Gastroenterology 2015;148:547–555

CLINICAL—LIVER

Nonalcoholic Steatohepatitis Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States

Robert J. Wong,[1] Maria Aguilar,[1] Ramsey Cheung,[2,3] Ryan B. Perumpail,[2] Stephen A. Harrison,[4] Zobair M. Younossi,[5,6] and Aijaz Ahmed[2]

[1]Division of Gastroenterology and Hepatology, Alameda Health System, Highland Hospital Campus, Oakland, California; [2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, California; [3]Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; [4]Division of Gastroenterology, Department of Medicine, San Antonio Military Medical Center, Fort Sam Houston, Texas; [5]Center of Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, Virginia; and [6]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, Virginia

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this CME exercise, successful learners will be able to explain the impact of the rising prevalence of nonalcoholic steatohepatitis on liver transplant waitlist registrations in the US.

See Covering the Cover synopsis on page 459; see editorial on page 493.

BACKGROUND & AIMS: Nonalcoholic steatohepatitis (NASH) has been predicted to become the leading indication for liver transplantation (LT) in the United States. However, few studies have evaluated changes in the etiology of liver diseases among patients awaiting LT, and none have focused on the effects of NASH on liver transplant waitlists in the United States. **METHODS:** We collected data from the United Network for Organ Sharing and Organ Procurement and Transplantation Network registry from 2004 through 2013, on liver transplant waitlist registrants with hepatitis C virus (HCV) infection, NASH, alcoholic liver disease (ALD), or a combination of HCV infection and ALD. We compared differences in survival within 90 days of registration (90-day survival) and probability of LT among patients with different diseases using Kaplan-Meier and multivariate logistic regression models. **RESULTS:** Between 2004 and 2013, new waitlist registrants with NASH increased by 170% (from 804 to 2174), with ALD increased by 45% (from 1400 to 2024), and with HCV increased by 14% (from 2887 to 3291); registrants with HCV and ALD decreased by 9% (from 880 to 803). In 2013, NASH became the second-leading disease among liver transplant waitlist registrants, after HCV. Patients with ALD had a significantly higher mean Model for End-Stage Liver Disease score at time of waitlist registration than other registrants. However, after multivariate adjustment, patients with ALD were less likely to die within 90 days when compared with patients with NASH (odds ratio [OR] = 0.77; 95% confidence interval [CI]: 0.67–0.89; $P < .001$); patients with HCV infection or HCV and ALD had similar odds for 90-day survival compared with NASH patients. Compared with patients with NASH, patients with HCV (OR = 1.45; 95% CI: 1.35–1.55; $P < .001$), ALD (OR = 1.15; 95% CI: 1.06–1.24; $P < .001$), or HCV and ALD (OR = 1.29; 95% CI: 1.18–1.42; $P < .001$) had higher odds for 90-day survival. **CONCLUSIONS:** Based on data from US adult LT databases, since 2004 the number of adults with NASH awaiting LTs has almost tripled. However, patients with NASH are less likely to undergo LT and less likely to survive for 90 days on the waitlist than patients with HCV, ALD, or HCV and ALD.

Keywords: Fatty Liver; UNOS/OPTN; Waitlist Mortality; MELD.

The rising prevalence of nonalcoholic fatty liver disease is a direct consequence of the worldwide obesity epidemic and the associated increase in the prevalence of diabetes and metabolic syndrome.[1–5] Hepatic steatosis in association with inflammation and ballooning defines nonalcoholic steatohepatitis (NASH), which can progress to increasing stages of fibrosis and ultimately cirrhosis and cirrhosis-related complications such as hepatocellular carcinoma (HCC).[5–8]

Despite the steady rise in the prevalence of NASH, hepatitis C virus (HCV) remains the leading etiology of chronic liver disease among HCC and non-HCC patients undergoing liver transplantation (LT).[9–12] A recent study utilizing data from the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) registry focused specifically on HCC patients undergoing LT in the United States and demonstrated that although HCV remains the leading etiology of HCC among liver transplant

Abbreviations used in this paper: **ALD, alcoholic liver disease; BMI, body mass index; CC, cryptogenic cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplantation; MELD, Model for End Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; UNOS, United Network for Organ Sharing.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.11.039

recipients in 2012, NASH was the most rapidly rising etiology, increasing 4-fold from 2002 to 2012.[10] Using data from the Scientific Registry of Transplant Recipients from 2001 to 2009, Charlton et al[9] demonstrated that NASH was the third leading indication for LT in the United States and predicted that NASH would become the leading indication for LT in the next 10 to 20 years.

Although analyses of LT trends can offer important insight into the changing clinical characteristics of liver transplant recipients, an evaluation of liver transplant waitlist trends can provide an earlier glimpse of the changing LT epidemiology. For example, Kim et al[13] utilized liver transplant waitlist data from the UNOS/OPTN registry to demonstrate the decreasing incidence of hepatitis B virus–related hepatic decompensation that resulted from widespread application of hepatitis B virus antiviral therapy. More recently, Biggins et al[14] also utilized the UNOS/OPTN registry data to demonstrate the increasing burden of HCV among an aging population on liver transplant waitlists in the United States. However, no study to date has specifically evaluated the impact of NASH on liver transplant waitlist registrations in the United States. Using the most recent UNOS/OPTN data from 2004 to 2013, we retrospectively evaluated trends in adult liver transplant waitlist registrations in the United States, with a focus on NASH-related chronic liver disease.

Methods

Study Population

Adult patients (aged 18 years and older) with chronic liver disease who were registered on the waitlist for liver transplants in the United States from 2004 to 2013 were evaluated using UNOS/OPTN registry data. The etiology of chronic liver disease leading to waitlist registration was determined based on disease diagnosis coding in UNOS/OPTN. Among patients with HCC, the underlying liver disease was determined based on the secondary disease diagnosis codes provided. Patients with both HCV and alcoholic liver disease (ALD) listed as etiologies were grouped into a separate category of combined HCV/ALD. Using methods similar to earlier studies, we created a modified NASH category that included patients given a diagnosis of NASH in addition to obese (body mass index >30 kg/m^2) patients with cryptogenic cirrhosis (CC).[9,10] Our current analysis focused on the top 4 leading etiologies of chronic liver disease among liver transplant waitlist registrants: HCV, ALD, NASH, and HCV/ALD.

Statistical Analysis

Clinical and demographic characteristics among liver transplant waitlist registrants were stratified by etiology of chronic liver disease; categorical variables were presented as proportions and frequencies and continuous variables were presented as mean ± SD or median and range as appropriate. Comparisons between groups utilized χ^2 testing for categorical variables and analysis of variance for continuous variables. Etiology-specific annual trends in new liver transplant waitlist registrations were calculated. The probability of 90-day waitlist survival and probability of receiving liver transplant at 90 days among waitlisted patients were evaluated using Kaplan–Meier methods and log-rank testing. Univariate and multivariate logistic regression models were utilized to evaluate the crude and adjusted probability of 90-day waitlist survival and probability of receiving liver transplant within 90 days on the waitlist. Forward stepwise regression methods included variables that were biologically significant (eg, age and sex) and those that demonstrated significant associations in the univariate models ($P < .10$). The final multivariate model was adjusted for sex, age, race/ethnicity, etiology of liver disease, presence of diabetes, Model for End Stage Liver Disease (MELD) score, ascites, and concurrent HCC. Statistical significance was met with a 2-tailed P value $<.05$. All statistical analyses were performed using the Stata statistical package (version 10, Stata Corp, College Station, TX). This study was exempt from Institutional Review Board after Stanford University Medical Center Institutional Review Board review.

Results

Overview

From 2004 to 2013, the overall 4 leading etiologies of chronic liver disease among adult liver transplant waitlist registrants were HCV, ALD, NASH, and HCV/ALD, accounting for 35.2%, 18.3%, 15.8%, and 9.7% of liver transplant waitlist registrants, respectively.

Characteristics of Study Cohort

Compared with patients with NASH, there was a significantly greater proportion of men among patients with HCV (69.8%, n = 21,620), ALD (76.5%, n = 12,338), and HCV/ALD (83.1%, n = 7,111) (Table 1). Waitlist patients with NASH were older at the time of waitlist registration when compared with patients with HCV (58.0 ± 8.7 years vs 55.0 ± 7.1 years; $P < .001$) or ALD (58.0 ± 8.7 years vs 54.2 ± 8.7 years; $P < .001$). NASH patients also had significantly higher body mass index (BMI) when compared with HCV patients (median, 31.6 vs 28.0 kg/m^2; $P < .001$) or ALD patients (31.6 vs 27.6 kg/m^2; $P < .001$). Although the majority of liver transplant waitlist patients were non-Hispanic white, there was a greater proportion of blacks among the HCV and HCV/ALD groups and a greater proportion of Hispanics among the HCV/ALD group (Table 1). HCV patients on the liver transplant waitlist had the highest proportion of concurrent HCC (24.6%, n = 7632), followed by patients with NASH (21.0%, n = 2925), HCV/ALD (13.2%, n = 1128), and ALD (7.5%, n = 1212) (Table 1). Compared with all other patients, ALD patients had the highest MELD score at time of liver transplant waitlist registration, and one of the highest proportions of ascites and hepatic encephalopathy at time of waitlist registration. ALD patients on the waitlist had the highest serum creatinine, and the lowest creatinine was seen among HCV patients. However, the lowest glomerular filtration rate was noted in NASH patients (55.2 ± 20.0 mL/min/1.73 m^2) (Table 1). Patients with NASH and HCV had relatively lower prevalence of hepatic encephalopathy at time of waitlist registration. Compared with all other patients, NASH patients had significantly higher proportion of concurrent diabetes mellitus (46.3% [NASH] vs 21.3%