Nonalcoholic Steatohepatitis Is the Most Rapidly Growing Indication for Liver Transplantation in Patients With Hepatocellular Carcinoma in the U.S.

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Nonalcoholic steatohepatitis (NASH) is currently the third leading indication for liver transplantation (LT) in the U.S. and is predicted to become the leading indication for LT in the near future. The trends in NASH-related hepatocellular carcinoma (HCC) among LT recipients in the U.S. remain undefined. We performed a retrospective cohort study to evaluate trends in the etiology of HCC among adult LT recipients in the U.S. from 2002 to 2012, using national data from the United Network for Organ Sharing registry. From 2002-2012, there were 61,868 adults who underwent LT in the U.S., including 10,061 patients with HCC. The total number and proportion of HCC LT recipients demonstrated a significant increase following the implementation of the Model for Endstage Liver Disease (MELD) scoring system in 2002 (3.3%, n = 143 in 2000 versus 12.2%, n = 714 in 2005 versus 23.3%, n = 1336 in 2012). The proportion of hepatitis C virus (HCV)-related HCC increased steadily from 2002 to 2012, and HCV remained the leading etiology of HCC throughout the MELD era (43.4% in 2002 versus 46.3% in 2007 versus 49.9% in 2012). NASH-related HCC also increased significantly, and NASH is the second leading etiology of HCC-related LT (8.3% in 2002 versus 10.3% in 2007 versus 13.5% in 2012). From 2002 to 2012, the number of patients undergoing LT for HCC secondary to NASH increased by nearly 4-fold, and the number of LT patients with HCC secondary to HCV increased by 2-fold. Conclusion: NASH is the second leading etiology of HCC leading to LT in the U.S. More important, NASH is currently the most rapidly growing indication for LT in patients with HCC in the U.S. (Hepatology 2014;59:2188-2195)

Hepatocellular carcinoma (HCC) is the sixth leading cause of cancer and the second leading cause of cancer-related deaths worldwide.1 In the U.S, HCC is the fifth and ninth most common cause of cancer-related deaths among men and women, respectively, with nearly 20,000 new cases diagnosed each year.2,3 Despite improvements in HCC screening and treatment, overall 5-year survival remains poor at less than 20%.2,3 Chronic liver disease and cirrhosis secondary to hepatitis B virus (HBV), hepatitis C virus (HCV), and alcoholic liver disease (ALD) are the leading causes of HCC.4 However, several studies have reported on the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) and project that nonalcoholic steatohepatitis (NASH), a subset of NAFLD with progressive histologic liver damage, will become the leading indication for liver transplantation (LT) in the U.S.5-7

The incidence of HCC among patients with NASH is not clearly defined. While NASH is associated with increased risk of HCC development, several studies have indicated that the overall risk of HCC among patients with NASH-related cirrhosis is significantly lower than the risk among patients with cirrhosis due to viral etiologies.5-8

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; CC, cryptogenic cirrhosis; CLD, cholestatic liver diseases; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for Endstage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; UNOS/OPTN, United Network for Organ Sharing and Organ Procurement and Transplantation Network.

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secondary to other forms of chronic liver disease, such as HBV or HCV. For example, Ascha et al. reported an HCC incidence of 2.6%/year among patients with NASH-related cirrhosis compared with 4.0%/year among patients with HCV-related cirrhosis. Despite the low incidence of HCC among NASH patients, the increasing prevalence of NASH resulting from the obesity epidemic in the U.S. may in fact lead to NASH becoming a leading indication for LT and a leading cause of HCC.

Understanding the impact of NASH on HCC patients requiring LT is especially important given the significant mortality and morbidity associated with HCC. In addition, the current shortage of organs available for LT emphasize the need to better understand LT trends that would allow targeted research and interventions aimed at optimizing the allocation of donor allografts among patients with chronic liver diseases. The burden of NASH among HCC patients requiring LT is not well defined. Our study uses a large national LT registry in the U.S. to evaluate recent trends in patients with HCC undergoing LT, to investigate the changing epidemiology of HCC and the impact of NASH among this cohort.

Materials and Methods

Study Population. The study included 61,868 adult patients (18 years or older) who underwent LT in the U.S. from the 2002-2012 United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) database. Among this cohort, 10,061 patients underwent LT for primary HCC. The diagnosis of HCC was based on primary or secondary diagnosis coding of LT recipients in UNOS. Other liver malignancies that were not primary HCC were excluded. The underlying etiology of HCC was determined based on additional primary or secondary diagnosis coding of liver disease etiology among patients with HCC undergoing LT. Underlying liver disease etiologies of HCC were categorized by UNOS as acute (acute or fulminant liver disease) or chronic. Chronic liver disease etiologies included HBV, HCV, NASH, cryptogenic cirrhosis (CC), cholestatic liver diseases (CLD) (i.e., primary biliary cirrhosis and primary sclerosing cholangitis), autoimmune hepatitis (AIH), ALD, ALD/HCV (i.e., concurrent ALD and HCV), metabolic diseases (e.g., Wilson's disease, hemochromatosis, and alpha-1 antitrypsin disease), and unknown. HCC patients with unknown etiology did not have one of the aforementioned chronic liver disease etiologies listed as a diagnosis.

A significant proportion of CC patients are believed to represent undiagnosed NASH patients. Previous studies have included CC patients into the NASH category. For example, Charlton et al. evaluated long-term trends in the frequency and outcomes of NASH patients undergoing LT in the U.S. and recategorized NASH using two different methods: NASH plus 50% of CC patients and NASH plus obese (body mass index [BMI] >30 kg/m²) CC patients. Our study employed similar methods to more accurately ascertain the prevalence of NASH diagnoses among our cohort. We created a modified NASH category that included LT recipients who were given a primary or secondary diagnosis of NASH plus obese patients with primary or secondary diagnosis of CC and unknown. The Model for Endstage Liver Disease (MELD) scoring system was implemented in 2002 as an objective method of prioritizing patients waiting for LT.

Statistical Analysis. Our study evaluated trends in HCC-related LT in the U.S. with a focus on changes in the underlying etiology of HCC among LT recipients. Frequencies of overall adult LT and HCC-related LT were reported for 1995, 1997, 2000, 2001, and 2002-2012 MELD era to demonstrate the significant rise in HCC-related LT following the implementation of the MELD scoring system in 2002. Frequencies of NASH, obese CC, and obese unknown etiology patients were calculated to demonstrate the method for creating our modified NASH category. The proportion of obese cryptogenic patients and obese unknown etiology patients included in the modified NASH category was calculated by dividing each obese cohort by the total number of patients in each cohort (e.g., cryptogenic and unknown). Trends in the distribution of underlying HCC etiology among HCC-related LT recipients were evaluated from 2002 to
2012. Frequencies of HCC etiologies were reported for each year, and the proportion of HCC that each etiology represented was calculated by dividing each etiology by the total number of HCC for each year. Nonparametric trend analyses were performed for each HCC etiology to determine whether there was a significant change in the proportion represented with time. Clinical and demographic characteristics were compared between NASH-related HCC and non-NASH-related HCC using chi-square testing for categorical variables and Student t test for continuous variables. All statistical analyses were performed using the Stata statistical package (v. 10, College Station, TX).

Results

From 2002-2012, there were 61,868 adult LT recipients in the U.S., including 10,061 HCC patients that received LT. The total number and proportion of HCC-related LT recipients demonstrated a significant increase following the implementation of the MELD system in 2002 (2.1%, n = 73 in 1995 versus 9.9%, n = 472 in 2002 versus 17.3%, n = 1013 in 2007 versus 23.3%, n = 1336 in 2012) (Table 1).

The etiologies of liver disease among HCC-related LT recipients are presented in Table 1. Rates of HCV patients with HCC (HCV-HCC) undergoing LT increased steadily over the MELD era and HCV remained the leading etiology of HCC among LT recipients in 2012 (n = 205/472 [43.4%] in 2002 versus n = 471/1013 [46.3%] in 2007 versus n = 666/1336 [49.9%] in 2012) (Table 1). Significant increases were also noted among NASH-related HCC (n = 0/472 [0%] in 2002 versus n = 41/1013 [4.0%] in 2007 versus n = 81/1336 [6.0%] in 2012) and among concurrent alcoholic liver disease and HCV-related HCC (ALD/HCV-HCC) (n = 23/472 [4.9%] in 2002 versus n = 66/1013 [6.5%] in 2007 versus n = 85/1336 [6.4%] in 2012), whereas HBV-related HCC demonstrated a significant decrease (n = 48/472 [10.2%] in 2002 versus n = 84/1013 [8.3%] in 2007 versus n = 61/1336 [4.6%] in 2012) (Table 1). The other etiologies of liver disease of HCC-related LT recipients did not change significantly during the MELD era.

A substantial proportion of CC patients are believed to represent undiagnosed NASH. As a result, the true frequency and proportion of NASH as an etiology of HCC among our cohort is likely to be underrepresented when only including patients who were specifically coded with NASH diagnoses. Using methods employed by Charlton et al.,5 we created a modified NASH category by combining NASH patients with obese CC and obese unknown etiology patients (Table 2). The frequency of obesity (BMI > 30 kg/m²) was 25.0%-50.0% among CC patients and 19.5%-38.8% among patients with unknown etiology (Table 2). This is similar to Charlton et al.,5 who found obesity rates of 31.4%-43.4% among CC patients. This modified NASH category as an etiology of HCC-related LT recipients did not change significantly during the MELD era.
The second leading etiology of HCC-related LT in 2012 (8.3% in 2002 versus 10.3% in 2007 versus 13.5% in 2012).

Figure 1 presents the changing epidemiology of HCC-related LT recipients from 2002-2003 to 2007-2008 to 2011-2012. While HCV remained the leading etiology of liver disease in HCC-related LT recipients in all periods, the proportion of HCC-related LT recipients with modified NASH continued to increase and became the second leading etiology of HCC-related LT (Fig. 1). Furthermore, with time the proportion of obese CC and obese unknown etiology patients decreased while patients coded as NASH increased, reflecting a marked increase in the proportion of patients with modified NASH who were accurately coded with a diagnosis of NASH in UNOS (Fig. 1).

Figure 2 presents the annual trend in the total number of HCC patients receiving LT in the MELD era and the associated liver disease etiology of HCC during this time. Recognizing that the risk of NASH also increases among overweight individuals with BMI >25, we included an additional category of modified NASH that includes overweight patients with CC and unknown etiologies of HCC referred to as modified NASH (BMI >30 kg/m²) in Fig. 2. We distinguished this from our original modified NASH category that used obese patients with CC and unknown etiologies of HCC (modified NASH [BMI >30]). While HCV remained the leading etiology of HCC during the entire MELD era, modified NASH (BMI >30) emerged as the second leading etiology of HCC beginning in 2006, whereas modified NASH (BMI >25) was already the second leading etiology of HCC in 2002. For the entire MELD era from 2002 to 2012, the number of patients with HCC-related LT increased by 364% for modified NASH (BMI >30) and increased by 263% for modified NASH (BMI >25), whereas the number of patients with HCC-related LT secondary to HCV increased by 225% (Fig. 2).

We performed a subanalysis of NASH-related HCC trends stratified by sex (male versus female), age (age >60 years versus age <60 years), BMI (BMI >30 versus BMI <30), and diabetes status. Even after adjusting for these additional variables, the increasing trend in NASH-related HCC persisted. Comparisons of clinical and demographic characteristics between NASH-related HCC and non-NASH-related HCC demonstrated significant differences (Table 3). Non-NASH-related HCC patients were more likely to be men (79.2% versus 70.6%, P < 0.001) and were younger at time of LT (57.2 ± 7.6 versus 59.3 ± 7.3, P < 0.001). NASH-related patients had significantly higher BMI (33.6 ± 4.3 versus 27.3 ± 4.9, P < 0.001) and higher rates of diabetes (42.8% versus 20.8%, P < 0.001). There were also significantly more non-Hispanic whites in the NASH-related HCC group and more Asians in the non-NASH-related HCC group (Table 3).

### Discussion

Since the implementation of the MELD scoring system for prioritization of patients for LT, the number and proportion of HCC patients undergoing LT has increased significantly. HCV remains the leading etiology of HCC-related LT, but beginning in 2006 NASH has become the second leading etiology of HCC-related LT. Using a modified NASH category that more accurately reflects the true prevalence of NASH, our current study demonstrates that HCC-related LT secondary to NASH has experienced a
nearly 4-fold increase since 2002, whereas HCC-related LT secondary to HCV increased by 2-fold. In 2012, HCV and NASH remain the two leading etiologies among HCC patients undergoing LT in the U.S.

The increasing prevalence of obesity in the U.S. is a major public health concern, and several studies have reported on the concurrent obesity-related increase in the prevalence of NAFLD and NASH. A recent study by Charlton et al. demonstrated a significant increase in the proportion of patients undergoing LT for NASH from 1.2% in 2001 to 9.7% in 2009, making NASH the third leading indication for LT. However, the true prevalence of NASH among LT recipients is likely to be significantly underestimated. Previous studies have suggested that a significant proportion of patients with CC may in fact have undiagnosed NASH.

CC patients have clinical features that are very similar to...
NASH patients, and the rate of posttransplant development of NASH among CC patients is similar to that seen among those patients who were assigned a pretransplant diagnosis of NASH.28,29 Furthermore, NASH as a diagnostic category in transplant center databases was implemented in 2001 and may have been underutilized in the earlier years after its availability.5,23 In a comprehensive study evaluating the frequency and outcomes of NASH-related LT in the U.S., Charlton et al. used two different methods to better capture the true prevalence of NASH among the LT recipients: 50% of patients with CC were included in the NASH group and obese (BMI >30 kg/m²) patients with CC were included in the NASH group.5 The latter method resulted in the inclusion of 31.4%-43.4% of CC patients into the NASH group. Our current study used similar methods and included 25.0%-50.0% of CC patients and 19.5%-38.8% of patients with unknown HCC etiology.

The association of NASH with development of HCC is well known. However, compared to other liver diseases such as HCV, the incidence of HCC among patients with NASH is significantly lower. In a large single-center study inclusive of 510 patients with cirrhosis, Ascha et al.9 reported a 2.6% annual incidence of HCC among NASH patients and 4.0% annual incidence among HCV patients. This significantly

![Fig. 2. Annual trends in HCC patients receiving liver transplantation stratified by leading liver disease etiologies in the MELD era.](image-url)

<p>| Table 3. Clinical and Demographic Characteristics of Non-NASH-Related HCC vs. NASH-Related HCC |
|------------------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Non-NASH HCC</th>
<th>NASH HCC</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>79.2% 7,066</td>
<td>70.6% 807</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>57.2 ± 7.6</td>
<td>59.3 ± 7.3</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (mean ± SD)</td>
<td>27.3 ± 4.9</td>
<td>33.6 ± 4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Non-Hispanic White</td>
<td>63.3% 5,582</td>
<td>75.3% 852</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>10.3% 907</td>
<td>6.4% 72</td>
<td></td>
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<tr>
<td>Asian</td>
<td>12.5% 1,098</td>
<td>2.5% 28</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13.9% 1,227</td>
<td>15.9% 180</td>
<td></td>
</tr>
<tr>
<td>MELD (mean ± SD)</td>
<td>13.7 ± 7.4</td>
<td>14.0 ± 7.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.6% 1,743</td>
<td>42.8% 450</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>3.2% 88</td>
<td>5.3% 13</td>
<td>0.08</td>
</tr>
<tr>
<td>Ascites</td>
<td>55.0% 4,900</td>
<td>59.1% 672</td>
<td>0.01</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>39.8% 3,541</td>
<td>41.5% 472</td>
<td>0.27</td>
</tr>
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</table>

Comparisons are presented as proportion (%) and frequency (n) unless otherwise indicated.

NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; BMI, body mass index; MELD, model for endstage liver disease.
lower rate of HCC development among NASH patients has been reported in several additional studies.\textsuperscript{10-17} Despite the low incidence of HCC among NASH patients, the overall increasing prevalence of NAFLD will undoubtedly lead to increased prevalence of NASH and a subsequent increased prevalence of NASH-related HCC. Our study is the first to demonstrate that NASH is the second leading etiology of HCC among LT recipients in the U.S. While HCV currently remains the leading etiology of HCC among LT recipients, the advent of more effective antiviral therapy for HCV may lead to a decline in HCV-related HCC in the near future. The increasing prevalence of obesity and NAFLD have already led to predictions that NASH will be the leading indication for LT in the next 10-20 years, and it may follow that NASH will also become the leading etiology of HCC.

Our study used a large population-based LT registry in the U.S., the 2002-2012 UNOS database. The inclusion of 11 years of data from the MELD era allowed for consistency of analyses as well as the ability to evaluate long-term trends in HCC-related LT. However, notable limitations existed that result from the use of large registry type data. The assignment of HCC as a primary or secondary diagnosis among LT recipients is not subject to any specific confirmatory mechanism, and thus errors in miscoding of HCC may occur. The same is true with respect to identifying the underlying etiology of HCC-specific etiologies selected from a drop-down menu without any need for confirmatory cross-checking. However, there is no specific reason to expect that any errors in diagnostic coding would be differential, and thus, if any nondifferential misclassification were to occur, this would bias our conclusions towards the null hypothesis. It has also been suggested that some degree of ascertainment bias may contribute to the increasing frequency of NASH as an indication for LT in the U.S. since the availability of NASH as a diagnostic category in 2001.\textsuperscript{5} In addition, the increasing trend in NASH as a diagnosis of liver disease may in part be affected by the increasing recognition of this etiology and the ability to document this in medical diagnosis coding systems. While our study captured the predominant etiology of HCC using the availability of UNOS coding, it is also possible that some patients may have had more than one concurrent chronic liver disease contributing to HCC (e.g., HCV and NASH). The limitation of the UNOS diagnosis coding system prevented the inclusion of coexisting chronic liver diseases among HCC patients undergoing LT. However, using obesity (BMI \textgreater{} 30 kg/m\textsuperscript{2}) as a surrogate of NASH, we found significant rates of obesity among HCV-related HCC (30.6\%) and ALD-related HCC (36.5\%), and lower rates among HBV-related HCC (12.5\%). Nevertheless, we recognize that solely using obesity as a surrogate of NASH has significant limitations. Additional potential biases need to be considered when evaluating our study outcomes. In our study, we used a modified NASH category that included HCC-related LT patients who were specifically coded with a primary or secondary diagnosis of NASH in addition to obese patients (BMI \textgreater{} 30 kg/m\textsuperscript{2}) with CC and unknown etiology of HCC. While this approach may have included patients without “true” NASH, this method is similar to that employed by Charlton et al.,\textsuperscript{5} and likely still represents an underestimation of NASH rather than an overestimation. Furthermore, while the prevalence of NASH is higher among obese patients, NASH does occur in patients with overweight and normal BMI categories, which further raises the possibility that our methods actually underestimate the prevalence of NASH among this cohort. For this reason, we included in Fig. 2 an additional analysis that included overweight patients with CC and unknown etiologies of HCC. In addition, our methods using BMI cutoffs in defining our modified NASH category is subject to potential selection bias, especially if overweight or obesity itself is associated with increased HCC risk. Racial/ethnic differences in the impact of BMI on risk of NASH, especially among Asians, where overweight and obesity may be more accurately categorized at lower cutoffs compared to other race groups, may have impacted our estimation of NASH diagnoses. In our study, HCC patients with unknown etiology did not have any other chronic liver disease as a primary or secondary diagnosis, and thus were presumed to be cryptogenic. Despite these limitations, the use of a large national LT database using methods consistent with prior studies adds considerable strength and value to our analysis of longitudinal trends in HCC-related LT in the U.S.

In summary, the frequency and proportion of HCC patients receiving LT in the U.S. has increased significantly following the implementation of the MELD scoring system in 2002. During the MELD era, HCV remains the leading etiology of HCC among LT recipients. However, the prevalence of NASH-related HCC has increased nearly 4-fold during the MELD era, and NASH has become the second leading etiology of HCC among LT recipients since 2006. The increasing prevalence of obesity and obesity-related diseases is a major public health concern, and NASH will soon become the leading indication for LT and the leading etiology of HCC in the U.S. Additional research is needed to better understand the impact of obesity on the development and natural history of NAFLD, NASH, and NASH-related HCC. Interventions targeted at reducing the obesity epidemic will have an
impact in reducing the overall prevalence of NAFLD, which will lead to decreased rates of NASH-related HCC and NASH-related hepatic decompensation requiring LT.

References