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Disparities in the Effects of Acuity Circle–based Liver Allocation on Waitlist and Transplant Practice Between Centers

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Background. Liver allocation in the United States was updated on February 4, 2020, by introducing the acuity circle (AC)–based model. This study evaluated the early effects of the AC-based allocation on waitlist outcomes. **Methods.** Adult liver transplant (LT) candidates listed between January 1, 2019, and September 30, 2021, were assessed. Two periods were defined according to listing date (pre- and post-AC), and 90-d waitlist outcomes were compared. Median transplant Model for End-stage Liver Disease (MELD) score of each transplant center was calculated, with centers categorized as low- (<25 percentile), mid- (25–75 percentile), and high-MELD (>75 percentile) centers. **Results.** A total of 12 421 and 17 078 LT candidates in the pre- and post-AC eras were identified. Overall, the post-AC era was associated with higher cause-specific 90-d hazards of transplant (csHR, 1.32; 95% confidence interval [CI], 1.27-1.38; $P < 0.001$) and waitlist mortality (cause-specific hazard ratio [csHR], 1.20; 95% CI, 1.09-1.32; $P < 0.001$). The latter effect was primarily driven by high-MELD centers. Low-MELD centers had a higher proportion of donations after circulatory death (DCDs) used. Compared with low-MELD centers, mid-MELD and high-MELD centers had significantly lower cause-specific hazards of DCD-LT in both eras (mid-MELD: csHR, 0.47; 95% CI, 0.38-0.59 in pre-AC and csHR, 0.56; 95% CI, 0.46-0.67 in post-AC and high-MELD: csHR, 0.11; 95% CI, 0.07-0.17 in pre-AC and csHR, 0.14; 95% CI, 0.10-0.20 in post-AC; all $P < 0.001$). Using a structural Bayesian time-series model, the AC policy was associated with an increase in the actual monthly DCD-LTs in low-, mid-, and high-MELD centers (actual/predicted: low-MELD: 19/16; mid-MELD: 21/14; high-MELD: 4/3), whereas the increase in monthly donation after brain death–LTs were only present in mid- and high-MELD centers. **Conclusions.** Although AC-based allocation may improve waitlist outcomes, regional variation exists in the drivers of such outcomes between centers.

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The Final Rule states that organ allocation shall not be based on the candidate's residence or place of listing.[1] The regional disparity of liver transplant (LT) access has been an issue and has been extensively discussed. In July 2018, a lawsuit was filed against Health Resources and Services Administration regarding the disparity or LT access between areas and called for the Organ Procurement and Transplantation Network/United Network for Organ

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The data that support the findings of this study are available from the Organ Procurement and Transplantation Network (OPTN). Restrictions apply to the availability of these data, which were used under license for this study. Data are available OPTN at https://optn.transplant.hrsa.gov/data/request-data/ with the permission of OPTN and the United Network of Organ Sharing.

United Network of Organ Sharing and the centers participating in the Organ Procurement and Transplantation Network are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis of the conclusions derived by the authors.

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Sharing (OPTN/UNOS) to implement a new liver allocation policy not based on arbitrary Donation Service Areas or Region Areas but rather as a zone-based liver distribution policy.[2] In response, OPTN/UNOS introduced the new liver allocation policy, called acuity circle (AC)–based model, in February 2020.[3] The new model is based on radially oriented zones around potential donors and involves converting each transplant center's median Model for End-stage Liver Disease (MELD) score at transplant to reflect transplants performed within a 250 nautical mile radius.

The OPTN/UNOS and LT society have been trying to address the concerns about regional variation in LT access.[4] One of the recent modifications in the LT allocation was the "Share 35 rule," introduced in 2013,[5] which was only applied within individual UNOS regions, and the discrepancies in transplant MELD score between regions remained.[6] The AC-based model was proposed to further alleviate the concerns about the disparity in transplant access. The donor service area–based allocation was discarded, and donated livers were shared based on radially oriented zones from the donor hospitals. This has the potential to dramatically change LT practice, along with having a downstream impact on patient outcomes. It is therefore imperative to assess the effects of the AC-based allocation on LT waitlist and transplant practice.

Recently, Chyou et al[7] reported the first 6-mo effects of AC-based allocation, demonstrating that adult non–status 1 deceased donor LT decreased by 2.7%. However, this report evaluated the data from March 2020 to August 2020, during which time the coronavirus disease 2019 (COVID-19) pandemic was declared, which significantly impacted LT practice. The effect of the policy outside of a period affected by the impact of COVID-19 remains to be fully elucidated. Consequently, it may be beneficial to evaluate the initial impact of AC-based allocation on LT waitlist outcomes and practice using data in a period when the effects of COVID-19 have subsided.[8] Wey et al[9] recently also studied the effects of AC-based allocation using more current data, demonstrating that MELD 29–32 candidates consistently had the largest differences in deceased donor LT and offer rates compared with before the implementation of the AC. However, the study by Wey et al[9] did not evaluate possible regional variation in the effects of AC-based allocation. One of the main purposes of introducing AC-based allocation was to reduce the regional discrepancy of LT access. Therefore, thorough evaluations of this aspect are crucial.

In this study, we hypothesized that there would be regional differences in the effects of the AC-based allocation on waitlist and transplant practice. We aimed to evaluate the early impact of the AC-based allocation on LT waitlist outcomes and transplant characteristics and determine possible regional variations.

MATERIALS AND METHODS

Patient Selection

This study uses data from the OPTN/UNOS Standard Transplant and Research file, containing information from all patients registered for LT in the United States until September 30, 2021. For the analysis of waitlist outcomes, candidate age <18 y at listing, hepatocellular carcinoma (HCC) exception cases, patients who were listed between February 5, 2020, and May 9, 2020 (COVID-19 onset period),[8] or who were listed before 2019 were excluded. The study was approved for an institutional review board waiver after institutional review board review.

Because AC-based allocation was introduced on February 4, 2020, 2 time periods were defined according to the date of LT listing: a pre-AC era from January 1, 2019, to February 3, 2020, and a post-AC era from May 10, 2020, to September 30, 2021. May 10, 2020, was selected as the cutoff because the COVID-19 effects have been deemed to have stabilized according to UNOS after that (COVID stabilization era).[8]

The median MELD score of each center from January 1, 2019, to February 3, 2020, (inclusive) was defined according to the median MELD calculated based on MELD scores of patients who received an LT, were age 12 or over, were not status 1A or status 1B, did not receive a living donor graft, did not receive a donation after circulatory death (DCD) graft, and donors from hospitals located >500 nautical miles from the recipient transplant hospital. This calculation of median score followed the way of MELD score at transplant calculation by OPTN/UNOS. Quantiles were defined as <25 percentile as a MELD score ≤23, 25 percentile to 75 percentile as a MELD score between 23 and 29, and >75 percentile as a MELD score ≥29. According to this, transplant centers were defined as lower, mid, and higher MELD center groups.

Analysis of Waitlist Outcomes

Ninety-day waitlist outcomes were analyzed using a competing risk analysis with outcomes, including improvement on the waitlist (removal code 12), transplantation (removal codes 2–4, 18, 19, 21, and 22), or death (including removal for being too sick) (removal codes 5, 8, and 13). To eliminate the effects of 2 different allocation policies, patients listed in the pre-AC era were censored on February 4, 2020, if none of the abovementioned events had occurred. Because differences in follow-up time can result in withdrawal bias, patients who were registered in either era were censored on the last day of the respective era (February 4, 2020, and October 1, 2021, respectively).[10] Patients who received living donor liver transplantation were included in the waitlist outcome analyses because they were also on deceased donor LT waitlist but were censored at the time of living donor liver transplantation receipt in the waitlist outcome analyses.[11] Outcomes were compared between pre- and post-AC eras. Ninety-day waitlist outcomes were also compared between eras in each MELD region group. For the 90-d competing risk of donation after brain death (DBD) and DCD transplant, receipt of DCD and DBD transplant was considered a competing event, respectively.

For comparisons of variables in patients who received a transplant, the 2 groups included patients listed pre-AC and transplanted pre-AC and patients listed post-AC and transplanted post-AC. Patients listed pre-AC but transplanted post-AC were thus excluded from the pre-AC group in the abovementioned bivariate analysis (Figure 1). Patients who received living donor liver transplantation were not included in the analyses of transplant characteristics.

Structural Bayesian Time-series Model

To estimate the causal effect of the AC policy on monthly transplant listings, DBD and DCD transplants, a time series analysis was performed. Specifically, this analysis used a structural Bayesian time-series model to estimate how monthly

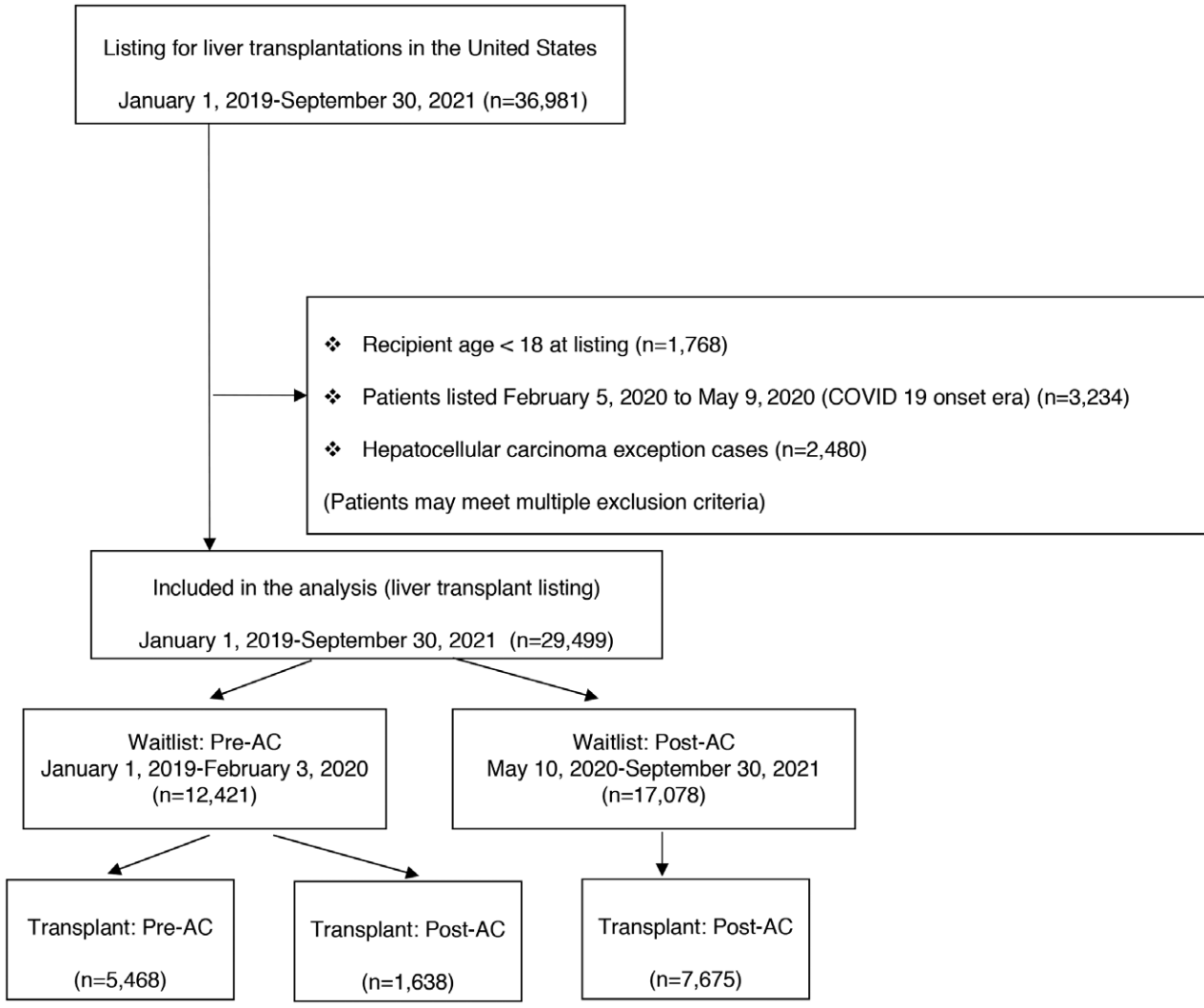

FIGURE 1. Strengthening the Reporting of Observational Studies diagram of cohorts included and excluded. AC, acuity circle; COVID-19, coronavirus disease 2019.

transplant listings, DBD and DCD transplants at low-, mid-, and high-MELD centers might have evolved after the AC policy if the policy had not occurred. Similarly, a sensitivity analysis was performed to evaluate monthly listings with a MELD score of >35 at listing in the low-, mid-, and high-MELD centers. A fully Bayesian time-series estimate of the effect is computed; it uses model averaging to construct the most appropriate synthetic control for modeling the counterfactual.[12] In this time series analysis, the pre- and post-AC periods were defined as previously noted. Covariates selected for the modeling were chosen based on the assumption that they would not be affected by the AC policy and included albumin level at LT, LT candidate factors (height, weight, body mass index, primary payment source at LT), and donor factors (height). Quantitative summaries are provided as tables displaying actual activity (what were the transplant rates with the policy), predicted activity (what would the transplant rates have been without the policy), absolute effect (with 95% confidence interval [CI]), relative effect (with 95% CI), the posterior tail-area probability *P*, and the posterior probability of a causal effect. A detailed description of the structural Bayesian time-series method used is shown in **Text S1** (**SDC**, http://links.lww.com/TXD/A439).

Statistical Analysis

Descriptive data for continuous variables were expressed as means with SD if the distribution was normal and medians with interquartile range if the distribution was non-normal. These were compared using the Student *t* test and Mann-Whitney *U* test, respectively. Categorical variables were expressed as numbers and percentages and were compared using chi-square and Fisher exact test. For the waitlist analysis, a cause-specific competing risk approach was used to account for the presence of competing risks of transplant and waitlist dropout because of mortality/being too sick for transplant.[13] To evaluate the effect of the exposure (AC policy) on competing events, cause-specific hazard ratios (csHRs) were reported after adjustment for confounders. Variables that were considered confounders were used for multivariable adjustment included age at listing, MELD score at listing, gender, diabetes, functional status at listing (Karnofsky score 3 categories 70%–100%, 40%–60%, 10%–30%), life support at listing, dialysis week before listing, hepatic encephalopathy at listing, alcohol-related liver disease, hepatitis C virus, exception point case, and HCC. Quantitative summaries are provided as tables displaying actual activity (what were the

TABLE 1.

Patient characteristics stratified by AC era

Waitlist patient characteristics	Pre-AC (N = 12421)	Post-AC (N = 17078)	P
Gender, male, n (%)	4900 (39.4)	6653 (39.0)	0.39[a]
Age at listing, median (IQR), y	57 (48–64)	56 (47–63)	<0.001[b]
BMI at listing, median (IQR), kg/m^2	28.4 (24.6–32.9)	28.1 (24.4–32.6)	<0.001[b]
MELD at listing, median (IQR)	20 (14–27)	21 (14–29)	<0.001[b]
Life support at listing, n (%)	564 (4.5)	742 (4.5)	0.82[a]
N-missing	5	542	
Liver-kidney listing, n (%)	1332 (10.7)	1678 (9.8)	<0.001[a]
Dialysis week before listing, n (%)	1252 (10.1)	1989 (11.6)	<0.001[a]
N-missing	11	3	
Non-HCC exception patients, n (%)	555 (4.5)	503 (2.9)	<0.001[b]
Primary liver disease, n (%)			
Alcohol-related liver disease	4794 (38.6)	7172 (42.0)	<0.001[a]
Nonalcoholic steatohepatitis	3027 (24.4)	3958 (23.2)	0.02[a]
Hepatitis C virus–related liver disease	1575 (12.7)	1657 (9.7)	<0.001[a]
Functional status at listing			<0.001[a]
N-missing	238	947	
70%–100%, n (%)	2430 (19.9)	3738 (23.2)	
40%–60%, n (%)	4574 (37.5)	5617 (34.8)	
10%–30%, n (%)	5179 (42.5)	6776 (42.0)	
MELD center			0.22[a]
N-missing	16	48	
Low, n (%)	3678 (29.6)	4894 (28.7)	
Mid, n (%)	5396 (43.5)	7538 (44.3)	
High, n (%)	3331 (26.9)	4598 (27.0)	
Transplant patient characteristics	Pre-AC (N = 5468)[c]	Post-AC (N = 7675)	
Distance donor hospital to transplant center (nautical miles), median (IQR)	74 (9–216)	148 (40–314)	<0.001[a]
Share type, n (%)			<0.001[b]
Local	3423 (62.6)	2712 (35.3)	
Regional	1754 (32.1)	2275 (29.6)	
National	291 (5.3)	2688 (35.0)	
DCD, n (%)	423 (8.2)	627 (8.6)	0.41[b]
N-missing	282	357	
CIT, median (IQR), h	5.5 (4.3–6.8)	5.7 (4.6–6.9)	<0.001[a]
Donor age, median (IQR), y	40 (28–53)	39 (28–52)	0.71[a]
Recipient age at transplant, median (IQR), y	56 (47–63)	55 (45–62)	<0.001[a]
Recipient BMI at transplant, median (IQR), kg/m^2	28.6 (24.8–32.9)	28.3 (24.5–32.9)	0.09[a]
MELD at transplant, median (IQR)	27 (20–35)	28 (21–35)	<0.001[a]
Life support at transplant, n (%)	678 (12.4)	803 (10.5)	<0.001[b]
N-missing	0	14	
Liver-kidney, n (%)	490 (9.0)	728 (9.5)	0.31[b]
Dialysis week before transplant, n (%)	1122 (20.6)	1748 (22.9)	0.003[b]
N-missing	34	30	
Primary liver disease, n (%)			
Alcohol-related liver disease	2331 (42.6)	3802 (49.5)	<0.001[b]
Nonalcoholic steatohepatitis	1325 (24.2)	1714 (22.3)	0.01[b]
Hepatitis C virus–related liver disease	493 (9.0)	545 (7.1)	<0.001[b]
Functional status at transplant			<0.001[b]
N-missing	95	159	
70%–100%, n (%)	2015 (37.5)	3049 (40.6)	
40%–60%, n (%)	2126 (39.6)	2702 (35.9)	
10%–30%, n (%)	1232 (22.9)	1765 (23.5)	
MELD center			<0.001[b]
N-missing	0	12	
Low, n (%)	1969 (36.0)	2516 (32.8)	
Mid, n (%)	2327 (42.6)	3467 (45.2)	
High, n (%)	1172 (21.4)	1680 (21.9)	

[a]Kruskal-Wallis rank-sum test.
[b]Pearson chi-square test.
[c]Includes a comparison of only patients who received a LT—pre-AC includes only patients listed pre-AC and transplanted pre-AC.
AC, acuity circle; BMI, body mass index; CIT, cold ischemia time; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-stage Liver Disease.

transplant rates with the policy), predicted activity (what would the transplant rates have been without the policy), absolute effect (with 95% CI), relative effect (with 95% CI), the posterior tail-area probability *P* (1-sided), and the posterior probability of a causal effect. The posterior distribution of the response variable (monthly DBD or DCD transplants) expected in the absence of the intervention (AC policy). The actual response is then compared with this posterior distribution. The tail-area probability is the probability under the calculated posterior that the response is at least as extreme (away from the expected value) as the one observed. A 2-sided $P < 0.05$ was considered statistically significant for all other analyses. All statistical analyses were performed using R (R version 4.1.1 [2021-08-10], R foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). The structural Bayesian time-series analysis was performed using the package "CausalImpact" version 1.2.7.[12]

RESULTS

Patient Characteristics

During the study period, 36 981 patients were listed for LT. Recipient age <18 y at listing (n = 1768), those who were listed between February 5, 2020, and May 9, 2020 (n = 3234), and HCC exception cases (n = 2480) were excluded (Figure 1). There were 12 421 and 17 078 patients who were listed and met the inclusion criteria in the pre- and post-AC eras, and a total of 5468 and 9313 patients were listed and received LT in the pre- and post-AC eras. The distance from donor hospital to transplant center was longer in the post-AC era (74–148 miles; $P < 0.001$), and the proportion of national sharing of organs (sharing >250 nautical miles radius) was statistically significantly higher (5.3%–35.0%; $P < 0.001$). The cold ischemia time was significantly longer in the post-AC era (median 5.5 h pre-AC to 5.7 h post-AC; $P < 0.001$). The proportion of LTs done was significantly lower in the lower MELD center group post-AC (36.0% to 32.8%; $P < 0.001$) (Table 1).

When comparing characteristics in each MELD score center group, a longer distance from the donor hospital to the transplant center and a larger proportion of national sharing in the post-AC era were observed in all center groups (Table 2). Notably, the proportion of DCD LTs in the post-AC era was numerically higher in the lower MELD center group, but this did not reach statistical significance (10.9%–12.0%; $P = 0.27$). Similarly, the proportion of DCD LTs was not statistically significantly different between eras in the mid (8.5%–8.6%; $P = 0.91$) and higher MELD center groups (2.5%–3.2%; $P = 0.31$).

Comparisons of Waitlist Outcomes Between Eras

Waitlist outcomes were compared between the eras. In the entire cohort, the 90-d probability of waitlist mortality was not statistically significantly different ($P = 0.34$), although the 90-d transplant probability was statistically significantly higher in the post-AC era ($P < 0.001$) (**Figure S1**, **SDC**, http://links.lww.com/TXD/A439). After risk-adjustment using transplant candidate characteristics, the cause-specific hazard of 90-d waitlist mortality associated with the post-AC era was statistically significantly higher compared with the pre-AC era (reference: pre-AC adjusted csHR, 1.20; 95% CI, 1.09-1.32; $P < 0.001$). This effect was primarily attributed to the high-MELD center groups. Moreover, post-AC was associated with a higher 90-d cause-specific hazard of transplant compared with the pre-AC era (reference: pre-AC [csHR], 1.32; 95% CI, 1.27-1.38; $P < 0.001$) (Table 3).

Next, 90-d waitlist outcomes were compared stratifying by MELD score center grouping. The 90-d transplant probability was statistically significantly higher in all groups in the post-AC era. The 90-d probability of waitlist mortality was statistically significantly higher in the post-AC era in only the high-MELD center group (**Figure S2**, **SDC**, http://links.lww.com/TXD/A439). In the lower MELD center group, although the adjusted cause-specific hazard of 90-d waitlist mortality was not statistically significantly different between the eras (90-d mortality: csHR, 1.05; 95% CI, 0.85-1.29; $P = 0.64$), the post-AC era was associated with a higher cause-specific hazard of 90-d transplant (csHR, 1.17; 95% CI, 1.09-1.25; $P < 0.001$). Similarly, in the mid-MELD center group, the post-AC was associated with a nonstatistically significantly different cause-specific hazard of waitlist mortality (csHR, 1.15; 95% CI, 0.99-1.33; $P = 0.06$) and a statistically significantly higher cause-specific hazard of 90-d transplant (csHR, 1.45; 95% CI, 1.36-1.53; $P < 0.001$). In the higher MELD center group, post-AC was associated with a statistically significantly higher cause-specific hazard of 90-d waitlist mortality compared with pre-AC (csHR, 1.35; 95% CI, 1.15-1.59; $P < 0.001$). Lastly, and similar to the low- and mid-MELD center groups, the post-AC era was associated with a higher cause-specific hazard of 90-d transplant than the pre-AC era (csHR, 1.37; 95% CI, 1.26-1.49; $P < 0.001$) (Table 3).

Comparisons of 90-d Probability and Cause-specific Hazard of Transplantation Between Center Groups According to Donor Type

Because the AC-based model was designed to enhance broader sharing of liver grafts from DBD donors, DBD and DCD LT probabilities were examined separately. The 90-d DBD LT probability was statistically significantly higher post-AC in the low-, mid-, and high-MELD center groups (low-MELD pre-AC 43.4% versus post-AC 45.4%; $P < 0.001$; mid-MELD pre-AC 35.0% versus post-AC 41.5%; $P < 0.001$; and high-MELD pre-AC 29.0% versus post-AC 35.7%; $P = 0.002$, <0.001, and <0.001, respectively) (**Figure S3**, **SDC**, http://links.lww.com/TXD/A439). When comparing this between MELD center groups in each era, the 90-d DBD LT probability was significantly higher in the lower MELD center group than in the mid or higher center groups in the pre-AC era ($P < 0.001$), and this remained highest in the lower MELD region group in the post-AC era ($P < 0.001$). Nonetheless, the difference between centers was reduced in terms of the 90-d DBD transplant probability in the post-AC era (Figure 2A and B). After risk-adjustment, the mid-MELD (csHR, 0.64; 95% CI, 0.59-0.69; $P < 0.001$) and high-MELD (csHR, 0.41; 95% CI, 0.38-0.45; $P < 0.001$) center groups had a significantly lower probability of DBD LT in the pre-AC era compared with the low-MELD group. In the post-AC era, these differences were attenuated. The cause-specific DBD LT hazard remained significantly higher in the low-MELD, compared with mid-MELD (reference low: csHR, 0.78; 95% CI, 0.74-0.83; $P < 0.001$) and the high-MELD center groups (csHR, 0.47; 95% CI, 0.44-0.51; $P < 0.001$) (Table 4).

When comparing the 90-d DCD LT probability between eras in each MELD center group, the low-MELD center group had a nonstatistically significantly higher DCD LT probability post-AC (pre-AC 7.3% versus post-AC 8.3%; $P = 0.27$),

TABLE 2.

Transplant donor characteristics for MELD centers stratified by AC era

Low-MELD centers	Pre-AC (N = 1969)[a]	Post-AC (N = 2516)	P
Distance donor hospital to transplant center, median (IQR), nautical miles	87 (9–249)	155 (42–314)	<0.001[b]
Share type, n (%)			<0.001[c]
Local	1198 (60.8)	874 (34.7)	
Regional	605 (30.7)	757 (30.1)	
National	166 (8.4)	885 (35.2)	
DCD, n (%)	207 (10.9)	290 (12.0)	0.27[c]
N-missing	65	90	
CIT, median (IQR), h	5.1 (4.2–6.4)	5.6 (4.6–6.7)	<0.001[b]
Donor age, median (IQR), y	40 (29–53)	41 (30–54)	0.14[b]
Mid-MELD centers	Pre-AC (N = 2327)[a]	Post-AC (N = 3467)	
Distance donor hospital to transplant center, median (IQR), nautical miles	72 (10–198)	140 (37–307)	<0.001[b]
Share type, n (%)			<0.001[c]
Local	1496 (64.3)	1277 (36.8)	
Regional	743 (31.9)	1073 (30.9)	
National	88 (3.8)	1117 (32.2)	
DCD, n (%)	189 (8.5)	284 (8.6)	0.91[c]
N-missing	116	179	
CIT, median (IQR), h	5.6 (4.5–6.9)	5.7 (4.5–6.9)	0.95[b]
Donor age, median (IQR), y	40 (28–53)	40 (29–53)	0.78[b]
High-MELD centers	Pre-AC (N = 1172)[a]	Post-AC (N = 1680)	
Distance donor hospital to transplant center, median (IQR), nautical miles	55 (8–204)	166 (49–322)	<0.001[b]
Share type, n (%)			<0.001[c]
Local	729 (62.2)	554 (33.0)	
Regional	406 (34.6)	445 (26.5)	
National	37 (3.2)	681 (40.5)	
DCD, n (%)	27 (2.5)	51 (3.2)	0.31[c]
N-missing	101	88	
CIT, median (IQR), h	5.8 (4.4–7.2)	5.8 (4.7–7.0)	0.26[b]
Donor age, median (IQR), y	37 (27–50)	36 (26–48)	0.006[b]

[a]Includes a comparison of only patients who received a LT—pre-AC includes only patients listed pre-AC and transplanted pre-AC.
[b]Kruskal-Wallis rank-sum test.
[c]Pearson chi-square test.
AC, acuity circle; CIT, cold ischemia time; DCD, donation after circulatory death; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-stage Liver Disease.

TABLE 3.

Impact of era (post-AC vs pre-AC) on 90-d waitlist outcomes (cause-specific hazard)

	Reference: pre-AC	
Outcome	Cause-specific HR (95% CI)	P
Overall[a]		
Mortality	1.20 (1.09-1.32)	<0.001
Transplant	1.32 (1.27-1.38)	<0.001
Low-MELD center group[a]		
Mortality	1.05 (0.85-1.29)	0.64
Transplant	1.17 (1.09-1.25)	<0.001
Mid-MELD center group[a]		
Mortality	1.15 (0.99-1.33)	0.06
Transplant	1.45 (1.36-1.53)	<0.001
High-MELD center group[a]		
Mortality	1.35 (1.15-1.59)	<0.001
Transplant	1.37 (1.26-1.49)	<0.001

[a]Adjusted for age at listing, MELD score at listing, gender, diabetes, functional status at listing, life support at listing, dialysis week before listing, hepatic encephalopathy at listing, alcohol-related liver disease, hepatitis C virus, exception point case, and hepatocellular carcinoma.
AC, acuity circle; CI, confidence interval; HR, hazard ratio; MELD, Model for End-stage Liver Disease.

statistically significantly higher in the mid-MELD centers (pre-AC 3.9% versus post-AC 4.9%; $P = 0.02$), whereas it was nonstatistically significantly numerically higher in high-MELD centers (high-MELD pre-AC 0.8% versus post-AC 1.3%; $P = 0.14$) (**Figure S4, SDC**, http://links.lww.com/TXD/A439). The 90-d DCD LT probability was significantly higher in the lower MELD center group both in the pre- and post-AC eras (pre-AC era low 7.3% versus mid 3.9% versus 0.8%; $P < 0.001$). This difference remained in the post-AC era (post-AC low 8.3% versus mid 4.9% versus high 1.3%; $P < 0.001$) (Figure 2C and D). This was corroborated by a consistently lower adjusted cause-specific hazard of DCD LT in the mid- and high-MELD groups relative to the low-MELD group in both the pre- and post-AC era. Notably, both the mid- and high-MELD groups had a lower cause-specific hazard of DCD transplant in the post-AC era ([reference low-MELD] pre-AC mid-MELD csHR, 0.47; 95% CI, 0.38-0.59 to post-AC csHR, 0.56; 95% CI, 0.46-0.67 and pre-AC high-MELD csHR, 0.11; 95% CI, 0.07-0.17 to post-AC csHR, 0.14; 95% CI, 0.10-0.20; all $P < 0.001$) (Table 4).

Bayesian Structural Time Series Analysis

The monthly transplant listings were examined using Bayesian structural time series analysis. There was a

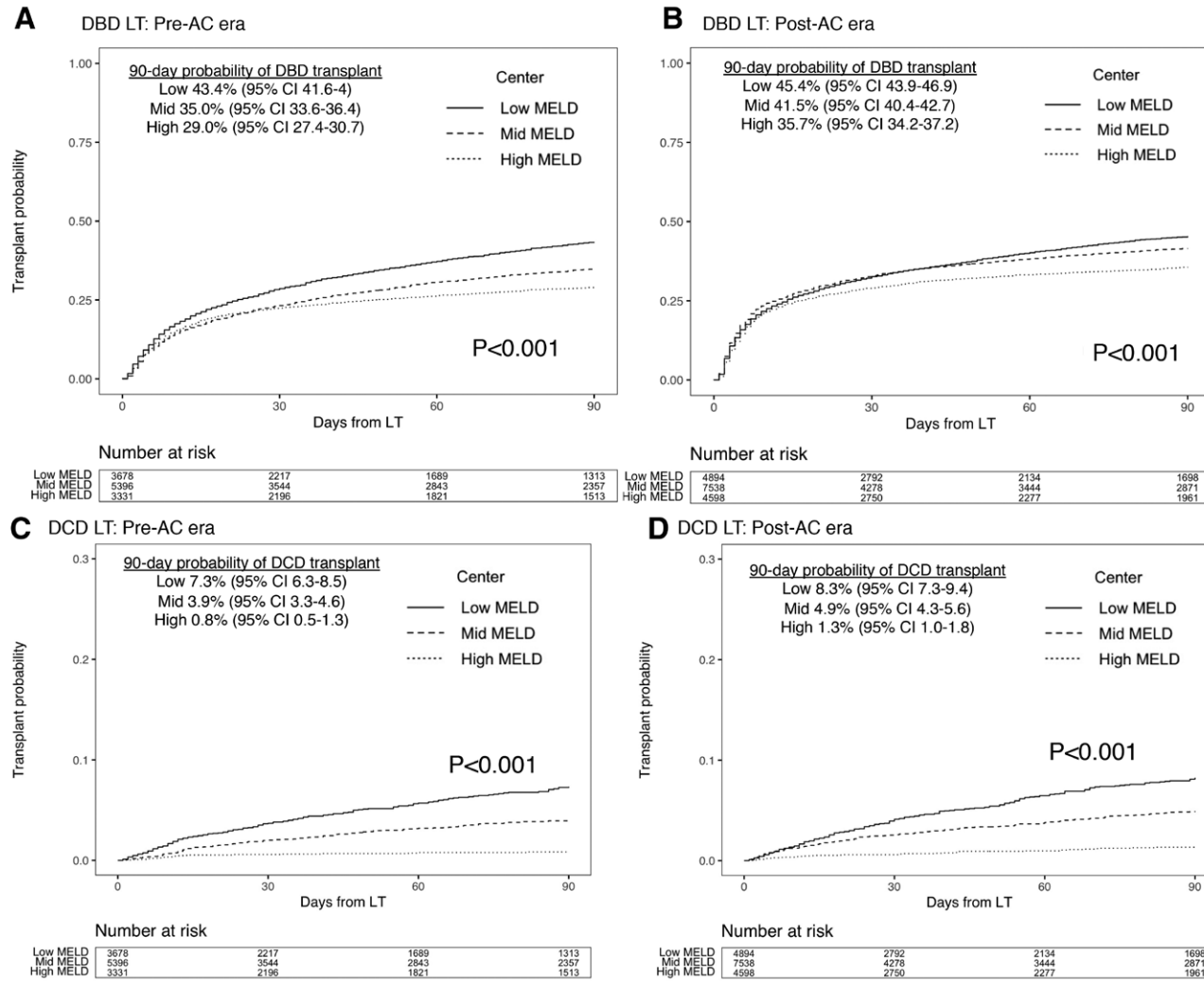

FIGURE 2. Comparisons of the 90-d cumulative incidence of DBD donor transplant and DCD donor transplant between MELD center groups: (A) DBD LT pre-AC era, (B) DBD LT post-AC era, (C) DCD LT pre-AC era, and (D) DCD LT post-AC era. AC, acuity circle; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplantation; MELD, Model for End-stage Liver Disease.

statistically significant increase in the monthly listings in the low-, mid-, and high-MELD centers. On a sensitivity analysis, this effect remained even for patients with an initial MELD >35 at the time of listing in the low-, mid-, and high-MELD centers.

We then evaluated the effect of the policy on monthly DCD and DBD transplants within each center group. For the low-MELD centers, the policy had a positive effect on the monthly DCD numbers (actual 19, predicted [SD] 16 [2]), corresponding to a relative increase of +20% (95% CI, –2% to –42%) (Figure 3A). The probability of obtaining this effect by chance was deemed to be very small (Bayesian 1-sided tail-area probability $P = 0.04$, meaning that the causal effect could be considered statistically significant). Similarly, the causal effect of the AC policy on the monthly DCD transplants in mid- and high-MELD centers was examined, and the relative effect of the increase was higher than seen for the monthly DCD in low-MELD centers (relative increase low-MELD centers +20% [95% CI, –2% to –42%]; mid-MELD +46% [95% CI, 21%-72%]; high-MELD +57% [95% CI, 31%-84%]) (Figure 3C and E). In contrast, there was no causal effect of the policy on the monthly DBD transplants the low-MELD centers but was associated with a relative increase in monthly DBD transplants in both mid- and high-MELD centers (relative effect low-MELD –3% [not statistically significant]; mid-MELD +26% [95% CI, 15%-36%]; high-MELD +51% [95% CI, 34%-70%]) (Figure 3B, D, and F).

DISCUSSION

This study examined the early effects of AC-based liver allocation on waitlist outcomes and transplant practice. We observed that the AC policy was associated with both an increased 90-d transplant probability and waitlist mortality overall. The effect on waitlist mortality was primarily driven by high-MELD centers. Although the low-MELD centers had the highest 90-d probability of transplantation in both the pre- and post-AC era, the disparity between these rates was reduced in the post-AC era. The difference in the 90-d probability of DCD transplant remained in the post-AC era, with the low-MELD regions having a higher probability of DCD transplantation relative to the mid- and high-centers in both the pre-and post-AC era. This was further corroborated by the time-series analysis, evaluating the causal impact of the policy

TABLE 4.

Impact of MELD region (low [reference] vs mid vs high) on 90-d DBD and DCD cause-specific hazard

	Reference: low-MELD center group	
Outcome	**Cause-specific HR (95% CI)**	***P***
DBD		
Pre-AC era[a]		
Mid-MELD center group	0.64 (0.59-0.69)	<0.001
High-MELD center group	0.41 (0.38-0.45)	<0.001
Post-AC era[a]		
Mid-MELD center group	0.78 (0.74-0.83)	<0.001
High-MELD center group	0.47 (0.44-0.51)	<0.001
DCD		
Pre-AC era[a]		
Mid-MELD center group	0.47 (0.38-0.59)	<0.001
High-MELD center group	0.11 (0.07-0.17)	<0.001
Post-AC era[a]		
Mid-MELD center group	0.56 (0.46-0.67)	<0.001
High-MELD center group	0.14 (0.10-0.20)	<0.001

[a] Adjusted for age at listing, MELD score at listing, gender, diabetes, functional status at listing, life support at listing, dialysis week before listing, hepatic encephalopathy at listing, alcohol-related liver disease, hepatitis C virus, exception point case, and hepatocellular carcinoma.
AC, acuity circle; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; HR, hazard ratio; MELD, Model for End-stage Liver Disease.

on monthly DCD transplants, which demonstrated the policy to have a positive effect on monthly DCD transplants in low-, mid-, and high-MELD centers. Although the AC policy was associated with a statistically significant increase in the DBD monthly LTs in mid- and high-MELD centers, it did not have a similar effect in low-MELD centers. The number of monthly listings increased in low-, mid-, and high-MELD centers. Although transplant access improved, this might not suffice the increased needs of donated livers for very sick patients, which could result in the increased risk of waitlist mortality. Consequently, the AC-based allocation decreased the discrepancies in LT access between the centers, mainly for DBD LT. This study revealed that the new allocation has been functioning as expected and seemed to appropriately alleviate the concerns with the disparity of LT access.

It should be acknowledged that the early effects of AC-based allocation were previously evaluated using the first 6-mo national LT data,[7] which demonstrated that the volume of adult non–status 1 deceased donor LT decreased by 2.7%. The study period of their study overlapped the declaration of the COVID-19 pandemic. Although LT practice must have been significantly affected by the COVID-19 pandemic nationwide, the impact would have differed among regions and states, especially at the beginning of the pandemic. To reduce these effects, we considered the post-AC era after May 10, 2020, as the impact of the COVID-19 pandemic on transplant activity has been deemed to have stabilized by UNOS (COVID 19 stabilization era).[8] Although this study cohort would not entirely eliminate the effects of the COVID-19 pandemic, the findings should support the significant effects of the AC-based allocation observed in this study.

Before the introduction of the AC-based allocation, there were concerns that broad sharing of donated livers might jeopardize waitlist outcomes in certain areas where MELD scores at transplant were relatively low because it was expected that a number of the donated livers in these areas would be shipped out to other areas, leading to a lower chance of LT in these areas.[14] According to the findings of this study, the post-AC era was associated with both an increased cause-specific waitlist mortality and transplant hazard overall, the former primarily driven by its effect in the high-MELD center group but not in the low- or mid-MELD center group. Therefore, the concern of possible adverse impact of AC-based allocation only in the low-MELD centers was alleviated. However, the increase in waitlist mortality in the high-MELD center group was unexpected and further investigations would be warranted.

The low-MELD centers had the highest probability of DCD transplants compared with the mid- and high-MELD centers in both the pre- and post-AC eras. Although the AC policy had an effect of increasing DCD monthly transplants in low-, mid-, and high-MELD centers, it had a statistically significantly positive effect on monthly DBD transplants only in mid- and high-MELD-center groups. Moreover, the relative positive effect of DCD monthly transplants was highest in high-MELD centers. In the new allocation policy, DCD donors and elderly donors (70 y or older) are allocated based on the different logistics from those for DBD donors or younger donors (<70 y).[5] Although DBD donors are broadly allocated based on AC, local allocation remains for DCD donors and the disparities in DCD donor use between centers remained significant. Low-MELD centers having the highest probability of DCD transplantation in both the pre- and post-AC era may be reflection of the threshold for acceptability of such grafts. Consequently, transplant centers which had many candidates with a low-MELD score might have more transplant offers of DCD donors. They may therefore need to accept more livers from DCD donors to maintain their LT activities. Posttransplant outcomes in DCD LT had become comparable with brain death donor LT.[15,16] However, those excellent post-LT outcomes were reported from well-experienced centers, and it remains unclear if satisfactory outcomes in DCD LT can be universally achieved. This study was unable to assess post-LT outcomes because of the limited posttransplant follow-up period. It is crucial to evaluate the possible adverse impact on outcomes secondary to the increase in the utilization of DCD donors and/or other types of marginal donors in certain areas/transplant centers.[17]

Because the AC-based model might have a greater impact on DBD donor liver allocation,[3] this study evaluated the DBD LT access in each group and assessed the regional discrepancies before and after introducing the AC-based allocation. Notably, the disparity in the probability of 90-d DBD LT decreased between regions in the post-AC era, largely driven by increases in the mid- and high-MELD centers rather than a decrease in low-MELD centers (low: 43.4%–45.4%, mid: 35.0%–41.5%, and high: 29.0%–35.7%). This reduced disparity suggests that the purposes of the introduction of the AC-based allocation have been successfully achieved. Notably, although the AC-based model improved LT access, we did not observe improvement in waitlist mortality. The AC-based model changed geographic allocation, whereas the medical urgency (patients' ranking on the waitlist) remained to be determined by the MELD-sodium (MELD-Na) score. Recently, MELD 3.0 was proposed by Kim et al.[18] According to their report, MELD 3.0 could better identify waitlist mortality than MELD-Na, and they concluded that MELD 3.0 addresses the gender disparity in LT access. It should be noted that the improvement in the MELD 3.0 model was subtle. Our group recently created a waitlist mortality prediction

model using a neural network, a machine learning technique, which had a significantly better performance of waitlist mortality prediction than the MELD-Na and the MELD 3.0 based model.[19] To achieve further improvements in LT waitlist outcomes, improvements in the determination LT candidates' medical urgency would be crucial as well.

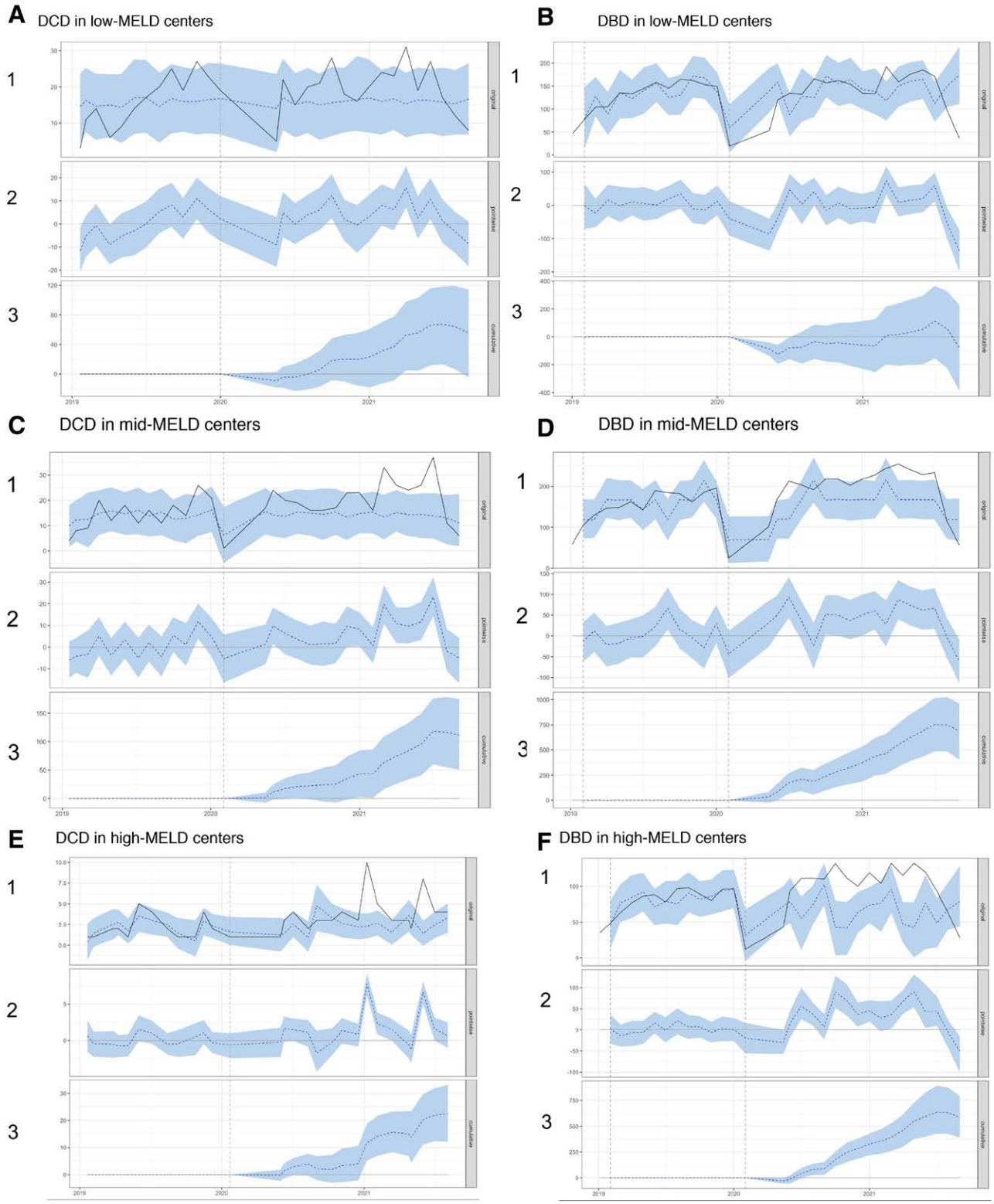

FIGURE 3. Time series analysis of monthly transplant trends pre- and post-AC policy. Each figure is comprised of 3 panels. 1. Original time series (monthly transplant rates) and the counterfactual estimate (the light blue shaded area [what the monthly transplant rate would have been had the policy not occurred]). 2. Difference between the observed data and the counterfactual estimate (point-wise causal effect). 3. Cumulative causal effects over time. A, DCD in low-MELD centers, (B) DBD in low-MELD centers, (C) DCD in mid-MELD centers, (D) DBD in mid-MELD centers, (E) DCD in high-MELD centers, and (F) DBD in high-MELD centers. AC, acuity circle; DBD, donation after brain death; DCD, donation after circulatory death; MELD, Model for End-stage Liver Disease.

Overall, the AC-based model provided positive changes in the liver allocation. It should be noted that those improvements in waitlist outcomes occurred along with dramatic changes in LT practice of transplant centers, which include the substantial increase in the travel distance. Consequently, cold ischemia time became significantly longer in all MELD score center groups in the post-AC era. Broad organ sharing by the AC-based model allocation might enhance the utilization of the donated livers for sicker patients with a high-MELD score. Also, the characteristics of LT recipients have been changing recently, which is represented by older age and significant medical comorbidities such as obesity, diabetes, and cardiovascular diseases.[20] These patient populations may have less tolerance in using donor livers with prolonged cold ischemia time.[21,22] Therefore, possible adverse effects of longer cold ischemia time should be evaluated in follow-up studies. Additionally, possible financial burden secondary to longer travel distances, and potentially higher cost for posttransplant care for sicker patients and DCD graft pursuit, needs to be carefully assessed. Recently, Wall et al[23] reported an increase in cost associated with liver acquisition that may be a threat to financial viability of transplant centers. Possible financial effects of the AC-based allocation may be significant, for which further studies would be warranted.

The limitations of this study should be acknowledged. The OPTN/UNOS registry may contain the potential for misclassification. It is not possible to attribute a causal effect of the AC-based allocation on outcomes in LT candidates, given the nonrandomized, retrospective design with the potential for unmeasured and residual confounding even despite the multivariable analyses performed. The post-AC era was chosen as post–May 10, 2020, according to the UNOS's deemed stabilization of the COVID-19 effect on transplant activity.[8] Within this context, there may be residual effects of the COVID-19 pandemic and may represent the potential of being a residual confounder for these results. However, it should be acknowledged that the impact of COVID-19 pandemic on the LT practice was not uniform across the nation, and this might persist and affect the practice differently during the study period of our study. Therefore, future studies are necessary to examine the effects of AC-based allocation after the end of the pandemic. Notwithstanding the COVID-19 pandemic having an adverse impact on LT activities,[24] a significant improvement in LT access was observed in the post-AC era.

In conclusion, although the AC-based liver allocation improved waitlist outcomes related to receipt of transplant, regional variation of positive effects was observed. Although there were significant differences in LT access between center groups, these were successfully reduced by the introduction of the AC-based allocation. Although the disparity between centers with DBD transplants has decreased, the disparity of DCD transplants between centers remained, with the AC policy having a positive effect on the monthly DCD transplants in low-, mid-, and high-MELD centers, but with positive effects in monthly DBD transplants limited to mid- and high-MELD centers. Notably, the changes in LT practice may be the result of the allocation change, represented by the significant increase in travel distance and the regional variation of DCD utilization, and the possible impact of these practice changes on post-LT outcomes has not yet been determined. Continuous evaluations are necessary to evaluate how those changes affect the center- and region-level waitlist and post-LT outcomes.

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REFERENCES

1. Organ Procurement and Transplantation Network. Final rule. 2000. Available at https://optn.transplant.hrsa.gov/governance/about-the-optn/final-rule/. Accessed November 23, 2021.
2. Pullen LC. Lawsuits drive transplant community debate over liver allocation. *Am J Transplant*. 2019;19:1251–1256.
3. Organ Procurement and Transplantation Network. OPTN policy notice liver and intestine distribution using distance from donor hospital. 2018. Available at https://optn.transplant.hrsa.gov/media/2788/liver_policynotice_201901.pdf. Accessed November 24, 2021.
4. Gentry SE, Massie AB, Cheek SW, et al. Addressing geographic disparities in liver transplantation through redistricting. *Am J Transplant*. 2013;13:2052–2058.
5. Organ Procurement and Transplantation Network. Redesigning liver distribution, OPTN/UNOS liver and intestinal organ transplantation committee. 2016. Available at https://optn.transplant.hrsa.gov/media/1913/liver_redesigning_liver_distribution_20160815.pdf. Accessed December 1, 2021.
6. Bowring MG, Zhou S, Chow EKH, et al. Geographic disparity in deceased donor liver transplant rates following share 35. *Transplantation*. 2019;103:2113–2120.
7. Chyou D, Karp S, Shah MB, et al. A 6-month report on the impact of the Organ Procurement and Transplantation Network/United Network for Organ Sharing acuity circles policy change. *Liver Transpl*. 2021;27:756–759.
8. Organ Procurement and Transplantation Network. Fifteen-month monitoring report of liver and intestine acuity circle allocation removal of DSA and region as units of allocation. 2021. Available at https://optn.transplant.hrsa.gov/media/tk2f5vch/data_report_liver_full_15moallocation_20210903_508_compliant.pdf. Accessed December 1, 2021.
9. Wey A, Noreen S, Gentry S, et al. The effect of acuity circles on deceased donor transplant and offer rates across model for end-stage liver disease scores and exception statuses. *Liver Transpl*. 2022;28:363–375.
10. Ivanics T, Vianna R, Kubal CA, et al. Impact of the acuity circle model for liver allocation on multivisceral transplant candidates. *Am J Transplant*. 2022;22:464–473.
11. Nagai S, Chau LC, Schilke RE, et al. Effects of allocating livers for transplantation based on model for end-stage liver disease-sodium scores on patient outcomes. *Gastroenterology*. 2018;155:1451–1462.e3.
12. Brodersen KH, Gallusser F, Koehler J, et al. Inferring causal impact using Bayesian structural time-series models. *Ann Appl Stat*. 2015;9:247–274.
13. Varadhan R, Weiss CO, Segal JB, et al. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care*. 2010;48:S96–S105.
14. Organ Procurement and Transplantation Network. Liver and intestine distribution using distance from donor hospital. 2018. Available at https://optn.transplant.hrsa.gov/governance/public-comment/liver-and-intestine-distribution-using-distance-from-donor-hospital/. Accessed December 3, 2021.
15. Bohorquez H, Seal JB, Cohen AJ, et al. Safety and outcomes in 100 consecutive donation after circulatory death liver transplants using a protocol that includes thrombolytic therapy. *Am J Transplant*. 2017;17:2155–2164.
16. Kalisvaart M, de Haan JE, Polak WG, et al. Comparison of postoperative outcomes between donation after circulatory death and donation after brain death liver transplantation using the comprehensive complication index. *Ann Surg*. 2017;266:772–778.

17. Schlegel A, Kalisvaart M, Scalera I, et al. The UK DCD risk score: a new proposal to define futility in donation-after-circulatory-death liver transplantation. *J Hepatol*. 2018;68:456–464.
18. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. *Gastroenterology*. 2021;161:1887–1895.e4.
19. Nagai S, Nallabasannagari AR, Moonka D, et al. Use of neural network models to predict liver transplantation waitlist mortality. *Liver Transpl*. 2022;28:1133–1143.
20. Nagai S, Collins K, Chau LC, et al. Increased risk of death in first year after liver transplantation among patients with nonalcoholic steatohepatitis vs liver disease of other etiologies. *Clin Gastroenterol Hepatol*. 2019;17:2759–2768.e5.
21. Guorgui J, Ito T, Younan S, et al. The utility of extended criteria donor livers in high acuity liver transplant recipients. *Am Surg*. 2021;87:1684–1689.
22. Grąt M, Wronka KM, Patkowski W, et al. Effects of donor age and cold ischemia on liver transplantation outcomes according to the severity of recipient status. *Dig Dis Sci*. 2016;61:626–635.
23. Wall AE, da Graca B, Asrani SK, et al. Cost analysis of liver acquisition fees before and after acuity circle policy implementation. *JAMA Surg*. 2021;156:1051–1057.
24. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. *Am J Transplant*. 2020;20:1809–1818.