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https://escholarship.org/uc/item/00z9n56d

Journal

Liver Transplantation, 26(5)

ISSN

1527-6465

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Publication Date

2020-05-01

DOI

10.1002/lt.25701

Peer reviewed

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Author manuscript

Liver Transpl. Author manuscript; available in PMC 2022 January 11.

Published in final edited form as:

Liver Transpl. 2020 May ; 26(5): 662–672. doi:10.1002/lt.25701.

Unfair Advantages for Hepatocellular Carcinoma Patients Listed for Liver Transplant in Short-Wait Regions Following 2015 Hepatocellular Carcinoma Policy Change

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Abstract

For patients with hepatocellular carcinoma (HCC) listed for liver transplantation (LT), United Network for Organ Sharing (UNOS) enacted policy changes in 2015 to improve equity between HCC and non-HCC patients. We evaluated the impact of these changes on regional disparities in wait-list dropout and LT. We included patients in the UNOS database listed with Model for End-Stage Liver Disease HCC exceptions in long-wait regions (LWRs), mid-wait regions (MWRs), and short-wait regions (SWRs) before these policy changes (era 1, January 1 to December 31, 2013) and after (era 2, October 7, 2015, to October 7, 2016). Cumulative incidence of wait-list dropout and LT were evaluated using competing risk regression. Median time to LT increased by 3.6 months (3.1 to 6.7 months) in SWRs and 1.3 months (6.9 to 8.2 months) in MWRs ($P < 0.001$), with a slight decrease in LWRs (13.4 to 12.9 months; $P = 0.02$). The 2-year cumulative incidence of dropout increased from 9.7% to 14.8% in SWRs ($P = 0.03$) and from 18.9% to 22.6% in MWRs ($P = 0.18$) but decreased in LWRs from 26.7% to 24.8% ($P = 0.31$). Factors predicting wait-list dropout included listing in era 2 (hazard ratio [HR], 1.17), in LWRs (HR, 2.56), and in MWRs (HR, 1.91). Regional differences in wait-list outcomes decreased with policy changes, but HCC patients in SWRs remain advantaged. Recent policy change may narrow these disparities.

The United Network for Organ Sharing (UNOS) introduced the Model for End-Stage Liver Disease (MELD) priority exception system for hepatocellular carcinoma (HCC) in 2002 to establish equitable dropout rates between HCC and non-HCC patients awaiting liver transplantation (LT).(1) Even with policy adjustments in 2003 and 2005, HCC patients

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Potential conflict of interest: Nothing to report.

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continued to receive excess priority[2–4] and an unfair advantage in access to LT compared with non-HCC patients. Specifically, the 12-month wait-list dropout over a 3-year span from 2005 to 2008 was 11.5% for HCC patients versus 17.7% for all non-HCC patients nationally.[2] Thus, UNOS introduced additional revisions in October 2015: a 6-month delay in awarding HCC exception points and a MELD exception cap at 34 points.[5] These changes reflected simulation data that predicted that a 6-month delay would promote equity between HCC and non-HCC patients.[6] Additionally, a cap of 34 points would reduce regional sharing for HCC patients under the Share 35 policy, limiting competition for organs for non-HCC patients with increased urgency.

Although much of this UNOS policy at the national level has focused on disparities between HCC and non-HCC patients, efforts to adjust the HCC exception policy have been confounded by regional disparities with regard to wait-list dropout.[7] Through each era of policy change from 2002 to 2015, patients with HCC in regions with longer wait times experienced higher rates of wait-list dropout compared with those in regions with shorter wait times.[7–9] Specifically, between 2005 and 2014, LT wait times for HCC patients increased by a median of 6.0 months in long-wait regions (LWR; regions 1, 5, and 9) versus 1.3 months in short-wait regions (SWR; regions 3, 10, and 11).[9]

A recent analysis by Ishaque et al. showed the 2015 policy changes of a 6-month exception delay and MELD cap achieved their goal, at least at a national level. In the 2 years preceding the revision, HCC patients had a 37% lower wait-list mortality/dropout rate versus non-HCC patients (hazard ratio [HR], 0.63 95% CI 0.54–0.73) compared with a nearly equitable wait-list mortality/dropout rate after policy implementation (HR, 0.95 95% CI 0.81–1.11).[10] To our knowledge, no regional analysis of post-2015 wait times has been completed, and therefore, the impact of this policy change on the wait-list mortality and dropout rates in SWRs versus mid-wait regions (MWRs) versus LWRs remains unknown.

Given previous evidence of regional disparities and the fact that 2015 policy adjustments were not directly aimed at addressing geographic differences, further policy adjustments have been proposed by the Organ Procurement and Transplantation Network (OPTN) whereby HCC exception points would be assigned based on median Model for End-Stage Liver Disease score at transplant (MMAT) minus 3 points.[11] The proposed policy would calculate MMAT based on median MELD score for patients undergoing LT within a 250-nautical-mile circle around the center of where the HCC patient is listed.[12] As a result of ongoing litigation, these policy adjustments have not yet been implemented. As of May 24, 2019, OPTN approved applying the MMAT calculation for LT candidates based on the donation service area (DSA) in which the candidate is listed.[13]

As regional allocation of organs drastically changes, it is crucial to understand the current, real-world outcomes that have prompted the MMAT approach so that the impact of this new policy can be clearly understood. We therefore investigated the impact of the 2015 UNOS policy changes on geographical trends in probabilities of LT and wait-list dropout in HCC patients in order to better characterize the regional impact of these policies and to facilitate future assessment as this new approach takes shape.

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Patients and Methods

This study included consecutive patients with HCC in the UNOS database aged 18 years and older who were initially listed within Milan criteria stage T2 and were approved for a MELD exception. The patients were split into 2 cohorts before and after the 2015 policy changes. Era 1 represented patients with HCC MELD exceptions first approved between January 1 and December 31, 2013, whereas era 2 included patients from October 7, 2015, to October 7, 2016. Wait-list follow-up data were available through March 2018. Excluded patients were those listed for multiorgan transplant, those who underwent living donor transplant, and those whose radiographic tumor burden exceeded Milan criteria either at HCC diagnosis or on any submitted exception petition. Study variables collected from the UNOS database at the time of listing with MELD exception included age, sex, race/ethnicity, etiology of liver disease, body mass index (BMI), laboratory MELD and Child-Pugh score, size and number of HCCs, alpha-fetoprotein (AFP), and type of locoregional therapy (LRT) received. Date of MELD exception approval and UNOS region where each patient was listed were captured to assess temporal and regional changes. Additional UNOS data on recovered donors were also queried for analysis of organ procurement.

The 11 UNOS regions were subdivided into wait-time regions based on median time from listing to LT from 2010 to 2014.[9] Regions were categorized as LWR (regions 1, 5, and 9), MWR (regions 2, 4, 6, 7, and 8), and SWR (regions 3, 10, and 11).

The primary outcome was dropout from the LT waiting list for death without LT or being too sick to undergo LT. The secondary outcome was LT including median time from initial MELD exception to LT. Outcomes were assessed for the overall cohort and stratified by both wait-time region and era to investigate geographic and temporal disparities, respectively.

STATISTICAL ANALYSIS

Patient and tumor characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical variables. Characteristics were stratified by pre- and post-policy eras as well as wait-time regions and were compared with Wilcoxon rank sum, Kruskal-Wallis, and Pearson’s chi-square tests, as appropriate.

Observed cumulative incidence and 95% confidence intervals (CIs) of wait-list dropout and LT were estimated while accounting for competing risks[14] and were stratified by wait-time region and era. Patient follow-up time was measured from the date of first MELD exception approval to the first event of the following:

1. Wait-list outcome (dropout or LT).
2. Last date on the waiting list within the study period.
3. 24 months after exception approval.

For dropout, follow-up terminated on the date of dropout with LT considered a competing event. For LT, patient follow-up ended at the date of LT with dropout for death or being too sick considered competing events. Patients removed from the waiting list for other reasons

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or remaining on the waiting list were censored at the last date on the waiting list or 24 months.

Univariate and multivariate subdistribution HRs and 95% CIs for risk of wait-list dropout were estimated using Fine and Gray competing risk regression. Characteristics with a univariate *P* value of <0.1 were included in the multivariate analysis with the final model selected by backward elimination (*P* for removal >0.05). Interactions were assessed between listing era and wait-time region. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC) and Stata/IC, version 14.2 (StataCorp, College Station, TX). This study was approved by the University of California, San Francisco, Committee for Human Research.

Results

NEW HCC REGISTRATIONS

To inform the geographic context of HCC, the proportion of listed patients with HCC exceptions was assessed at the wait region level across both eras. The percentages of listed patients with approved HCC exceptions were 26.3% and 24.9% during eras 1 and 2, respectively ($P = 0.04$). Within the LWRs, the percentages of newly approved HCC exceptions per listing were 33.4% and 27.8% for eras 1 and 2 ($P < 0.001$), whereas MWRs (26.2% and 26.6%; $P = 0.67$) and SWRs (20.1% and 20.2%; $P = 0.90$) maintained a consistent percentage of HCC approvals across eras. The proportion of transplants for HCC among candidates listed in eras 1 and 2 were 33.4% and 27.9%, respectively ($P < 0.001$). This decrease was observed across all wait regions. The percentage of HCC transplants for eras 1 and 2 were 43.1% and 31.0% for LWRs ($P < 0.001$), 35.7% and 32.0% for MWRs ($P = 0.02$), and 25.4% and 22.3% ($P = 0.02$) for SWRs.

CHARACTERISTICS OF PATIENTS LISTED WITH HCC

Baseline demographics and clinical characteristics of the study population with HCC are stratified by era and summarized in Table 1. Across era 1 (n = 2162) and era 2 (n = 2195), 32.3% of the cohort were listed in LWRs, 42.9% in MWRs, and 24.8% in SWRs. Hepatitis C virus (HCV) was the most common etiology of liver disease, and the median laboratory MELD score at listing in both eras was 10. Patients in era 2 were slightly older at listing (62 versus 60 years) with lower mean AFP (8 versus 11 ng/mL), a higher proportion with Child-Pugh class A cirrhosis (46.3% versus 42.1%), and had fewer tumors (81.6% with single lesion versus 72.1%; all $P \leq 0.02$). The percent of patients receiving LRT for HCC also significantly increased from era 1 (81.3%) to era 2 (89.5%; $P < 0.001$). Patients in SWRs (69.9% versus 90.7%; $P < 0.001$) and MWRs (84.0% versus 89.9%; $P < 0.001$) accounted for much of the increase, whereas this proportion was similar in LWRs (86.0% versus 87.8%; $P = 0.31$).

To account for regional demographic differences, baseline characteristics are also summarized by wait region in Supporting Table 1. Tumor characteristics, AFP, and MELD scores at listing were not meaningfully different across wait regions. LWRs had a higher proportion of Hispanic (24.8%) and Asian (13.1%) patients compared with other regions

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($P < 0.001$). LWRs also had a higher proportion of Child-Pugh class A patients (52.1%) compared with MWRs (42.3%) and SWRs (37.6%; $P < 0.001$). LWRs and MWRs had higher proportions of ablation (86.8% and 87.1%) compared with SWRs (80.7%; $P < 0.001$).

TRANSPLANT CENTER CHARACTERISTICS

Characteristics of transplant centers were also assessed for practice pattern variations that might influence LT and wait times. The number of older donors (age >70 years) and deceased donor liver transplantations (DDLTs) among HCC patients were evaluated at the center level. The total number of older donors was 57 in era 1 and 52 in era 2 across all centers. Of 114 centers, 51 did not perform any DDLTs. The median percentages of transplants among HCC patients who received DDLTs are summarized by region and era in Supporting Table 2. The median percent of DDLTs in era 1 was 0 across all 3 wait regions and remained similar when removing centers with 0 DDLTs (10.0% in LWRs versus 12.2% in MWRs versus 8.0% in SWRs). Only 2 centers had a statistically significant change in the percent of transplants that were DDLT from era 1 to era 2, and there was no significant change in DDLT percentage at the wait region level between eras.

With regard to our local organ procurement organization (OPO) and transplant center, which reside in an LWR, data were queried from the UNOS eligible donor database for both eras and in more recent years, as summarized in Supporting Table 3. The number of recovered donors at the local OPO level remained consistent between era 1 and era 2, and it remains similar as of 2018. The number of recovered donors has increased at the wait region level over the same time period. The percentage of DDLTs and older donors (age >70 years) also did not significantly change at our transplant center, which is consistent with LWR more broadly.

LT AND TRANSPLANT WAIT TIMES

Wait-list outcomes for the study cohort are summarized in Table 2. Of the 4357 patients, 1522 (70.4%) from era 1 and 1390 (63.3%) from era 2 underwent LT. Median time to LT increased from 6.5 months (IQR, 3.0–12.7 months) in era 1 to 7.8 months (IQR, 6.4–11.9 months) in era 2. SWRs experienced the greatest increase in median wait time (from 3.1 to 6.7 months) between eras, although time to LT remained significantly longer in era 2 for MWR (8.2 months; $P < 0.001$) and LWR (12.9 months; $P = 0.02$). At the end of study follow-up in era 2, 104 (16.0%) patients in LWRs remained listed for LT versus 4.2% in MWRs and 1.6% in SWRs.

Cumulative incidence of LT within 2 years of listing with initial HCC exception decreased overall between era 1 (0.746; 95% CI, 0.726–0.765) and era 2 (0.669; 95% CI, 0.678–0.720; $P < 0.001$). This decrease was largely driven by the significant decline in SWR LT incidence from 0.886 (95% CI, 0.854–0.912) to 0.826 (95% CI, 0.790–0.856; $P = 0.03$). However, the cumulative incidence of LT in both era 1 and era 2 remained higher in SWRs compared with other regions (Fig. 1A–C).

Among patients with HCC who received transplant over the study period, median exception MELD at LT in eras 1 and 2 was 28 (IQR, 25–31) and 28 (IQR, 28–31), respectively ($P < 0.001$) reflecting a slight increase in MMAT in era 2. This increase was largely driven by a

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3-point increase in median MMAT within SWRs from era 1 (25; IQR, 22–25) to era 2 (28; IQR, 28–28; $P < 0.001$). LWRs (31 [IQR, 29–34] to 31 [28–33]; $P = 0.002$) and MWRs (28 [IQR, 25–31] to 28 [IQR, 28–29]; $P < 0.001$) had statistically significant but numerically small shifts in MMAT.

WAIT-LIST DROPOUT

Overall cumulative incidence of dropout within 2 years of listing with MELD exception was similar from era 1 (19.5%; 95% CI, 17.8%-21.3%) to era 2 (21.2%; 95% CI 19.4%-23.1%). Probability of dropout within 2 years of listing increased in SWR from 9.7% (7.3%-12.5%) to 14.8% (11.9%-18.1%); $P = 0.03$; Fig. 2A). Probability of dropout within 2 years of listing did not significantly change in MWR (0.189 to 0.226; $P = 0.18$) and LWR (0.267 to 0.248; $P = 0.31$) across eras (Fig. 2B,C). Median time to dropout was 6.5 months in era 1 and 6.7 months in era 2 and was not significantly different across eras by wait region (Table 2).

The multivariate competing risk model of wait-list dropout showed that listing in era 2 was associated with an increased risk of dropout (HR 1.17; 95% CI, 1.01–1.35; $P = 0.03$ compared with era 1), with much of the difference accounted for by SWRs (HR, 2.06; 95% CI, 1.40–3.02; $P < 0.001$ compared with era 1; Table 3). MWRs also showed an increased risk of wait-list dropout for era 2 compared with era 1 (HR, 1.30; 95% CI, 1.05–1.62; $P = 0.02$) but not LWR (HR, 0.87; 95% CI, 0.70–1.08; $P = 0.20$). Interaction testing between waiting time and era showed that these multivariate dropout HRs for era 2 versus era 1 in MWR (HR, 1.30) and SWR (HR, 2.06) differed significantly from LWRs (HR, 0.87; interaction $P = 0.009$ versus MWRs and $P < 0.001$ versus SWRs).

The multivariate model also demonstrated an increased risk of dropout for patients listed in LWRs (HR, 2.56; 95% CI, 2.07–3.18; $P < 0.001$) and MWRs (HR, 1.91; 95% CI, 1.54–2.37; $P < 0.001$) compared with SWRs across both eras. This increased risk of dropout conferred by listing in an LWR compared with a SWR significantly decreased from era 1 (HR, 4.03; 95% CI, 2.89–5.63; $P < 0.001$) to era 2 (HR, 1.70; 95% CI, 1.28–2.26; $P < 0.001$; interaction $P < 0.001$). Similar results were found for dropout in MWRs compared with SWRs from era 1 (HR, 2.46; 95% CI, 1.75–3.47; $P < 0.001$) to era 2 (HR, 1.56; 95% CI, 1.19–2.04, $P = 0.001$; interaction $P = 0.04$; Table 3).

CLINICAL FACTORS ASSOCIATED WITH WAIT-LIST DROPOUT

Clinical factors that significantly impacted wait-list dropout in the multivariate model are summarized in Table 3 and include increasing age, Child-Pugh and MELD scores, listing AFP, and tumor burden as well as receipt of LRT and having blood type O (compared with AB or B; all $P \leq 0.001$). Child-Pugh class C (HR, 2.08; 95% CI, 1.59–2.71) and class B (HR, 1.56; 95% CI, 1.32–1.86) predicted higher risk of dropout compared with class A, as did all levels of AFP >20 ng/mL at listing. Risk of dropout also increased with tumor burden for a single lesion >3 cm (HR, 1.49; 95% CI, 1.25–1.76), 2 lesions at listing (HR, 1.39; 95% CI, 1.16–1.68), or 3 lesions at listing (HR, 1.88; 95% CI, 1.41–2.51) compared with 1 lesion ≤3 cm. Receipt of LRT was protective from wait-list dropout with an HR of 0.69 (95% CI, 0.57–0.83).

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POST-LT PATIENT SURVIVAL

The 1-year post-LT patient survival among HCC patients was similar for those listed in era 1 (92.1%; 95% CI, 90.6%-93.4%) compared with era 2 (93.3%; 95% CI, 91.6%-94.7%; $P = 0.52$). This was consistent across wait regions. LWRs (era 1, 93.6%; 95% CI, 91.0%-95.5%; era 2, 94.5%; 95% CI, 90.1%-97.0%; $P = 0.67$), MWRs (era 1, 91.2; 95% CI, 88.6%-93.2%; era 2, 91.8; 95% CI, 88.9%-94.0%; $P = 0.28$), and SWRs (era 1, 91.8%; 95% CI, 88.8%-94.0%; era 2, 94.6%; 95% CI, 91.8%-96.4%; $P = 0.40$) demonstrated no significant differences in survival. No differences in 1-year graft survival were detected among HCC patients by era.

Beyond our study population, 1-year post-LT patient survival was similar for HCC and non-HCC patients listed in era 1 (HCC, 92.1%; 95% CI, 90.6%-93.4%; non-HCC 92.0%, 95% CI, 91.0%-93.0%; $P = 0.44$) and era 2 (HCC, 93.3%; 95% CI, 91.6%-94.7%; non-HCC, 93.0%; 95% CI, 92.0%-93.8%; $P = 0.65$). No differences were identified between HCC and non-HCC groups when stratified by region. No differences in 1-year graft survival were detected between HCC and non-HCC patients in eras 1 or 2.

Discussion

Despite numerous UNOS policy adjustments since 2002, optimizing the allocation of organs for LT and achieving equity between patient groups has remained a challenge. Establishing equitable policies for HCC and non-HCC patient access to LT is an important objective, as the incidence of HCC continues to increase.[15] The burden of HCC from chronic HCV is not expected to peak until 2030, and increasing rates of nonalcoholic fatty liver disease (NAFLD) represent the fastest growing indication for LT in patients with HCC.[16–18] HCC now accounts for nearly 25% of all LTs performed in the United States compared with 15% from 2002 to 2005.[19,20]

Ishaque et al.[10] demonstrated that 2015 updates to the HCC policy accomplished the goal of reducing the differences in rates of HCC and non-HCC wait-list mortality/dropout at a national level. This change was largely driven by an increased risk of wait-list dropout for HCC patients compared with non-HCC patients with HR increasing from 0.8 before to 1.9 after policy implementation. Although their study did note a decrease in the rate of LT for HCC patients at the regional level, no comparisons were performed with regard to intraregional differences. This regional analysis is crucial to better understand ongoing geographic disparities in access to LT for HCC patients.

Our analysis has shown that HCC patients in the post-2015 era experienced longer wait times for LT and higher rates of wait-list dropout/delisting than in previous eras, which is largely driven by increased delays in SWRs. The proportion of transplants performed for HCC also decreased across all wait regions, despite the proportion of listings for HCC exceptions in MWRs and SWRs remaining unchanged. These findings were expected in the context of a 6-month delay in assigning HCC exception points and a revised MELD cap below the Share 35 threshold. The goal of this policy change was to make access to transplant more similar between HCC and non-HCC patients, regardless of geography. It was observed that in LWRs, access to transplant and wait-list dropout rates were already

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similar between HCC and non-HCC patients. Therefore, by increasing waiting time in SWRs without further disadvantaging LWRs, the 2015 policy adjustments did inadvertently impact geographic equity. However, it is important to recognize that geographic disparity overall remains inadequately addressed, as demonstrated by the current findings. HCC patients in LWRs and MWRs remained disadvantaged compared with SWRs, with a 1.70-fold and 1.56-fold probability of dropout/delisting, respectively, compared with SWR patients in the post-2015 policy change era. Interaction analysis confirmed the significance of these disparities. Additionally, cumulative incidence of wait-list dropout remains highest in LWRs by a substantial margin.

There were also notable temporal differences between the eras with regard to clinical data. Patients in era 2 were significantly older at listing with lower AFP, lower tumor burden, and higher proportion with compensated liver disease and, thus, no alternate indication for LT besides HCC. Our multivariate analysis confirmed that these clinical factors are associated with wait-list dropout, with increasing tumor burden, AFP, MELD, and Child-Pugh scores conferring higher probability of dropout, whereas receiving LRT appears protective. This trend of decreasing clinical acuity at the time of exception listing may indicate reduced urgency of LT and, potentially, reduced survival benefit. Because many patients with a small HCC and well-preserved liver function may achieve complete and sustained response to regional ablative therapy, thus precluding the need for immediate LT,[21] further consideration regarding selection for LT may be prudent.

The drivers of this ongoing geographic disparity remain unclear. We do note that the burden of HCC among patients listed for transplant and ultimately transplanted is higher in LWRs than in MWRs or SWRs. Although the proportion of patients listed and transplanted with HCC decreased in LWR in era 2 (likely a consequence of the 6-month delay in listing), it does remain higher than in other regions. This higher burden of HCC likely explains the higher MMAT in LWRs for HCC patients. Slightly higher rates of ablation in LWRs may also explain some of the increased wait times, although this practice is, in turn, likely a response to anticipated longer delays in transplant. Use of DDLT and older donors, while variable at the center level, did not significantly vary between eras or regions within our study population, making practice patterns at the center level an unlikely driver of overall disparities.

Revisions to HCC exception policy over time have achieved their intended goal of reducing disparities between HCC and non-HCC patients, but regional differences remain an area of great concern. Our data support the conclusions of UNOS regarding the need for ongoing efforts to address geographic disparities in LT. A recent transition from 11 regional review boards to a single National Liver Review Board for awarding MELD exceptions took place in May 2019.[22] This unified review board should help to mitigate potential regional disparities by allowing for more consistent review of MELD exceptions across different regions. As reviewers are drawn from a national pool to review anonymous exception requests, there is hope for improved consistency in how these exceptions are awarded. Broader sharing of livers across a wider geographic area and the introduction of the MMAT minus 3 points and concentric circle liver allocation policies could ameliorate geographic inequities by more accurately reflecting the differences in MELD score that are necessary to

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receive a LT in different parts of the country. The MMAT minus 3 points approach assigns HCC exception points in a way that is geographically normalized, such that circles around transplant centers with higher median MELD scores (typically in LWRs) will assign greater priority to HCC patients. Liver allocation will now also follow a concentric circle model: candidates with highest medical urgency (status 1A and 1B) listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital will receive priority, followed by candidates with MELD scores ≥37 in increasingly broad circles of 150, 250, and 500 nautical miles until a recipient is identified.[23] This new system effectively eliminates organ allocation based on regions or DSAs and, over time, is predicted to reduce geographic disparity in access to transplant both for HCC and non-HCC patients. This policy has been formally adopted and is awaiting implementation.

Although review board consistency and geographic normalization will likely help achieve equity, consideration should also be given to methods of improving organ procurement in LWRs. Efforts to improve rates of both organ donation and utilization, especially in LWRs, are essential to addressing geographic disparities. OPO liver donation rates per 100 eligible deaths range from as low as 44.9 to as high as 87.3, with many of the OPOs in LWRs representing lower ranges.[24] Any improvement in these OPO metrics in LWRs could markedly reduce the high wait-list dropout rate without disadvantaging traditionally shorter-wait regions, and indeed, the number of recovered donors does appear to be increasing nationally. Our analysis did not demonstrate an increase in recovered donors at the OPO level across eras, but increased recognition of this issue may lead to improvements in OPO performance. For example, under direction of a new chief executive officer, concerted efforts are currently underway within the California Transplant Donor Network to increase organ procurement and utilization.

Our analysis establishes a timely baseline for geographic and temporal disparities in LT as new policies take effect. With over 4000 patients across 2 eras of policy revisions, we have characterized robust trends at the national, regional, and clinical level to inform ongoing debates about inequity in organ allocation. Moreover, by demonstrating current differences in wait times and wait-list dropout, we are better equipped to prospectively assess the impacts of new HCC and liver allocation guidelines within the concentric circles model. We are optimistic that the geographic normalization introduced by the MMAT approach will reduce incentives for HCC patients to travel from longer- to shorter-wait regions[9] and address perceptions of regional inequity with regard to organ allocation.

Limitations of this study include the relatively short length of follow-up for patients listed in era 2 and the inherent limits of the UNOS database. Specifically, 16.0% of era 2 patients in LWRs remained listed for LT at the end of study follow-up, which may limit our power to detect changes in rates of dropout between eras in LWRs. Moreover, the relatively short study period limited our ability to evaluate practice differences at the center level. With only a total of 109 older donors and 229 DDLT donors over the study period, our assessment of practice pattern variation at the center level is not definitive. Our study also excluded patients who underwent downstaging of their tumor burden prior to listing. Because era 1 preceded formal adoption of downstaging at the national level,[25] we could not ensure a homogeneous approach to listing of downstaged patients across eras and, thus, opted to

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exclude these patients who exceeded Milan criteria T2 at any point. We also could not meaningfully assess post-LT outcomes over this timeline given how recently era 2 patients underwent LT. The response to LRT is an important surrogate of tumor biology and a factor predicting wait-list dropout, but this information is not available in the UNOS database.[21,26]

In conclusion, in this large national study evaluating temporal and regional trends in wait-list outcomes among patients with HCC, we observed ongoing geographic disparities. Although disparities between HCC and non-HCC patients improved at a national level as intended by the 2015 UNOS policy adjustments, the gap between LWRs, MWRs, and SWRs with regard to wait-list dropout for HCC patients persists. These findings support the policies now approved by UNOS to assign MELD exception points based on MMAT minus 3 points, as well as allocation of organs based on a concentric circles model to narrow these wait-list disparities. This approach is based largely on simulation data of various MMAT minus n scenarios that suggest improved regional equity in allocation of organs compared with prior HCC policies. The 6-month delay in awarding HCC exception points will remain in place.[27] As we shift into a new era with policies directly targeting regional inequality, our findings provide a more definitive understanding of the geographic disparities that preceded it.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Clinical and Translational Core of the University of California, San Francisco, Liver Center (P30 DK026473).

Abbreviations:

AFP	alpha-fetoprotein
BMI	body mass index
CI	confidence interval
DDLT	deceased donor liver transplantation
DSA	donation service area
EtOH	alcohol
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio

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IQR	interquartile range
LRT	locoregional therapy
LT	liver transplantation
LWR	long-wait region
MELD	Model for End-Stage Liver Disease
MMAT	median Model for End-Stage Liver Disease score at transplant
MWR	mid-wait region
NAFLD	nonalcoholic fatty liver disease
NS	not significant
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplantation Network
SWR	short-wait region
UNOS	United Network for Organ Sharing

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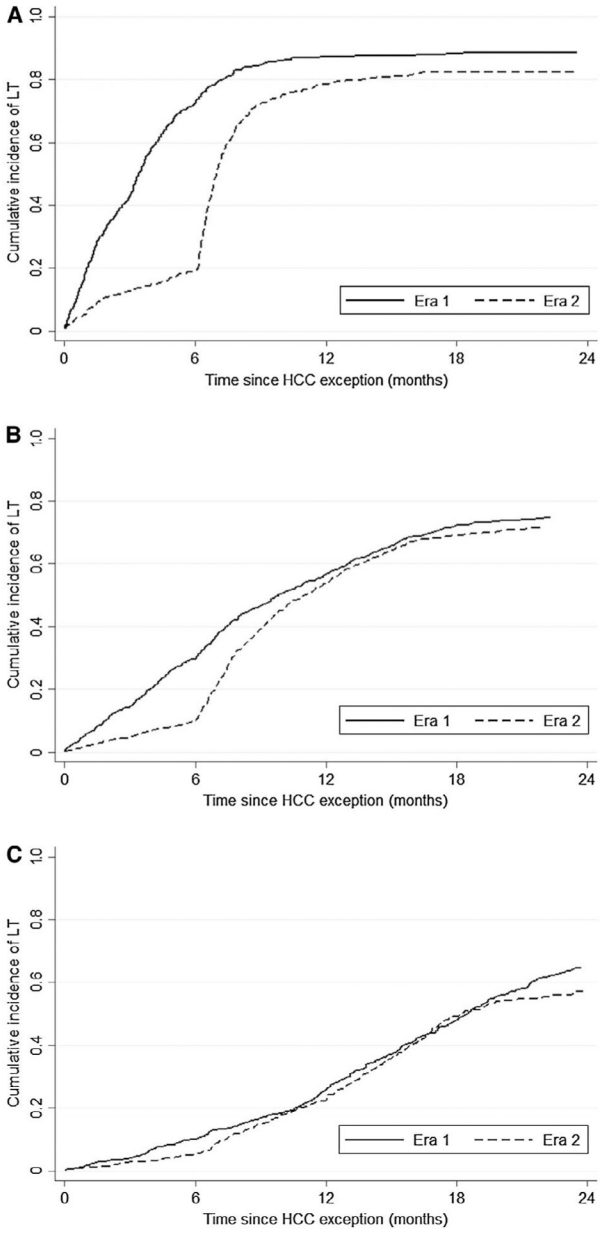

FIG. 1.

Cumulative probability of LT stratified by MELD exception in era 1 (January 1 to December 31, 2013) versus era 2 (October 7, 2015, to October 7, 2016) for UNOS (A) SWRs (P = 0.03), (B) MWRs (P = 0.18), and (C) LWRs (P = 0.31).

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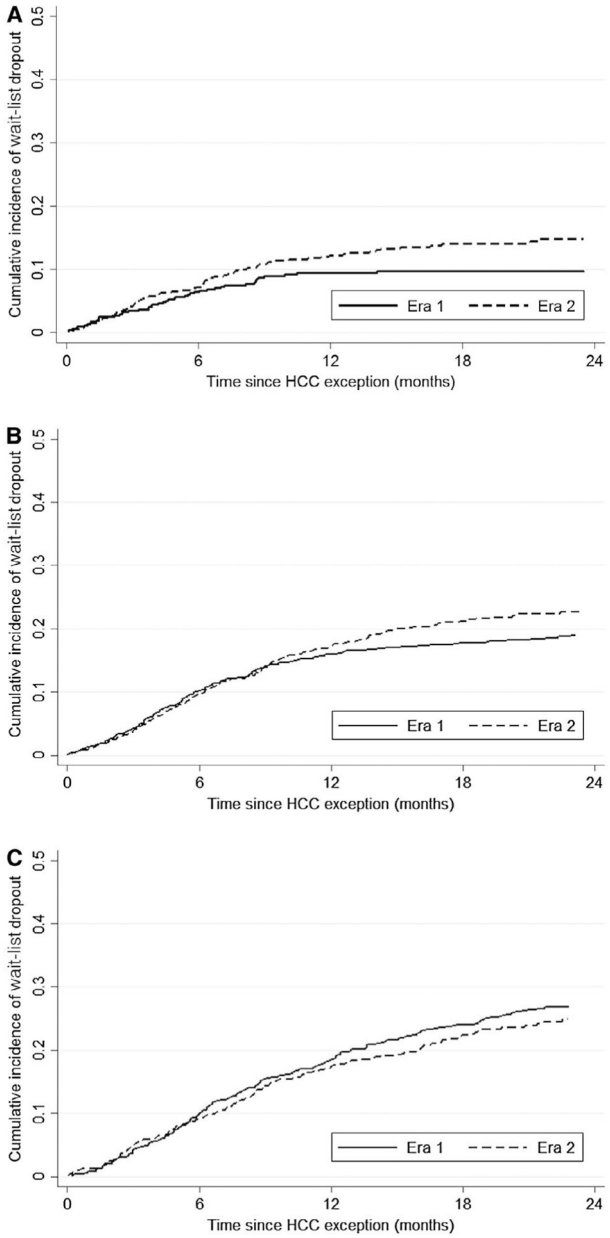

FIG. 2.

Cumulative probability of wait-list dropout in era 1 (January 1 to December 31, 2013) and era 2 (October 7, 2015, to October 7, 2016) for UNOS (A) SWRs ($P = 0.03$), (B) MWRs ($P = 0.18$), and (C) LWRs ($P = 0.31$).

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TABLE 1.

Baseline Characteristics of Patients With HCC Listed for LT by Listing Era

	Overall (n = 4357)	Era 1 (n = 2162)*	Era 2 (n = 2195)†	*P* Value
UNOS wait region				<0.001
LWR	1409 (32.3)	762 (35.2)	647 (29.5)	
MWR	1867 (42.9)	879 (40.7)	988 (45.0)	
SWR	1081 (24.8)	521 (24.1)	560 (25.5)	
Age, years	61 (57–65)	60 (56–64)	62 (57–65)	<0.001
Sex, male	3317 (76.1)	1649 (76.2)	1668 (76.0)	0.83
Ethnicity				
Caucasian	2825 (64.8)	1398 (64.7)	1427 (65.0)	0.04
Hispanic	712 (16.3)	341 (15.8)	371 (16.9)	
African American	442 (10.1)	216 (10.0)	226 (10.3)	
Asian	320 (7.3)	183 (8.5)	137 (6.2)	
Other	58 (1.3)	24 (1.1)	34 (1.5)	
Etiology				<0.001
HCV	2548 (58.5)	1287 (59.5)	1261 (57.4)	
NAFLD	472 (10.8)	192 (8.9)	280 (12.8)	
EtOH	431 (9.9)	175 (8.1)	256 (11.7)	
HBV	222 (5.1)	124 (5.7)	98 (4.5)	
Other	684 (15.7)	384 (17.8)	300 (13.7)	
BMI, kg/m^2	28.5 (25.1–32.2)	28.3 (25.0–32.0)	28.6 (25.3–32.4)	0.03
Listing MELD	10 (8–15)	10 (8–16)	10 (8–15)	0.48
Child-Pugh class				0.02
A	1927 (44.2)	911 (42.1)	1016 (46.3)	
B	1853 (42.5)	948 (43.8)	905 (41.2)	
C	573 (13.2)	299 (13.8)	274 (12.5)	
Missing	4 (0.0)	4 (0.0)	0 (0.0)	
AFP, ng/mL	9 (5–28)	11 (5–38)	8 (4–20)	<0.001
Listing HCC burden				<0.001
1 lesion 2–3 cm	2388 (54.8)	1123 (51.9)	1265 (57.6)	

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	Overall (n = 4357)	Era 1 (n = 2162)*	Era 2 (n = 2195)†	*P* Value
1 lesion 3.1–5 cm	964 (22.1)	438 (20.2)	526 (24.0)	
2 lesions	798 (18.3)	462 (21.4)	336 (15.3)	
3 lesions	207 (4.8)	139 (6.4)	68 (3.1)	
Received LRT	3721 (85.4)	1757 (81.3)	1964 (89.5)	<0.001
LWR	1223 (86.8)††	655 (86.0)††	568 (87.8)††	0.31
MWR	1626 (87.1)††	738 (84.0)††	888 (89.9)††	<0.001
SWR	872 (80.7)††	364 (69.9)††	508 (90.7)††	<0.001

NOTE: Data are given as n (%) or median (IQR). LWRs are regions 1, 5, and 9; MWRs are regions 2, 4, 6, 7, and 8; and SWRs are regions 3, 10, and 11.

*HCC patients listed for transplant with first approved MELD exception from January 1 to December 31, 2013.

†HCC patients listed for transplant with first approved MELD exception from October 7, 2015, to October 7, 2016.

††Percentages calculated based on number of patients in these wait regions by era (top row of table).

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TABLE 2.

Outcomes on the LT Waiting List for HCC Patients by Region and Era

	Era 1 (n = 2162)*	Era 2 (n = 2195)†	*P* Value
Received an LT	1522 (70.4)	1390 (63.3)	<0.001
LT by region‡			
LWR	463 (60.8)	325 (50.2)	<0.001
MWR	610 (69.4)	625 (63.3)	0.004
SWR	449 (86.2)	440 (78.6)	0.004
Time to LT, months	6.5 (3.0–12.7)	7.8 (6.4–11.9)	<0.001
Time to LT by region, months			
LWR	13.4 (8.4–18.3)	12.9 (8.4–16.2)	0.02
MWR	6.9 (3.6–11.5)	8.2 (6.6–11.4)	<0.001
SWR	3.1 (1.2–4.8)	6.7 (6.2–7.7)	<0.001
Remained listed for LT at end of study follow-up‡			<0.001
LWR	10 (1.3)	104 (16.0)	
MWR	7 (0.8)	42 (4.2)	
SWR	0 (0.0)	9 (1.6)	
Dropout for death/delisting	421 (19)	424 (19)	0.35
Dropout by region‡			
LWR	204 (27)	148 (23)	0.03
MWR	168 (19)	200 (20)	NS
SWR	49 (9.4)	76 (14)	0.004
Time to dropout, months	6.5 (3.7–12.2)	6.7 (3.4–11.0)	0.37
Time to dropout by region, months			
LWR	8.2 (4.8–14.1)	7.8 (3.7–12.7)	0.18
MWR	5.9 (3.4–10.5)	6.5 (3.7–10.5)	0.57
SWR	4.5 (2.2–7.2)	5.8 (2.6–8.7)	0.23

NOTE: Data are given as n (%) or median (IQR). LWRs are regions 1, 5, and 9; MWRs are regions 2, 4, 6, 7, and 8; and SWRs are regions 3, 10, and 11.

*HCC patients listed for transplant with first approved MELD exception from January 1 to December 31, 2013.

†HCC patients listed for transplant with first approved MELD exception from October 7, 2015, to October 7, 2016.

‡The long wait time regions include regions 1, 5, and 9; the percentages are calculated based on the n value for this region in era 1 (n = 762) and in era 2 (n = 647). The mid wait time regions include regions 2, 4, 6, 7, and 8; the percentages are calculated based on the n value for this region in era 1 (n = 879) and in era 2 (n = 988). The short wait time regions include regions 3, 10, and 11; the percentages are calculated based on the n value for this region in era 1 (n = 521) and era 2 (n = 560).

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TABLE 3.

Multivariate Competing Risk Model for Wait-List Dropout Due to Death or Delisting Among Patients With HCC by Region and Era

Predictor	Multivariate HR (95% CI)	*P* Value	Interaction *P* Value
Region-related factors			
MELD exception listing era			
Era 2 versus era 1 (all regions)	1.17 (1.01–1.35)	0.03	
Era 2 versus era 1 among LWRs	0.87 (0.70–1.08)	0.20	0.009 *
Era 2 versus era 1 among MWRs	1.30 (1.05–1.62)	0.02	<0.001 †
Era 2 versus era 1 among SWRs	2.06 (1.40–3.02)	<0.001	
LWRs versus SWRs			
Overall	2.56 (2.07–3.18)	<0.001	
LWRs versus SWRs among era 1	4.03 (2.89–5.63)	<0.001	<0.001
LWRs versus SWRs among era 2	1.70 (1.28–2.26)	<0.001	
MWRs versus SWRs			
Overall	1.91 (1.54–2.37)	<0.001	
MWRs versus SWRs among era 1	2.46 (1.75–3.47)	<0.001	0.04
MWRs versus SWRs among era 2	1.56 (1.19–2.04)	0.001	
Clinical factors			
Blood type AB+B (versus O)	0.71 (0.57–0.88)	0.001	
Age (per year)	1.02 (1.01–1.04)	<0.001	
MELD at listing (per point)	1.03 (1.02–1.05)	<0.001	
Child-Pugh B (versus A)	1.56 (1.32–1.86)	<0.001	
Child-Pugh C (versus A)	2.08 (1.59–2.71)	<0.001	
AFP at listing, ng/mL	1.34 (1.12–1.61)	0.001	
21–100 ng/mL (versus ≤20 ng/mL)	2.24 (1.84–2.73)	<0.001	
101–1000 ng/mL (versus ≤20 ng/mL)	4.26 (2.93–6.22)	<0.001	
>1000 ng/mL (versus ≤20 ng/mL)			
Listing tumor burden			
1 lesion 3.1–5 cm (versus 1 lesion ≤3 cm)	1.49 (1.25–1.76)	<0.001	
2 lesions (versus 1 lesion ≤3 cm)	1.39 (1.16–1.68)	0.001	
3 lesions (versus 1 lesion ≤3 cm)	1.88 (1.41–2.51)	<0.001	

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Predictor	Multivariate HR (95% CI)	*P* Value	Interaction *P* Value
Received LRT prior to LT	0.69 (0.57–0.83)	<0.001	

*Indicates that multivariate HRs (0.87 versus 1.30) differ significantly.

†Indicates that multivariate HRs (0.87 versus 2.06) differ significantly.