Original Article

The prevalence of cirrhosis in patients transplanted for severe alcohol-associated hepatitis—clarification essential

Gina Choi[1,2], Akshay Shetty[1,2], Elena G. Saab[2], Jung Yum[2], Sammy Saab[1,2]

[1]Departments of Medicine, University of California at Los Angeles, Los Angeles, CA, USA; [2]Departments of Surgery, University of California at Los Angeles, Los Angeles, CA, USA

Contributions: (I) Concept and design: G Choi, S Saab; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: EG Saab, J Yum; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sammy Saab, MD, MPH, AGAF, FAASLD. 200 Medical Plaza, Suite 214, Los Angeles, CA 90095, USA. Email: SSaab@mednet.ucla.edu.

Background: Severe alcoholic-associated hepatitis (AH) is a serious complication of excessive alcohol consumption associated with high mortality. Select patients not responding to medical treatment may require liver transplantation (LT). Patients who respond to medical treatment are generally felt to have recovered from this insult. However, it is unclear if patients with AH actually have acute-on-chronic liver failure. Thus, we studied the severity of underling liver disease in patients transplanted for AH.

Methods: This is a single-center retrospective study examining the histopathologic findings of patients with a diagnosis of AH who underwent LT between September 2019 and December 2021. We used the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia criteria to define AH. Demographic and clinical events were recorded. Laboratory and histological data were also collected. Descriptive statistics using mean with standard deviation (SD) or percentage were utilized.

Results: A total of 18 patients who met the strict definition of AH were included in this study. The mean (SD) age of the cohort was 41.3 (10.4) years and two-thirds of the patients were male. Non-Hispanic Whites attributed for 55.6% of the study group. The median (SD) duration of alcohol abstinence was 8.4 (4.5) weeks. In total, 83.3% of patients met the histologic criteria for AH, while 94.4% patients showed evidence of at least hepatocyte ballooning with Mallory-Denk bodies. Cirrhosis was noted in over three-quarters of all explants in our cohort.

Conclusions: Background cirrhosis in patients transplanted for AH is common. While severe AH is an acute process, patients needing LT are likely those with an acute on chronic process. Patients who recover without transplantation may still be at risk of hepatic decompensation and other liver related complications.

Keywords: Alcohol cirrhosis; alcohol-associated hepatitis (AH); liver transplantation (LT)

Received: 10 June 2022; Accepted: 13 November 2022; Published: 30 December 2022.
doi: 10.21037/dmr-22-41
View this article at: https://dx.doi.org/10.21037/dmr-22-41

Introduction

Alcohol related liver disease remains a growing challenge. Treatment is limited and rife with complex socioeconomic factors and controversy. Severe alcohol-associated hepatitis (AH) is a unique clinical entity in the setting of excessive alcohol use with rapid onset of jaundice with <60 days of alcohol abstinence (1). Prednisolone, the mainstay of medical treatment, has limited efficacy with significant side effects. Therefore, the mortality rate remains high, quoted as 30–50% at 28 days and 70% at 6 months (2,3). Historically, early liver transplantation (LT) for severe AH, in fact for all alcohol related liver disease, has been limited due to required 6-month abstinence prior to LT. In 2011,

Mathurin *et al.* published a study that showed early LT for severe AH refractory to medical therapy without a period of abstinence improved survival (4). As a result, the last decade has seen a change in the perception of LT for alcoholic liver disease and severe AH in light of increasing literature supporting excellent outcomes accompanied with low recidivism rates (4,5). Specifically, LT for AH has increased 5-fold from 2014 to 2019 (6). This prompts examination of our practices. Review of the literature reveals inconsistent terminology as many patients included in these studies had acute on chronic liver failure or decompensated alcohol related cirrhosis (7-10). In 2016, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia published a definition of AH to assist clinical trials (1). Despite these efforts, significant challenges remain in correctly assigning the diagnosis, particularly in retrospective studies due to the heterogeneity and ambiguity associated with the diagnosis of severe AH.

The aim of this study was to review explant pathology of patients transplanted for severe AH and assess if they had severe AH without cirrhosis or severe AH overlying cirrhosis. While severe AH is an acute process, patients needing LT are likely those with underlying cirrhosis. This cohort represents a unique group warranting early LT to improve outcomes. They also warrant special attention as we re-evaluate transplant criteria amidst the scarcity of organs. We present the following article in accordance with the STROBE reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-41/rc).

Methods

Study design

This single-center retrospective study examined inpatients referred for LT with a diagnosis of severe AH between September 2019 and December 2021. Beginning in September 2019, the criteria for LT evaluation was expanded at our center to include a diagnosis of severe AH. Prior to this date, our center denied transplant evaluation for patients with less than 6 months sobriety. Severe AH was defined according to the NIAAA Alcoholic Hepatitis Consortia inclusion criteria: onset of jaundice within 8 weeks of last alcohol use in patients with ongoing excessive alcohol consumption; aspartate aminotransferase (AST) >50 IU/L, AST/alanine aminotransferase (ALT) ratio of >1.5 and both values <400 IU/L, and total bilirubin of >3.0 mg/dL (1). Liver biopsies were not performed in our cohort. Inclusion criteria included patients over the age of 18, hospitalized with a diagnosis of severe AH who completed the LT evaluation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of University of California Los Angeles (No. 20-002295) and individual consent for this retrospective analysis was waived.

Evaluation process

The LT evaluation process includes consultations by hepatology, transplant surgery, cardiology, pulmonary, nursing, social work, psychiatry, and nutrition. Specifically, the social work assessment included review of housing, social support (our institution requires two caregivers), and the therapeutic relationship between the patient, their family, and the transplant team. Psychiatric review assessed patient's insight into their liver disease and potential risk of alcohol relapse. Hepatology assessed for clinical severity of AH, including indication for, and likelihood of response to, steroid therapy. Candidacy disagreements were resolved by consensus during a weekly multi-disciplinary patient selection committee meeting where all specialties were personally represented.

Laboratory tests included but were not limited to complete blood count, comprehensive metabolic panel, prothrombin time/international normalized ratio (INR), viral and autoimmune serologies, and urine toxicology screens. Abdominal imaging was performed with abdominal computerized tomography and/or ultrasound. Explants were reviewed by dedicated liver pathologists.

Statistical analysis

Descriptive statistics were reported using mean with standard deviation (SD) or percentage where appropriate.

Results

During the study period, a total of 18 patients with a diagnosis of severe AH underwent LT (*Table 1*). The mean (SD) age of the cohort was 41.3 (10.4) years old and two-thirds of the patients were male. Non-Hispanic and Hispanic Whites accounted for most patients transplanted. Over half of the cohort had a household income between $50,000 and $74,999 per year. Medical comorbidities were uncommon in our cohort (*Table 2*). Four (22.2%) patients had hypertension, and 1 (5.6%) patient had diabetes. The

Table 1 Demographics of patients with alcoholic hepatitis

Variables	Results
Number	18
Age (years), mean (SD)	41.3 (10.4)
Gender, n (%)	
Male	12 (66.7)
Female	6 (33.3)
Race/ethnicity, n (%)	
Non-Hispanic White	10 (55.6)
Hispanic or Latino	6 (30.0)
Non-Hispanic Asian	1 (5.6)
Non-Hispanic Black	1 (5.6)
Socioeconomic status, n (%)	
$50,000 to $74,999	10 (55.6)
$75,000 to $99,999	6 (33.3)
$100,000 to $149,000	1 (5.6)

SD, standard deviation.

Table 2 Medical co-morbidities and hepatic complication (n=18)

Variables	Number of patients (%)
Medical co-morbidities	
Hypertension	4 (22.2)
Diabetes mellitus	1 (5.6)
Obese*	9 (50.0)
Clinical liver associated complications	
Ascites	13 (72.2)
Hepatic encephalopathy	12 (66.7)
Variceal bleeding	5 (27.8)
Hemodialysis	13 (72.2)

*, BMI (kg/m^2) greater than 30. BMI, body mass index.

mean (SD) body mass index (BMI) was 31.8 (6.8) kg/m^2. Half our cohort had BMI greater than 30. In regard to overt hepatic manifestations, 13 (72.2%) patients had ascites and 12 (66.7%) patients had hepatic encephalopathy prior to LT. All patients were jaundiced. In total, 88.9% of our cohort had at least one manifestation of ascites, esophageal variceal bleeding, and/or hepatic encephalopathy. Five (27.8%) patients had a history of variceal bleeding and 72.2% were on hemodialysis at the time of LT.

Table 3 Alcohol and other substance use in patients accepted for LT (n=18)

Variables	Number of patients (%)
Duration of sobriety (days)	
<30	2 (11.1)
30–90	14 (77.8)
>90	2 (11.1)
History of DUI	
Rehabilitation programs (AA/NA)	11 (61.1)
Tobacco use	9 (50.0)
Cannabis use	4 (22.2)
Illicit substance use	2 (11.1)

LT, liver transplantation; DUI, driving under the influence; AA, alcoholic anonymous; NA, narcotic anonymous.

The mean (SD) time from referral to initiation of LT evaluation and time from evaluation to final committee decision was 3.1 (2.8) and 9.1 (6.5) days, respectively (*Table 3*). The mean (SD) time from final committee decision to LT was 11.1 (11.5) days. The median (SD) duration of alcohol abstinence was 8.4 (4.5) weeks. The duration of sobriety was <30, 30 to 90, and >90 days in 2 (11.1%), 14 (77.8%), and 2 (11.1%) patients, respectively. Eleven (61.1%) patients had a prior driving under the influence (DUI) citation, and 11 (61.1%) patients had participated in an alcohol rehabilitation program. Illicit substance use was uncommon (16.7%). Nine (50.0%) patients had a history of tobacco use, and 4 (22.2%) had a history of cannabinoid use.

Laboratory values are shown in *Table 4*. The mean (SD) AST/ALT ratio was 3.3 (1.6) and the mean (SD) model for end-stage liver disease sodium (MELD-Na) was 39.7 (4.3). All patients underwent abdominal imaging prior to LT (*Table 5*). Fifteen (83.3%) patients underwent computerized topography and 3 (16.7%) had abdominal ultrasounds. Of the 18 patients, nodular appearing liver, hepatomegaly, and splenomegaly were seen in 12 (66.7%), 11 (61.1%), and 14 (77.8%) patients, respectively. Seventeen (94.4%) patients had radiographic evidence of ascites. Both nodular liver and hepatomegaly were seen in 6 (33.3%) patients.

Fifteen (83.3%) of the explants fulfilled histologic criteria for alcoholic steatohepatitis (*Table 6*). The explant of one patient lacked steatosis hepatocyte ballooning, Mallory-

Table 4 Laboratory data time of listing LT

Laboratory	Mean (SD)
Aspartate transaminase (IU/L)	92.2 (46.7)
Alanine transaminase (IU/L)	30.7 (30.7)
AST/ALT ratio	3.3 (1.6)
Bilirubin (mg/dL)	26.1 (7.8)
Creatinine	2.6 (1.8)
Platelet count ($\times 10^9$/L)	88.7 (58.6)
Albumin (g/dL)	3.3 (0.6)
Hemoglobin (g/dL)	8.5 (2.0)
Sodium (mEq/L)	134.1 (4.1)
INR	2.7 (0.7)
MELD-Na	39.7 (4.3)

LT, liver transplantation; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD-Na, model for end-stage liver disease sodium.

Table 5 Imaging findings in patients with alcohol hepatitis transplanted* (n=18)

Image finding	Number of patients (%)
Nodular appearing liver	12 (66.7)
Hepatomegaly	11 (61.1)
Splenomegaly	14 (77.8)
Ascites	17 (94.4)
Imaging method	
Computerized topography	15 (83.3)
Ultrasound	3 (16.7)

*, hepatomegaly defined as greater than 15 cm in the midclavicular line and splenomegaly as a length greater than 12 cm.

Table 6 Pathology of explants of liver transplant recipients with alcohol hepatitis (n=18)

Pathologic finding	Number of patients (%)
Cirrhosis	14 (77.8)
Steatosis	15 (83.3)
Neutrophil infiltration	6 (33.3)
Hepatocyte ballooning	16 (88.9)
Mallory-Denk body	17 (94.4)

Denk bodies, and neutrophil infiltrates. Hepatocyte ballooning and Mallory-Denk bodies were found in the two explants, but no steatosis. Cirrhosis was noted in over three-quarters of all the explants in our cohort transplanted for severe AH. The mean (SD) weight of the explanted liver was 2,360.5 (789.2) grams. In the 4 patients without cirrhosis, 3 had bridging fibrosis and one patient had pericellular fibrosis. All 4 of the patients had steatosis, hepatocyte ballooning, and Mallory-Denk bodies.

Discussion

Since the expansion of LT criteria to include the diagnosis of severe AH at our center, there has been a significant rise in inpatient referrals for these patients (11). Similar to most tertiary care centers, outside hospital referrals remain a major source of our severe AH population, but growing awareness and acceptance in early LT for AH has led to a slow change in the referral pattern. Our study population was more diverse than recent reports with non-Hispanic Whites only attributing for 55% of the study group compared to the U.S. national 5-year trend between 2014–2019 reporting 77% of patients undergoing early LT for severe AH were non-Hispanic Whites (6). When assessing disease severity, our study population had similar severity in MELD score and Maddrey's Discriminant Function, but more patients in our cohort required renal replacement therapy at time of LT than the national average (5,12-14).

Patients at our center were diagnosed with severe AH according to NIAAA Alcoholic Hepatitis Consortia (1). Given their clinical presentation, cirrhosis was suspected in two-thirds of the study group based on imaging findings, while 89% of patient had at least one manifestation of hepatic decompensation aside from jaundice at presentation. Explant review supported this diagnosis in all but one patient, with 83% of patients meeting all histologic criteria for AH, while 94% patients showed evidence of at least hepatocyte ballooning with Mallory-Denk bodies. Histologic presence of AH in our population is higher than recently reported literature of patients transplanted for AH (5,12,13). Steatosis was missing in three patients, most likely due to their recent sobriety as steatosis is known to improve earliest, usually within a few weeks

of sobriety. Background cirrhosis in our population was noted in 75% of patients, which is lower than recently reported rates of 88–96% of patients with AH undergoing LT (5,12,13). We suspect that the variance in histologic findings is due to the difference in patient selection criteria at our center compared to the studies discussed above. In the largest multicenter study (5), only 79% of patients retrospectively met NIAAA Alcoholic Hepatitis Consortia criteria when including patients with severe disease. In addition, by nature of the multicenter design, significant heterogeneity is likely to exist with patient selection across centers in the severe AH population due to its variable clinical presentation and lack of standardized diagnostic criteria. Lastly, our center's sample size remains small and could potentially be attributing to the variance when compared to the multi-center study.

Literature from 5-decade ago reviewing retrospective liver biopsies in AH patients suggested a small percentage of patients (27%) had underlying cirrhosis, while 10–20% of patients with AH were expected to annually progress to cirrhosis (14,15). More recent single center retrospective review of patients presenting with AH from 2008 to 2013, reported that 61% patients with histologic data had underlying cirrhosis (8). In a recent histologic prognostication scoring system for AH, Alcoholic Hepatitis Histologic Score, 82% of AH patients were noted to have underlying cirrhosis (9). Comparing these to patients being evaluated in treatment studies for prednisone who had undergone liver biopsies reported that the majority of patients (86–93.7%) had underlying background cirrhosis (10,16). Similarly, high rates were noted in recent publication of patients undergoing LT for severe AH, with rates reported between 88–96% of patients with background cirrhosis (5,12,13). The later studies that focused on treatment, whether with corticosteroids or early LT, had significantly higher rates of patients with cirrhosis, and in our study, three out of the four patients who did not have cirrhosis, had advanced fibrosis on their biopsy. From a pathophysiologic standpoint, this reinforces the adage that severe AH, despite its acute clinical presentation, remains a chronic and maybe even a recurring process. The severity of AH may be dependent on the quantity of alcohol use in the patient, while the clinical course is likely dependent on the underlying hepatic reserve, where those with advanced fibrosis or cirrhosis are less likely to improve with abstinence alone and hence the majority, if not all patients have underlying cirrhosis in treatment studies. Histologic review of chronically decompensated patients with alcohol-related cirrhosis with recent alcohol use revealed features of alcohol hepatitis in up to 94% of biopsies, with moderate to severe hepatitis noted in up 27% of cases (17). This raises the question of how to differentiate between severe AH patients versus acute on chronic decompensated cirrhosis patients. Currently clinical history of prior decompensation remains the sole consideration.

Given the acute on chronic nature of severe AH, a revision in terminology should be considered for severe AH to one that is suggestive of its chronic nature, such as acute on chronic alcoholic hepatitis. The terminology should be more granular in describing this heterogeneous clinical entity to better direct care and prognosticate outcome. Should liver biopsies be considered in this patient subset who are being considered for LT? In the age of growing non-invasive testing options, consideration should be given to quantitative liver function tests to assess the hepatic reserve so we may allocate transplant resources to those who are less likely to recover without LT. In addition, multiple arguments against liver biopsy persist due to the risks associated in clinically ill patients with coagulopathy while lack of clinical improvement or failure of medical treatment currently remains the key consideration for LT evaluation among these patients.

Limitations in our study include its retrospective study design. The cohort is small, and obtained from a single center. The exact amount of alcohol use is not available. Instead, the amount of alcohol use was deemed excessive which varies from person to person. Despite these limitations, the study provides essential data to the variable presentation of severe AH. As national trends continue to evolve with growing acceptance of AH as an indication for LT, careful patient selection due to the scarcity of organs is paramount.

In conclusion, the majority of patients in our series with a clinical diagnosis of severe AH have underlying cirrhosis. Patients who recovered from their severe AH may be at risk of further liver complications from underlying cirrhosis.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-41/rc

Data Sharing Statement: Available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-41/dss

Peer Review File: Available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-41/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-41/coif). SS serves as an unpaid editorial board member of *Digestive Medicine Research* from April 2022 to March 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of University of California Los Angeles (No. 20-002295) and individual consent for this retrospective analysis was waived.

References

1. Crabb DW, Bataller R, Chalasani NP, et al. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785-90.
2. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619-28.
3. 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;71:306-33.
4. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790-800.
5. 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.
6. Cotter TG, Sandıkçı B, Paul S, et al. Liver transplantation for alcoholic hepatitis in the United States: Excellent outcomes with profound temporal and geographic variation in frequency. Am J Transplant 2021;21:1039-55.
7. Galambos JT. Natural history of alcoholic hepatitis. 3. Histological changes. Gastroenterology 1972;63:1026-35.
8. Roth NC, Saberi B, Macklin J, et al. Prediction of histologic alcoholic hepatitis based on clinical presentation limits the need for liver biopsy. Hepatol Commun 2017;1:1070-84.
9. Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146:1231-9.e1-6.
10. Mathurin P, Duchatelle V, Ramond MJ, et al. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. Gastroenterology 1996;110:1847-53.
11. Choi G, Benhammou JN, Yum JJ, et al. Barriers for Liver Transplant in Patients with Alcohol-Related Hepatitis. J Clin Exp Hepatol 2022;12:13-9.
12. Lee BP, Chen PH, Haugen C, et al. Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis. Ann Surg 2017;265:20-9.
13. Weeks SR, Sun Z, McCaul ME, et al. Liver Transplantation for Severe Alcoholic Hepatitis, Updated Lessons from the World's Largest Series. J Am Coll Surg 2018;226:549-57.
14. Lischner MW, Alexander JF, Galambos JT. Natural history of alcoholic hepatitis. I. The acute disease. Am J Dig Dis 1971;16:481-94.
15. Schwartz JM, Reinus JF. Prevalence and natural history of alcoholic liver disease. Clin Liver Dis 2012;16:659-66.
16. Ramond MJ, Poynard T, Rueff B, et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. N Engl J Med 1992;326:507-12.
17. Katoonizadeh A, Laleman W, Verslype C, et al. Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. Gut 2010;59:1561-9.

doi: 10.21037/dmr-22-41

Cite this article as: Choi G, Shetty A, Saab EG, Yum J, Saab S. The prevalence of cirrhosis in patients transplanted for severe alcohol-associated hepatitis—clarification essential. Dig Med Res 2022;5:54.