Alcohol and Alcoholism, 2018, 53(6) 716–718
doi: 10.1093/alcalc/agy056
Advance Access Publication Date: 7 August 2018
Rapid paper

Rapid paper

Early Liver Transplantation is a Viable Treatment Option in Severe Acute Alcoholic Hepatitis

Puneet Puri[1,†], George Cholankeril[2,†], Thomas Y. Myint[3], Aparna Goel[2], Shiv Kumar Sarin[4], Ann M. Harper[5], and Aijaz Ahmed[2,*]

[1]Division of Gastroenterology and Hepatology, Hunter Holmes McGuire Veterans Affairs and Virginia Commonwealth University Medical Center, Richmond, VA 23298, USA, [2]Divison of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA 94304, USA, [3]Department of Medicine, Santa Clara Valley Medical Center, San Jose, CA 95128, USA, [4]Institute of Liver and Biliary Sciences, New Delhi 110070, India, and [5]Department of Research and Data Analytics, United Network for Organ Sharing, Richmond, VA 23219, USA

*Corresponding author: Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 750 Welch Road, Suite # 210, Palo Alto, CA 94304, USA. Tel: +650-498-6091; Fax: +650-498-5692. E-mail: aijazahmed@stanford.edu

[†]Authors share first co-authorship.

Received 17 February 2018; Revised 10 July 2018; Editorial Decision 10 July 2018; Accepted 13 July 2018

Abstract

Liver transplantation is lifesaving for patients with severe acute alcoholic hepatitis (SAH) with preliminary data demonstrating favorable early post-transplant outcomes. Using the United Network for Organ Sharing database, we demonstrate that liver transplantation for SAH in the USA has steadily increased and is associated with similar 1- and 3-year post-transplant survival as well as comparable 30-day waitlist mortality to acute liver failure due to drug-induced liver injury.

INTRODUCTION

Severe acute alcoholic hepatitis (SAH) is associated with high short-term mortality and medical therapy offers no significant survival benefit (Mathurin *et al.*, 2011). In a European pilot study, Mathurin *et al.* (2011) first demonstrated that in carefully selected patients with SAH who had appropriate psycho-social support in the absence of severe comorbidities, liver transplantation provided a clear survival benefit for patients with a low risk for recidivism. Despite these encouraging results, liver transplantation for SAH in the USA remains controversial without 6 months of sobriety.

Data using the United Network for Organ Sharing (UNOS) registry have demonstrated comparable post-transplant outcomes among liver transplant (LT) recipients with SAH and alcoholic cirrhosis (Singal *et al.*, 2012). With an increasing alcoholic liver disease burden in the USA, preliminary results from institution-specific and consortium-based protocols have suggested an favorable 1-year post-transplant survival with early (<6 months of sobriety) LT surgery in patients with SAH (Im *et al.*, 2016; Cholankeril and Ahmed, 2017; Weeks *et al.*, 2018). Compared to SAH, patients with acute liver failure (ALF) due to drug-induced liver injury (DILI) have a similar acuity in the onset of presentation in the absence of underlying chronic liver disease and may also face similar psycho-social concerns prior to listing for LT surgery. However, current allocation policies in the USA do not prioritize patients with SAH as they do for ALF due to DILI. Therefore, we studied temporal trends and associated LT outcomes among patients listed with SAH and those with ALF due to DILI undergoing liver transplantation in the USA.

MATERIALS AND METHODS

Using the UNOS database, all patients listed for LT in the USA from 2011 to 2016 with a primary diagnosis of SAH or ALF-related to DILI were analyzed. Patients listed for DILI were further categorized into acetaminophen (APAP) and non-APAP cohorts. All other patients with ALF including those listed for acute viral hepatitis or unknown etiology were excluded. Demographic and clinical characteristics were compared using Chi-square test for categorical variables including gender, ethnicity, proportion with Model for End-Stage

Liver Disease (MELD) >26 and hepatic encephalopathy. Kruskal–Wallis test was utilized to compare quantitative variables including recipient age, MELD score at listing, total bilirubin, international normalized ratio for prothrombin time and time to transplant. Cumulative incidence and 95% confidence intervals (CIs) for waitlist death or mortality were calculated while accounting for competing risk of undergoing liver transplantation. Gray's method was used to test differences between multiple cohorts. Kaplan Meier survival methods with log-rank test were used for the 1- and 3-year survival following LT. All statistical analyses were performed using the SAS statistical package (version 9.4, Cary, NC). Statistical significance was met with P-value < 0.05.

RESULTS

From 2011 to 2016, 186 patients were registered (new additions) on the LT waitlist with the diagnosis of SAH. Of these SAH waitlist registrants, 67.7% (n = 126) underwent LT surgery. In comparison, 36.3% (n = 88) of these newly registered patients on the LT waitlist with APAP (n = 241) and 58.2% (n = 402) with non-APAP (n = 690) underwent LT surgery. Median time to LT was 10 days (IQR, 5–24 days) in patients with SAH. The number of LT centers increased steadily from 10 centers in 2011 to 27 centers in 2016 that registered patients with SAH to their LT waitlist. As a result, the annual number of SAH-related LT registrants increased from 14 registrants in 2011 to 58 in 2016. Patients with APAP were predominantly females and had more severe liver disease at the time of registration on the LT waitlist (Table 1). At the time of LT waitlist registration, patients with SAH had a median MELD score of 32 with nearly three-quarters of the patients having a MELD score >26. Patients with SAH also had a higher prevalence of severe hepatic encephalopathy at registration compared to APAP and non-APAP patients. Patients with APAP were noted to have the higher 7-day, 15-day and 30-day LT waitlist mortality compared to SAH (Table 1). One- and three-year post-transplant survival rates were comparable among the three cohorts (Table 2). Notably, SAH post-transplant survival rate at 3 years surpassed that of APAP and non-APAP.

DISCUSSION

Our study provides the first 'real-world' national experience on early liver transplantation in the setting of SAH in the USA. The key findings regarding early liver transplantation over 5 years relates to (i) a 4-fold increase in the listing of patients with SAH, and (ii) nearly three-times increment in the number of centers performing early liver transplantation. More importantly, early liver transplantation for SAH is associated with similar one- and three-year post-transplant survival as well as comparable 30-day waitlist mortality to ALF due to DILI.

These observations further support the recommendations of experts to refer carefully selected SAH patients with MELD score >26 who fail medical therapy for a comprehensive evaluation for early liver transplantation due to high overall mortality rate if managed conservatively (Mitchell *et al.*, 2017). Early referral of

Table 1. Comparison of clinical characteristics and waitlist mortality and post-transplant survival among liver transplant registrants listed for SAH, and APAP as well as non-APAP related acute liver failure from 2011 to 2016

Waitlist outcomes				
	SAH (n = 186)	APAP (n = 241)	Non-APAP (n = 690)	P -value
Median age [IQR]	46.6 [36–56]	34.7 [25–44]	55.2 [51–62]	<0.001
Gender (%)				<0.001
Male	121 (65.1%)	48 (19.9%)	506 (73.3%)	
Ethnicity (%)				<0.001
Caucasian	141 (75.8%)	194 (80.5%)	361 (52.3%)	
African-American	8 (4.3%)	15 (6.2%)	89 (12.9%)	
Hispanic	26 (14.0%)	21 (8.7%)	98 (14.2%)	
Other	11 (5.9%)	11 (4.6%)	142 (20.6%)	
Median MELD score, [IQR]	32 [25–40]	34 [29–41]	21 [11–31]	<0.001
MELD score >26 (%)	138 (74.2%)	206 (85.5%)	209 (30.3%)	<0.001
Median total Bilirubin, [IQR]	20.0 [6.3–29.3]	5.8 [1.8–6.4]	8.4 [1.2–11.2]	<0.001
Median INR [IQR]	2.2 [1.6–2.5]	5.0 [2.8–6.4]	2.1 [1.2–2.3]	<0.001
Severe HE (%)	35 (18.8%)	36 (14.9%)	25 (3.6%)	<0.001
7-Day waitlist mortality %, (95% CI)	1.6 (2.1–4.4)	8.0 (4.9–12.0)	1.3 (0.7–2.4)	<0.001
15-Day waitlist mortality %, (95% CI)	4.5 (2.1–8.2)	8.0 (4.9–12.0)	2.3 (1.4–3.7)	<0.001
30-Day waitlist mortality %, (95% CI)	6.9 (3.7–11.3)	11.4 (6.4–18.0)	3.3 (2.1–4.8)	0.05
LT surgeries (%)	126 (67.7%)	88 (36.3%)	402 (58.2%)	<0.001

Table 2. Comparison of post-transplant survival among liver transplant recipients listed for SAH, and APAP as well as non-APAP related acute liver failure from 2011 to 2016

Post-transplant survival				
	SAH (n = 126)	APAP (n = 88)	Non-APAP (n = 402)	P -value
Median time to transplant in days [IQR]	10 [5–24]	3 [2–4]	45 [2–260]	<0.001
1-Year post-transplant survival %, (95% CI)	89.5 (81.8–94.1)	87.7 (78.3–93.3)	90.9 (87.5–93.4)	0.59
3-Year post-transplant survival %, (95% CI)	87.8 (79.0–93.0)	77.4 (65.3–85.7)	85.9 (81.5–89.3)	0.19

appropriately selected patients is paramount as further acute decompensation due to infection or altered mental status could preclude them from a comprehensive medical and psycho-social LT evaluation. Utilization of predictive tools including the Maddrey Discriminant Function and the Lille Model Score can aid in identifying patients who are likely to spontaneous recover as well as those who have a low likelihood of responding to conventional medical therapy (Mitchell *et al.*, 2017).

In the past, strict 6-month sobriety rule often precluded patients with SAH from undergoing liver transplantation. However, many transplant centers are re-evaluating 6-month sobriety rule in a subset of patients with SAH. Our study utilizing the UNOS database revealed that in 2016 alone, 27 LT centers in the US performed early liver transplantation in patients with SAH. With alcohol use and other substance addictions being viewed as chronic medical conditions and just not self-inflicting diseases, the indication of early liver transplantation for SAH should be re-examined. Recent studies have demonstrated that new therapeutic development for SAH should focus on liver injury in the short-term and alcohol consumption in the long term (Louvet *et al.*, 2017).

Our study is limited by its retrospective design, inability to evaluate recidivism, medical therapy and onset of disease presentation. Behavioral factors including alcohol use, smoking use and clinical comorbidities including cardiovascular disease were not available in the UNOS registry. Moreover, center-specific variation in listing diagnoses for SAH and alcoholic liver disease is due to variability in centers differentiating patients with and without advanced fibrosis or cirrhosis. Requiring LT centers to report this data prior to listing could help identify the appropriate patient cohort with SAH without underlying advanced fibrosis.

While our post-transplant outcomes data are promising, these need to be confirmed in a prospective fashion, which should pave the path to further assess the role of early liver transplantation in SAH in the USA.

ACKNOWLEDGMENTS

This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the USA Government.

CONFLICT OF INTEREST

None declared.

FUNDING

P.P. is supported by National Institutes of Health grant from NIAAA K23AA021179.

AUTHORS' CONTRIBUTIONS

P.P. and G.C.—Study concept and design; acquisition of data; analysis and interpretation of data; drafting and critical revision of the manuscript; and study supervision. T.Y.M. and A.G.—Analysis and interpretation of data; and drafting and critical revision of the manuscript. S.K.S., A.M.H. and A.A.—Study concept and design; analysis and interpretation of data; drafting and critical revision of the manuscript; and study supervision.

ABBREVIATIONS

SAH	severe acute alcoholic hepatitis
APAP	acetaminophen
DILI	drug-induced liver failure
ALF	acute liver failure
LT	liver transplant
MELD	Model for End-Stage Liver Disease; non-acetaminophen
USA	United States of America
UNOS	United Network for Organ Sharing

REFERENCES

Mathurin P, Moreno C, Samuel D, *et al.* (2011) Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* **365**:1790–1800.

Singal AK, Bashar H, Anand BS, *et al.* (2012) Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology* **55**:1398–1405.

Cholankeril G, Ahmed A. (2017) Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* **16**:31418–20.

Im GY, Kim-Schluger L, Shenoy A, *et al.* (2016) Early liver transplantation for severe alcoholic hepatitis in the United States—a single-center experience. *Am J Transplant* **16**:841–9.

Weeks SR, Sun Z, McCaul ME, *et al.* (2018) Liver transplantation for severe alcoholic hepatitis, updated lessons from the World's largest series. *J Am Coll Surg* **226**:549–57.

Mitchell MC, Friedman LS, McClain CJ. (2017) Medical management of severe alcoholic hepatitis: expert review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol* **15**: 5–12.

Louvet A, Labreuche J, Artru F, *et al.* (2017) Main drivers of outcome differ between short term and long term in severe alcoholic hepatitis: a prospective study. *Hepatology* **66**:1464–73.