ACCESS TO LIVER TRANSPLANTATION UNDER THE NEW EXCEPTION POLICY FOR HCC AND NON-HCC CANDIDATES

by

Tanveen Ishaque

A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science

Baltimore, Maryland
April, 2017

ABSTRACT

BACKGROUND: In October 2015, the Organ Procurement and Transplantation Network (OPTN) implemented a revised liver exception point policy to address the disparity between Hepatocellular Carcinoma (HCC) and non-HCC patients in access to deceased-donor liver transplant (DDLT). Under the new policy, HCC patients obtain exception points only after 6 months on the waitlist. The impact of this policy change on access to DDLT and waitlist mortality for HCC and non-HCC patients has not been described.

METHODS: Using Scientific Registry of Transplant Recipients (SRTR) data on 29,759 adult, first-time DDLT waitlist registrants from 2014 to 2016, we compared access to DDLT and mortality risk in HCC vs. non-HCC patients, pre-implementation (10/8/2014-10/7/2015) and post-implementation (10/8/2015-6/30/2016). Waitlist dropout due to deteriorating condition was classified as mortality. We estimated cumulative incidence of DDLT accounting for the competing risk of waitlist mortality overall and for four different strata of calculated MELD (6-10, 11-18, 19-24, and 25-40). We used Cox regression to model cause-specific hazard, and Fine and Gray methods to model mortality accounting for the competing risk of transplantation, adjusting for age, gender, race, and time-varying calculated MELD.

RESULTS: During the pre-implementation period, HCC patients had 5-fold higher access to DDLT than non-HCC patients (aCSHR = $_{5.32}$ 5.61 $_{5.91}$, $p<0.001$). During the post-implementation period, HCC and non-HCC patients had comparable chances of receiving

DDLT experiencing access to DDLT (aCSHR = $_{0.81}$ 0.93 $_{1.07}$, p>0.1). After accounting for the reduction in mortality due to transplant in both groups, risk of waitlist mortality/dropout for HCC candidates compared to non-HCC candidates increased from 1.3-fold higher risk of waitlist mortality/dropout pre-implementation (asHR =$_{1.15}$ 1.30 $_{1.46}$, p=0.005) to 2.18-fold higher risk of waitlist mortality/dropout post-implementation (aSHR = $_{1.69}$ 2.18 $_{2.80}$, p<0.001).

CONCLUSIONS: The October 2015 HCC exception policy change eliminated the disparity in access to DDLT between HCC and non-HCC patients. However, risk of waitlist mortality/dropout increased in HCC candidates compared to non-HCC candidates.

Co-advisors:

Thesis advisor

Allan B. Massie, PhD, MHS

Assistant Professor, School of Medicine, Epidemiology (Joint)

Academic advisor

Anne Rositch, PhD, MSPH

Assistant Professor, Epidemiology

Acknowledgments

The work presented in this thesis would not be possible without the incredible support from my advisors, family members, colleagues and friends. First, I would like to thank my thesis advisor Dr. Allan B. Massie for his diligence, dedication and careful guidance throughout the whole process. When I first started working with Dr. Massie, I had little knowledge about the HCC and liver transplantation policy. He kindly welcomed me in their group, shared his expertise, and helped me to grow as an epidemiologist to develop this project. I will always be grateful for his gracious behavior towards me. I would also like to express my gratitude for Dr. Anne Rositch, who is my academic advisor and had an enormous impact on my two year journey in this master's program. I am also grateful to Dr. Dorry Segev who not only gave me an opportunity to work with Epidemiological Research Group in Organ Transplantation (ERGOT) but also graciously shared his insight on this project. I acknowledge the incredible help and support from my colleagues in ERGOT especially from Mary Grace Bowring, Xun Luo, Alvin Thomas, Jessica Ruck, Samantha Halpern, Corey Wickliffe and Nicole Zonnenberg. I want to specially thank Samantha Halpern for her constructive suggestions to improve my writing. My heartfelt gratitude to my parents and younger sister without whom I would not be at this prestigious platform. At last I want to express my sincere thanks to my husband for his unconditional love and support at each step to fulfil my dreams.

Table of Contents

List of Tables

List of figures

BACKGROUND

Hepatocellular carcinoma (HCC) is primary malignancy of the liver resulting from the abnormal growth of hepatocytes. Major risk factors for developing HCC include hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, heavy alcohol consumption, chronic liver disease, and cirrhosis (1). Obesity (2, 3), non-alcoholic fatty liver disease (1, 4), and diabetes (3, 5) have also been found to be associated with development of HCC.

Global epidemiology of HCC

Globally, the burden of HCC varies according to geographic region, occurring predominantly in men and following the distribution of endemic HBV infection (6). According to the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2012, HCC was the fifth most common cancer among men and ninth most common cancer in women, representing 7.5% (554,000 cases) of all male cancer cases and 3.4% (228,000 cases) of all female cancer cases. In 2012, HCC was the second most common cause of cancer-related death worldwide with an estimated 746,000 deaths (including male and female). Altogether, 9.1% of all cancer deaths in the world occur due to HCC, with the highest incidence of and mortality due to HCC occurring in Eastern Asia for both men and women. In 2012, the estimated age-standardized incidence rate of HCC for men in Eastern Asia was about 31.96 per 100,000 persons per year, while for women the estimated age-standardized incidence rate was about 10.02 per 100,000 persons per year. The estimated age-standardized rates of mortality due to HCC for men and women in Eastern Asia were about 30 per 100,000 persons per year and 9 per 100,000 persons per year respectively (7).

Epidemiology of HCC in the United States

According to the 2013 Surveillance, Epidemiology, and End Results (SEER), HCC is relatively rare in the United States. Based on reported cases in 2009-2013, the age-adjusted incidence rate of combined liver and bile duct cancer is 8.4 per 100,000 per year. In 2016, there were an estimated 39,230 new liver and bile duct cancer cases, representing 2.3% of all new cancer cases. However, the incidence rate has increased by 3% per year over the last ten years (8). Between 2000 and 2010, HCC incidence increased by 5.4% per year (2000-2007) and then 2.3% per year (2007-2010). The rate of increase was highest among persons aged 50-64 years. Between 2000 and 2010, there was also a rising of HCC incidence rate among white, black and Hispanic persons, while HCC incidence among Asians/Pacific Islanders showed a decreasing trend from 2002 to 2010. Overall age and race-specific incidence rates are higher among men compared to women (9).

Mortality of HCC in the United States

Based on 2009-2013 cancer deaths, the combined age-adjusted mortality rate for liver and bile duct cancer in the United States is 6.1 per 100,000 persons per year. In 2016, there were an estimated 27,170 deaths due to liver and bile duct cancer representing about 4.6% of all cancer deaths. The mortality rate for liver and bile duct cancer has been increasing by 2.5% per year for the last decade. Based on 2006-2012 SEER data, only 17.5% of liver and bile duct cancer patients survived 5 or more years after being diagnosed. However, if diagnosed at a localized stage, about 43% of liver and bile duct cancer patients survived 5 or more years after being diagnosed (8). In a study conducted using 1992-2005 SEER data,

age-adjusted mortality rates due to liver and bile duct cancer were found to be the highest among Asians/Pacific Islanders in the 35-49 and 65+ age groups (9). The same study showed that among those in the 50-65 age group, mortality was highest in Black, followed by Hispanics, Asians/Pacific Islanders, and Whites. Mortality rate also differs by state, ranging from 2.3-6.8 per 100,000 people with the highest mortality rate in Washington, DC and gulf coast states (5.6-5.8 per 100,000 people) (9). Between 2000 and 2010, mortality rate increased among persons aged 50-64 years in most states while it either decreased or remained constant among those aged 35-49 years (9).

Treatment options for HCC

Treatment selection for HCC depends primarily on the size, severity, and distribution of the underlying tumor and on the patient's physical condition. Tumor resection and liver transplantation are potentially curative treatment options for HCC (10, 11). Other treatment options for early HCC include radiofrequency ablation, microwave ablation, percutaneous ethanol injection (PEI), and percutaneous acetic acid injection (PAI). For intermediate and advanced stage HCC, treatment options are trans-arterial chemoembolization (TACE) and, in some cases, systemic chemotherapy (10-12).

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT) is usually suitable for early stage HCC patients with either a single lesion ≤5cm, or ≤3 nodules, each ≤3cm without any vascular or extrahepatic spread (10, 12). Several studies reported recurrence-free survival following OLT, and, in most cases, overall survival is better for liver transplant recipients compared to patients

undergoing surgical resection (10, 13, 14). A study of 11,187 HCC cases, using 2001-2009 SEER data, found that mortality within 2 years of HCC diagnosis for the surgical resection (N=2150) group was 44%, while it was only 29% for the liver transplant (N=296) group ($p<0.001$) (10)

Liver transplantation in the United States

In the United States, liver transplantation is performed using both living donors (LDLT) and deceased donors (DDLT). In 2012, a meta-analysis reported similar one, three and five year survival and recurrence rates of HCC for LDLT and DDLT recipients (15). However, controversy remains regarding the relative advantages of LDLT and DDLT (16, 17). Nevertheless, in the US more than 95% of OLT are DDLT (18, 19). Due to ethical debate regarding donor health, adult LDLT continues to be stagnant (19). Saidi et al. used data reported to the United Network for Organ Sharing (UNOS) to conduct a study of 6,028 HCC candidates who underwent LT (5,858 DDLT and 170 LDLT) between 1990 and 2009. In this study, there was an increase in the number of DDLT cases from 337 (2.3%) in 2002 to 1,142 (8.75%) in 2009 ($p<0.001$) among HCC candidates. In contrast, the number of LDLT cases among HCC candidates was similar, decreasing slightly from 16 (5.7%) in 2002 to 14 in 2009 (5.7%) ($p=0.1$) (20). According to the 2015 SRTR annual report, 6,768 of 7,127 adult LT procedures in 2015 were DDLT (21).

Development of allocation system for DDLT

In the United States there are 140 liver transplant centers, each of which is affiliated with a local organ procurement organization (OPO) (22). Each OPO is connected with one to eight transplant centers and is responsible for retrieving, preserving, and transporting donor

livers to regional liver transplant centers (22). Due to a constant organ shortage, a system was developed to prioritize the patients waiting for donor organs (22). Before 1997, waitlisted transplant candidates were stratified according to their hospital status (ICU patients, non-ICU hospitalized patients, ambulatory outpatient). Within each stratum, patients were prioritized according to their accrued waiting time. In 1998, a new allocation system was developed to classify transplant candidates as status 1, status 2A, status 2B, and status 3 based on their hospital status, Child-Turcotte-Pugh (CTP) score, and presence of sequelae of end stage liver disease (22). Child-Turcotte-Pugh (CTP) score is calculated from clinical and biochemical parameters and the total score was used to classify each patient as CTP class A (5-6 points), B (7-9 points), or C (≥10 points) (22). Within each stratum, candidates were again ranked according to accrued waiting time (22). As such, some patients with less medical urgency could have higher priority to receive a donor liver than patients with heightened medical urgency on the basis of longer accumulated waiting time (22). In addition, this system was highly dependent on subjective clinical assessment from physicians, which cannot be standardized (22).

The Model for End-Stage Liver Disease (MELD) score

Liver allocation policy was changed on February 27, 2002, granting priority to waitlisted candidates based only on their medical urgency as determined by the Model for End-Stage Liver Disease (MELD) score as opposed to on accrued waiting time (22). MELD score is a reliable measure of short-term mortality risk for patients with liver failure (27) which is calculated from serum bilirubin, serum creatinine, and international normalized ratio (INR) and ranges from 6 (least urgent) to 40 (most urgent) (23).

Factors related to DDLT

Using data from the Scientific Registry of Transplant Recipients (SRTR), a study, conducted on 57,503 adult waitlisted transplant candidates from 2002 to 2008, reported that blood group, and donation service area (the geographic area served by single OPO) were associated with access to DDLT (24). According to the findings of this study, candidate age, height, diagnosis, hospitalization, and combined liver-intestine or liver-kidney listing were associated with higher rates of DDLT (24). In contrast, female sex, higher serum creatinine (S. Cr), higher bilirubin, dialysis, and prior liver transplant were associated with lower rates of DDLT (24). In another study using 2002-2007 SRTR data, Black transplant candidates were found to have similar access to DDLT compared to white candidates, while Hispanic and Asian candidates had lower rates of DDLT compared to white transplant candidates (25).

Eligibility criteria for HCC Liver transplantation candidates

In 1996, Mozzafero et al. studied the outcomes of 48 cirrhosis patients with HCC who underwent OLT and found overall and recurrence-free survival at four years post-OLT to be 85% and 92% respectively for HCC patients with small tumors inside the Milan criteria (single nodule ≤5 cm; up to three nodules ≤3cm; and without macrovascular invasion or extra hepatic disease) (26). However, in cases in which the tumor exceeded the parameters specified by the Milan criteria, overall and recurrence-free survival rates decreased to 50% and 59% respectively (26). A later single center study of 489 HCC patients undergoing liver transplantation between 1985 and 2003 reconfirmed the bad prognosis following OLT

for HCC patients with tumors falling outside the Milan criteria (27). In 1998, the Organ Procurement and Transplantation Network (OPTN) adopted the Milan criteria and considered HCC candidates fulfilling these criteria to be eligible for DDLT (28).

Liver allocation system for eligible HCC candidates

HCC candidates who meet the Milan criteria usually have low MELD scores since underlying liver functions are often well preserved in these patients (22). Thus, if HCC candidates are only evaluated for transplant according to their calculated MELD scores, they will endure long waiting times prior to transplantation. During this time, HCC candidates' tumors will either grow larger or spread to other parts of the body, making these candidates ineligible for transplant (outside of Milan criteria). Therefore, the chances of waitlist mortality/dropout are heightened for HCC candidates if they are assessed only by their calculated MELD scores (22). To establish a fair chance of liver allocation for HCC candidates and to avoid higher rates of waitlist dropout, HCC candidates are granted MELD exception points equivalent to certain MELD scores from the beginning of the MELD era (29). This change results in higher DDLT rate, shorter median time to DDLT, and lower dropout rate for HCC candidates compared to the previous era (28).

Modification of policy regarding exception score for HCC candidates

To increase the efficiency of the organ allocation system and to establish an equity between HCC and non-HCC candidates, the policy regarding standardized MELD exception scores was modified on several occasions, the first of which occurred in 2002 (Table 1) (30). In 2005, the exception point policy was revised such that HCC candidates fulfilling the Milan

criteria automatically received MELD scores of 22, 25, and 28 during initial application, first extension (3 months) and second extension (6 months), respectively (31).

Disparity in access to DDLT

Even after changing the initial exception point from 24 to 22, there was concern about disparities in organ allocation for HCC candidates compared to non-HCC candidates (32, 33). A study by Sharma et al. reported that HCC candidates had a 26% higher chance of getting transplanted compared to non-HCC patients (24, 34). In addition, non-HCC candidates also had higher rates of waitlist mortality/dropout compared to HCC exception patients at 30 (6% vs 1.8%), 60 (8.4% vs 3.6%), 90 (10.2% vs. 5.1%), 180 (13.6% vs. 8.6%) and 365 (17.7% vs. 11.5%) days (32, 34). The odds of waitlist dropout were also significantly higher among non-HCC candidates compared to HCC candidates (33, 35, 36). Additionally, the risk of waitlist removal increased over time for non-HCC candidates, but remained stable for HCC candidates (33).

Revised policy for exception point allocation in October 2015

To reduce the disparity in access to DDLT between HCC and non-HCC candidates, OPTN changed the policy regarding MELD exception points again in October 2015. Under the new policy, HCC candidates who meet the Milan criteria acquire a first exception score of 28 six months after their initial exception point application (37). Under this policy, HCC candidates are registered at their calculated MELD scores during initial application for exception points and also at first extension (3 months) (37). The October 2015 exception point policy also states that the exception point will be capped at 34 for all candidates. For

candidates who already had MELD exception scores of 35-40, it would also be capped at 34 (31, 37, 38).

Study rationale and objectives

To assess the effectiveness of the revised MELD exception point policy (October 2015), OPTN's public comment proposal suggested a pre- vs. post-policy implementation analysis at six-month intervals with fixed metrics, including waitlist outcomes (probability of removal for transplant, mortality, dropout due to deteriorating condition) for approved requests (39). In response to the OPTN proposal, and to address the question of changes in access to DDLT for HCC and non-HCC patients following the recent policy change, we conducted a retrospective cohort study using national registry data to estimate the association between access to transplant and HCC in both the pre-policy-implementation and post-policy-implementation periods. We also explored the risk of waitlist mortality or dropout for HCC and non-HCC candidates before and after the policy change.

The findings from this study will inform the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee as to whether the new policy achieves the desired equity in access to DDLT between HCC and non-HCC candidates without modifying the risk of waitlist mortality.

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 Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere (40, 41). 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.

This study utilized de-identified data and has been exempted by the Johns Hopkins School of Medicine Institutional Review Board (study number NA_00042871).

Study population

Our study population consisted of 29,249 adult first-time transplant candidates prevalently listed for DDLT at any time between October 8, 2014 and July 1, 2016. We excluded candidates who first became active on the waitlist before January 1, 2007 to prevent any possible effects of different organ allocation policies on access to transplantation. We also excluded live donor recipients and patients who were ever classified as Status 1 (Figure 1).

Person-time

Time of origin for waitlisted candidates was their date of enrollment for this study (the later of their first date of waitlist registration or October 8, 2014). All waitlisted candidates were either administratively censored on July 31, 2016 or removed due to transplant, waitlist

mortality/dropout, or censored if removed from the waitlist for reasons such as transfer to another center, transplant at a different center, or improved condition.

Outcome ascertainment

The primary outcome of this study was DDLT, which was ascertained from the SRTR registry. Patient mortality was ascertained from SRTR and supplemented with linkage to the Social Security Death Master File. Removal from the waitlist due to deteriorating condition (dropout) was treated as equivalent to waitlist mortality.

Exposure ascertainment

Hepatocellular carcinoma: Candidates were considered to have hepatocellular carcinoma (HCC) if they received a MELD exception point for HCC. Candidates with no MELD exception and who did not have a diagnosis of HCC were regarded as non-HCC candidates. Candidates with a diagnosis of HCC who did not receive a MELD exception (N=1097), or who received a MELD exception but who had no diagnosis of HCC (N=382), were excluded from analysis.

Policy era: The change in allocation policy for DDLT with regards to MELD exception points was implemented on October 8, 2015. We therefore divided transplant candidates in our study population into two eras: pre-implementation (October 8, 2014 to October 7, 2015) and post-implementation (October 8, 2015 to July 31, 2016). HCC patients who applied for MELD exception during the pre-implementation era, and non-HCC patients who entered the study during the pre-implementation era, were classified as "pre-

implementation" even after October 8, 2015; in other words, era was not a time-varying exposure.

Other variables

Model of End-stage Liver Disease (MELD) score: MELD score for each individual was calculated from the laboratory values of creatinine, bilirubin, and INR (42) and was designated "calculated MELD (cMELD)" for this study. We also used "allocation MELD (aMELD)" to denote MELD score that was used to decide a candidate's priority for liver allocation. In nonexception cases, allocation MELD and calculated MELD had the same value. For exception cases, allocation MELD was the larger of calculated MELD or exception MELD. MELD score was treated as time-varying due to variation in MELD score over time depending on a candidate's physical condition. Candidates who were temporarily inactive on the waitlist were not excluded from the primary analysis since they were still at risk for death.

Age and race: Age was dichotomized as 18-49 years and >50 years, based on Martingale residual plots. Race was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and Other.

Statistical analysis

Descriptive analysis: All statistical analyses were performed using Stata 14.2 for Linux (Stata Corp., College Station, TX). HCC and non-HCC candidates were compared using chi-squared and Fisher's exact tests for categorical variables and unpaired t-tests or

Wilcoxon rank sum tests for continuous variables with normal or non-normal distributions respectively. 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 (4).

Cumulative incidence of waitlist mortality/dropout and transplantation: Cumulative incidence of DDLT accounting for the competing risk of waitlist mortality/dropout was estimated for each era as described by Coviello et al. (43); for each era, we estimated the cumulative incidence of DDLT overall and for each of four different strata of calculated MELD (6-10, 11-18, 19-24, and 25-40). Cumulative incidence of waitlist mortality/dropout accounting for the competing risk of DDLT was estimated using the same techniques.

Transplant rates for HCC and non-HCC patients pre- and post-policy change: We used a Cox proportional hazards model to compare rates of DDLT among HCC versus non-HCC patients, both pre- and post-policy change, adjusting for age, gender, race, and calculated MELD. This model treated the competing event as a censored observation and did not assume independence between the two events. Thus, cause specific hazard ratio (CSHR) provides only the association between the exposure and the outcome and should not be interpreted directly as a cumulative incidence function (44). Similarly, we conducted a competing risk analysis using the Fine and Gray method (45) to account for the fact that waitlist mortality/dropout prevents access to DDLT.

Waitlist mortality/dropout for HCC and non-HCC patients, accounting for the competing risk of transplantation: We compared mortality/dropout for HCC versus non-HCC

patients, accounting for the competing risk of transplant, pre- and post-policy implementation using the Fine and Gray method (45). This method models subdistribution hazard ratio (sub-HR) for both events between HCC and non-HCC candidates after accounting for the fact that the two events preclude each other. In this method, candidates were not censored even if they had the competing event and were allowed direct modeling of sub-distribution cumulative incidence function (CIF) (44). Competing risks analyses were performed for the entire cohort, and stratified by MELD category as described above. We also constructed a separate model using Cox regression to compare rates of waitlist mortality/dropout among HCC versus non-HCC patients.

Sensitivity analysis

Although candidates who were temporarily inactive on the waitlist were at risk of mortality, they were not considered eligible for DDLT. Therefore, we excluded candidates who were inactive on the waitlist at any point during the study period and ran the same models as a sensitivity analysis.

RESULTS

Study population

During the pre-implementation era, 4,716 of 21,984 candidates (21.4%) had HCC compared to 2,084 of 7,775 candidates (26.8%) during the post-implementation era. Compared to non-HCC candidates in both eras, HCC candidates were older (median (IQR) age 61 (57-65) years vs. 57 (57-65) years, $p<0.001$), and were more likely to be male (76% vs. 59%, $p<0.001$). The racial distribution was similar in both eras and most HCC and non-HCC waitlist candidates were white (pre-implementation 63% vs. 72.4%, $p<0.001$; post-implementation 64% vs. 71.9%, $p<0.001$). Among HCC and non-HCC candidates during both periods, blood type O was the most common (pre-implementation 47.3% vs. 46.5%; post-implementation 46.8% vs. 47.0%) (Table 2).

At baseline, HCC candidates had median calculated MELD of 10 (IQR 8-14) in both eras. Pre-implementation, median calculated MELD among non-HCC candidates was 15 (IQR 11-20), while post-implementation, median calculated MELD among non-HCC candidates was 19 (IQR 14-26). In the pre-implementation era, allocation MELD was higher for HCC candidates compared to non-HCC candidates (median (IQR) aMELD 22 (22-25) vs. 16 (11-22), $p<0.001$). However, in the post-implementation era, allocation MELD was significantly lower among HCC candidates compared to non-HCC candidates (median (IQR) aMELD 11 (8-15) vs. 20 (15-28), $p<0.001$). Hepatitis C cirrhosis (pre-implementation 39.6% vs post-implementation 35.9%), hepatoma with cirrhosis (pre-implementation 19.5% vs post-implementation 21.9%), alcoholic cirrhosis (pre-implementation 11.7% vs post-implementation 12.9%), and hepatoma without cirrhosis (pre-implementation 12.1% vs post-implementation 10.7%) were the most common

primary diagnoses for HCC candidates regardless of the policy era. Alcoholic cirrhosis (pre-implementation 30.3% vs post-implementation 33.7%), fatty liver disease (pre-implementation 15.3% vs post-implementation 20.2%), and hepatitis C cirrhosis (pre-implementation 22.4% vs post-implementation 13.1%) were the most common primary diagnoses for non-HCC waitlist candidates.

Access to DDLT

During the pre-implementation era, the incidence of DDLT was 35.7% among HCC candidates compared to 18.7% among non-HCC candidates. Conversely, during the post-implementation era, the incidence of DDLT was 42.7% among non-HCC candidates compared to 11.2% among HCC candidates (Figure 2).

Access to DDLT across MELD strata

Pre-implementation, the incidence of DDLT at 6 months was higher among HCC candidates compared to non-HCC candidates in calculated MELD strata 6-10 (29.5 % vs. 0.59%), 11-18 (30.8 % vs. 4.5%), and 19-24 (22.2% vs. 12.9%). In calculated MELD stratum 25-40, HCC candidates had lower access to DDLT compared to non-HCC candidates (32.8% vs. 44.3%) (Figure 3).

Post-implementation, HCC and non-HCC candidates had similar incidence of DDLT at 6 months in calculated MELD strata 6-10 (5.1% vs. 3.7%) and 11-18 (12.0% vs. 15.8%). However, HCC candidates had lower incidence of DDLT compared to non-HCC

candidates in calculated MELD strata 19-24 (13.3% vs. 33.7%) and 25-40 (67.0% vs. 27.4%) (Figure 4).

Waitlist mortality/dropout

Among all transplant candidates, HCC candidates had slightly lower incidence of waitlist mortality/dropout compared to non-HCC candidates in both eras (pre-implementation 6% vs. 9%; post implementation 6% vs. 10%) (Figure 5).

Waitlist mortality/dropout across MELD strata

Pre-implementation, incidence of waitlist mortality/dropout was higher among HCC candidates compared to non-HCC candidates in MELD strata 6-10 (3.1% vs. 1.3%), 11-18 (5.7% vs. 3.5%), 19-24 (11.0% vs. 5.7%) and 25-40 (25% vs. 19.9%) (Figure 6).

Post-implementation, incidence of waitlist mortality/dropout was 1.64% for both HCC and non-HCC candidates in MELD stratum 6-10. However, HCC candidates had slightly higher incidence of waitlist mortality/dropout in MELD strata 11-18 (5.8% vs. 3.9%) and 19-24 (9.8% vs. 5.8%). In MELD stratum 25-40, waitlist mortality/dropout was 44.5% among HCC candidates versus 21.8% among non-HCC candidates (Figure 7).

HCC and DDLT rate pre-and post-implementation

In an adjusted model, access to DDLT was 5-fold higher for HCC candidates compared to non-HCC candidates during the pre-implementation period (aCSHR = $_{5.32}$ 5.61 $_{5.91}$, $p<0.001$) (Table 3). During the post implementation era, there was no evidence of a difference in access to DDLT among HCC and non-HCC candidates (aCSHR= $_{0.81}$ 0.93

$_{1.07}$, p>0.1). The change in association between HCC and access to DDLT from pre-implementation to post-implementation was statistically significant (interaction p<0.001) (Table 3).

Waitlisted candidates older than 50 years of age had 1.11 fold higher access to DDLT compared to candidates aged 18-50 (aCSHR = $_{1.06}$ 1.11 $_{1.17}$, p<0.001). Female candidates had 18% lower access to DDLT compared to male candidates (aCSHR = $_{0.79}$ 0.82 $_{0.86}$, p<0.001). Compared to white candidates, Black candidates had similar access to DDLT (aCSHR = $_{0.90}$ 0.97 $_{1.04}$, p>0.1). However, compared to white candidates, Hispanic candidates and those of other races had 35% (aCSHR = $_{0.61}$ 0.65 $_{0.69}$, p<0.001) and 19% lower access to DDLT (aCSHR = $_{0.74}$ 0.81 $_{0.89}$, p<0.001) respectively. Access to DDLT for waitlisted candidates was 2.25 fold higher with 5 points increase in calculated MELD scores (aCSHR = $_{2.23}$ 2.25 $_{2.28}$, p<0.001) (Table 3). Table-3 also showed the result from the competing risk model.

HCC and DDLT rate across MELD strata

Calculated MELD 6-10: Pre-implementation, HCC candidates had 114.49 fold greater access to DDLT compared to non-HCC candidates after adjusting for age, gender, race, and calculated MELD (aCSHR = $_{82.26}$ 114.49 $_{159.35}$, p <0.001). Post-implementation, the association between HCC and access to DDLT persisted, but was attenuated to only 2.91 fold higher access to DDLT for HCC candidates compared to non-HCC candidates (aCSHR = $_{1.64}$ 2.91 $_{5.18}$, p<0.001). The difference in pre- and post-implementation association between HCC and access to DDLT was statistically significant (interaction p<0.001) (Table 5).

Calculated MELD 11-18: Pre-implementation, HCC candidates had 10.70 fold higher access to DDLT compared to non-HCC candidates (aCSHR = $_{9.67}$ 10.70 $_{11.83}$, $p<0.001$). Post-implementation, HCC and non-HCC candidates had similar access to DDLT (aCSHR = $_{0.75}$ 0.94 $_{1.18}$, $p>0.1$). The difference in pre- and post-implementation association between HCC and access to DDLT was statistically significant (interaction $p<0.001$) (Table 5).

Calculated MELD 19-24: Pre-implementation, HCC candidates had 2.18 fold higher access to DDLT compared to non-HCC candidates (aCSHR = $_{1.85}$ 2.18 $_{2.57}$, $p<0.001$). Post-implementation, access to DDLT was attenuated for HCC candidates compared to non-HCC candidates: HCC candidates had 61% lower access to DDLT compared to non-HCC candidates (aCSHR = $_{0.27}$ 0.39 $_{0.58}$, $p<0.001$). The difference in pre- and post-implementation association between HCC and access to DDLT was statistically significant (interaction $p<0.001$) (Table 5).

Calculated MELD 25-40: Pre-implementation, HCC candidates had 42% lower access to DDLT than non-HCC candidates (aCSHR = $_{0.48}$ 0.58 $_{0.69}$, $p<0.001$). Post-implementation, access to DDLT was substantially reduced for HCC candidates compared to non-HCC candidates after adjustment. HCC candidates had 73% lower access to DDLT compared to non-HCC candidates (aCSHR = $_{0.18}$ 0.27 $_{0.40}$, $p<0.001$). The difference in pre- and post-implementation association between HCC and access to DDLT was statistically significant (interaction $p<0.001$) (Table 5).

HCC, DDLT, and waitlist mortality/dropout pre- and post-implementation

After taking into account the fact that transplantation precludes waitlist mortality/dropout, HCC candidates were at higher risk of waitlist mortality/dropout compared to non-HCC candidates when adjusting for age, gender, race, and calculated MELD. Pre-implementation, the risk of waitlist mortality/dropout was 1.30 fold higher for HCC candidates compared to non-HCC candidates (asHR = $_{1.15}$1.30 $_{1.46}$, p<0.001). Post-implementation, the risk of waitlist mortality/dropout for HCC candidates increased further up to 2.18 folds higher compared to non-HCC candidates (asHR = $_{1.69}$ 2.18 $_{2.80}$, p<0.001). The difference in pre- and post-implementation association between HCC and waitlist mortality/dropout was statistically significant (interaction p<0.001) (Table 4).

Age >50 years (asHR = $_{1.75}$ 1.93 $_{2.12}$, p<0.001), female gender (asHR = $_{1.06}$ 1.15 $_{1.24}$, p<0.001) and 5 point increase in calculated MELD score (asHR = $_{1.69}$ 1.72 $_{1.75}$, p<0.001) were identified as risk factors for increased risk of waitlist mortality/dropout. White and Hispanic candidates had similar risks of waitlist mortality/dropout (asHR= $_{0.88}$ 0.97 $_{1.07}$, p>0.1). Black and those of other race had 23% (asHR = $_{0.66}$ 0.77 $_{0.89}$, p<0.001) and 20% (asHR=$_{0.67}$ 0.80 $_{0.96}$, p=.017) lower risks of waitlist mortality/dropout compared to white respectively (Table 4).

HCC, DDLT, and waitlist mortality/dropout across MELD strata

Calculated MELD 6-10: Within this stratum, the risk of waitlist mortality/dropout was 39% higher among HCC candidates compared to non-HCC candidates in the pre-implementation era (asHR = $_{1.01}$ 1.39 $_{1.92}$, p=0.046) Post-implementation, HCC and non-

HCC candidates had comparable risks of waitlist mortality/dropout (asHR = $_{0.18}$ 0.53 $_{1.54}$, p>0.1) (Table 5). The difference in pre- and post-implementation association between HCC and risk of waitlist mortality/dropout was not statistically significant (interaction p=0.08)

Calculated MELD 11-18: Pre-implementation, HCC and non-HCC candidates had comparable risks of waitlist mortality/dropout (asHR = $_{0.98}$ 1.18 $_{1.43}$, p=0.08). Post-implementation, HCC candidates had 1.71 times higher risks of waitlist mortality/dropout compared to non-HCC candidates (asHR = $_{1.02}$ 1.71 $_{2.86}$, p=0.04) (Table 5). The difference in pre- and post-implementation association between HCC and risk of waitlist mortality/dropout was not statistically significant (interaction p-value >0.1).

Calculated MELD 19-24: Pre-implementation, the risk of waitlist mortality/dropout for HCC candidates was 1.64 folds higher (asHR = $_{1.27}$ 1.64 $_{2.11}$, p<0.001) compared to non-HCC candidates. Risk of waitlist mortality/dropout increased to 1.82 fold among HCC candidates compared to non-HCC candidates post-implementation (asHR = $_{1.02}$ 1.82 $_{3.25}$, p=0.04). The difference in pre- and post-implementation association between HCC and risk of waitlist mortality/dropout was not statistically significant (interaction p-value >0.1) (Table 5).

Calculated MELD 25-40: Pre-implementation, the risk of waitlist mortality/dropout for HCC candidates was found to be 1.31 fold higher than that for non-HCC candidates (asHR = $_{1.08}$ 1.31 $_{1.58}$, p<0.01). Post-implementation, the risk of waitlist mortality/dropout increased to 3.11 fold higher for HCC candidates compared to non-HCC candidates (asHR

= 2.19 3.11 4.42, p<0.001). The difference in pre- and post-implementation association between HCC and risk of waitlist mortality/dropout was statistically significant (interaction p<0.001).

DISCUSSION

In this study of access to DDLT among HCC and non-HCC candidates before and after the October 2015 policy change regarding MELD exception points for HCC candidates, we found that, compared to non-HCC candidates, HCC candidates had higher access to DDLT in the pre-implementation period. However, in the post-implementation period, HCC and non-HCC candidates had similar access to DDLT. Additionally, the risk of waitlist mortality/dropout for HCC candidates increased from 1.3-fold in the pre-implementation era to 2.18-fold in the post-implementation period compared to non-HCC candidates.

We found that, in the pre-implementation period, HCC candidates had a higher rate of DDLT compared to non-HCC candidates. Previous studies by Washburn et al. and Goldber et al. found that the current liver allocation system favors HCC candidates over non-HCC candidates, as evidenced by the lower rate of waitlist mortality/dropout among HCC candidates (32, 33). Northup et al. also reported similar findings, indicating a higher rate of DDLT and lower rate of waitlist mortality/dropout for candidates with exception points, such as HCC candidates (34). Our current study showed that these disparities between HCC and non-HCC candidates with regards to the rates of DDLT and waitlist mortality/dropout persisted until the October 2015 MELD exception point policy change. Our group also previously used 2002-2010 OPTN data to describe these disparities, finding that HCC candidates were advantaged with regards to DDLT organ allocation in the pre-implementation period as compared to non-HCC candidates (36). The present study extends our prior work by reporting the rate of DDLT across strata of calculated MELD,

and by comparing rates of DDLT in the pre-implementation and post-implementation periods.

We reported that HCC and non-HCC candidates had similar access to DDLT in the post-implementation period. Two studies have previously predicted a reduced disparity in access to DDLT between HCC and non-HCC candidates accounting for the 6 month delay in exception point allocation using UNOS data from the pre-implementation period (46, 47). Applying liver simulation allocation modeling (LSAM) on waitlisted candidates from the year 2010, Heimbach et al. predicted that a 6 month delay in exception point allocation would diminish the disparity in access to DDLT between HCC and non-HCC candidates (44.2 vs. 33.9 per 100 person-years) (46). Similarly, Alver et al. used 2009-2014 UNOS data to construct a non-parametric multistate model for predicting probabilities of transplant and waitlist mortality/dropout for HCC and non-HCC candidates in both the pre-implementation and post-implementation eras. In this study, Alver et al. reported lower access to DDLT for HCC candidates compared to non-HCC candidates (8.2% vs. 41.2%) at 6 months and improved equity at 1 year (45.9% vs. 46.8%). Our study findings are consistent with these predictions, demonstrating that the overall rate of DDLT was similar between HCC and non-HCC candidates during the post-implementation period (aCSHR = $_{0.81}$ 0.93 $_{1.07}$). However, in the same study, Alver et al. also predicted that this improved equity in access to DDLT among HCC and non-HCC candidates would subsequently diminish after 1 year, again resulting in an advantage for HCC candidates compared to non-HCC candidates (70.2% vs. 50.1% at 18 month, 78.3% vs. 52.2% at 24 month and 83.8% vs. 54.9% at 36 months) (47). Since our study is limited to only the first 8 months

post-implementation, further studies are needed to investigate the equity in transplant rate between HCC and non- HCC candidates after 6 month.

In a recent study, Marvin et al. used 2005-2009 UNOS data to predict the probabilities of waitlist mortality/dropout and transplantation considering the six month delay in exception point allocation (48). Using multistate models in different strata of an alternative MELD score named equivalent MELD ($MELD_{EQ}$ = max[$MELD_{CALQ-EQ}$, calculated MELD]), in which $MELD_{CALQ-EQ}$ was determined by equating the hazards of waitlist dropout for HCC and non-HCC candidates based on other covariates and their calculated MELD scores, Marvin et al. reported an increased risk of waitlist mortality/dropout among HCC candidates with higher $MELD_{EQ}$ versus a decreased risk of waitlist mortality/dropout among HCC candidates with lower $MELD_{EQ}$ (48). The results of our study extend Marvin et al.'s findings by showing that this relationship holds in the post-implementation era and after accounting for the competing risk of transplantation. Furthermore, our finding that, in the post-implementation period, HCC candidates in higher MELD strata (19-24, 25-40) had a lower rate of DDLT and a higher risk of waitlist mortality/dropout bolsters Marvin et al.'s case that an improved system is needed for prioritizing HCC patients with higher calculated MELD (48).

Our study must be understood in the context of several limitations. Due to concerns about potential reporting bias we are only able to study waitlist mortality/dropout for the first 8 months following the October 2015 exception point policy change. Thus, it remains uncertain whether the patterns we identified will persist. 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 what factors were available in this database; for instance, we were unable to adjust for factors such as pre-transplant HCC treatment as such covariates were not available in our data. 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 rates of DDLT and risk of waitlist mortality/dropout in light of recent changes to the policy regarding exception point allocation for HCC liver transplant 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/dropout.

In conclusion, our findings from this national registry-based study of access to DDLT among HCC and non-HCC transplant candidates suggest that post implementation of the October 2015 MELD exception point allocation policy, the disparity in access to DDLT among HCC and non-HCC candidates was eliminated while the risk of waitlist mortality/dropout increased almost 2-fold for HCC candidates compared to non-HCC candidates. The relationship between HCC and rate of DDLT varied across different strata

of calculated MELD in both the pre- and post-implementation periods. In lower MELD strata (6-10, 11-18), discrimination regarding organ allocation between HCC and non-HCC candidates was reduced post-implementation, however the risk of waitlist mortality/dropout did not change. In higher MELD strata (19-24, 25-40), there was decreased access to DDLT for HCC candidates in the post-implementation period along with a corresponding increase in the risk of waitlist mortality/dropout for HCC candidates compared to non-HCC candidates.

Further research is needed to explore post-transplant outcomes for HCC candidates who had a 6 month delay in getting their first exception point. Additional investigation is also necessary to explore geographic disparity in access to DDLT under the new policy since several studies reported about existing geographic disparity in liver allocation (49, 50)..

Our study findings show that after the policy change, there was a reducion in disparity between HCC and non-HCC candidates within lower calculated MELD strata (6-10, 11-18). However, under the new policy, HCC candidates within higher calculated MELD strata (19-24, 25-40) also had lower access to DDLT. Therefore, revision to the exception point allocation policy for HCC candidates may be warranted.

APPENDICES

Table 1: Modification of standardized exception score from 2002-2015

HCC	Initial standardized MELD exception score				
	Feb 2002	Feb 2003	Apr 2004	Mar 2005	Oct 2015
Stage I	24	20	Calculated MELD	Calculated MELD	Calculated MELD
Stage II	29	24	24	22	Calculated MELD

Table 2. Baseline characteristics of the study population

	Pre-implementation (N=21984)		Post-implementation (N=7775)	
	HCC	Non-HCC	HCC	Non-HCC
N (%)	4716 (21.4%)	17268 (78.6%)	2084 (26.8%)	5691 (73.2%)
Median Age (IQR) age	61 (57-65)	57 (50-62)	61 (57-65)	56 (48--62)
Female (%)	23.6	40.3	24.0	40.8
Race				
White (%)	63.3	72.4	64.3	71.9
Black (%)	10.1	7.5	9.3	7.3
Hispanic/Latino (%)	17.2	15.4	18.1	15.7
Other (%)	9.3	4.6	8.2	4.8
Blood group type (%)				
O	47.3	46.5	46.8	47.0
A	37.1	38.6	36.8	36.8
B	12.5	12.1	12.9	12.2
AB	2.9	2.7	3.3	3.9
Median (IQR) calculated MELD	10 (8-14)	15 (11-20)	10 (8-14)	19 (14-26)
Median (IQR) allocation MELD	22 (22-25)	16 (11-22)	11 (8-15)	20 (15-28)
Primary Diagnosis (%)				
Hepatoma	12.1	0	10.7	0
Hepatoma with cirrhosis	19.5	0	21.9	0
Cirrhosis with Hepatitis C	39.6	22.4	35.9	13.1
Cirrhosis with Hepatitis B	3.3	1.8	2.5	1.6
Alcoholic cirrhosis with/without Hepatitis C	11.7	30.3	12.9	33.7
Fatty liver	6.1	15.3	8.8	20.2
Cryptogenic	1.6	6.3	1.9	6.0
Autoimmune	0.8	4.1	0.4	4.2
Other	4.9	19.6	4.6	20.9

Table 3. DDLT candidate characteristics associated with access to DDLT, regardless of mortality/dropout (Cox) and accounting for waitlist mortality/dropout as a competing risk (CR)

	Cox	**CR**
HCC (pre-implementation)	5.61 (5.32 5.91)	4.43 (4.14 4.74)
HCC (post-implementation)	0.93 (0.81 1.07)	0.71 (0.61 0.83)
Age >50 year	1.11 (1.06 1.17)	0.92 (0.86 0.97)
Female	0.82 (0.79 0.86)	0.82 (0.77 0.86)
White	ref	ref
Black	0.97 (0.90 1.04)	1.01 (0.91 1.10)
Hispanic/Latino	0.65 (0.61 0.69)	0.70 (0.65 0.75)
Other	0.81 (0.74 0.89)	0.85 (0.76 0.95)
Calculated MELD (per 5 units)	2.25 (2.23 2.28)	1.64 (1.62 1.67)
p-value for HCC and policy intercation	<0.001	<0.001

Cox= Cox regression; CR=competing risk analysis

Table 4. DDLT candidate characteristics associated with waitlist mortality/dropout, regardless of access to DDLT (Cox) and accounting for access to DDLT as a competing risk (CR)

	Cox	CR
HCC (pre-implementation)	1.61 (1.45 1.79)	1.30 (1.15 1.46)
HCC (post-implementation)	1.57 (1.24 1.99)	2.18 (1.69 2.80)
Age >50 year	1.99 (1.82 2.17)	1.93 (1.75 2.12)
Female	1.01 (0.93 1.07)	1.15 (1.06 1.24)
White	ref	ref
Black	0.75 (0.66 0.86)	0.77 (0.66 0.89)
Hispanic/Latino	0.78 (0.72 0.86)	0.97 (0.88 1.07)
Other	0.65 (0.55 0.77)	0.80 (0.67 0.96)
Calculated MELD/5	2.85 (2.79 2.90)	1.72 (1.69 1.75)
p-value for HCC and policy intercation	0.8	<0.001

Cox= Cox regression; CR=competing risk analysis

Table 5. Access to DDLT and waitlist mortality/dropout, pre- & post implementation across MELD strata HCC candidate's pre- and post-policy change

	DDLT rate: HCC vs non-HCC		Waitlist mortality/dropout accounting for competing risk of DDLT: HCC vs non-HCC	
MELD range	Pre-implementation	Post-implementation	Pre-implementation	Post-implementation
6-10	114.49 (82.26 159.35)	2.91 (1.64 5.18)	1.39 (1.01 1.92)	0.53 (0.18 1.54)
11-18	10.70 (9.67 11.83)	0.94 (0.75 1.18)	1.18 (0.98 1.43)	1.71 (1.02 2.86)
19-24	2.18 (1.85 2.57)	0.39 (0.27 0.58)	1.64 (1.27 2.11)	1.82 (1.02 3.25)
25-40	0.58 (0.48 0.69)	0.27 (0.18 0.40)	1.31 (1.08 1.58)	3.11 (2.18 4.42)

Figure 1. Study Population

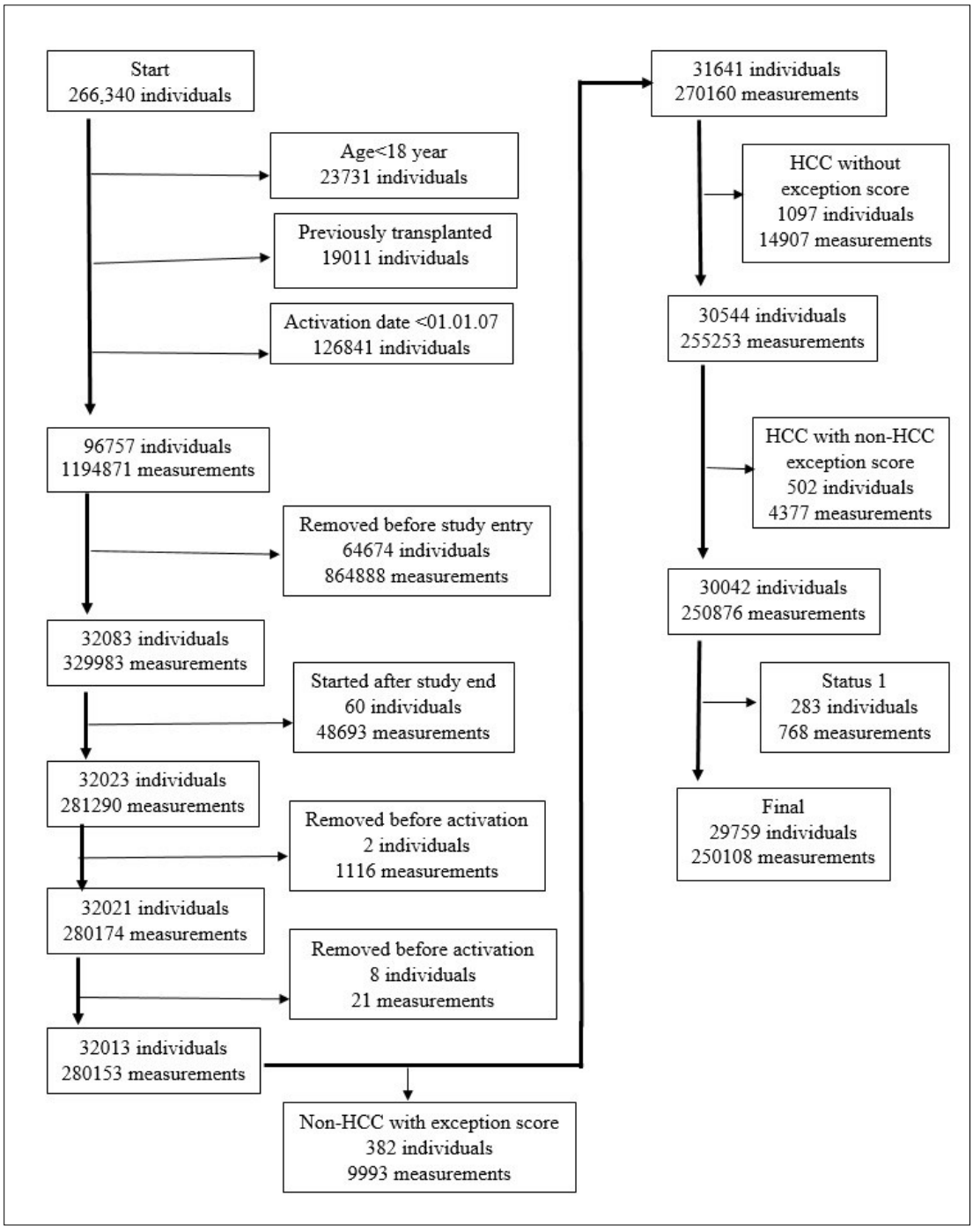


Figure 2. Cumulative incidence of DDLT for HCC and non-HCC candidates, treating waitlist mortality/dropout as a competing risk. Pre-implementation, cumulative incidence of transplantation was substantially higher for HCC candidates than for non-HCC candidates; post-implementation, cumulative incidence of transplantation was lower for HCC candidates.

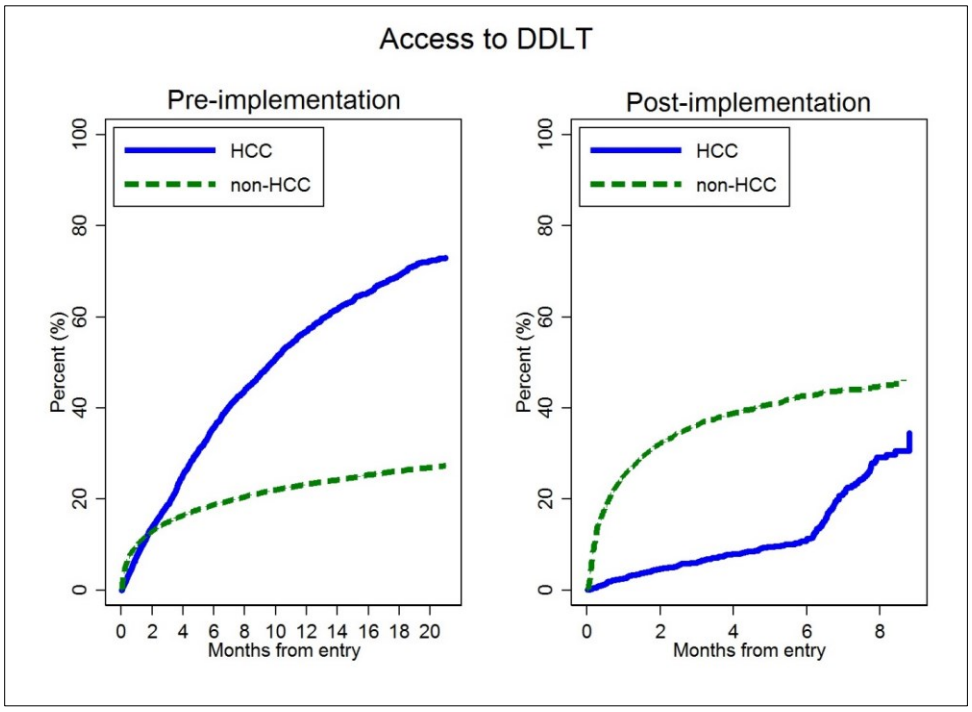


Figure 3. Access to DDLT for HCC and non-HCC candidates, pre-implementation, across MELD strata, treating waitlist mortality/dropout as a competing risk. Cumulative incidence of transplantation was substantially higher for HCC candidates than for non-HCC candidates in MELD strata 6-10, 11-18 and 19-24 but lower in MELD strata 25-40.

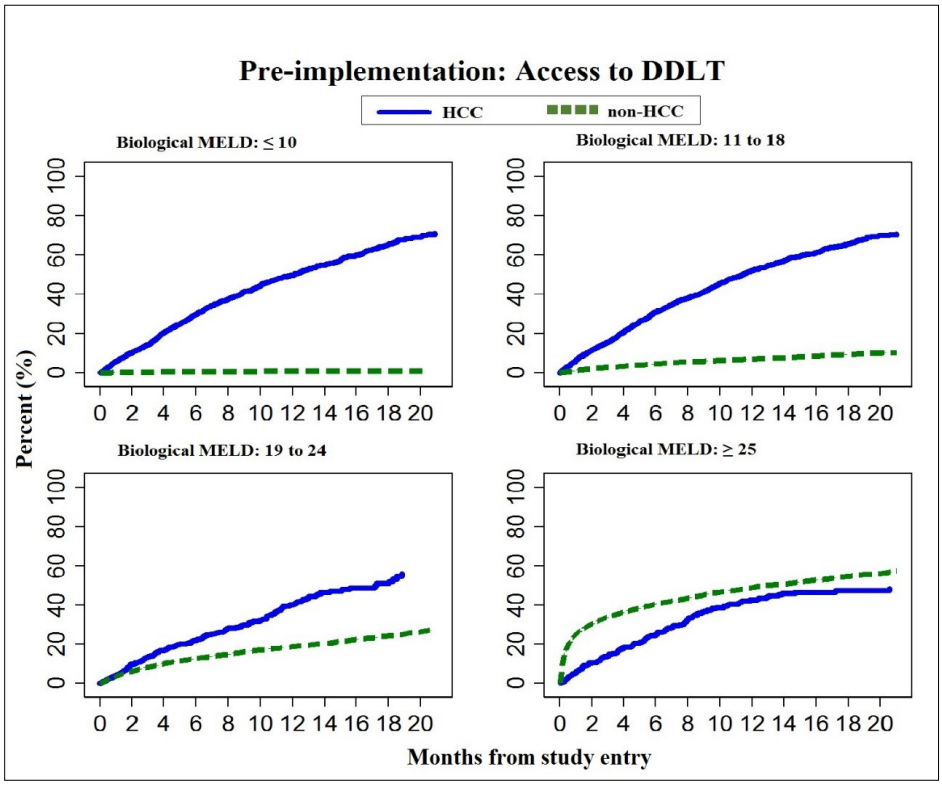


Figure 4. Access to DDLT for HCC and non-HCC candidates, post-implementation, stratified by MELD strata, treating waitlist mortality/dropout as a competing risk. Cumulative incidence of transplantation was similar for HCC and non-HCC candidates in MELD strata 6-10 & 11-18 but lower for HCC candidates compared to non-HCC candidates in MELD strata 19-24 & 25-40.

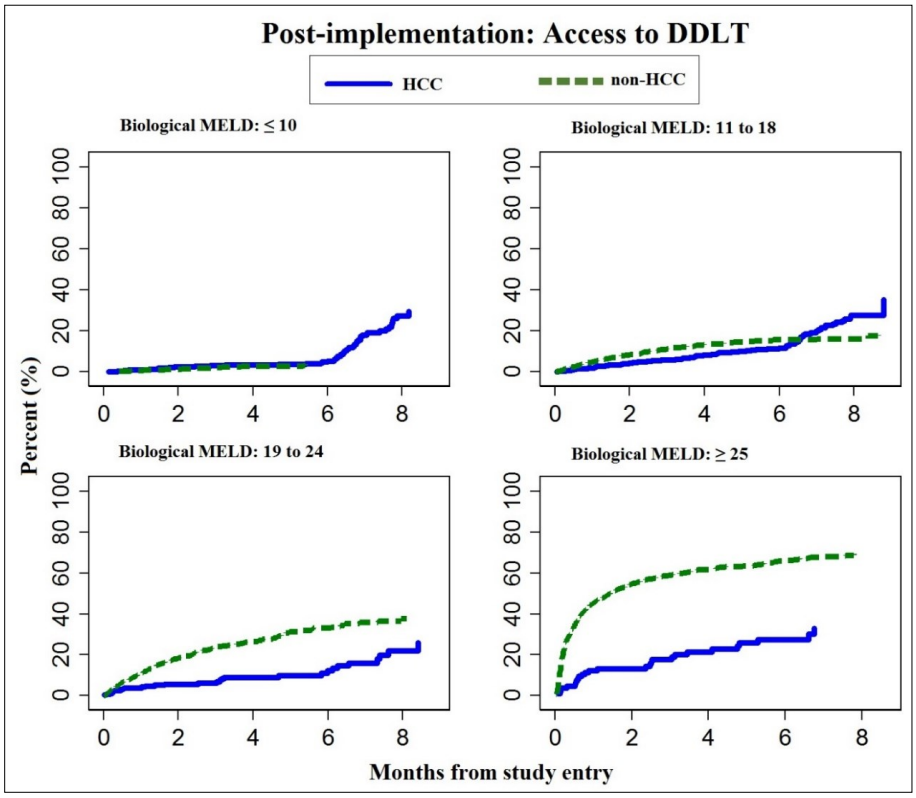


Figure 5: Waitlist mortality/dropout risk for HCC and non-HCC candidates, treating access to DDLT as a competing risk. Among all waitlist candidates, cumulative incidence of waitlist mortality/dropout was slightly higher for non-HCC candidates than for HCC candidates in both pre-implementation and post-implementation era

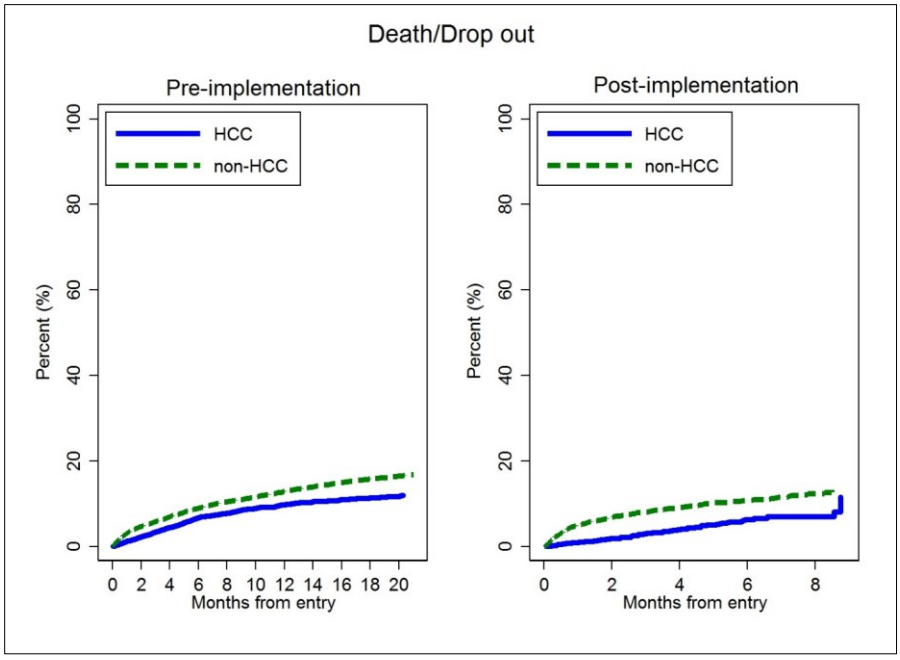


Figure 6. Waitlist mortality/dropout risk for HCC and non-HCC candidates, pre-implementation, stratified by calculated MELD, treating access to DDLT as a competing risk across MELD strata (Pre-implementation era). Cumulative incidence of mortality/dropout was similar for HCC and non-HCC candidates in MELD strata 6-10 & 11-18 but slightly higher for HCC candidates than for non-HCC candidates in MELD strata 19-24 and 25-40.

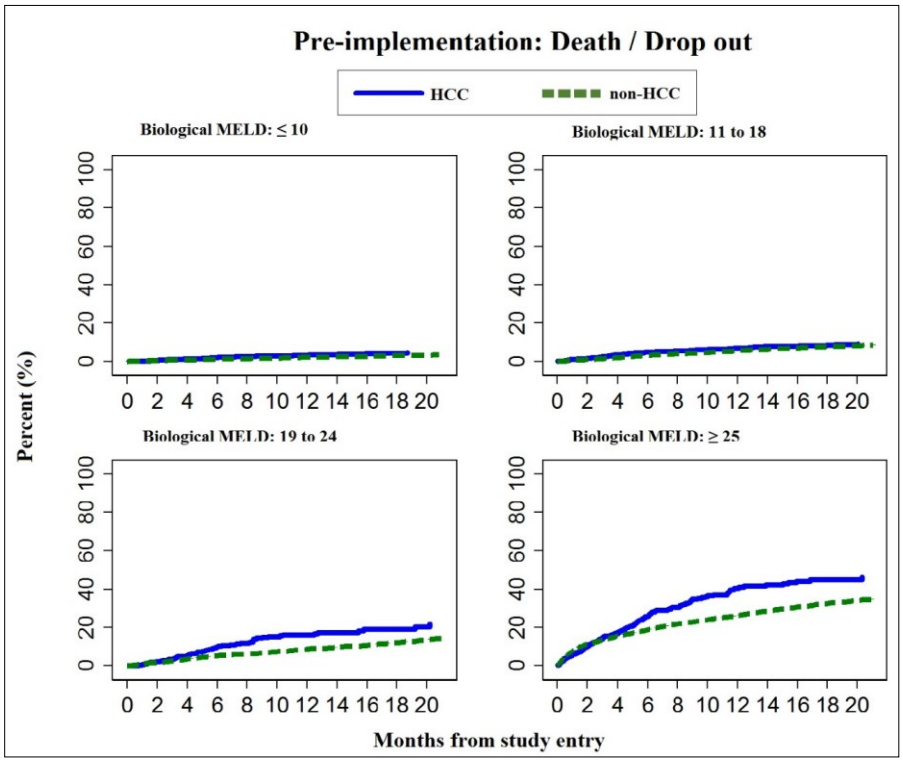
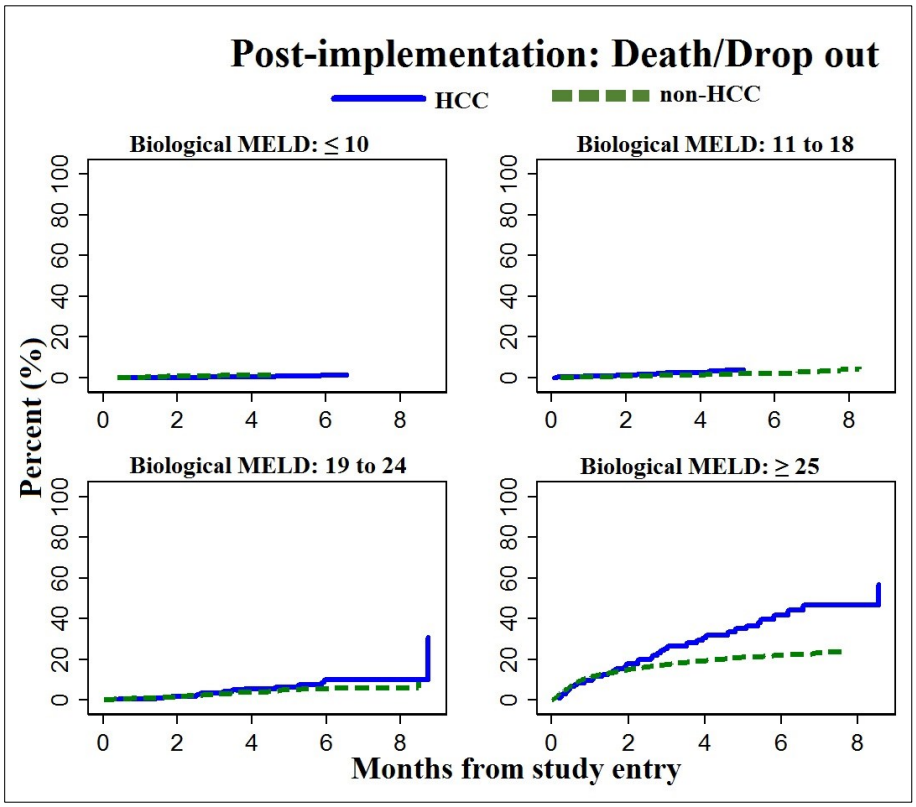


Figure 7. Waitlist mortality/dropout risk for HCC and non-HCC candidates, post-implementation, stratified by calculated MELD, treating access to DDLT as a competing risk across MELD strata (Pre-implementation era). Cumulative incidence of mortality/dropout was similar for HCC and non-HCC candidates in MELD strata 6-10 & 11-18 but slightly higher for HCC candidates than for non-HCC candidates in MELD strata 19-24 and 25-40.



REFERENCES:

1. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. Hepatology Research. 2007;37:S88-S94.
2. Saunders D, Seidel D, Allison M, Lyratzopoulos G. Systematic review: the association between obesity and hepatocellular carcinoma – epidemiological evidence. Alimentary Pharmacology & Therapeutics. 2010;31(10):1051-63.
3. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults. Cancer research. 2016;76(20):6076-83.
4. White DL, Kanwal F, El–Serag HB. Association Between Nonalcoholic Fatty Liver Disease and Risk for Hepatocellular Cancer, Based on Systematic Review. Clinical Gastroenterology and Hepatology. 2012;10(12):1342-59.e2.
5. Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: A systematic review and meta-analysis of cohort studies. International Journal of Cancer. 2012;130(7):1639-48.
6. Mittal S, El-Serag HB. Epidemiology of HCC: Consider the Population. Journal of clinical gastroenterology. 2013;47(0):S2-S6.
7. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. [Internet]. 2013 [cited 21/03/2017]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
8. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2013): National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission.; [Available from: https://seer.cancer.gov/statfacts/html/livibd.html.
9. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. The American journal of gastroenterology. 2014;109(4):542-53.
10. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine. 2017;96(9):e5904.
11. Fitzmorris P, Shoreibah M, Anand BS, Singal AK. Management of hepatocellular carcinoma. Journal of Cancer Research and Clinical Oncology. 2015;141(5):861-76.
12. Madkhali AA, Fadel ZT, Aljiffry MM, Hassanain MM. Surgical Treatment for Hepatocellular Carcinoma. Saudi Journal of Gastroenterology : Official Journal of the Saudi Gastroenterology Association. 2015;21(1):11-7.
13. Adam R, Bhangui P, Vibert E, Azoulay D, Pelletier G, Duclos-Vallee JC, et al. Resection or transplantation for early hepatocellular carcinoma in a cirrhotic liver: does size define the best oncological strategy? Annals of surgery. 2012;256(6):883-91.
14. Rahman A, Assifi MM, Pedroso FE, Maley WR, Sola JE, Lavu H, et al. Is resection equivalent to transplantation for early cirrhotic patients with hepatocellular carcinoma? A meta-analysis. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2012;16(10):1897-909.
15. Liang W, Wu L, Ling X, Schroder PM, Ju W, Wang D, et al. Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma:

a meta-analysis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2012;18(10):1226-36.
16. Cheng SJ, Pratt DS, Freeman RB, Jr., Kaplan MM, Wong JB. Living-donor versus cadaveric liver transplantation for non-resectable small hepatocellular carcinoma and compensated cirrhosis: a decision analysis. Transplantation. 2001;72(5):861-8.
17. Di Sandro S, Slim AO, Giacomoni A, Lauterio A, Mangoni I, Aseni P, et al. Living donor liver transplantation for hepatocellular carcinoma: long-term results compared with deceased donor liver transplantation. Transplantation proceedings. 2009;41(4):1283-5.
18. Porret PM, Olthoff KM. Current state of living donor liver transplantation. Clinical Liver Disease. 2013;2(4):160-4.
19. Brown RS. Live Donors in Liver Transplantation. Gastroenterology. 2008;134(6):1802-13.
20. Saidi RF, Li Y, Shah SA, Jabbour N. Living Donor Liver Transplantation for Hepatocellular Carcinoma: It Is All about Donors? International journal of organ transplantation medicine. 2013;4(4):137-43.
21. Kim WR, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, et al. OPTN/SRTR 2015 Annual Data Report: Liver. American Journal of Transplantation. 2017;17:174-251.
22. Coombes JM, Trotter JF. Development of the Allocation System for Deceased Donor Liver Transplantation. Clinical Medicine and Research. 2005;3(2):87-92.
23. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology (Baltimore, Md). 2000;31(4):864-71.
24. Sharma P, Schaubel DE, Messersmith EE, Guidinger MK, Merion RM. Factors That Affect Deceased Donor Liver Transplantation Rates In the United States In Addition to Model for End Stage Liver Disease Score. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2012;18(12):1456-63.
25. Mathur AK, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Racial and ethnic disparities in access to liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2010;16(9):1033-40.
26. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. The New England journal of medicine. 1996;334(11):693-9.
27. Löhe F, Angele MK, Gerbes AL, Löhrs U, Jauch KW, Schauer RJ. Tumour size is an important predictor for the outcome after liver transplantation for hepatocellular carcinoma. European Journal of Surgical Oncology.31(9):994-9.
28. U.S. Organ Procurement and Transplantation Network policies: Policy 9: Allocation of Livers and Liver-Intestines. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI; December, 2014. p. 108.

29. Elwir S, Lake J. Current Status of Liver Allocation in the United States. Gastroenterology & hepatology. 2016;12(3):166-70.
30. Rahimi RS, Trotter JF. Liver transplantation for hepatocellular carcinoma: outcomes and treatment options for recurrence. Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology. 2015;28(3):323-30.
31. US Organ Procurement and Transplantation Network: Revised liver policy regarding HCC exception scores October 6, 2015 [Available from: https://optn.transplant.hrsa.gov/news/revised-liver-policy-regarding-hcc-exception-scores/.
32. Washburn K, Edwards E, Harper A, Freeman R. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(7):1643-8.
33. Goldberg D, French B, Abt P, Feng S, Cameron AM. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2012;18(4):434-43.
34. Northup PG, Intagliata NM, Shah NL, Pelletier SJ, Berg CL, Argo CK. Excess mortality on the liver transplant waiting list: unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation. Hepatology (Baltimore, Md). 2015;61(1):285-91.
35. Charlton M. The lethal and enduring inequity of deceased donor liver allocation policy for hepatocellular carcinoma in the United States. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(11):2794-6.
36. Massie AB, Caffo B, Gentry S, Hall EC, Axelrod D, Lentine KL, et al. MELD Exceptions and Rates of Waiting List Outcomes. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(11):2362-71.
37. Schilsky ML, Moini M. Advances in liver transplantation allocation systems. World journal of gastroenterology. 2016;22(10):2922-30.
38. U.S. Organ Procurement and Transplantation Network policies: Policy 9: Allocation of Livers and Liver-Intestines. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI; December, 2014. p. 111-2.
39. Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review: public comment proposal [press release]. U.S. Organ Procurement and Transplantation Network.
40. Leppke S, Leighton T, Zaun D, Chen SC, Skeans M, Israni AK, et al. Scientific Registry of Transplant Recipients: collecting, analyzing, and reporting data on transplantation in the United States. Transplantation reviews (Orlando, Fla). 2013;27(2):50-6.

41. Massie AB, Kucirka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014;14(8):1723-30.
42. Freeman RB, Jr., Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2004;4 Suppl 9:114-31.
43. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. STATA journal. 2004;4:103-12.
44. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. American journal of epidemiology. 2009;170(2):244-56.
45. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.
46. Heimbach JK, Hirose R, Stock PG, Schladt DP, Xiong H, Liu J, et al. Delayed Hepatocellular Carcinoma MELD Exception Score Improves Disparity in Access to Liver Transplant in the US. Hepatology (Baltimore, Md). 2015;61(5):1643-50.
47. Alver SK, Lorenz DJ, Marvin MR, Brock GN. Projected outcomes of 6-month delay in exception points versus an equivalent Model for End-Stage Liver Disease score for hepatocellular carcinoma liver transplant candidates. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2016;22(10):1343-55.
48. Marvin MR, Ferguson N, Cannon RM, Jones CM, Brock GN. MELDEQ : An alternative Model for End-Stage Liver Disease score for patients with hepatocellular carcinoma. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2015;21(5):612-22.
49. Yeh H, Smoot E, Schoenfeld DA, Markmann JF. Geographic Inequity in Access to Livers for Transplantation. Transplantation. 2011;91(4):479-86.
50. Rana A, Riaz IB, Gruessner AC, Gruessner RW. Geographic inequity results in disparate mortality: a multivariate intent-to-treat analysis of liver transplant data. Clinical transplantation. 2015;29(6):484-91.

CURRICULUM VITAE

Tanveen Ishaque

Email: tishaqu1@jhmi.edu

Phone: 4438577629

EDUCATION

- Masters of Science (2nd year -3rd term), Department of Epidemiology August 31 to Present

  Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; GPA: 3.95
- Masters in Public Health January, 2012 –April, 2013

  North South University, Dhaka, Bangladesh; GPA: 3.85 (WES-3.84 out of 4.0)
- Bachelor of Medicine and Surgery April, 2004 – December, 2009

  Dhaka Medical College, Dhaka, Bangladesh; Marks: 3200 (74%) (Honors in Anatomy)(WES-4.0/ 4.0)

RESEARCH EXPERIENCE

Research Assistant June, 2016 to till now

Epidemiologic Research group of Organ Transplantation, Dept. of Surgery, JHMI.

- Data analysis and manuscript preparation
  - Project: Access to transplant and HCC after the exception policy change

Project Coordinator June, 2016 to August, 2016

Epidemiology department, JHBSPH

- Data collection and other administrative support.
  - Project: Oral HPV infection and persistence in HIV positive and HIV negative individuals

Senior Research Associate December, 2014 to July, 2015

Research and Evaluation Division, BRAC, Dhaka, Bangladesh

- Proposal writing, Field supervision, Data management, Report writing, Manuscript preparation

- Project: Incidence and predictors of recurrent pulmonary tuberculosis among successfully treated cohort under DOTS program

Research Fellow October, 2013 to November, 2014

Emerging diseases and immunobiology, Centre for food and water borne disease, icddr,b, Dhaka, Bangladesh

- Data Analysis, Manuscript Preparation
- Project:-
    - Mortality of Guilain Barre Syndrome in Bangladesh;
    - Risk factors of respiratory failure in Guillain-Barre syndrome patients in a low income country: a prospective study.
- Data collection, Data entry and Field supervision
    - Project:
    - Prospective hospital based surveillance on Encephalitis in Bangladesh: clinical features, diagnostic imaging and etiology
    - International GBS outcome study

Research Associate October, 2012 to September, 2013

Research and Evaluation Division, BRAC, Dhaka, Bangladesh

- Qualitative study: Proposal writing, study design, data collection, data analysis, report writing
    - Project: Client satisfaction: user and provider perspective on facility-based obstetric care in rural Bangladesh
- Data Analysis for health survey:
    - Project: Improved MNCS in rural Bangladesh-evidence from end line survey"

Research Physician

CRF project of BIRDEM, Dhaka, Bangladesh January, 2011 to September, 2012

- Data collection, Data cleaning, exploratory data analysis
    - Project: Study on therapeutic efficacy in controlling long term progression of nephropathy in Diabetics - BNDC Trial (Blood pressure, Nephropathy & Dyslipidemia Control Trial)- Patient recruitment 2008-10 and follow-up up to 2013 (1st Phase)

Intern December, 2009 to December, 2010

Dhaka Medical College, Dhaka, Bangladesh

• Rotatory placement in Medicine, Surgery and Gynecology wards to get hand on training on clinical care

HONORS & AWARDS

- Young Investigator Award for the American Transplant Congress (ATC) 2017
- Jonathon Pembroke Australasia award, 2014
- Government education board scholarship

PUBLICATION: JOURNAL ARTICLE

- Assessing community based Improved Maternal Neonatal Child Survival (IMNCS) program in rural Bangladesh [PLoS One. 2015; 10(9)]

  Mahfuzar Rahman, Fatema Tuz Jhohura, Sabuj Kanti Mistry, Tridib Roy Chowdhury, Tanveen Ishaque, Rasheduzzaman Shah and Kaosar Afsana

- High mortality of Guillain-Barré syndrome in Bangladesh , Journal of the peripheral nervous system [Accepted]

  Tanveen Ishaque, Mohammad B. Islam, Gulshan Ara, Hubert P. Endtz, Quazi D. Mohammad, Bart C. Jacobs, Zhahirul IslamJournal of the Peripheral Nervous System

POSTER: CONFERENCE PAPER

- Access to liver transplantation under the new HCC exception policy

  Tanveen Ishaque, Allan Massie, , Mary Bowring, Jessica Ruck, Andrew MacGregor Cameron, Benjamin Philosophe and Dorry Segev

- Risk factors of respiratory failure in Guillain-Barre syndrome patients in a low income country: a prospective study.

  Mohammad B. Islam, Tanveen Ishaque, A. Ul. Alam Gulshan Ara, Quazi D. Mohammad, Zhahirul Islam

PUBLICATION: REPORT

- Incidence and predictors of recurrent pulmonary tuberculosis among successfully treated cohort under DOTS program

  Tanveen Ishaque, Morsheda Banu,Mahmuda Akter Sarkar, Khadiza Begum,Shayla Islam, Md Akramul Islam and Mahfuzar Rahman

- Bound to be satisfied: user and provider perspective on facility-based obstetric care in rural Bangladesh.

  Tanveen Ishaque, Khadiza Begum