATE-AH	American Consortium of Early Liver Transplantation for Alcoholic Hepatitis
AH	alcoholic hepatitis
ALD	alcohol-associated liver disease
LT	liver transplantation
UNOS	United Network for Organ Sharing

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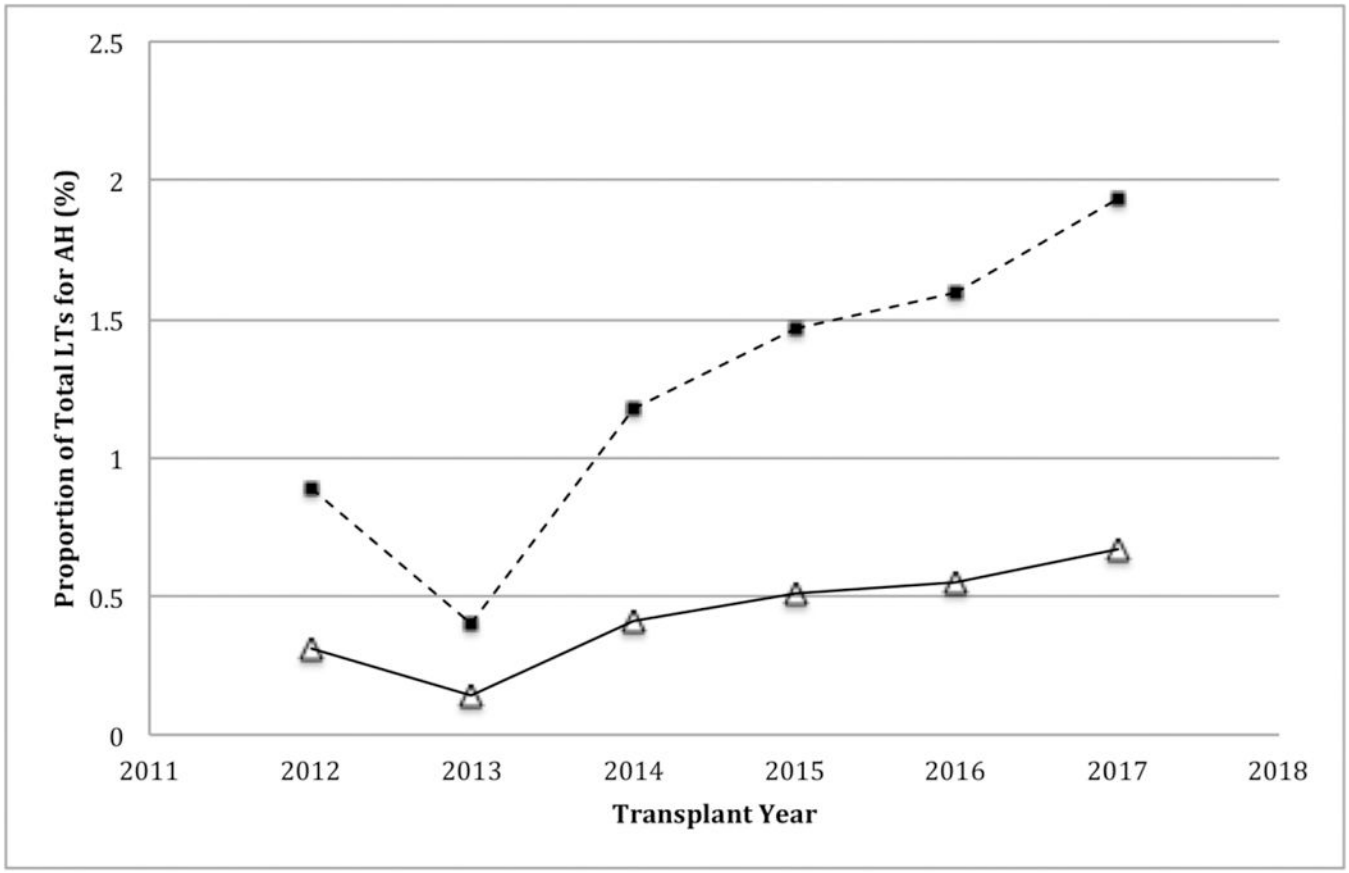

Figure 1. UNOS vs. Estimate of Actual Number and Proportions of Liver Transplants Performed for Alcoholic Hepatitis in the United States.

The proportion of total LTs performed with a primary UNOS listing diagnosis of AH increased from 0.31% (17 / 5,414) in 2012 to 0.67% (48 / 7,125) in 2017 (**solid line**). In a sensitivity analysis assuming the same rate of alternate classification amongst all LT centers as ACCELERATE-AH sites (i.e. assuming only 35% of LT recipients for AH coded in UNOS with listing diagnosis of AH), the actual proportion of LT for AH among total U.S. LTs may be as high as 1.3% (482 / 37,112) between 2012–2017, and 1.9% (138 / 7,077) of the total LTs in 2017 **(dashed line)**.

Table 1:

Patient Characteristics in ACCELERATE-AH Patients Classified as AH vs. Non-AH in UNOS Database

	Classified With AH as UNOS Diagnosis?		
Characteristic	**Yes (n=43)**	**No (n=81)**	**p**
Age – yr – median (IQR)	39 (34–51)	43 (37–50)	0.36
Male, n (%)	34 (79)	52 (64)	0.09
Caucasian, n (%)	34 (79)	71 (88)	0.21
Employed, n (%)	29 (67)	36 (44)	0.02
Medical Insurance Private, n (%) Medicare, n (%) Medicaid, n (%)	27 (63) 6 (14) 10 (23)	58 (72) 7 (9) 16 (20)	0.54
Married / Stable Companion, n (%)	25 (58)	52 (64)	0.51
History of Co-Morbid Psychiatric Disease, n (%)	17 (40)	30 (37)	0.78
History of Non-THC Illicit Substance Use[a], n (%)	6 (14)	9 (11)	0.61
History of Failed Rehabilitation Attempt, n (%)	13 (30)	20 (25)	0.51
History of Alcohol-Related Legal Issues, n (%)	13 (30)	20 (25)	0.51
Alcohol Consumption Immediately Prior to Hospitalization[b] – units/day – median (IQR)	12 (8–15)	8 (5–16)	0.16
Years of Heavy Drinking[c] – median (IQR)	12 (6–20)	17 (8–25)	0.23
Received Corticosteroids Pre-LT for AH, n (%)	29 (67)	45 (56)	0.20
Sodium at LT – mg/dL – median (IQR)	135 (133–139)	136 (134–140)	0.09
INR at LT – median (IQR)	2.0 (1.8–2.5)	2.2 (1.8–2.7)	0.20
Bilirubin at LT – mg/dL – median (IQR)	27.2 (21.3–34.6)	23.4 (15.2–32.2)	0.11
Creatinine at LT – mg/dL – median (IQR)	2.8 (1.7–4.6)	2.1 (1.3–3.5)	0.06
Mechanical Ventilation at LT, n (%)	3 (7)	14 (17)	0.11
Renal Replacement Therapy at LT, n (%)	25 (58)	47 (58)	0.99
Na-MELD Score at LT - median (IQR)	38 (36–40)	39 (35–40)	0.74

[a] 1 missing value in Yes group

[b] 2 missing values: 1 in Yes group, 1 in No group

[c] 3 missing values: 1 in Yes group, 2 in No group

Table 2.

Classification of ACCELERATE-AH Patients (n=124) in UNOS Database

Classified with AH as UNOS Diagnosis?	n (%)
Yes	43 (35)
No *	81 (65)
Coordinator unawareness of AH diagnosis code	44 (54)
Concomitant chart documentation of AH/alcoholic cirrhosis	13 (16)
Uncertainty at listing regarding AH versus acute-decompensated alcoholic cirrhosis	12 (15)
Data entry error	12 (15)

* 80 (64%) were listed as alcoholic cirrhosis; 1 (1%) as fulminant hepatic necrosis

Abbreviations: ACCELERATE-AH, American Consortium of Early Liver Transplantation for Alcoholic Hepatitis; UNOS, United Network for Organ Sharing; AH, alcoholic hepatitis

Table 3.

UNOS vs. Estimate of Actual Number and Proportions of Liver Transplants Performed for Alcoholic Hepatitis in the United States

Transplant Year	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Total Adult LTs Performed in U.S. *	5,414	5,591	5,848	6,236	6,898	7,077
LTs for AH as UNOS Listing Diagnosis	17	8	24	32	38	48
Proportion of LT for AH as UNOS Listing Diagnosis (%)	0.31	0.14	0.41	0.51	0.55	0.67
Estimate of Actual ** Number of LTs for AH	49	23	69	92	110	138
Estimate of Actual ** Proportion of LT for AH (%)	0.89	0.40	1.18	1.47	1.59	1.93

Abbreviations: LT, liver transplant; AH, alcoholic hepatitis; UNOS, United Network of Organ Sharing

* All adult LTs performed in U.S., excluding HIV and re-transplants

** Numbers calculated from sensitivity analysis assuming the same rate of alternate classification amongst all LT centers as ACCELERATE-AH sites (i.e. assuming only 35% of LT recipients for AH coded in UNOS with listing diagnosis of AH)