Differential Impact of Age Among Liver Transplant Candidates With and Without Hepatocellular Carcinoma

Giuseppe Cullaro, Jessica B. Rubin, Neil Mehta, and Jennifer C. Lai

Division of Gastroenterology and Hepatology, Department of Medicine, University of California, San Francisco, San Francisco, CA

Hepatocellular carcinoma (HCC) is the fastest-rising cause of cancer-related mortality in the United States and is a leading indication for liver transplantation (LT). Changes have been noted in the age of the population with chronic liver disease, but how this change affects patients with HCC is unknown. This study aims to characterize trends and transplant-associated outcomes among patients ≥65 years old listed for LT with HCC. Using the United Network for Organ Sharing database, we analyzed all patients ≥18 years old listed for LT during 2003–2017 in the United States in 2 groups (<65 or ≥65 years). Time trends between HCC and non-HCC patients were compared and stratified by disease etiology. Competing-risks and Cox proportional hazards regressions associated HCC and age with wait-list and post-LT survival. There were 161,724 LT candidates included: 14% were ≥65 years old at listing and 25% had HCC. The proportion of patients ≥65 years old rose significantly faster among those with HCC, as compared with those without HCC (Δ = 0.80; P < 0.001). Age ≥65 years was significantly associated with both wait-list mortality (adjusted subhazard ratio, 1.51; 95% confidence interval [CI], 1.40–1.64) and post-LT mortality (adjusted hazard ratio, 1.50; 95% CI, 1.41–1.60) in the multivariate analysis. There were significant interactions between age and HCC on both wait-list (P < 0.001) and post-LT mortality (P = 0.04), suggesting that older age does not impact patients with HCC as much as patients without HCC. The proportion of older adults with HCC listed for LT has nearly tripled from 2003 to 2017, and the rapidly growing population of older adults with HCC may provide an opportunity to expand LT access without compromising outcomes.

Liver Transplantation 26:349–358 2020 AASLD.
Received July 26, 2019; accepted October 7, 2019.

The burden of hepatocellular carcinoma (HCC) is rising rapidly with an incidence that has nearly tripled in the United States over the past several decades.(1–4) As a result, HCC has become the fastest-growing cause of cancer-related mortality in the United States.(2,3) These trends have significantly impacted the liver transplantation (LT) population: Not only has the proportion of LT recipients with HCC increased more than 6-fold over the last 2 decades,(5,6) but HCC currently represents the most common indication for LT in the United States.(7)

The rising incidence of HCC is believed to be due to an increased prevalence of cirrhosis in the United States—the biggest risk factor for HCC—among those with chronic hepatitis C virus (HCV) as well as the rapid emergence of the obesity-related liver disease known as nonalcoholic fatty liver disease (NAFLD). It is well documented that these changes in liver disease etiology have resulted in an older LT population in the United States.(8–10) However, it is not known how these evolving demographics have specifically impacted patients with HCC, which may have important implications for HCC-related morbidity and mortality. In the present study, we aimed to characterize aging trends in the HCC population and their impact on transplant-related outcomes among HCC patients.

Abbreviations: aSHR, adjusted subhazard ratio; CI, confidence interval; DAA, direct-acting antiviral; DRI, donor risk index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IQR, interquartile range; KPS, Karnofsky Performance Status; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; SHR, subhazard ratio; UNOS, United Network for Organ Sharing.

Address reprint requests to Jennifer C. Lai, M.D., M.B.A., Division of Gastroenterology and Hepatology, Department of Medicine, University of California, San Francisco, 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143. Telephone: 415-476-2777; FAX: 415-476-0659; E-mail: jennifer.lai@usf.edu
Patients and Methods

All adult (≥18 years) patients listed for LT in the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) registry from January 1, 2003 through December 31, 2017 were evaluated for inclusion in this study.

RECIPIENT AND DONOR CHARACTERISTICS

Data used in this analysis were obtained from the UNOS/OPTN registry as of April 6, 2018. The Model for End-Stage Liver Disease (MELD) score at listing and at transplant or wait-list removal was calculated and capped at 6 and 40.\(^\text{(11)}\)\(^\text{(12)}\) Because serum sodium was not routinely collected in the UNOS/OPTN database until 2014, we used MELD instead of MELD–sodium scores in this study looking at longterm trends. Ascites and hepatic encephalopathy were considered present if they were recorded at either listing or wait-list removal/transplant. Liver donor characteristics included those used to calculate the donor risk index (DRI), which is a summary metric to quantify liver allograft quality.\(^\text{(13)}\)

AGE GROUPS

Older patients were defined as those ≥65 years at the time of listing, whereas younger patients were defined as those <65 years at listing. An age of 65 years is a commonly used cutoff for older adults in the medical and LT literature.\(^\text{(9,14,15)}\)

HCC AND CIRRHOSIS ETIOLOGY

Patients were categorized as having HCC if any of the following were true:

1. They were granted HCC exception points.
2. Their primary or secondary diagnosis at listing or transplant was HCC.
3. They were designated as ever having had HCC.

Listing diagnoses were grouped into the following common diagnostic categories: HCV, nonalcoholic steatohepatitis (NASH; including cryptogenic cirrhosis), alcohol-related cirrhosis, autoimmune etiologies (including primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis), and other etiologies of cirrhosis (any other listing code that met the inclusion criteria). For the time trend analyses, these diagnoses were further grouped into HCV, NASH, and non-HCV/ non-NASH, which included all other categories.

OUTCOMES

To better understand the impact of an aging LT cohort, we analyzed the impact of age in those with and without HCC on 2 outcomes:

1. Wait-list mortality, defined as the combined outcome of death before transplant or removal for being too sick for transplant.
2. Post-LT mortality.

For wait-list mortality, patient follow-up began on the date of listing for LT and ended at the time of death, removal from the waiting list, or transplant. Patients removed from the waiting list for recovery of hepatic function, social reasons, or living donor LT were censored at the time of their removal. For post-transplant mortality, follow-up time was defined as the time between the date of transplant and the date of death or last follow-up. Patients remaining alive at last follow-up were censored at that time.
STATISTICAL ANALYSIS

Demographics Analysis

Categorical variables were compared between age and HCC groups by the chi-square test. Continuous variables were compared between groups by the Wilcoxon rank sum test given nonparametric distributions.

Trend Analysis

We determined the percentage of patients ≥65 years by listing year from 2003 to 2017. This was first completed in all patients with and without HCC. We then determined the percentage of patients ≥65 years in those with and without HCC stratified by the etiology of cirrhosis (ie, HCV, NASH, and non-HCV/non-NASH). To test for statistical trends over time, we evaluated the percentage of patients ≥65 years old stratified by HCC status, treating the listing year as the continuous variable. We tested for differences in the trends over time using nonparametric tests and standardized regression coefficients (Fig. 1).

To evaluate the correlation between the changes in screening recommendations for HCV, the introduction of direct-acting antiviral (DAA) therapy, and the percentage of older patients with HCC, we compared regression coefficients for patients listed before and after January 1, 2014. This date was chosen because during 2013, national guidelines were changed to recommend universal HCV screening for all patients born from 1945 to 1965, and the US Food and Drug Administration approved the first

---

**FIG. 1.** Trends in the proportion of patients listed for LT in the United States between 2003 and 2017 who are ≥65 years at time of listing. (A) Proportion of all listed patients ≥65 years by HCC status. (B) Proportion of listed patients ≥65 years with HCV cirrhosis by HCC status. (C) Proportion of listed patients ≥65 years with NASH cirrhosis by HCC status. (D) Proportion of listed patients ≥65 years with non-HCV/non-NASH cirrhosis by HCC status. β represents regression coefficient.
DAA, sofosbuvir.\(^{(16-18)}\) Era of transplantation was categorized as 2003-2005, 2006-2009, 2010-2013, and 2014-2017. Eras were selected a priori based on the following:

1. Significant improvements in both wait-list and post-LT mortality over time.
2. Several updates to HCC transplantation policies and management strategies.
4. Availability of DAA therapy in early 2014.\(^{(9,16-22)}\)

**Survival Analysis**

For the outcome of wait-list mortality, a competing-risks regression was used to associate age $\geq 65$ years with wait-list mortality, accounting for LT. For the outcome of post-LT mortality, Cox proportional hazards regression models were used to associate age $\geq 65$ years with posttransplant mortality. To account for center variability, all models were adjusted for region and era of transplantation, and they were clustered on transplant center. We formally tested the interaction between HCC and age.

Covariables with $P < 0.2$ were considered for inclusion in multivariate models. Backward elimination was used for final models, with covariables not reaching significance of $P < 0.05$ being sequentially eliminated, and 2-sided $P$ values of $< 0.05$ were considered statistically significant. Wait-list and posttransplant patient mortality were estimated by age and HCC status using Kaplan-Meier plots. Plots were compared using a log-rank test.

**Software and Database**

All analyses were performed using STATA, version 15.0 (StataCorp., College Station, TX). This study was approved by the institutional review board at the University of California, San Francisco.

**Results**

**DEMOGRAPHICS AND CLINICAL CHARACTERISTICS BY AGE AND HCC STATUS**

There were 161,724 adult patients listed for LT during the study period. Of these, 35.5% were female, and 70.8% were non-Hispanic white. The median age at listing was 55 years [interquartile range (IQR), 49-61 years], with 22,092 (14%) patients $\geq 65$ years at listing. Among the 40,293 (25%) patients with HCC, the median age was 59 years (IQR, 54-64 years), with 20.6% of these patients $\geq 65$ years at listing. In comparison among patients without HCC, the median age was 54 years (IQR, 47-60 years), with 11.4% of patients $\geq 65$ years at listing (Table 1).

Among the 40,293 patients with HCC, those $\geq 65$ years, as compared with those <65 years, were more likely to be female (28.1% versus 21.4%; $P < 0.001$) and to have NASH cirrhosis (21.2% versus 8.2%; $P < 0.001$). They were also less likely to have decompensated cirrhosis, as measured by ascites (17.2% versus 20.0%; $P < 0.001$) and hepatic encephalopathy (7.1% versus 8.5%; $P < 0.001$). Among the 121,431 non-HCC patients, those $\geq 65$ years were also more likely to be female (45.8% versus 39.0%; $P < 0.001$) and to have NASH cirrhosis (37.7% versus 16.3%; $P < 0.001$). In contrast to those with HCC, in this cohort, the rates of ascites and hepatic encephalopathy were clinically similar between age groups.

**TRENDS IN PERCENTAGE OF PATIENTS $\geq 65$ YEARS**

Among all patients with HCC, median age at listing increased from 54 (49-63) years in 2003 to 62 (57-66) years; among all patients without HCC, the median age at listing increased, but at a slower rate, from 52 (46-57) years to 56 (47-62) years. Among all patients with HCC, the percentage of patients $\geq 65$ years increased from 13.9% in 2003 to 33.2% in 2017 ($\beta = 1.44$; $P < 0.001$). Although the percentage of patients $\geq 65$ years also increased from 2003 to 2017 among those without HCC ($\beta = 0.64$; $P < 0.001$), the rise was significantly faster among those with HCC ($\Delta = 0.80$; $P < 0.001$; nonparametric test for trend, $P < 0.001$; Fig. 1A). The proportion of patients $\geq 65$ years also increased by era of transplantation, as shown in Fig. 2.

To evaluate the differential increase of the proportion of patients $\geq 65$ years by HCC status in more detail, we performed a trend analysis stratified by primary etiology of cirrhosis. Among all patients listed with HCV cirrhosis, the percentage of patients $\geq 65$ years among those with HCV cirrhosis with HCC rose from 9.9% in 2003 to 30.2% in 2017 ($\beta = 1.41$; $P < 0.001$). Simultaneously, among those with HCV cirrhosis without HCC, the percentage $\geq 65$ years rose
TABLE 1. Characteristics and Outcomes of Patients Listed for LT in the United States During 2003-2017 by HCC Status and Age

<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>No HCC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age ≥65 Years (n = 8300)</td>
<td>Age &lt;65 Years (n = 31,993)</td>
<td>P Value</td>
<td>Age ≥65 Years (n = 13,792)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>2335 (28)</td>
<td>6840 (21)</td>
<td>&lt;0.001</td>
<td>6318 (46)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5388 (65)</td>
<td>20,621 (64)</td>
<td>&lt;0.001</td>
<td>10,741 (78)</td>
</tr>
<tr>
<td>Black</td>
<td>660 (8)</td>
<td>3203 (10)</td>
<td></td>
<td>733 (5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1287 (16)</td>
<td>5199 (16)</td>
<td></td>
<td>1744 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>878 (11)</td>
<td>2505 (8)</td>
<td></td>
<td>464 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>87 (1)</td>
<td>465 (1)</td>
<td></td>
<td>110 (1)</td>
</tr>
<tr>
<td>Liver diagnosis</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1043 (13)</td>
<td>2826 (9)</td>
<td>2403 (17)</td>
<td>21,059 (20)</td>
</tr>
<tr>
<td>HCV</td>
<td>3444 (41)</td>
<td>19,627 (61)</td>
<td>2272 (16)</td>
<td>35,040 (33)</td>
</tr>
<tr>
<td>NASH/cryptogenic</td>
<td>1758 (21)</td>
<td>2635 (8)</td>
<td>5193 (38)</td>
<td>17,597 (16)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>326 (4)</td>
<td>758 (2)</td>
<td>2079 (15)</td>
<td>14,149 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>1729 (21)</td>
<td>6147 (19)</td>
<td>1845 (13)</td>
<td>19,794 (18)</td>
</tr>
<tr>
<td>Days on the waiting list</td>
<td>188 (71-349)</td>
<td>184 (64-92)</td>
<td>0.03</td>
<td>132 (26-447)</td>
</tr>
<tr>
<td>MELD of listing</td>
<td>11 (8-14)</td>
<td>11 (8-15)</td>
<td>&lt;0.001</td>
<td>17 (13-24)</td>
</tr>
<tr>
<td>MELD at transplant</td>
<td>12 (8-18)</td>
<td>13 (9-19)</td>
<td>&lt;0.001</td>
<td>21 (15-30)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>591 (7)</td>
<td>2732 (9)</td>
<td>&lt;0.001</td>
<td>2956 (21)</td>
</tr>
<tr>
<td>Ascites</td>
<td>1427 (17)</td>
<td>6412 (20)</td>
<td>&lt;0.001</td>
<td>5920 (43)</td>
</tr>
<tr>
<td>KPS</td>
<td>70 (60-80)</td>
<td>70 (60-80)</td>
<td>0.60</td>
<td>60 (50-80)</td>
</tr>
<tr>
<td>DRI</td>
<td>1.5 (1.2-1.8)</td>
<td>1.5 (1.2-1.8)</td>
<td>&lt;0.001</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Private insurance</td>
<td>2369 (29)</td>
<td>20,038 (63)</td>
<td>&lt;0.001</td>
<td>3672 (27)</td>
</tr>
<tr>
<td>Wait-list outcomes</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still waiting</td>
<td>1460 (18)</td>
<td>4359 (14)</td>
<td>2976 (22)</td>
<td>25,292 (23)</td>
</tr>
<tr>
<td>Death/sickness</td>
<td>1565 (19)</td>
<td>5027 (16)</td>
<td>4316 (31)</td>
<td>24,591 (23)</td>
</tr>
<tr>
<td>Living donor LT</td>
<td>99 (1)</td>
<td>433 (1)</td>
<td>301 (2)</td>
<td>2404 (2)</td>
</tr>
<tr>
<td>Deceased donor LT</td>
<td>5176 (62)</td>
<td>22,174 (69)</td>
<td>6199 (45)</td>
<td>55,352 (51)</td>
</tr>
<tr>
<td>Posttransplant mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 year</td>
<td>536 (10)</td>
<td>1801 (8)</td>
<td>&lt;0.001</td>
<td>846 (14)</td>
</tr>
<tr>
<td>At 5 years</td>
<td>1108 (21)</td>
<td>4433 (20)</td>
<td>0.02</td>
<td>1396 (23)</td>
</tr>
</tbody>
</table>

NOTE: Data are presented as n (%) or median (IQR).

from 4.5% to 12.4% (β = 0.52; P < 0.001). The relative increase between 2003 and 2017 in the percentage of patients ≥65 years was significantly larger among those with HCC compared with those without (Δ = 0.89; P < 0.001; nonparametric test for trend, P < 0.001), as shown in Fig. 1B. Trend analysis confirmed that there was a significant increase in the rate of rise of the percentage of patients ≥65 years among those with HCV after the implementation of national screening policies and the introduction of DAA therapy (Δ = 2.43; P < 0.001; nonparametric test for trend, P < 0.001).

Among patients with NASH and HCC, the percentage of patients ≥65 years rose from 28.6% in 2003 to 45.6% in 2017 (β = 1.41; P < 0.001) compared with a rise from 17.3% to 29.4% among those without HCC (β = 0.73; P < 0.001). Similar to patients with HCV, the rise in the proportion of patients ≥65 years was significantly faster among those with HCC compared with those without HCC (Δ = 0.68; P < 0.001; nonparametric test for trend, P < 0.001; Fig. 1C).

Similarly, among those with non-HCV/non-NASH and HCC, the percentage of patients ≥65 years rose from 19.7% in 2003 to 32.1% in 2017 (β = 1.08; P < 0.001) compared with a smaller rise from 9.3% to 12.7% among those with non-HCV/non-NASH cirrhosis without HCC (β = 0.31, P < 0.001; Δ = 0.77,
Fig. 1D).  

**WAIT-LIST OUTCOMES BY AGE AND HCC STATUS**  

Among all patients, 22.0% experienced wait-list mortality. By HCC status, wait-list mortality was 23.8% among those without HCC and 16.4% among those with HCC ($P < 0.001$). By age, wait-list mortality was 26.6% among those $\geq 65$ years compared with 21.2% among those $< 65$ years ($P < 0.001$; Table 1).

In a univariate competing-risks regression analysis, age $\geq 65$ years was significantly associated with wait-list mortality (subhazard ratio [SHR], 1.43; 95% confidence interval [CI], 1.36–1.50; $P < 0.001$). Other factors associated with wait-list mortality included female sex (SHR, 1.19; 95% CI, 1.10–1.28), NASH compared with alcohol-related cirrhosis (SHR, 1.15; 95% CI, 1.02–1.31), final MELD (SHR, 1.05; 95% CI, 1.02–1.08), hepatic encephalopathy (SHR, 2.84; 95% CI, 2.09–3.87), and private insurance (SHR, 0.76; 95% CI, 0.71–0.81). HCC was not significantly associated with wait-list mortality on univariate analysis (SHR, 0.83; 95% CI, 0.66–1.05; $P = 0.12$). In multivariate regression, age $\geq 65$ years remained independently associated with wait-list mortality (adjusted subhazard ratio [aSHR], 1.51; 95% CI, 1.40–1.64; Table 2).

There was a significant interaction between age $\geq 65$ years and HCC status on wait-list mortality ($P < 0.001$), with age $\geq 65$ years being associated with a significantly lower risk of wait-list mortality in those with HCC compared with those without HCC.

**POST-LT OUTCOMES BY AGE AND HCC STATUS**  

Among the 161,724 listed for deceased donor LT, 88,901 patients underwent deceased donor LT (55.0%). Among these patients, 1- and 5-year post-LT mortality rates were 9.8% and 19.0% respectively (Table 1). Among the patients with HCC, the rates of 1- and 5-year mortality differed less for patients $\geq 65$ years and $< 65$ years (1-year: 10.4% versus 8.1%, $P < 0.001$; 5-year: 21.4% versus 20.0%, $P = 0.02$) than it did for patients $\geq 65$ years and $< 65$ years without HCC (1-year: 13.7% versus 10.0%, $P < 0.001$; 5-year: 22.5% versus 18.1%, $P < 0.001$). Among all patients who underwent deceased donor LT, age $\geq 65$ years (hazard ratio [HR], 1.39;
95% CI, 1.33-1.45) was associated with increased post-LT mortality as was presence of HCC (HR, 1.13; 95% CI, 1.09-1.18). Other factors associated with post-LT mortality were as follows: HCV compared with alcohol-related cirrhosis (HR, 1.26; 95% CI, 1.21-1.32), NASH compared with alcohol-related cirrhosis (HR, 1.06; 95% CI, 1.01-1.12), baseline Karnofsky Performance Status (KPS; HR, 0.97 per 10 points; 95% CI, 0.96-0.97), MELD at transplant (HR, 1.01; 95% CI, 1.01-1.01), waiting list time (HR, 0.99 per 90 days; 95% CI, 0.98-0.99), hepatic encephalopathy (HR, 1.21; 95% CI, 1.16-1.26), and DRI (HR, 1.38 per 0.1 points; 95% CI, 1.30-1.47). In multivariate analysis, age ≥65 years remained independently associated with post-LT mortality (adjusted HR, 1.50; 95% CI, 1.41-1.60; P < 0.001; Table 3).

Similar to wait-list mortality, there was a significant interaction between age and HCC on post-LT mortality (P = 0.04). Among patients <65 years, HCC was
associated with an average increased risk of post-LT mortality by 37% (95% CI, 23%-52%; \( P < 0.001 \)), but among those \( \geq 65 \) years, the risk associated with HCC was significantly lower (30%; 95% CI, 12%-48%; \( P < 0.001 \)).

**Discussion**

In this national study of more than 160,000 patients listed for LT in the United States, we observed that the proportion of older adults with HCC listed for transplant has nearly tripled between 2003 and 2017, with over one-third of patients listed for LT with HCC aged 65 years or older by 2017. Although older age was a risk factor for both wait-list and post-LT mortality, it was more strongly associated with mortality among non-HCC patients compared with those with HCC. Although prior studies have reported on the aging US LT population,\(^{(8,10,23)}\) our study is the first to explore how the rising age among patients with chronic liver disease specifically impacts patients listed for LT with HCC.

Why has the population of HCC patients seeking LT aged faster than the population of non-HCC patients? Our analyses suggest that this is driven in large part by the aging of patients with HCV-related liver disease. In the United States, the peak HCV antibody prevalence occurred in individuals born between 1940 and 1965—the Baby Boomers—with most having been infected between the ages of 20-35 years.\(^{(24,25)}\) The majority of these individuals are now \( \geq 65 \) years and have had HCV infection for >30 years, both of which have been shown to be independent risk factors for HCC.\(^{(26)}\) In addition, US guidelines changed in 2013 to recommend universal HCV screening for all Baby Boomers, increasing the diagnosis rate of HCV. Many of these patients had cirrhosis at diagnosis and, therefore, were screened for HCC.\(^{(27-29)}\) Although the widespread treatment of HCV-infected individuals with DAA therapy significantly reduces the lifetime risk of HCC, those who have advanced fibrosis at the time of DAA therapy remain at risk for HCC at older ages, rather than dying of hepatic decompensation.\(^{(30)}\)

Another major explanation for the rapid rise in older LT patients with HCC is the obesity epidemic, which has led to a burgeoning population of patients with NAFLD. Given the relatively slow progression of obesity-related liver disease, cirrhosis related to NAFLD often does not develop until more advanced ages in comparison with other liver diseases. Therefore, as the underlying etiology driving the development of HCC more frequently becomes NAFLD, the age of patients listed for transplant with HCC is expected to increase.

The temporal trends in advancing age that we observed among patients seeking LT for HCC are particularly relevant in the context of their transplant-related outcomes. In contrast to previous studies suggesting that older patients universally have worse LT outcomes,\(^{(8,23)}\) our findings demonstrate that the relationship between age and posttransplant outcomes is more nuanced. With regard to wait-list mortality, older HCC patients had half the risk of death of older non-HCC patients. Similarly, among patients <65 years, HCC was associated with a substantially increased risk of post-LT mortality, whereas HCC was associated with a smaller, though still increased, risk of posttransplant mortality among patients \( \geq 65 \) years. This may be explained by increased clinical reserve among the cohort of patients \( \geq 65 \) years selected to undergo LT compared with those \( \geq 65 \) years with decompensated cirrhosis.

We acknowledge the following limitations to our study. First, given that we analyzed data from a national administrative database, we were unable to fully account for center-specific policies that might influence the age of HCC patients being considered for LT. However, given that center-specific policies, when present, typically impose age limits on LT rather than liberalize age cutoffs, we would anticipate that such policies would lead to underestimation of age trends among patients with HCC nationwide. Furthermore, our survival analyses were clustered by center, and therefore, any center-based variation in outcomes should have been accounted for. Second, because national HCV screening guidelines changed around 2013, it is possible that our findings reflected increased screening practices rather than true increased incidence or earlier HCC diagnosis resulting in lead-time bias. Finally, we acknowledge that by using the UNOS/OPTN database, there is the possibility of a selection bias of only including older patients deemed to have the functional reserve to undergo transplant. This limits the conclusions that can be made regarding all older patients with HCC, but we believe our finding that age impacts those with HCC less than those without HCC highlights the need to reassess how we are capturing age-associated risk among LT candidates.
Our findings have significant implications for the management of older patients with chronic liver disease and HCC. We demonstrated that the median age of the HCC population is rising rapidly in the United States, significantly faster than those without HCC. Given the increased HCV screening among the Baby Boomers, increasing availability of DAA therapy, and the ongoing epidemic of obesity-related liver disease—all of which may be contributing to the aging of the HCC population—our observations may represent merely the tip of the iceberg. In light of the favorable interaction that we observed between HCC and older age on both wait-list and posttransplant mortality, our findings suggest that older HCC patients may present an opportunity to expand LT access to adults at older ages without significantly compromising outcomes. However, we also confirmed that age is a risk factor for wait-list and post-LT mortality in all populations, including HCC. Thus, patient selection for LT remains essential in this population; future research should focus on developing better metrics—perhaps one based on comorbidities and frailty—to more accurately risk stratify older HCC patients and evaluate their candidacy for LT.

REFERENCES

25) Demnistan MM, Jiles RB, Drobeniecu J, Klevens RM, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection