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Early Impact of MMaT-3 Policy on Liver Transplant Waitlist Outcomes for Hepatocellular Carcinoma

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Background. To reduce the disparity in access to liver transplant (LT), United Network for Organ Sharing implemented an exception policy in May 2019, which capped hepatocellular carcinoma (HCC) exception score to the median Model for End-Stage Liver Disease (MELD) at transplant within the donor service area minus 3 points (MMaT-3) after the 6-mo wait period. We aimed to evaluate how this policy affected HCC waitlist outcomes. **Methods.** Using United Network for Organ Sharing data, we analyzed waitlist outcomes in HCC patients at the time they received exception points from in the pre-MMaT era (August 15, 2017, to November 15, 2018) and MMaT era (June 1, 2019, to August 30, 2020). Comparisons were made within the HCC group and HCC versus non-HCC (at time of listing) groups in the pre-MMaT and MMaT eras and regions were grouped as low, medium, and high MELD based on MMaT. **Results.** HCC group: LT probability within HCC patients decreased by 20% (subhazard ratio [sHR], 0.78; 95% confidence interval [CI], 0.74-0.85) between the eras and decreased by 41% in low MELD regions (sHR, 0.59; 95% CI, 0.52-0.66). Waitlist dropout was unchanged. Matched HCC versus non-HCC groups: HCC patients had 80% higher LT probability (sHR, 1.84; 95% CI, 1.71-1.99) than non-HCC patients in the pre-MMaT era; which decreased to a 14% higher LT probability in MMaT era. In low and medium regions, HCC patients had over twofold higher LT probability in the pre-MMaT era, which decreased to a ~20% higher probability (sHR, 1.14; 95% CI, 1.06-1.23) in the MMaT era. After implementation of the acuity circle policy, HCC patients had lower LT probability (sHR, 0.84; 95% CI, 0.74-0.94) than non-HCC patients. **Conclusions.** The geographic disparity between HCC and non-HCC patients has improved with the MMaT-3 policy. Despite lower LT probability for HCC patients, waitlist dropout was not adversely impacted.

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In 2002, The Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) adopted the Model for End-Stage Liver Disease (MELD) score for liver organ allocation purposes to prioritize liver candidates by medical urgency.[1] Consequently, waitlist mortality has improved substantially, with overall

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improvement in liver transplant (LT) outcomes. Although MELD has shown to accurately measure 90-d mortality for those with chronic liver disease, it does not reflect mortality caused by cancer spread including hepatocellular carcinoma (HCC), one of the leading indications for LT.[2,3]

LT is the only curative treatment for HCC. Eligible HCC transplant candidates with T2 lesions typically do not have severe liver dysfunction at presentation, and their mortality is largely driven by tumor burden.[4] Therefore, laboratory MELD score is not applicable for HCC patients, making prioritization in access to LT for HCC challenging.[5,6] From 2005 onwards, the OPTN/UNOS has implemented several allocation policies to grant HCC patients exception scores, instead of the laboratory MELD score, in an attempt to reflect true mortality[7] and therefore ensure equitable access for HCC and non-HCC patients.[8] These exception policies, which artificially increase HCC patients MELD score, inadvertently overprioritized HCC patients for LT compared with non-HCC patients with chronic liver disease.[9]

In 2015, the HCC exception policy implemented a 6-mo delay from listing to receive HCC exception points and capped the MELD exception score granted to 34.[10] As a result, an initial exception score of 28 was given 6 mo after listing as it equates to 35% waitlist mortality at 3 mo. An extension was submitted every 3 mo, which would increase an additional 3 points and cap at 34. Despite the 6-mo wait period, HCC patients continue to benefit from over prioritization for LT.[7,9,11] To reduce this disparity in access to LT, OPTN/UNOS implemented a new exception policy on May 15, 2019, which capped the first HCC exception score received to the median MELD at transplant within the donor service area minus 3 points (MMaT-3) after the 6-mo wait period, with an increase every 3 mo similar to prior policy.[2] There are no published data to confirm whether this goal has been achieved. Therefore, our aim was to evaluate the early impact of the MMaT-3 policy on waitlist outcomes including access to LT and waitlist dropout.

PATIENTS AND METHODS

Utilizing data collected from the UNOS LT registry, we retrospectively analyzed clinical outcomes among all adult (aged 18 y or older) LT registrants waitlisted in the United States from August 15, 2017, to March 1, 2021. Patients listed as status 1A or for simultaneous organ transplant and/or living donor transplant were excluded. Using the Standard Transplant Analysis and Research file, we evaluated only patients listed with HCC exception using the Standard Transplant Analysis and Research identifier "EXC_HCC as HCC," "HCC_DIAG," "HCC_DIAGNOSIS_TCR," and "HCC_EVER_APPR."

Our primary objective was to compare waitlist outcomes including receipt of LT and waitlist dropout between patients who received HCC MELD exception points before and those who received exception after the implementation of the MMaT-3 policy on May 15, 2019. We included all HCC patients in our analysis, and follow-up time was calculated after the date they received MELD exception points, beginning August 15, 2017, through August 30, 2020 (n = 5261). Patients were categorized into 2 era-based cohorts based on the current exception policy during the time period when they received initial HCC exception points. HCC patients who received exception points from August 15, 2017, to November 15, 2018, were categorized as the "pre-MMaT" era and those who received exception points from June 1, 2019, to August 30, 2020, were categorized as "MMaT" era. Since both the pre-MMaT and MMaT policies implemented a 6-mo waiting period on the waitlist before receiving MELD exception points, each candidate's index date into the analysis began at the date they received their exception points. Therefore, the initial 6-mo mandatory wait period from the initial waitlist registration date was not included. The end dates in each era were selected to ensure that all candidates had at least 180 d of follow-up after receiving exception points. Patients who received MELD exception during the pre-MMAT policy period had their last follow-up censored after May 15, 2020. Patients who received exception during the MMAT era were followed through March 1, 2021.

In a secondary analysis, we examined whether the MMaT policy improved access to LT for all candidates by comparing waitlist outcomes between HCC and non-HCC patients in the pre-MMaT and MMaT eras, respectively. Non-HCC patients (n = 21 345) were compared at the time of listing to HCC patients (n = 5261) at the time of receiving their MELD exception score. Patients in the non-HCC cohort that were listed as status 1A had simultaneous organ transplant and/or underwent prior LT were excluded. To eliminate bias and to ensure appropriate comparison, patients with HCC (cases) were matched in a 1:1 manner to non-HCC patients (controls) by age (± 5), gender, transplant region (categorized as high, medium, or low MELD), and era seen in **Table S1** (**SDC**, http://links.lww.com/TXD/A414). UNOS regions were categorized into terciles based on the MMaT within these regions during the study period, as shown in **Table S2** (**SDC**, http://links.lww.com/TXD/A414). This was calculated using the mean of the monthly allocation MMAT score for each region (obtained from the UNOS data) over each era. In the pre-MMaT era, low MELD regions (regions 3, 10, and 11) had a MMAT cutoff under 28, medium MELD regions (regions 2, 4, 6, 7, and 8) had a MMaT between 28 and 30, and high MELD regions (regions 1, 5, and 9) had a MMaT above 30. The same MMaT thresholds were used in the MMaT era; however, region 8 was categorized as a medium MELD region in the pre-MMaT era and low MELD region in the MMaT era. All other regions remained within the same MELD region during both eras.

Waitlist Outcomes

Waitlist outcomes included the rate for waitlist dropout and LT during each policy era. Waitlist dropout was defined as removal from the waitlist caused by either death or clinical deterioration (coded as too sick for transplant in UNOS). In exploratory analyses, we analyzed regional variation in waitlist outcomes (dropout and LT) between high, medium, and low MELD regions.

Sensitivity Analyses

On February 4, 2020, the acuity circle (AC) policy was implemented to replace donation service area (DSA) and regional boundaries previously used in liver distribution with a system based on distance between donor hospital and transplant hospital. The purpose of the policy was to prioritize patients with high MELD or acuity of illness, which may have impacted LT outcomes between HCC and non-HCC patients in the MMaT

era. To evaluate potential differences from the AC policy, we compared LT outcomes in the pre-AC and AC policies within the MMaT era. Patients who received exception points from May 1, 2019, to October 31, 2019, were included in the "pre-AC" policy, and those who received exception points from March 1, 2020, to August 30, 2020, were included in the AC policy. Patients listed in the pre-AC policy were censored after February 29, 2020, and all patients had at least 90-d follow-up. As previously described, HCC and non-HCC patients were matched 1:1 by age, gender, transplant region (low, medium, and high MELD region), and era as shown in **Table S3** (**SDC**, http://links.lww.com/TXD/A414). Allocation MMaT for each region was calculated every 6 mo and consequently changed the regional MELD categories at separate time points during the AC policy. Therefore, several medium and high MELD regions interchanged MELD categories during the AC policy, and we were not able to accurately categorize medium and high MELD regions. Low MELD regions (3, 8, 10, and 11) remained the same during the entirety of the MMaT era including the 6-mo intervals with the AC policy and were included in the subanalyses.

Statistical Analysis

Clinical and demographic characteristics are presented as frequencies and proportions for categorical variables and median with interquartile range (IQR) for continuous variables. Clinical comparisons between the pre-MMaT and MMaT eras were made using chi-square for categorical variables and Mann–Whitney *U* test for continuous variables. Because of small aggregate number in waitlist dropout during each era, waitlist dropout was not stratified regionally. Transplant probability and waitlist dropout rates were compared using Fine–Gray proportional hazard regression models. The Gray test and Fine–Gray models allow for the analysis of competing risk events, which, in our study, were waitlist removal caused by death, clinical deterioration or clinical improvement, and transplant. Subhazard ratios (sHRs) and 95% confidence intervals (CIs) were estimated by modeling the cumulative incidence function. Statistical significance was met with a $P < 0.05$. All statistical analyses were completed using STATA 14.0 (College Station, TX). This study was approved by the Institutional Review Board at Baylor College of Medicine, and the Institutional Review Board waived the need for patient consent.

RESULTS

HCC Patient Characteristics

In the pre-MMaT era, 2776 patients received HCC exception points, whereas 2485 patients received exception points in the MMaT era. Patients in the MMaT-3 era were older and had a higher percentage of those with nonalcoholic steatohepatitis and lower percentage with chronic hepatitis C virus. Clinical characteristics of HCC patients in each era are shown in Table 1.

Waitlist Outcomes for HCC Patients in Pre-MMaT and MMaT Eras

HCC Liver Transplantation

The proportion of HCC patients who underwent LT decreased from 68.2% to 60.1% in the MMaT era ($P < 0.001$). Median time to LT was 73 d (IQR, 28-154 d) in the pre-MMaT era and decreased to 67 d (IQR, 29-142 d) in the MMaT era ($P = 0.002$). HCC patients had over a 20% decline in LT probability in the MMaT era (sHR, 0.78; 95% CI, 0.74-0.85) as shown in Figure 1.

Regional Differences for HCC Liver Transplantation

Half of all HCC patients were listed in high MELD regions, 30% in medium MELD regions, and 20% in low MELD regions. Time to LT decreased in medium and high MELD regions and increased in low MELD regions during the MMaT era (Table 2). Despite having the lowest number of HCC patients, low MELD regions had the highest proportion that underwent LT, followed by medium and high MELD regions, respectively. LT probability for HCC patients in high, medium, and low MELD regions in the pre-MMaT and MMaT eras are shown in Figure 2. Compared with the pre-MMaT era, LT probability in high MELD (sHR, 0.91; 95% CI, 0.80-1.03) regions were unchanged in the MMaT era (Figure 2A). In low and medium MELD regions, LT probability decreased by 41% (sHR, 0.59; 95% CI, 0.52-0.66) and

TABLE 1.

Comparison of sociodemographic and clinical characteristics at time of listing among HCC liver transplant candidates who received MELD exception score before and during the MMaT-3 policy change

	HCC exception candidates		
Characteristics	Pre-MMaT-3 (N = 2776)	MMaT-3 (N = 2485)	*P*
Mean age, SD, y	61.0 (0.13)	61.7 (0.15)	<0.001
Age >65, n (%)	741 (26.7)	836 (33.6)	<0.001
Gender, n (%)			0.64
Female	655 (23.6)	600 (24.1)	
Male	2121 (76.4)	1885 (75.8)	
Ethnicity/race, n (%)			0.08
White	1699 (61.2)	1581 (63.6)	
Black	237 (8.4)	168 (6.8)	
Hispanic	542 (19.5)	500 (20.1)	
Asian	240 (8.7)	195 (7.9)	
Other	58 (2.1)	41 (1.7)	
Etiology of liver disease, n (%)			
Chronic hepatitis C virus infection	1440 (51.9)	1048 (42.2)	<0.001
Alcoholic liver disease	366 (13.8)	332 (13.4)	0.85
Nonalcoholic steatohepatitis	388 (14.0)	514 (20.7)	<0.001
Diabetes, n (%)	1036 (37.3)	925 (37.2)	0.94
Obesity (BMI ≥30), n (%)	1176 (42.4)	1088 (43.8)	0.30
BMI <18.5, n (%)	21 (0.8)	21 (0.9)	0.72
Hepatic decompensation, n (%)			
Severe hepatic encephalopathy	51 (1.8)	60 (2.4)	0.15
Moderate ascites	1286 (46.3)	1115 (44.9)	0.29
Dialysis	12 (0.4)	17 (0.7)	0.22
History of SBP	65 (2.3)	68 (2.7)	0.36
Portal venous thrombosis	209 (7.5)	152 (6.1)	0.04
UNOS region, n (%)			
High MELD	894 (32.2)	901 (36.3)	0.002
Medium MELD	1215 (43.8)	890 (35.8)	<0.001
Low MELD	667 (24.03)	694 (27.9)	<0.001

BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MMaT-3, median Model for End-Stage Liver Disease at transplant minus 3; SBP, spontaneous bacterial peritonitis; UNOS, United Network for Organ Sharing.

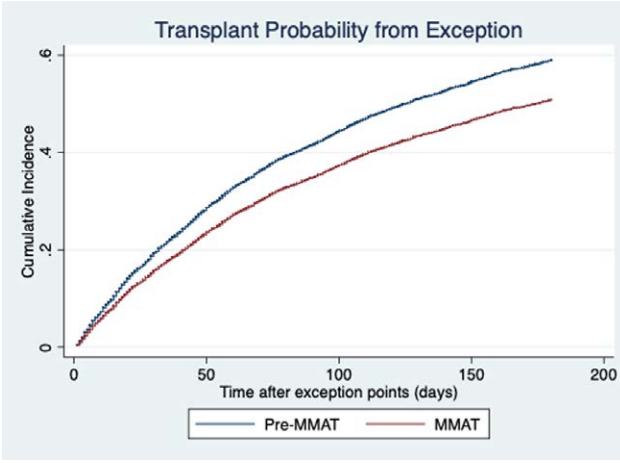

FIGURE 1. Transplant probability for hepatocellular carcinoma exception patients in the pre-MMaT and MMaT eras ([reference: pre-MMaT] sHR, 0.80; 95% CI, 0.74-0.85; $P < 0.001$). CI, confidence interval; MMaT, median Model for End-Stage Liver Disease at transplant; sHR, subhazard ratio.

17% (sHR, 0.83; 95% CI, 0.75-0.93), respectively, during the MMaT era (Figure 2B and C).

HCC Waitlist Dropout

Waitlist outcomes among those who received HCC exception points during the pre-MMaT and MMaT eras are described in Table 2. Median time from receiving exception points to waitlist dropout (death and/or clinical deterioration) increased from 127 d (IQR, 62-202 d) in the pre-MMaT era to 162 d (IQR, 78-254 d) in the MMaT era ($P = 0.003$). HCC waitlist dropout was unchanged ([reference: Pre-MMaT] sHR, 0.95; 95% CI, 0.80-1.13) as depicted in Figure 3. Similar findings were seen when assessing waitlist death and clinical deterioration separately (Table 2). There was lower percentage of HCC patients who were removed because of clinical improvement in the MMaT era ($P = 0.02$). Although there were no statistically significant regional differences in HCC waitlist dropout between eras, HCC patients in low MELD regions experienced a slightly higher waitlist dropout (sHR, 1.21; 95% CI, 0.80-1.84) and HCC patients in high MELD regions had a lower observed dropout (sHR, 0.80; 95% CI, 0.60-1.07) during the MMaT era.

TABLE 2.

Waitlist outcomes among HCC exception candidates before and during MMaT-3 policy

	Pre-MMaT-3 (N = 2766)	MMaT-3 (N = 2485)	*P*
Overall, n (%)			
Waitlist dropout	278 (10.5)	244 (9.8)	0.81
Waitlist death	68 (2.5)	59 (2.4)	0.86
Waitlist clinical deterioration	210 (7.6)	185 (7.4)	0.87
Removal due to clinical improvement	26 (0.9)	14 (0.6)	0.02
Liver transplant	1892 (68.2)	1493 (60.1)	<0.001
90-d outcomes, n (%)			
Waitlist dropout	106 (3.8)	71 (2.9)	0.05
Liver transplant	1090 (39.3)	905 (36.4)	0.03
180-d outcomes, n (%)			
Waitlist dropout	187 (6.7)	142 (5.7)	0.13
Liver transplant	1562 (56.3)	1248 (50.2)	<0.001
Regions			
High MELD, n	894	901	
Liver transplant, n (%)	498 (55.7)	463 (51.3)	0.07
Median time to transplant (IQR)	144 (56-257)	92 (37-185)	<0.001
Medium MELD, n	1215	890	
Liver transplant, n (%)	829 (68.2)	550 (61.8)	0.002
Median time to transplant (IQR)	75 (30-151)	68 (30-137)	0.40
Low MELD, n	667	694	
Liver transplant, n (%)	565 (84.7)	480 (69.2)	<0.001
Median time to transplant (IQR)	41 (16-81)	53 (21-102)	<0.001

HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MMaT-3, median Model for End-Stage Liver Disease at transplant minus 3.

Comparison of Waitlist Outcomes in HCC and Non-HCC patients in Pre-MMaT and MMaT Eras

Characteristics regarding matched HCC and non-HCC patients are described in **Table S1** (**SDC**, http://links.lww.com/TXD/A414). Figure 4 shows cumulative LT rates in the matched non-HCC and HCC cohorts in the pre-MMaT and MMaT eras. HCC patients had 80% higher LT rate than non-HCC patients during the pre-MMaT era (sHR, 1.84; 95% CI, 1.71-1.99), but this disparity decreased between eras with HCC patients having only a 14% higher LT rate (sHR, 1.14; 95% CI, 1.06-1.23) in the MMaT era (Figure 4A and B). This reduction in LT probability for HCC patients was also seen on a regional level as well (Figure 4C and D). Compared with non-HCC patients, HCC patients in low MELD regions (sHR, 2.56; 95% CI, 2.22-2.96) and medium MELD regions (sHR, 2.08; 95% CI, 1.85-2.34) had over a twofold higher LT probability in the pre-MMaT era, which decreased to approximately only a 20% higher transplant probability in the MMaT era (low MELD: sHR, 1.19; 95% CI, 1.06-1.23 and medium MELD: sHR, 1.21; 95% CI, 1.07-1.37) as shown in Table 3. The disparity in LT disparity was lower among HCC and non-HCC patients in high MELD regions, with HCC patients having a 33% higher probability in the pre-MMaT era (sHR, 1.33; 95% CI, 1.15-1.53), which decreased to a 7% higher probability in the MMaT era (sHR, 1.07; 95% CI, 0.94-1.23).

Sensitivity Analyses: Effect of Acuity Circle Allocation Policy During the MMaT era

In the MMaT era, 1288 patients received HCC exception points before the AC policy (pre-AC), and 1170 patients received exception points after implementation of the AC policy. With the pre-AC policy, median time to LT was 57 d (IQR, 28-98 d) and 51 d (IQR, 21-94 d) after the AC policy ($P = 0.045$) and decreased in medium and high MELD regions as well. LT probability among all HCC patients in the MMaT era did not change with the AC policy (sHR, 0.93; 95% CI, 0.83-1.05; $P = 0.25$). HCC patients in low MELD regions did, however, have a 27% lower LT probability (sHR, 0.73; 95% CI, 0.58-0.93; $P = 0.011$) with the AC policy.

Matched HCC Versus Non-HCC groups

LT probability between HCC and non-HCC patients did not change with the pre-AC policy, but HCC patients had a 16% lower probability (sHR, 0.84; 95% CI, 0.74-0.94) than non-HCC patients after the AC policy. In low MELD regions, HCC patients had a 40% higher LT probability with the pre-AC policy. However, after the AC policy, no statistical difference was seen in between HCC and non-HCC patients (**Table S4, SDC**, http://links.lww.com/TXD/A414).

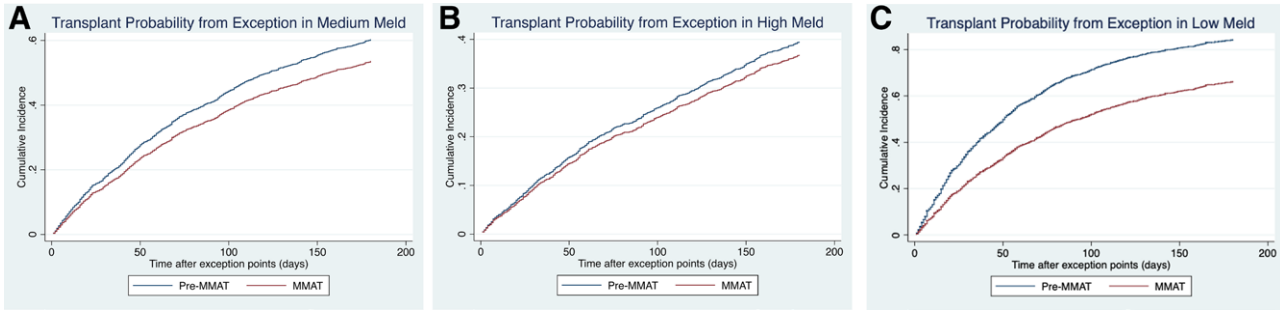

FIGURE 2. Regional comparison for transplant probability for HCC patients in the pre-MMaT-3 and MMaT-3 eras. A, Transplant probability for HCC patients in high MELD regions ([reference: pre-MMaT] sHR ratio, 0.91; 95% CI, 0.80-1.03; $P = 0.15$). B, Transplant probability for HCC patients in medium MELD regions ([reference: pre-MMaT] sHR, 0.83; 95% CI, 0.75-0.93; $P < 0.001$). C, Transplant probability for HCC patients in low MELD regions ([reference: pre-MMaT] sHR, 0.59; 95% CI, 0.52-0.66; $P < 0.001$). CI, confidence interval; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MMaT-3, median Model for End-Stage Liver Disease at transplant minus 3; sHR, subhazard ratio.

DISCUSSION

In this study of the MMaT-3 policy and its effect on HCC waitlist outcomes, we found encouraging results suggesting improvement in the disparity for access to LT. Although HCC patients experienced lower LT probability in the MMaT era, overall waitlist dropout remained unchanged. HCC patients had a 80% higher LT probability than non-HCC patients in pre-MMaT era, which decreased to a 14% higher probability in the MMaT era. Moreover, the disparity in LT probability between HCC and non-HCC patients narrowed in all MELD regions, thereby reducing geographic inequities in access to LT. The greatest improvement in this disparity was seen in low and medium MELD regions, where HCC patients had over twofold higher LT probability in the pre-MMaT era, which decreased to a 20% higher LT probability in MMaT era. These data suggest significant progress toward the overarching goal of the MMaT-3 policy of reducing the disparity in access to transplant between HCC and non-HCC patients without adversely impacting HCC waitlist dropout or overall LT probability for all candidates. Although there are several policy and pandemic-related factors that limit us in concluding improved outcomes definitively, this is the first real-world experience, and these data can help policymakers and stakeholders in improving disparities for access to LT.

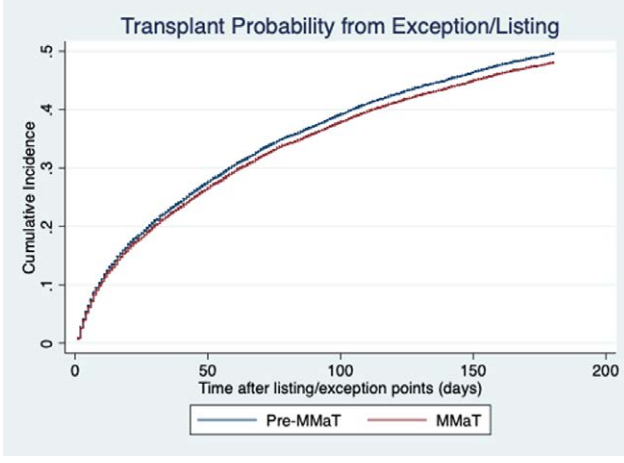

FIGURE 3. Comparison of waitlist dropout (death or clinical deterioration) for hepatocellular carcinoma exception patients in the pre-MMaT and MMaT eras ([reference: pre-MMaT] sHR, 0.95; 95% CI, 0.80-1.13; $P = 0.60$). CI, confidence interval; MMaT, median Model for End-Stage Liver Disease at transplant; sHR, subhazard ratio.

Reducing regional disparity for access to LT among HCC and non-HCC patients has been a significant challenge for policymakers and stakeholders. As low MELD regions transplant at lower MELD scores, receiving HCC exception points that go up to 34 in such regions lead to HCC patients being over prioritized.[11] These data suggest that MMaT policy has reduced over prioritization for HCC patients. The greatest improvement in this disparity was seen in low and medium MELD regions, where HCC patients had over twofold higher LT probability than non-HCC patients in the pre-MMaT era, which decreased to a 20% higher LT probability in MMaT era. Furthermore, with the MMaT policy, there was no significant difference in LT probability between HCC and non-HCC in high MELD regions, which account for half of all HCC patients. Although the increase in time to LT for HCC patients did not impact waitlist dropout on a national level, we did observe that HCC patients in low MELD regions had slightly higher waitlist dropout in the MMaT era, which should be evaluated further since a potential delay in LT from this policy could theoretically increase HCC waitlist dropout. Long-term analyses will help determine if policy adjustments may be needed.

The first documented case of coronavirus disease 2019 in the United States was reported on March 5, 2020, during the MMaT era and coinciding with the AC policy. During the early phases of the pandemic, the increasing demand and utilization of hospital resources adversely impacted the ability of transplant centers to list candidates and perform LT. In addition, there was wide geographic heterogeneity in transplant practices that correlated with the burden of coronavirus disease 2019 during varying phases of the pandemic.[12] Although

TABLE 3.

Transplant probability for HCC patients compared with non-HCC patients (reference) in the pre-MMaT and MMaT eras

	Pre-MMaT (n = 5366)		MMaT (n = 5030)	
	sHR (95% CI)	*P*	sHR (95% CI)	*P*
Overall	1.84 (1.71-1.99)	<0.001	1.14 (1.06-1.23)	<0.001
MELD region				
Low MELD	2.56 (2.22-2.96)	<0.001	1.19 (1.05-1.35)	0.007
Medium MELD	2.08 (1.85-2.34)	<0.001	1.21 (1.07-1.37)	0.002
High MELD	1.33 (1.15-1.53)	<0.001	1.07 (0.94-1.23)	0.28

Matched 1:1 on age, gender, MELD region, and era.
CI, confidence interval; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MMaT, median Model for End-Stage Liver Disease at transplant; sHR, subhazard ratio.

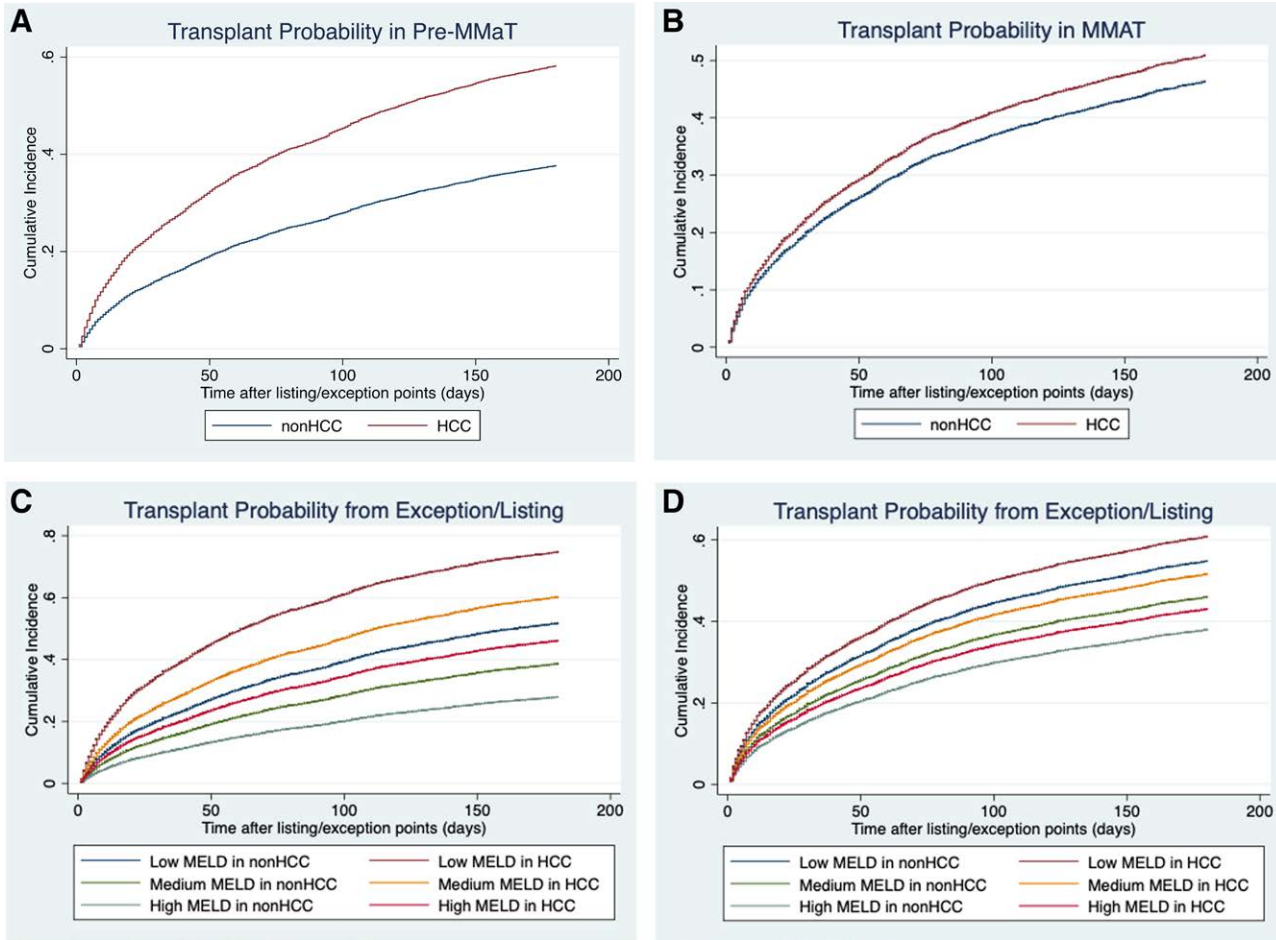

FIGURE 4. National and regional comparison of transplant probability for HCC vs non-HCC patients listed in the pre-MMaT and MMaT eras. A, Differences in transplant probability for HCC and non-HCC patients listed in the pre-MMaT era ([reference: non-HCC patients] sHR, 1.84; 95% CI, 1.71-1.99; $P < 0.001$). B, Differences in transplant probability for HCC and non-HCC patients listed in the MMaT era ([reference: non-HCC patients] sHR, 1.14; 95% CI, 1.06-1.23; $P < 0.001$). C, Regional differences in transplant probability for HCC vs non-HCC patients in the pre-MMaT era. D, Regional differences in transplant probability for HCC vs non-HCC patients in the MMaT era. CI, confidence interval; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MMaT, median Model for End-Stage Liver Disease at transplant; sHR, subhazard ratio.

LT volume had decreased substantially from March 2020 to April 2020, LT volume rapidly recovered, and waitlist outcomes, including LT and dropout for candidates, were not adversely impacted.[12,13,14] Additionally, the impact of the pandemic on LT from April 2020 onwards was studied, and no statistically significant difference was reported in percentage of patients transplanted with HCC overall during the pandemic.[15] Because of inherent limitations of available data from UNOS, we were unable to evaluate the pandemic's impact of stay at home orders, heterogenous center-specific practices, donor availability, and hospital resource utilization on these outcomes. We did observe a lower number of HCC exception points during the MMaT era, but it remains unclear if the pandemic was a contributing factor. Despite of the pandemic, real-world interim data are urgently needed for policy and stakeholders to evaluate the efficacy of the MMaT-3 policy in reducing geographic disparity in our LT allocation system.

Although our study has important clinical implications for LT in HCC patients, there are few limitations. Given the retrospective design and variation in transplant practices throughout the study period, residual confounders may be present. Because of the short follow-up time, we were unable to evaluate how this policy affected post-LT outcomes including tumor recurrence. Future long-term data are needed to evaluate how the reduced probability for LT in low MELD regions will affect waitlist dropout and posttransplant outcomes in low MELD regions. There also exists center-level variation in HCC eligibility criteria throughout the study period that could not be captured in UNOS. In the pre-MMaT policy, candidates would continue to receive incremental increases to their score extending past 1 y, which would further increase their probability for LT compared with those in the MMaT-3 policy.

There were other OPTN/UNOS policy revisions that should be taken into consideration. In December 2017, a national downstaging policy proposed by the University of California San Francisco allowed HCC patients who presented with HCC beyond Milan criteria to be eligible for LT if they were successfully downstaged within Milan criteria and did not exceed an alpha-feta protein level exceeding 1000 ng/mL.[16-18] Most patients in the pre-MMaT cohort were included after this policy came into effect. In addition, to reduce regional inconsistencies in granting exception requests, a national liver review board was instituted in May 1, 2019, to improve efficiency.[19] The MMaT era started after this national liver review board was instituted, which may confound our findings.

More recently, in February 2020, AC policy was implemented to replace DSA and regional boundaries previously used in liver distribution with a system based on distance between donor hospital and transplant hospital. The purpose of the policy was to prioritize patients with higher MELD or acuity of illness, which may have impacted LT outcomes during the MMaT era. In our subgroup analyses, we demonstrate that the AC policy further decreased LT probability within HCC patients but had similar probability compared with non-HCC patients. With the AC policy, MMaT for each transplant center is calculated every 6 mo, and the corresponding MMaT-3 fluctuated after the AC policy went into effect. This impacted medium and high MELD regions as several regions interchanged between medium and high MELD regions, and we were unable to assess regional impact during phases of the AC policy. However, low MELD regions, where the disparity for LT is most pronounced, remained within their regional MELD category through the entirety of the AC policy, and we found no difference in LT probability for HCC and non-HCC candidates after the AC policy was implemented. Further data are needed to determine the effect of the AC policy on LT outcomes.

Of note, OPTN/UNOS initially approved the AC policy to start alongside the MMaT policy in May 2019. However, the transition to the AC policy where liver distribution allocation was based on distance was temporarily blocked in federal court and reverted back to DSA-based distribution. In February 4, 2020, the new AC model was reinstated by UNOS for liver distribution.[20] That means MMaT-3 was calculated on DSA-level characteristics during the pre-AC period of MMaT policy and distance-level characteristics during the AC period of MMaT policy. Therefore, categorizing patients as low, medium, and high MELD based on UNOS regions subjects HCC recipients in both the MMaT analysis and AC subanalysis to misclassification of exposure and significant type II error. These dynamic changes in how MMaT was calculated over time (6 mo), DSA, and distance made it challenging to create a comparator group. For this reason, we opted to present these pre- and post-analyses using previous UNOS regions. Although it may be more comprehendible to the transplant community, it may not be generalizable to the current distribution and allocation practices. With longer follow-up, future studies should take the current AC distribution policy and evaluate how the current donor distance MMaT-3 policy compares to pre-MMaT-3 policy.

As previously mentioned, OPTN/UNOS reinstated the AC policy in February 2020. Although we were able to broadly evaluate effect of AC policy during the MMaT period, regionally, this may not be generalizable because of the change of the distribution system from DSA to distance for determining MMaT.

LT probability within HCC patients decreased but created a more equitable access to LT for all candidates. This improvement in LT probability was also seen on a regional level, thereby reducing the geographic disparity in access for LT among HCC and non-HCC candidates as was the intent of the policy. Low MELD regions that previously had a disproportionate advantage in LT for HCC candidates had over a 40% reduction in LT probability and also had a more equitable balance compared with non-HCC patients. Moreover, waitlist dropout did not significantly change for HCC patients. Long-term data will need to evaluate the efficacy of the policy in improving access to LT and effect on waitlist dropout.

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REFERENCES

1. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl*. 2001;7:567–580.
2. Heimbach JK. United States liver allocation. *Curr Opin Organ Transplant*. 2020;25:104–109.
3. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol*. 2017;15:767–775.e3.
4. Gosalia AJ, Martin P, Jones PD. Advances and future directions in the treatment of hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)*. 2017;13:398–410.
5. Piscaglia F, Camaggi V, Ravaioli M, et al. A new priority policy for patients with hepatocellular carcinoma awaiting liver transplantation within the model for end-stage liver disease system. *Liver Transpl*. 2007;13:857–866.
6. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology*. 2004;127:S261–S267.
7. Nagai S, Kitajima T, Yeddula S, et al. Effect of mandatory 6-month waiting period on waitlist and transplant outcomes in patients with hepatocellular carcinoma. *Hepatology*. 2020;72:2051–2062.
8. Yohanathan L, Heimbach JK. The impact of allocation changes on patients with hepatocellular carcinoma. *Clin Liver Dis*. 2020;24:657–663.
9. Durkin C, Kaplan DE, Bittermann T. T2 hepatocellular carcinoma exception policies that prolong waiting time improve the use of evidence-based treatment practices. *Transplant Direct*. 2020;6:e597.
10. Alver SK, Lorenz DJ, Marvin MR, et al. 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 Transpl*. 2016;22:1343–1355.
11. Rich NE, Parikh ND, Singal AG. Hepatocellular carcinoma and liver transplantation: changing patterns and practices. *Curr Treat Options Gastroenterol*. 2017;15:296–304.
12. Cholankeril G, Podboy A, Alshuwaykh OS, et al. Early impact of COVID-19 on solid organ transplantation in the United States. *Transplantation*. 2020;104:2221–2224.
13. Strauss AT, Boyarsky BJ, Garonzik-Wang JM, et al. Liver transplantation in the United States during the COVID-19 pandemic: national and center-level responses. *Am J Transplant*. 2021;21:1838–1847.
14. United Network for Organ Sharing. COVID-19 and solid organ transplant. 2021. Available at https://unos.org/covid/. Accessed March 26, 2021.
15. Cholankeril G, Goli K, Rana A, et al. Impact of COVID-19 pandemic on liver transplantation and alcohol-associated liver disease in the USA. *Hepatology*. 2021;74:3316–3329.
16. Yao FY, Xiao L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant*. 2007;7:2587–2596.
17. Organ Procurement and Transplantation Network. OPTN policies. 2020. Available at https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed December 22, 2020.
18. Merani S, Majno P, Kneteman NM, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. *J Hepatol*. 2011;55:814–819.
19. Organ Procurement and Transplantation Network. Liver review board guidance. 2020. Available at https://optn.transplant.hrsa.gov/resources/guidance/liver-review-board-guidance/. Accessed December 22, 2020.
20. Latt NL, Niazi M, Pyrsopoulos NT. Liver transplant allocation policies and outcomes in United States: a comprehensive review. *World J Methodol*. 2022;12:32–42.