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Transplantation and Waitlist Mortality for HCC and Non-HCC Candidates Following the 2015 HCC Exception Policy Change

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Abstract

Historically, exception points for hepatocellular carcinoma (HCC) led to higher transplant rates and lower waitlist mortality compared to non-HCC candidates. As of October 2015, HCC candidates must wait 6 months after initial application to obtain exception points; the impact of this policy remains unstudied. Using 2013–2017 SRTR data, we identified 39,350 adult, first-time, active waitlist candidates and compared deceased-donor liver transplant (DDLT) rates, and waitlist mortality/dropout for HCC versus non-HCC candidates before (10/8/2013–10/7/2015, pre-policy) and after (10/8/2015–10/7/2017, post-policy) the policy change using Cox and competing risks regression, respectively. Compared to non-HCC candidates with the same calculated MELD, HCC candidates had a 3.6-fold higher rate of DDLT pre-policy (aHR= $_{3.49}$ 3.69 $_{3.89}$) and a 2.2-fold higher rate of DDLT post-policy (aHR= $_{2.09}$ 2.21 $_{2.34}$). Compared to non-HCC candidates with the same allocation priority, HCC candidates had a 37% lower risk of waitlist mortality/dropout pre-policy (asHR= $_{0.54}$ 0.63 $_{0.73}$) and a comparable risk of mortality/dropout post-policy (asHR= $_{0.81}$ 0.95 $_{1.11}$). Following the policy change, the DDLT advantage for HCC candidates remained, albeit dramatically attenuated, without any substantial increase in waitlist mortality/dropout. In the context of sickest-first liver allocation, the revised policy seems to have established allocation equity for HCC and non-HCC candidates.

INTRODUCTION

The Organ Procurement and Transplantation Network (OPTN) implemented a revised policy in October 2015 to modify the timing and maximum value of exception points for hepatocellular carcinoma (HCC) candidates on the deceased donor liver transplant (DDLT) waitlist (1, 2). Before the policy change, HCC candidates received exception points of 22 for the first 3 months after initial application, followed by exception points of 25 for the first 3-

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DISCLOSURE

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month extension, 28 for the second 3-month extension, and 29 for the third 3-month extension (2). Since the October 2015 policy change, HCC candidates are listed at their calculated MELD scores for the first 3-months after initial application and for the first 3-month extension (2). Subsequently, they receive exception points of 28 for the second 3-month extension at 6 months and 29 for the third 3-month extension at 9 months (1–3). The revised policy also reduces the maximum exception points for HCC candidates from 40 to 34 (1–3).

Historically, HCC candidates have experienced a substantial advantage in deceased donor liver allocation with lower waitlist mortality/dropout within one year of listing compared to non-HCC candidates (11.5% vs. 17.7%) (4). Our group previously showed that HCC candidates had 1.6-fold higher odds of transplant and 53% lower odds of 90-day waitlist mortality/dropout (5). Additionally, waitlist mortality/dropout for HCC candidates was found not to increase with higher exception points (4.2% vs. 4.6% vs. 3.0% for exception points of 22, 25, and 28 respectively), as compared to non-HCC candidates for whom 90-day mortality/dropout increased with higher MELD scores (11.0% vs. 17.3% vs. 23.6% for MELD scores of 21–23, 24–26, 27–29 respectively) (6). Moreover, there was an increase in the proportion of waitlist candidates who obtained HCC exception points from 2005 to 2012 (15.7% to 21.6%) (7).

Prior to implementation of the revised policy, a simulation study conducted by Heimbach et al. predicted that a 6-month delay in exception point allocation would equalize the transplant and mortality/dropout rates for those with and without HCC exceptions (8). However, this delay might create a window period in which candidates with rapidly progressive HCC, who may have poor post-transplant outcomes, are removed from the waitlist (9). Therefore, the revised policy has the potential to increase the waitlist mortality or removal for HCC candidates, potentially overcorrecting the prior advantage and introducing a disadvantage for HCC candidates.

To better understand the effectiveness of the revised allocation policy and to address the OPTN public comments proposal requesting early post-implementation analysis (9), we conducted an analysis of prospectively maintained national registry data to estimate the association between HCC and DDLT, waitlist mortality/dropout before and after the policy change. In addition, we compared post-transplant outcomes for HCC DDLT recipients before and after implementation of the revised policy.

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the US, submitted by the members of the OPTN, and has been described elsewhere (10, 11). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study population

We identified 39,350 first-time, active, adult waitlist candidates listed for DDLT between October 8, 2013 and October 7, 2017. We excluded candidates who were prevalent on the waitlist on October 8, 2013 to prevent any possible effects of previous DDLT allocation policies. In addition, we excluded candidates diagnosed with HCC but not approved for HCC exception points, non-HCC candidates with exception points, and candidates ever listed as Status 1 (Figure 1). The primary exposure was HCC, and thus, we identified all candidates approved for HCC exception points (HCC candidates) and compared waitlist outcomes to candidates without any exception points who were never diagnosed with HCC (non-HCC candidates). Finally, to identify changes in waitlist and post-transplant outcomes among HCC candidates under the new policy, we defined two eras using the recent policy implementation date: pre-policy was defined as 10/8/2013–10/7/2015 and post-policy was defined as 10/8/2015–10/7/2017.

Deceased-donor liver transplant

Candidates entered the study at the time of approval of their exception (HCC candidates) or first active date on the waitlist (non-HCC candidates). Candidates were followed until DDLT, waitlist removal (for mortality/dropout or other reasons), or date of administrative censorship. Two-year of follow-up was available for post-policy candidates, and thus, we restricted our pre-policy follow-up period to two-year as well. In other words, candidates studied during the pre- and post-policy were administratively censored on October 7, 2015 and October 7, 2017, respectively. We used a Cox proportional hazards model to compare time to DDLT among HCC and non-HCC candidates in the pre- and post-policy eras, adjusting for age, sex, race, and time-varying calculated MELD score (cMELD). This model treated waitlist mortality/dropout as a censored observation and did not assume independence between DDLT and waitlist mortality/dropout. Thus, the reported hazard ratio (HR) indicates the association between HCC and DDLT and should not be interpreted directly as a cumulative incidence function (CIF) of DDLT (12). Under the policy, chance of DDLT was time varying for HCC candidates, and thus we estimated the hazard of DDLT within the first 6 months of HCC exception-point approval and the hazard of DDLT from 6–24 months after HCC exception-point approval. The overall hazard of DDLT within each policy-era is also presented. We tested the interaction between HCC and policy era to determine whether the advantage of HCC exception points in access to DDLT changed after the October 2015 policy. Results are reported stratified by policy era. To illustrate time to DDLT graphically, we estimated the cumulative incidence of DDLT accounting for waitlist mortality/dropout as a competing risk, as described by Coviello and Boggess (13).

Waitlist mortality/dropout

We used competing risk regression analysis to determine whether waitlist mortality/dropout associated with HCC changed under the October 2015 policy. Waitlist mortality/dropout was defined as removal from the waitlist due to death, deteriorating condition, or medical unsuitability (too sick for transplant); candidates removed for other reasons (e.g. living donor liver transplant, transplanted at another center) were censored. Patient mortality was ascertained using SRTR data supplemented with linkage to the Social Security Death Master

File. Using the Fine and Gray method (14), we estimated the association between waitlist mortality/dropout and HCC while accounting for the competing risk of transplantation. This method does not censor the transplanted candidates and therefore allows direct modeling of the sub-distribution CIF of waitlist mortality/dropout (12). Similar to the Cox regression model, we estimated the time-varying hazard of waitlist mortality/dropout, reporting the sub-hazard ratio (sHR) of mortality/dropout in the first six months after HCC exception point approval and between six to 24 months after HCC exception point approval. The overall sHR of waitlist mortality/dropout within each policy-era is also reported. The final model was adjusted for age, sex, race, and allocation MELD (aMELD) as determined by the OPTN based on cMELD or exception points. We tested the interaction between HCC and policy era to determine whether the risk of waitlist mortality/dropout for HCC patients changed under the new policy; results are reported stratified by policy era. To illustrate time to waitlist mortality/dropout graphically, we also estimated the cumulative incidence of waitlist mortality/dropout accounting for DDLT as a competing risk, as described by Coviello and Boggess (13).

Waitlist dropout

Waitlist dropout was defined as removal from the waitlist due to deteriorating condition, or medical unsuitability. We estimated the association between waitlist dropout and HCC while accounting for the competing risk of transplantation and waitlist mortality using Fine and Gray method (14) with adjustment for age, sex, race, and aMELD. As described above, we reported the sub-hazard ratio (sHR) of waitlist dropout for 0–6 months, 6–24 months, and 0–24 months. Similar to previous models, we tested the interaction between HCC and policy era to determine whether the risk of waitlist dropout for HCC patients changed under the new policy. We also estimated the cumulative incidence of waitlist dropout accounting for DDLT and waitlist mortality as a competing risk (13).

Waitlist mortality

We repeated the above analysis to estimate the association between waitlist mortality and HCC while accounting for the competing risk of transplantation and waitlist dropout before and after the policy change using Fine and Gray method (14) and adjusting for age, sex, race, and aMELD.

Regional variations in DDLT and waitlist mortality/dropout

To illustrate the changes in DDLT rate and waitlist mortality/dropout incidence pre- and post-policy by UNOS regions, we repeated the above analysis, stratified by region, and presented the results in figure 4.

All-cause graft failure

To determine whether post-transplant outcomes were affected by the delay in exception point allocation among HCC DDLT recipients under the new policy, we compared all-cause graft failure among HCC DDLT recipients pre- vs post-policy change. Since the DDLT rate for HCC candidates within the first 6 months of their exception point approval decreased substantially following the policy change, median post-DDLT follow up time in the post-

policy era was 8.8 months. As such, in our study of post-transplant graft failure we censored all participants at 1-year post-transplant. We estimated the cumulative incidence of all-cause graft failure (defined as re-transplant or death) within 1 year of transplantation for HCC DDLT recipients pre- and post-policy using Kaplan-Meier methods. We estimated the association between all-cause graft failure and the policy change among HCC recipients using Cox proportional hazards regression, adjusting for recipient age, sex, race, and donor risk index (DRI).

Statistical analysis

All statistical analyses were performed using Stata 14.2/SE for Linux (Stata Corp., College Station, TX). HCC and non-HCC candidates were compared using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Comparisons between HCC and non-HCC candidates were made separately for both eras. All tests were two-sided, and a p-value of ≤0.05 was considered statistically significant. Confidence intervals were reported as per the method of Louis and Zeger (15).

RESULTS

Study population

Characteristics of HCC and non-HCC candidates at study entry were compared to each other for the pre- and post-policy eras separately (Table 1). At study entry, HCC candidates were older than non-HCC candidates in both eras (pre-policy: median (IQR) age 61 (56–65) years vs. 56 (49–62) years, p<0.001; post-policy: median (IQR) age 62 (58–66) years vs. 56 (48–62) years, p<0.001) and less likely to be female (pre-policy: 23.3% vs. 39.2%, p<0.001; post-policy: 22.4% vs. 40.4%, p<0.001). In both eras, median cMELD at study entry was 10 (IQR: 8–13) for HCC candidates and 18 (IQR: 14–26) (p<0.001) for non-HCC candidates. In the pre-policy era, HCC candidates had higher aMELD at study entry compared to non-HCC candidates (median (IQR) aMELD 22 (22–22) vs. 18 (14–26), p<0.001). Conversely, in the post-policy era, HCC candidates had significantly lower aMELD at study entry compared to non-HCC candidates (median (IQR) aMELD 10 (8–15) vs. 21 (15–28), p<0.001) (Table 1).

HCC and DDLT rate

Pre-policy, 38.7% of HCC candidates received DDLT within 6 months of study entry, compared to 34.4% of non-HCC candidates. Post-policy, only 14.1% of HCC candidates received DDLT within 6 months of study entry, compared to 44.1% of non-HCC candidates (Figure 2). In both eras, more HCC candidates received DDLT within 24 months of study entry as compared to non-HCC candidates (pre-policy: 88.4% vs. 46.3%; post-policy: 90.6% vs. 57.2%) (Figure 2).

Pre-policy, HCC candidates had 2.83-fold higher DDLT rate compared to non-HCC candidates with the same cMELD within the first 6-months after study entry (aHR= $_{2.66}$ 2.83 $_{3.02}$, p<0.001), which increased to 9.02-fold higher between 6 and 24 months after study entry (aHR= $_{8.14}$ 9.02 $_{10.00}$, p<0.001). Over the 24 months as a whole, DDLT rate was 3.69-

fold higher for HCC candidates compared to non-HCC candidates (aHR= $_{3.49}$ 3.69 $_{3.89}$, p<0.001) (Table 2).

Post-policy, HCC candidates had 24% lower DDLT rate compared to non-HCC candidates with the same cMELD within the first 6 months of study entry (aHR= $_{0.69}$ 0.76 $_{0.83}$, p=0.001), which increased to 11.97-fold higher between 6 and 24 months post-study entry (aHR= $_{10.99}$ 11.97 $_{13.03}$, p<0.001). Over the 24 months as a whole, HCC candidates had 2.21-fold greater DDLT rate compared to non-HCC candidates (aHR= $_{2.09}$ 2.21 $_{2.34}$, p<0.001) (Table 2).

HCC and waitlist mortality/dropout

In both eras, waitlist mortality/dropout for HCC candidates was lower compared to non-HCC candidates within 6 months of study entry (pre-policy: 4.8% vs. 7.6%; post-policy: 4.9% vs. 5.9%) and also within 24 months of study entry (pre-policy: 8.7% vs. 14.1%; post-policy: 9.3% vs. 9.6%) (Figure 3a).

Pre-policy, the risk of waitlist mortality/dropout for HCC candidates was 41% lower within the first 6-months of study entry compared to non-HCC candidates with same aMELD (asHR= $_{0.50}$ 0.59 $_{0.70}$, p <0.001). HCC and non-HCC candidates had a similar risk of waitlist mortality/dropout between 6 and 24 months post-study entry (asHR= $_{0.68}$ 0.94 $_{1.29}$, p=0.7). Over the 24 months as a whole, HCC candidates had 37% lower risk of waitlist mortality/dropout compared to non-HCC candidates with same aMELD (asHR= $_{0.54}$ 0.63 $_{0.73}$, p <0.001) (Table 3a).

Post-policy, HCC and non-HCC candidates with the same aMELD experienced a comparable risk of waitlist mortality/dropout within the first 6 months post-study entry (asHR= $_{0.71}$ 0.86 $_{1.03}$, p=0.1), between 6 and 24 months post-study entry (asHR= $_{0.96}$ 1.25 $_{1.63}$, p=0.1), and over the 24 months as a whole (asHR= $_{0.81}$ 0.95 $_{1.11}$, p=0.5) (Table 3a).

HCC and waitlist dropout

Pre-policy, 2.2% of HCC candidates dropped out within 6 months of study entry, compared to 2.5% of non-HCC candidates. Post-policy, 3.3% of HCC candidates dropped out within 6 months of study entry, compared to 1.8% of non-HCC candidates (Figure 3b). In both eras, more HCC candidates dropped out within 24 months of study entry compared to non-HCC candidates (pre-policy: 4.8% vs. 4.6%; post-policy: 5.8% vs. 3.0%) (Figure 3b).

Pre-policy, the risk of waitlist dropout for HCC candidates was 27% lower within the first 6-months of study entry compared to non-HCC candidates with same aMELD (asHR= $_{0.57}$ 0.73 $_{0.93}$, p= 0.01). HCC and non-HCC candidates had a similar risk of waitlist dropout between 6 and 24 months post-study entry (asHR= $_{0.91}$ 1.44 $_{2.26}$, p=0.1). Over the 24 months as a whole, HCC candidates had comparable risk of waitlist dropout compared to non-HCC candidates with same aMELD (asHR= $_{0.64}$ 0.80 $_{1.01}$, p= 0.05) (Table 3b).

Post-policy, the risk of waitlist dropout for HCC candidates was 1.79-fold higher within the first 6-months of study entry compared to non-HCC candidates with same aMELD (asHR= $_{1.39}$ 1.79 $_{2.31}$, p<0.001), which increased to 2.39-fold higher between 6 and 24 months after

study entry (asHR= $_{1.65}$ 2.39 $_{3.47}$, p<0.001). Over the 24 months as a whole, risk of dropout was 1.93-fold higher for HCC candidates compared to non-HCC candidates with same aMELD (asHR= $_{1.54}$ 1.93 $_{2.42}$, p<0.001) (Table 3b).

HCC and waitlist mortality

In both eras, waitlist mortality for HCC candidates was lower compared to non-HCC candidates within 6 months of study entry (pre-policy: 2.6% vs. 5.1%; post-policy: 1.6% vs. 4.1%) and also within 24 months of study entry (pre-policy: 3.9% vs. 9.5%; post-policy: 3.5% vs. 6.6%) (Figure 3c).

In both eras, HCC candidates and non-HCC candidates had a similar mortality risk. Pre-policy, the risk of waitlist mortality for HCC candidates was 51% lower within the first 6-months of study entry compared to non-HCC candidates with same aMELD (asHR= $_{0.40}$ 0.49 $_{0.62}$, p <0.001). HCC and non-HCC candidates had a similar risk of waitlist mortality between 6 and 24 months post-study entry (asHR= $_{0.48}$ 0.74 $_{1.17}$, p=0.2). Over the 24 months as a whole, HCC candidates had 48% lower risk of waitlist mortality compared to non-HCC candidates with same aMELD (asHR= $_{0.43}$ 0.52 $_{0.64}$, p <0.001) (Table 3c).

Post-policy, the risk of waitlist mortality for HCC candidates was 54% lower within the first 6-months of study entry compared to non-HCC candidates with same aMELD (asHR= $_{0.34}$ 0.46 $_{0.62}$, p <0.001). HCC and non-HCC candidates had a similar risk of waitlist mortality between 6 and 24 months post-study entry (asHR= $_{0.52}$ 0.78 $_{1.17}$, p=0.2). Over the 24 months as a whole, HCC candidates had 47% lower risk of waitlist mortality compared to non-HCC candidates with same aMELD (asHR= $_{0.41}$ 0.53 $_{0.68}$, p <0.001) (Table 3c).

Regional variations in DDLT and waitlist mortality/dropout

Pre-policy, DDLT rate for HCC was much higher compared to non-HCC candidates in all regions. Post-policy, DDLT rate for HCC candidates was still higher compared to non-HCC candidates in all regions. However, the difference of DDLT rate between HCC and non-HCC candidates was attenuated in the post-policy era compared to the pre-policy era. The reduction in DDLT rate from pre- to post policy was statistically significant for all regions except region 1 and region 9 (Figure 4a).

Pre-policy, HCC candidates had substantially lower incidence of mortality/dropout compared to non-HCC candidates in regions 1, 2, 3, 5, 7, and 9. Post-policy, HCC and non-Candidates had comparable chance of waitlist mortality/dropout in all regions (Figure 4b).

HCC and all cause graft failure

Among HCC DDLT recipients, one-year graft failure was 7.5% pre-policy and 5.9% post-policy (log-rank p= 0.1). After adjusting for recipient age (splined at 40, 55, 75), race, sex, DRI (splined at 2.5), there was no evidence of association between the policy change and 1-year graft failure (aHR= $_{0.60}$ 0.79 $_{1.03}$; p=0.1; Figure 5).

DISCUSSION

In this national study of waitlist and post-transplant outcomes in liver waitlist registrants, we found that the substantial allocation advantage to HCC candidates in pre-policy era (aHR= 3.7 compared to non-HCC candidates) remained in attenuated form in post-policy era (aHR= 2.2). Furthermore, while HCC candidates had a 37% lower risk of waitlist mortality/dropout pre-policy (asHR=0.63), they experienced a comparable risk of mortality/dropout post-policy (asHR= 0.95) compared to non-HCC candidates with similar allocation priority. Both before and after the policy change, HCC candidates had substantially lower risk of waitlist mortality compared to non-HCC candidates (asHR= 0.5). However, while their risk of dropout was comparable to risk for non-HCC candidates before the policy change (asHR= 0.8), it was substantially higher than risk to non-HCC candidates after the policy change (asHR=1.9).

This study explored the equity in organ allocation for waitlist candidates in two years preceding the October 2015 policy change. Our findings that HCC candidates had a 37% lower risk of mortality/dropout due to 3.7-fold greater DDLT rate compared to non-HCC candidates in the pre-policy era are consistent with previous findings of lower waitlist mortality/dropout and higher DDLT rate for HCC candidates (4–7). The present study extended previous work by comparing DDLT rate for HCC and non-HCC candidates with the same cMELD in the pre- and post-policy eras. In post-policy era, for first time ever, HCC candidates had lower rates of transplant compared to non-HCC candidates with the same cMELD score, in the first six months after approval of their exception. However, after this six-month period, HCC candidates had 11-fold higher rates of transplant compared to non-HCC candidates with the same cMELD, such that overall HCC candidates continued to experience higher transplant rates.

Our findings reinforce the results of simulation studies conducted prior to the 2015 policy change. Using a liver simulation allocation model (LSAM) for waitlisted candidates in 2010, Heimbach and colleagues compared the effect of delaying exception point allocation on transplant rate and waitlist mortality/dropout for HCC and non-HCC candidates (8). Their prediction model found that a 6-month delay in exception point allocation would result in a closer alignment between DDLT rates for HCC and non-HCC candidates by 1 year post listing without substantial changes in the rate of waitlist mortality/dropout (8). Additionally, in another simulation study, Alver et al. compared the projected DDLT and waitlist mortality/dropout rate under an allocation system with 6-month delay (post-policy) and with $MELD_{EQ}$ (a novel HCC-specific scoring system based on cMELD, alpha-fetoprotein, and tumor characteristics), using a non-parametric multistate model on 2009–2014 UNOS data (18). Their prediction model found that a 6-month delay would result in reduced DDLT rate at 6 months, equivalent access at 12 months, and increased access at 18 months post-listing for HCC candidates compared to non-HCC candidates, with a consistently lower risk of mortality/dropout and similar post-transplant survival in each interval (16). In studying the real-world effects of this six-month delay in exception point allocation after implementation of the revised OPTN/UNOS policy, we have confirmed that the delay did, in fact, reduce the advantage HCC candidates previously experienced in access to DDLT, while maintaining a

comparable risk of waitlist mortality/dropout for HCC candidates compared to their non-HCC counterparts.

Our study must be understood in the context of several limitations. The hazard ratios for 6–24 months could be affected by survival bias, as they were estimated using only candidates who were not removed in first 6 months. We were only able to study post-transplant outcome for the first 12 months following the implementation of the October 2015 revised liver policy regarding HCC exception points. Thus, it remains uncertain whether the patterns we identified in post-transplant outcome will persist after 1 year. We also recognize the potential limitations of using registry-based data. OPTN data are gathered across hundreds of centers, potentially with varying degrees of quality control and different policies for checking and updating MELD scores. Additionally, we adjusted for a limited number of covariates based on which factors were available in this registry; for instance, we were unable to adjust for factors such as pre-transplant HCC treatment, as such, data were not available. However, despite these limitations, national registries constitute the only comprehensive data source for studies of changes in organ allocation at the national level.

Despite the aforementioned limitations, our study also has several key strengths. To our knowledge, this is the first study of changes in DDLT, risk of waitlist mortality, and post-transplant outcomes in light of recent modifications to the exception point allocation policy for HCC candidates. The sample size of our study was large enough to provide sufficient power in the stratified analysis. Other strengths include accounting for the dynamic nature of MELD and the use of competing risks methods to elucidate the relationship between allocation priority and waitlist mortality.

In conclusion, our findings suggest that allocation of DDLT remained higher for HCC candidates than non-HCC candidates with the same calculated MELD two years after the implementation of the 2015 revised liver allocation policy; although the magnitude of the difference in DDLT rate was attenuated in the post-policy era. Despite a significant reduction of the allocation advantage for HCC candidates following the 2015 policy change, waitlist mortality/dropout remained comparable for both HCC and non-HCC candidates. The revised HCC exception policy seems to have achieved its goal of establishing equity in waitlist mortality/dropout for HCC and non-HCC candidates. However, it will be important to carefully monitor waitlist and post-transplant outcomes as the length of follow-up time since policy implementation increases.

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Abbreviations

aHR	adjusted hazard ratio
aMELD	allocation MELD
asHR	adjusted sub-hazard ratio
CIF	cumulative incidence function
cMELD	calculated MELD
DDLT	deceased donor liver transplant
DRI	donor risk index
HCC	Hepatocellular carcinoma
HR	hazard ratio
HRSA	Health Resources and Services Administration
IRB	Institutional Review Board
LSAM	liver simulation allocation modeling
MELD	Model for end stage liver disease
OPTN	Organ procurement and Transplantation Network
sHR	sub-hazard ratio
SRTR	Scientific Registry of Transplant Recipients
UNOS	United Network for Organ Sharing

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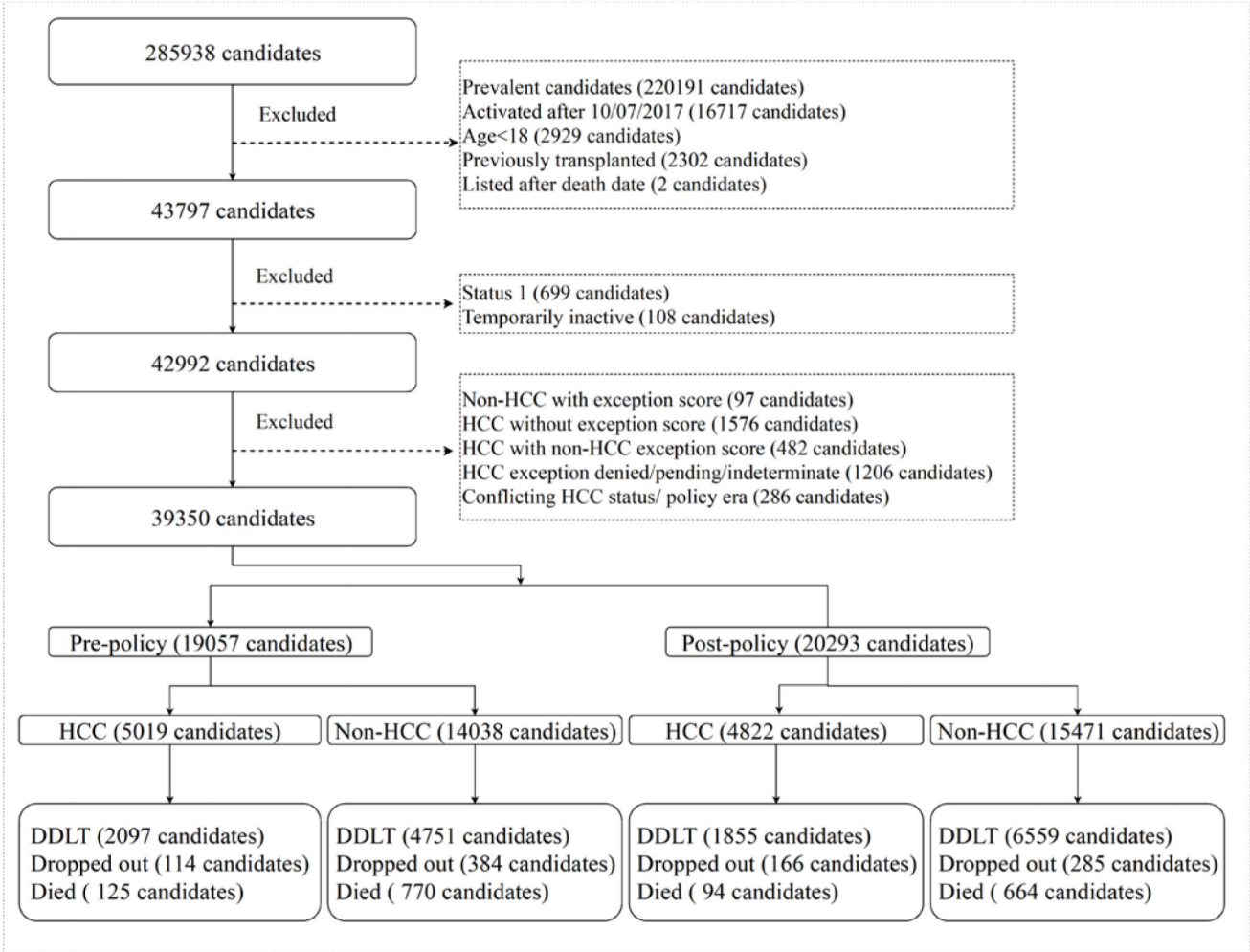

Figure 1.
Construction of the study population.

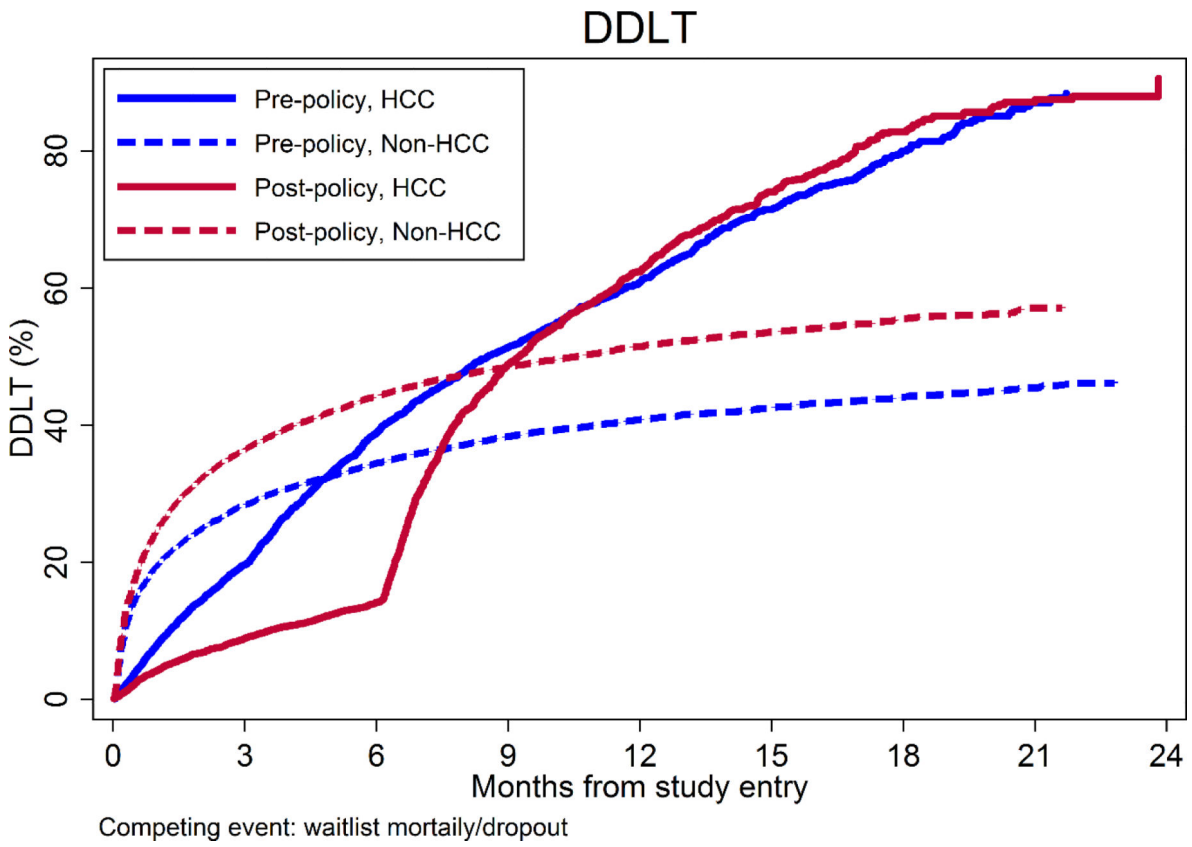

Figure 2.

Cumulative incidence of DDLT for HCC (solid) and non-HCC (dash) candidates. Pre-policy (blue), DDLT was substantially higher for HCC candidates than for non-HCC candidates at 24 months post-study entry (88.4% vs. 46.3%). Post-policy (red), DDLT was lower for HCC candidates until 6 months post-study entry (14.1% vs. 44.1%), started to increase sharply at 6 months post-study entry, and became higher than non-HCC candidates (90.6% vs. 57.2% after 24-month).

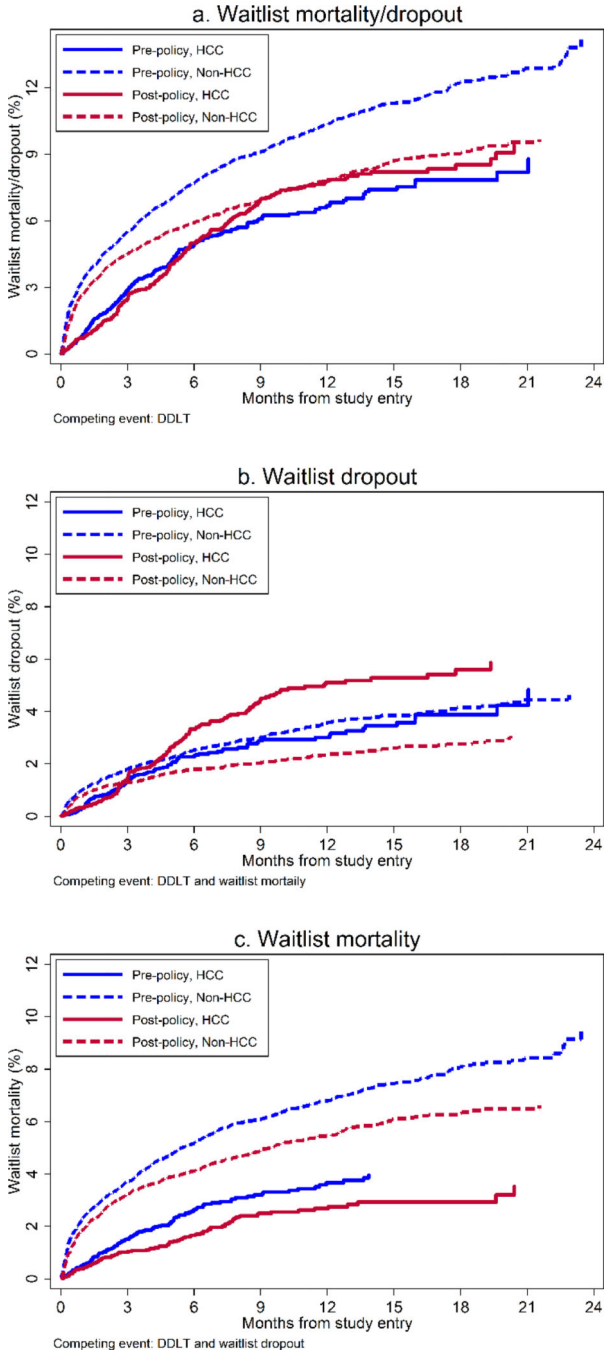

Figure 3.

Cumulative incidence of (a) waitlist mortality/dropout, (b) waitlist dropout (c) waitlist mortality for HCC (solid) and non-HCC (dash) candidates in pre-policy (blue) and post-policy (red) era.

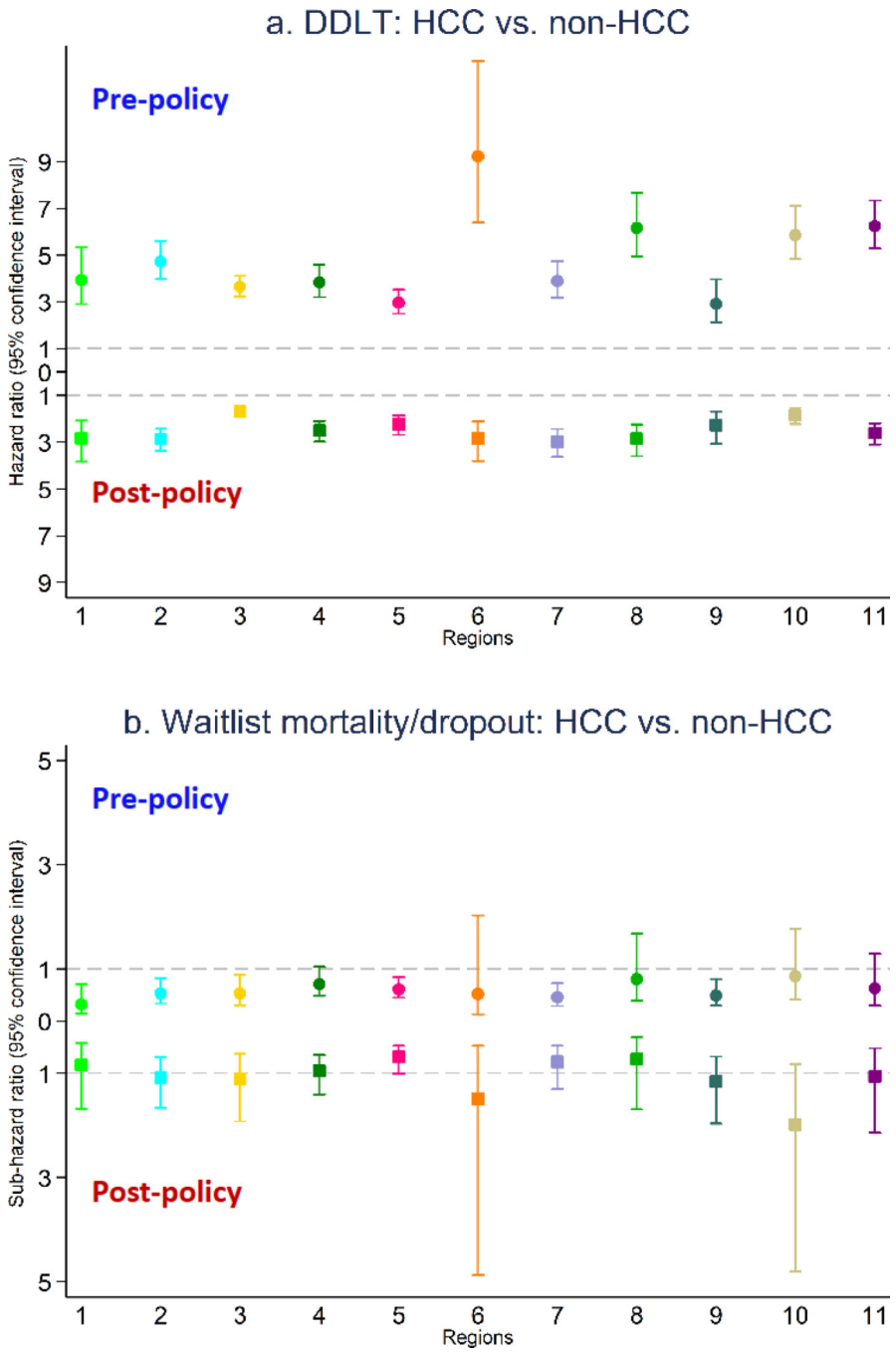

Figure 4.

(a) DDLT and (b) waitlist mortality/dropout for HCC vs. non-HCC candidates in pre-policy (circle) and post-policy (square) era, stratified by UNOS region.

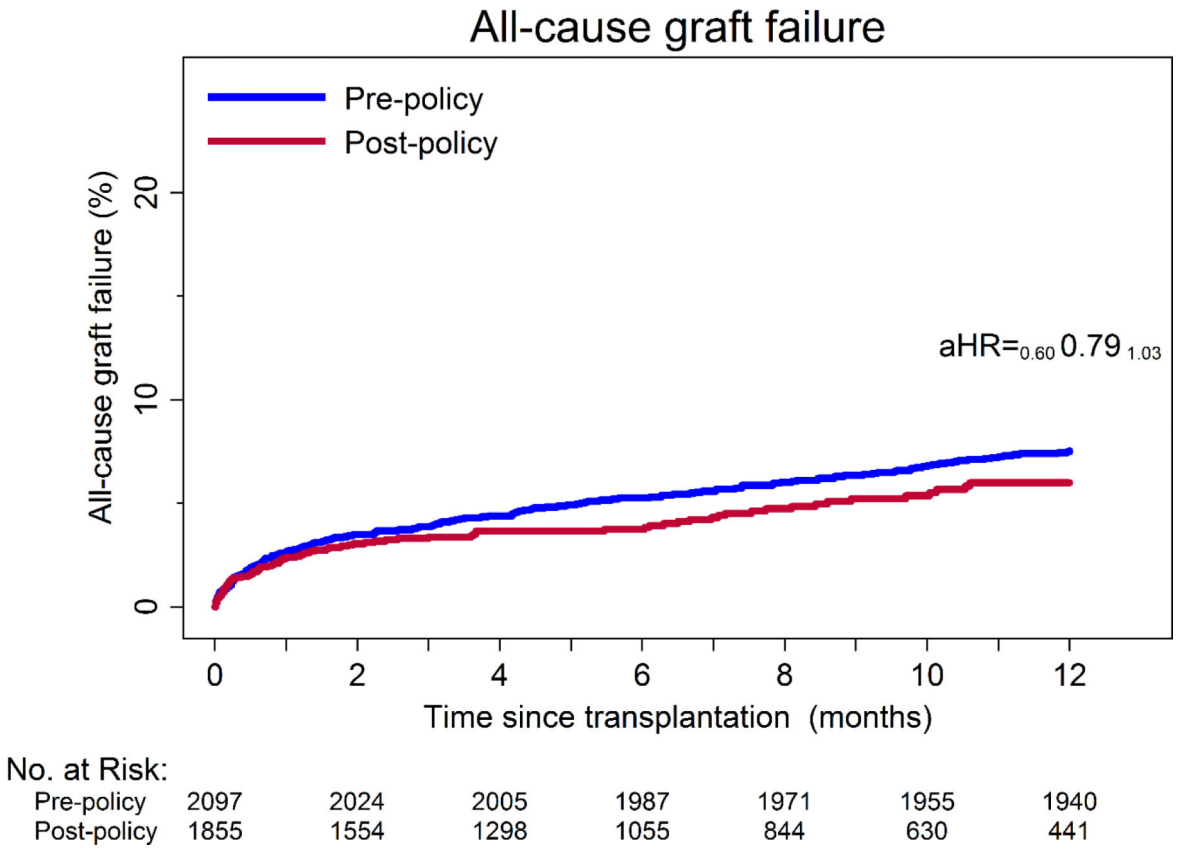

Figure 5.

Cumulative incidence of all-cause graft failure over one year, pre-policy (blue) and post-policy (red), among HCC DDLT recipients. There was no evidence of change in post-transplant outcomes for HCC recipients (aHR=$_{0.60}$ 0.79 $_{1.03}$, p=0.1).

Table 1.

Baseline characteristics of the study population comparing HCC vs. non-HCC candidates in pre-policy and post-policy era.

	Pre-policy (N=19057)			Post-policy (N=20293)		
	HCC	**Non-HCC**	**p-value**	**HCC**	**Non-HCC**	**p-value**
N	5019	14038		4822	15471	
Age, median (IQR)	61 (56–65)	56 (49–62)	<0.001	62 (58–66)	56 (48–62)	<0.001
Female, %	23.3	39.2	<0.001	22.4	40.4	<0.001
Race, %						
White	64.1	72.2	<0.001	64.9	72.8	<0.001
Black	10.6	8.6		9.9	7.2	
Hispanic/Latino	16.1	14.7		17.2	15.5	
Asian	7.8	3.0		6.6	3.0	
Other	1.4	1.6		1.4	1.5	
cMELD, median (IQR)	10 (8–13)	18 (14–26)	<0.001	10 (8–13)	18 (14–26)	<0.001
aMELD, median (IQR)	22 (22–22)	18 (14–26)	<0.001	10 (8–15)	21 (15–28)	<0.001

IQR=Interquartile range; cMELD= calculated MELD; aMELD= allocation MELD

Table 2.

DDLT for HCC vs. non-HCC candidates, pre-policy and post-policy, regardless of waitlist mortality (Cox). In the pre-policy era, HCC candidates had substantially higher DDLT rate than non-HCC candidates with comparable cMELD. Post-policy, HCC candidates had slightly lower DDLT rate than non-HCC candidates in the first 6 months of study entry (aHR=0.76), but a substantially higher DDLT rate between 6 and 24 months post-study entry (aHR=11.97). Within the first 24 months overall, HCC candidates had a 2.2-fold higher DDLT rate compared to non-HCC candidates (aHR=2.21).

	DDLT rate: HCC vs non-HCC recipients (Cox aHR)		
	Pre-policy	**Post-policy**	**interaction p**
0–6m	$_{2.66}$ **2.83** $_{3.02}$	$_{0.69}$ **0.76** $_{0.83}$	<0.001
6–24m	$_{8.14}$ **9.02** $_{10.00}$	$_{10.99}$ **11.97** $_{13.03}$	<0.001
0–24m	$_{3.49}$ **3.69** $_{3.89}$	$_{2.09}$ **2.21** $_{2.34}$	<0.001

Cox= Cox regression; aHR= adjusted Hazard ratio. Models adjusted for age (spline at 55), sex, race, and cMELD (spline at 12 & 35).

Table 3.

(a) Waitlist mortality/dropout, (b) waitlist dropout, and (c) waitlist mortality for HCC vs. non-HCC, pre-policy and post-policy, accounting for competing risks (CR). Pre-policy, HCC candidates had substantially lower incidence of waitlist mortality/dropout (asHR=0.59), dropout (asHR=0.73) and mortality (asHR=0.49) compared to non-HCC candidates at the same aMELD during the first six months after study entry, but comparable incidence of waitlist mortality/dropout, dropout, mortality at 6–24 months after study entry; Within the first 24 months overall, their mortality/dropout risk was substantially lower compared to non-HCC candidates (sHR=0.63). Post-policy, HCC and non-HCC candidates had similar incidence of waitlist mortality/dropout (sHR=0.95). However, risk of dropout was higher for HCC candidates compared to non-HCC candidates in post-policy era (sHR=1.93).

a. Waitlist mortality/dropout incidence accounting for competing risks of DDLT (asHR)

	Pre-policy	Post-policy	Interaction p
0–6m	0.50 **0.59** 0.70	0.71 0.86 1.03	0.004
6–24m	0.68 0.94 1.29	0.96 1.25 1.63	0.1
0–24m	0.54 **0.63** 0.73	0.81 0.95 1.11	<0.001

b. Waitlist dropout incidence accounting for competing risks of DDLT and waitlist mortality (asHR)

	Pre-policy	Post-policy	Interaction p
0–6m	0.57 **0.73** 0.93	1.39 **1.79** 2.31	<0.001
6–24m	0.91 1.44 2.26	1.65 **2.39** 3.47	0.05
0–24m	0.64 0.80 1.01	1.54 **1.93** 2.42	<0.001

c. Waitlist mortality incidence accounting for competing risks DDLT and waitlist dropout (asHR)

	Pre-policy	Post-policy	Interaction p
0–6m	0.40 **0.49** 0.62	0.34 **0.46** 0.62	0.7
6–24m	0.48 0.74 1.17	0.52 0.78 1.17	0.9
0–24m	0.43 **0.52** 0.64	0.41 **0.53** 0.68	0.9

asHR= adjusted sub-hazard ratio. Models adjusted for age (spline at 55), sex, race, and aMELD (spline at 12 & 35).