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UNOS policy change benefits high-priority patients without harming those at low priority

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The heart transplantation policy change (PC) has improved outcomes in high-acuity (Old 1A, New 1–3) patients, but the effect on low-priority (Old 1B/2, New 4–6) patients is unknown. We sought to determine if low-priority patient outcomes were compromised by benefits to high-priority patients by evaluating for interaction between PC and priority status (PS). We included adult first-time heart transplant candidates and recipients from the UNOS registry during a 19-month period before and after the PC. We compared clinical characteristics and performed competing risks and survival analyses stratified by PC and PS. There was a dependence of PC and PS on waitlist death/deterioration with an interaction sub-distribution hazard ratio (adjusted sdHR) of 0.59 (0.45–0.78), *p*-value < .001. There was a trend toward a benefit of PC on waitlist death/deterioration (adjusted sdHR: 0.86 [0.73–1.01]; $p = .07$) and an increase in heart transplantation (adjusted sdHR: 1.08 [1.02–1.14], $p = .007$) for low-priority patients. There was no difference in 1-year post-transplant survival (log-rank $p = .22$) when stratifying by PC and PS. PC did not negatively affect waitlisted or transplanted low-priority patients. High-priority, post-PC patients had a targeted reduction in waitlist death/deterioration and did not come at the expense of worse post-transplant survival.

KEYWORDS

clinical research/practice, health services and outcomes research, heart transplantation/cardiology, patient survival, registry/registry analysis, United Network for Organ Sharing (UNOS), waitlist management

1 | INTRODUCTION

The six-tiered prioritization scheme implemented with the 2018 United Network for Organ Sharing (UNOS) policy change was designed to prioritize the sickest patients awaiting heart transplantation with the goal of decreasing waitlist mortality and improving donor organ availability. Several analyses of the 2018 policy change have examined the effect of the policy change on either waitlist outcomes and/or short-term post-transplant survival. The main findings of these analyses have demonstrated a decrease in waitlist death/deterioration, an increase in rates of heart transplantation, and either worse or unchanged short-term post-transplant survival.[1–8]

Abbreviations: BMI, body mass index; IABP, intra-aortic balloon pump; IQR, interquartile range; MELD, model for end-stage liver disease; sdHR, sub-distribution hazard ratio; csHR, cause-specific hazard ratio; UNOS, United Network of Organ Sharing; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

Some analyses were limited in interpretation due to informative censoring and repeated analyses have begun to address this issue.[2,8–10]

An analysis of Status 1 patients bridged to heart transplantation with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) identified reduced waitlist mortality, with shorter waitlist times, and improved post-transplant survival.[3] Prior analyses demonstrated shorter waitlist times, reduced waitlist mortality and equivocal post-transplant survival in patients bridged to heart transplant with an intra-aortic balloon pump (IABP).[5,11,12] One current limitation is that most analyses have examined outcomes for either all statuses or have focused on high-priority (Status 1 and Status 2) patients alone. One recent study by Fuery et al.[13] provided an analysis of "low-priority" patients (Old 2, New 6) and contrasted these findings with "high-priority" patients (Old 1A, New 1 and 2). The authors found that low-priority patients had similar post-transplant survival before and after the UNOS policy change and longer waitlist times. Both low- and high-priority patients had shorter waitlist times after the policy change, however, lower priority patients received hearts from donors with greater comorbidities. While informative, this study did not assess for a potential interaction between the UNOS policy change and priority status and did not perform a competing risks analysis on waitlisted patients. As a result, it is currently unknown whether the observed benefits in waitlist and post-transplant outcomes in high-priority status patients negatively affect low-priority patients.

Thus, the purpose of this study was to evaluate the combined effect of priority status and policy change on waitlist and post-transplant outcomes for first-time adult heart transplant candidates and recipients and to determine if the gains seen in outcomes among high-priority patients came at a cost to low-priority patients.

2 | MATERIALS AND METHODS

2.1 | Database and patient cohort

After exempt status approval from the University of Southern California Institutional Review Board, we analyzed all adult (≥18 years old), first-time, heart transplant candidates that were single-organ heart transplant recipients from the UNOS Registry. Thus, a minority of heart transplant candidates in our cohort were listed for dual organ transplantation, but ultimately all recipients that underwent a heart transplant in our study cohort were single-organ recipients. We selected pre-policy (PRE) change and post-policy (POST) change time periods to address the differences in UNOS reporting requirements as have been discussed previously by Parker et al.[9] and Hanff et al.[4] Thus, the PRE time period was October 18, 2016 through May 30, 2018 and the POST time period was between October 18, 2018 through May 30, 2020. Inclusion into the competing risks cohort required waitlist registration within the PRE or POST time period, whereas inclusion in the survival analysis required both registration and transplantation within the PRE or POST time period. Like the study design of Goff et al,[2] we chose the May 30th cutoff date to maximize follow-up of all transplant recipients in the POST era. This was done to minimize the potential effects of informative censoring due to delayed reporting of continued survival compared to mortality.[9] Follow-up data was available through June 2021. There was a small number of patients that were either listed or transplanted with concurrent temporary mechanical circulatory support (tMCS) devices that had a "low-priority" status recorded in the UNOS registry. Due to this inconsistency, we chose to exclude these patients from our analysis as the presence of tMCS should have placed these patients in a "high-priority" status.

2.2 | Definition of priority status

High-priority status was defined as Status 1A and Status 1–3 for the pre- versus post-policy era cohorts, respectively. Similarly, Old Status 1B/2 and Status 4–6 were defined as low-priority status for the pre-versus post-policy eras, respectively. Priority status for waitlisted patients was based on the *initial* priority status at the time of registration, while priority status for patients that underwent heart transplantation was based on their *final* priority status at the time of transplantation.

2.3 | Statistical analysis

All analyses were performed with R Version 4.0.3. p-values for all analyses were two-sided with a significance level of .05.

2.3.1 | Baseline characteristics

Baseline clinical characteristics of heart transplant recipients (or candidates) and heart transplant donors are presented as median with interquartile range (IQR) or frequency (percentage). Group comparison between continuous variables was performed using the Kruskal-Wallis test. Pearson's Chi-squared test or Fisher's exact test, depending on cell counts, were used to compare categorical variables. Additional pairwise comparison of subgroups was performed depending on the results of group comparisons (e.g., Mann–Whitney tests) and clinical relevance.

2.3.2 | Competing risks analysis

A competing risks analysis was performed to calculate and compare the cumulative incidence between the following two events after being registered for heart transplantation: (1) death or deterioration or (2) heart transplantation. The competing risk analysis cohort was stratified by policy era (PRE or POST, as defined above). Unadjusted cumulative incidence curves for the outcome of interest (heart transplant or death/deterioration) between PRE and POST patients were compared using Gray's test.[14] Patients listed in the PRE cohort that did not undergo an event (death/deterioration or heart transplantation) by the time of the policy change were censored on October 18, 2018; to permit the same amount of time on

TABLE 1 Baseline clinical characteristics of heart transplant candidates stratified by initial priority status at listing (high vs. low) and policy-era (PRE vs. POST)

	High-priority status at listing				Low-priority status at listing			
	PRE ERA (*N* = 1434)	POST Era (*N* = 2000)	*p*-value	# Missing	PRE Era (*N* = 4261)	POST Era (*N* = 3379)	*p*-value	# Missing
1A (Old policy)	1434	-	-		-	-	-	-
1B (Old policy)	-	-	-		2749 (64.5)	-		-
2 (Old policy)	-	-	-		1512 (35.5)	-		-
1	-	218 (10.9)	-		-	-		-
2	-	1091 (54.5)	-		-	-		-
3	-	691 (34.5)	-		-	-		-
4	-	-	-		-	2134 (63.2)		-
6	-	-	-		-	1245 (36.8)		-
Age	55 [45, 63]	55 [44, 63]	.273	-	56 [46, 63]	56 [47, 63]	.888	-
Gender (% Male)	1048 (73.1)	1488 (74.4)	.408	-	3133 (73.5)	2445 (72.4)	.264	-
Ethnicity			.166	-			.275	-
Asian	56 (3.9)	89 (4.4)		-	119 (2.8)	96 (2.8)		-
Black	354 (24.7)	511 (25.6)		-	973 (22.8)	824 (24.4)		-
Hispanic	126 (8.8)	212 (10.6)		-	360 (8.4)	306 (9.1)		-
Other	19 (1.3)	17 (0.9)		-	52 (1.2)	32 (0.9)		-
White	879 (61.3)	1171 (58.6)		-	2757 (64.7)	2121 (62.8)		-
Body Mass Index (kg/m^2)	27.1 [23.6, 31.1]	27.1 [23.7, 31.5]	.663	4	27.9 [24.5, 31.7]	28.4 [24.8, 32.1]	<.001	-
Blood type							.762	8
A	575 (40.1)	736 (36.8)	.256		1562 (36.7)	1250 (37.0)		
AB	70 (4.9)	97 (4.9)			195 (4.6)	144 (4.3)		
B	231 (16.1)	347 (17.3)			567 (13.3)	429 (12.7)		
O	558 (38.9)	820 (41.0)			1937 (45.5)	1556 (46.0)		
History of cigarette use[a]	656 (45.7)	821 (41.0)	.007	-	1922 (45.1)	1498 (44.3)	.514	-
History of ischemic cardiomyopathy[a]	328 (22.9)	443 (22.1)	.646	-	809 (19.0)	538 (15.9)	.001	-
History of diabetes mellitus[a]	419 (29.2)	555 (27.8)	.366	-	1195 (28.0)	976 (28.9)	.434	-
Prior cardiac surgery[a]	563 (39.3)	678 (33.9)	.001	-	1665 (39.1)	1466 (43.4)	<.001	-
Dialysis after listing[a]	28 (2.0)	41 (2.1)	.902	-	31 (0.7)	16 (0.5)	.185	-
Implantable cardioverter defibrillator[a]	991 (69.1)	1287 (64.3)	.004	-	3335 (78.3)	2557 (75.7)	.008	-
On mechanical ventilation at listing	67 (4.7)	90 (4.5)	.876	-	-	-	NA	-
On intravenous inotropes at listing	638 (44.5)	918 (45.9)	.433	-	1117 (26.2)	729 (21.6)	<.001	-
Hemodynamics at listing								
Cardiac index (L/min/m^2)	2.11 [1.72, 2.58]	2.00 [1.64, 2.45]	<.001	260	2.12 [1.78, 2.51]	2.11 [1.79, 2.49]	.716	266
Pulmonary capillary wedge pressure, mm Hg	20 [13, 26]	21 [15, 27]	.006	466	17 [11, 24]	16 [10, 22]	<.001	327
IABP at listing (%)	230 (16.0)	636 (31.8)	<.001	-	-	-	-	-
VA-ECMO at listing (%)	94 (6.6)	152 (7.6)	.27	-	-	-	-	-

[a]Counts based on the number of confirmed affirmative responses in the database.

TABLE 2 Baseline clinical characteristics of heart transplant recipients stratified by priority status at the time of heart transplantation (high vs. low) and policy-era (PRE vs. POST)

	High-priority status at transplant				Low-priority status at transplant			
Recipient characteristics	PRE Era (*N* = 1863)	POST Era (*N* = 2447)	*p*-value	# Missing	PRE Era (*N* = 833)	POST Era (*N* = 639)	*p*-value	# Missing
1A (Old policy)	1863	-	-			-		
1B (Old policy)	-	-	-		766 (92.0)	-		
2 (Old policy)	-	-	-		67 (8.0)	-		
1	-	274 (11.2)	-		-	-		
2	-	1554 (63.5)	-		-	-		
3	-	619 (25.3)	-		-	-		
4	-	-	-		-	512 (80.1)		
6	-	-	-		-	127 (19.9)		
Age	57 [47, 63]	56 [46, 63]	.026	-	58 [48, 65]	58 [47, 64]	.713	-
Time on waitlist (days)	43 [16, 115]	15 [6, 52]	<.001	-	65 [23, 154]	62 [23.50, 153]	.995	-
Gender (Male, %)	1377 (73.9)	1811 (74.0)	.971	-	534 (64.1)	378 (59.2)	.059	-
Ethnicity			.329	-			.241	-
Asian	67 (3.6)	104 (4.3)			33 (4.0)	19 (3.0)		
Black	432 (23.2)	570 (23.3)			169 (20.3)	128 (20.0)		
Hispanic	154 (8.3)	235 (9.6)			82 (9.8)	62 (9.7)		
Other	22 (1.2)	22 (0.9)			11 (1.3)	2 (0.3)		
White	1188 (63.8)	1516 (62.0)			538 (64.6)	428 (67.0)		
Body mass index (kg/m^2)	26.93 [23.62, 30.58]	27.06 [23.63, 31.07]	.464	5	27.18 [23.92, 30.91]	27.80 [24.67, 31.17]	.02	-
Blood type			.311	-			.269	-
A	768 (41.2)	950 (38.8)			397 (47.7)	320 (50.1)		
AB	104 (5.6)	125 (5.1)			79 (9.5)	62 (9.7)		
B	288 (15.5)	397 (16.2)			138 (16.6)	117 (18.3)		
O	703 (37.7)	975 (39.8)			219 (26.3)	140 (21.9)		
History of cigarette use[a]	862 (46.3)	1017 (41.6)	.002	-	364 (43.7)	270 (42.3)	.616	-
History of ischemic cardiomyopathy[a]	553 (29.7)	654 (26.7)	.035	-	264 (31.7)	183 (28.6)	.228	-
Dialysis after listing[a]	33 (1.8)	50 (2.0)	.576	-	3 (0.4)	1 (0.2)	.637	-
Diabetes mellitus[a]	518 (27.8)	669 (27.3)	.761	-	234 (28.1)	172 (26.9)	.659	-
Prior cardiac surgery[a]	746 (40.0)	856 (35.0)	.001	-	308 (37.0)	244 (38.2)	.664	-
Implantable cardioverter defibrillator[a]	1428 (76.7)	1708 (69.8)	<.001	-	655 (78.6)	470 (73.6)	.026	-
Total bilirubin	0.70 [0.50, 1.10]	0.70 [0.50, 1.20]	.002	4	0.60 [0.40, 1.00]	0.60 [0.40, 0.90]	.069	2
Creatinine	1.16 [0.95, 1.43]	1.12 [0.90, 1.40]	.001	1	1.11 [0.91, 1.39]	1.15 [0.92, 1.40]	.259	-
MELD-XI Score	9.44 [5.90, 12.91]	9.34 [5.76, 12.86]	.637	4	8.74 [5.54, 11.86]	8.71 [5.17, 12.15]	.663	2
On mechanical ventilation	17 (0.9)	77 (3.1)	<.001	-	-	-	-	-
On intravenous inotropes	779 (41.8)	1192 (48.7)	<.001	-	347 (41.7)	151 (23.6)	<.001	-
IV antibiotics within 14-days of transplant[a]	206 (11.1)	312 (12.8)	.1	-	19 (2.3)	6 (0.9)	.076	-
Cardiac index (L/min/m^2)	2.22 [1.83, 2.68]	2.07 [1.71, 2.54]	<.001	177	2.20 [1.87, 2.62]	2.18 [1.87, 2.61]	.97	35

TABLE 2 (Continued)

Recipient characteristics	High-priority status at transplant PRE Era (*N* = 1863)	POST Era (*N* = 2447)	*p*-value	# Missing	Low-priority status at transplant PRE Era (*N* = 833)	POST Era (*N* = 639)	*p*-value	# Missing
Mean pulmonary artery pressure, mm Hg	26 [20, 34]	28 [21, 36]	<.001	143	24 [18, 32]	23 [17.75, 30]	.002	46
Pulmonary capillary wedge pressure, mm Hg	17 [11, 24]	20 [13, 25]	<.001	316	15 [10, 21]	14 [9, 20]	.007	48
VA-ECMO at time of transplant	28 (1.5)	179 (7.3)	<.001	-	-	-	-	-
IABP at time of transplant	253 (13.6)	1024 (41.8)	<.001	-	-	-	-	-

[a]Counts based on the number of confirmed affirmative responses in the database.

the waitlist; similar administrative censoring was performed on the POST cohort for patients not experiencing an event by October 18, 2020. Multivariable Fine-Gray proportional sub-distribution hazards models[15] and cause-specific Cox proportional hazards models were used to evaluate the adjusted policy-era and listing priority status effect on waitlist outcomes. For each outcome of interest, the initial multivariable model included demographic characteristics (i.e., gender, race, BMI, age) with additional clinical variables selected based on a priori clinical relevance and existing publications.[3,6,8,16] Hemodynamic measurements were not included in the multivariable models due to many missing observations.

2.3.3 | Survival analysis

Unadjusted post-transplant survival (freedom from death or graft failure) between PRE and POST patients was estimated using Kaplan–Meier curves and differences in survival were compared using a standard log-rank test. A multivariable Cox proportional hazards model[17] was used to evaluate the effect policy era had on post-transplant survival, adjusting for other variables. Patients registered for a heart transplant in the PRE era and transplanted in the POST era were censored as alive on October 18, 2018. Additionally, patients were censored at the time of the last follow-up or at 365-days post-heart transplant, whichever occurred first. Variable selection for our multivariable model was done like that described above for our competing risks analysis. To avoid issues of multicollinearity, we chose to only include one predictor when two or more highly correlated predictors (e.g., BMI and body surface area, MELD score, and creatinine or total bilirubin levels) are recommended for the multivariable model.

3 | RESULTS

3.1 | Comparison of baseline characteristics by priority status at the time of listing

See Table 1 for a comparison of baseline characteristics (stratified by policy era and priority status) at the time of listing.

3.1.1 | High-priority patients

There were significantly more patients listed at high priority status in the POST era (2000/5379 [37.2%] vs. 1434/5695 [25.2%], *p*-value < .001). The median age was similar at 55 years old. A similar majority of patients of the male gender was present in both eras. Fewer patients had implantable cardioverter defibrillators in the POST era (64.3% vs. 69.1%, *p* = .004). There were also fewer patients with a history of prior cardiac surgery in high-priority POST-era patients (39.3% vs. 33.9%, *p* = .001). There was a similar number of patients listed on mechanical ventilation (90 [4.5%] patients vs. 67 [4.7%] patients, *p* = .876) and VA-ECMO (152 [7.6%] patients vs. 94 [6.6%] patients, *p* = .27) in the POST and PRE eras, respectively. Consistent with prior studies, IABP use was significantly increased in the POST era (636 [31.8%] patients vs. 230 [16.0%] patients, *p* < .001). Cardiac index was significantly, but only marginally, lower in the POST-era at 2.00 L/min/m^2 versus 2.11 L/min/m^2, *p* < .001.

3.1.2 | Low-priority patients

The median age was similar between eras at 56 years old. Again, there was a similar majority of male patients in both eras. Fewer patients in the POST era were on IV inotropes at the time of listing (21.6% vs. 26.2%, *p* < .001). There was no difference in baseline cardiac index between the two eras (*p* = .716).

3.2 | Comparison of baseline characteristics by priority status at the time of heart transplantation

See Table 2 for a comparison of baseline characteristics (stratified by policy era and priority status) at the time of heart transplantation.

3.2.1 | High priority

More patients underwent heart transplantation from a high-priority status in the POST era compared to the PRE-era

TABLE 3 Donor clinical characteristics stratified by priority status at the time of heart transplantation (high vs. low) policy-era (PRE vs. POST)

	High-priority status at transplant				Low-priority status at transplant			
Donor characteristics	PRE Era (*N* = 1863)	POST Era (*N* = 2447)	*p*-value	# Missing	PRE Era (*N* = 833)	POST Era (*N* = 639)	*p*-value	# Missing
Donor age	31 [23, 39]	31 [24, 39]	.878	-	32 [24, 41]	33 [26, 43]	.002	-
Donor gender (male, %)	1298 (69.7)	1885 (77.0)	<.001	-	496 (59.5)	326 (51.0)	.001	-
Donor female, recipient male	264 (14.2)	231 (9.4)	<.001	-	123 (14.8)	101 (15.8)	.633	-
Donor ethnicity			.617	-			.209	-
Asian	26 (1.4)	39 (1.6)			15 (1.8)	8 (1.3)		
Black	309 (16.6)	403 (16.5)			139 (16.7)	84 (13.1)		
Hispanic	302 (16.2)	438 (17.9)			119 (14.3)	86 (13.5)		
Other	35 (1.9)	48 (2.0)			17 (2.0)	10 (1.6)		
White	1191 (63.9)	1519 (62.1)			543 (65.2)	451 (70.6)		
Donor body mass index (kg/m^2)	26.4 [23.2, 30.7]	26.7 [23.7, 31.0]	.02	2	26.0 [22.9, 30.3]	26.7 [23.1, 32.0]	.029	-
DONOR blood type			.011	-			.007	-
A	681 (36.6)	818 (33.4)			381 (45.7)	302 (47.3)		
AB	37 (2.0)	27 (1.1)			33 (4.0)	46 (7.2)		
B	175 (9.4)	250 (10.2)			130 (15.6)	109 (17.1)		
O	970 (52.1)	1352 (55.3)			289 (34.7)	182 (28.5)		
Donor total bilirubin	0.70 [0.50, 1.10]	0.70 [0.50, 1.10]	.682	5	0.70 [0.50, 1.20]	0.60 [0.40, 1.10]	.011	-
Donor creatinine	1.00 [0.75, 1.58]	1.05 [0.80, 1.60]	.009	5	0.95 [0.71, 1.40]	1.04 [0.75, 1.65]	.004	-
Donor MELD-XI	8.30 [3.52, 14.6]	8.76 [3.92, 14.8]	.061	5	7.84 [2.71, 13.8]	8.15 [3.25, 15.1]	.198	-
Ischemic time (hours)	3.10 [2.33, 3.72]	3.48 [2.92, 4.02]	<.001	19	2.97 [2.22, 3.62]	3.20 [2.38, 3.88]	<.001	10
Donor-hospital to recipient hospital distance	83 [13, 261]	259 [106, 412]	<.001	-	65 [11, 215]	150 [27, 335]	<.001	-
Donor history of hypertension	304 (16.3)	359 (14.7)	.149	-	127 (15.2)	125 (19.6)	.035	-
Donor history of diabetes	78 (4.2)	74 (3.0)	.049	-	30 (3.6)	33 (5.2)	.181	-
LVEF	60 [56, 65]	60 [55, 65]	.933	4	60 [58, 65]	60 [55, 65]	.204	1
PHS High-risk donor	591 (31.7)	849 (34.7)	.044	0	258 (31.0)	261 (40.8)	<.001	-
BMI ratio (donor/recipient)	0.99 [0.85, 1.17]	1.00 [0.86, 1.19]	.179	7	0.97 [0.84, 1.14]	0.98 [0.83, 1.16]	.435	-
Predicted heart mass ratio (donor/recipient)	1.01 [0.91, 1.13]	1.03 [0.93, 1.17]	<.001	2	1.00 [0.91, 1.11]	0.99 [0.90, 1.10]	.167	-
Donor cause of death			.07	0			<.001	-
Anoxia	740 (39.7)	1038 (42.4)			312 (37.5)	314 (49.1)		
CVA/Stroke	268 (14.4)	321 (13.1)			132 (15.8)	111 (17.4)		
Head trauma	806 (43.3)	1013 (41.4)			376 (45.1)	195 (30.5)		
CNS/Tumor	11 (0.6)	7 (0.3)			2 (0.2)	2 (0.3)		
Other	38 (2.0)	68 (2.8)			11 (1.3)	17 (2.7)		

(2447/3086 [79.2%] vs. 1863/2696 [69.1%], p-value < .001). Time on the waitlist was notably shorter in the high-priority POST era patients (15 days vs. 43 days, p < .001). The median age was between 56 and 57 years old in the two groups. Approximately 74% of high-priority heart transplant recipients, both PRE and POST, were male gender. In stark contrast to the similar

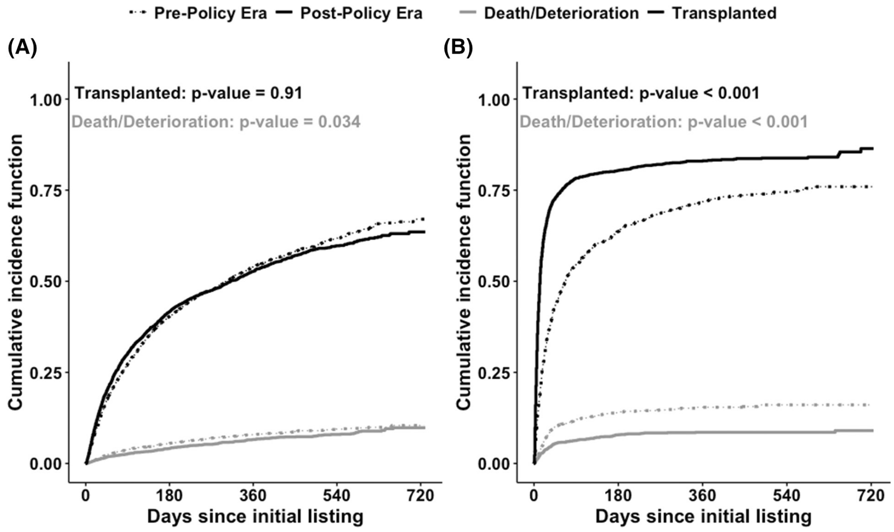

FIGURE 1 Cumulative incidence plots for the waitlist (death/deterioration and heart transplantation) for patients in the low (left - A) and high (right - B) priority statuses. Gray's test *p*-values included in the plot.

TABLE 4 Multivariable competing risks analysis looking at waitlist outcomes of death/deterioration or heart transplantation using a Fine-Gray proportional sub-distribution hazards model

	Waitlist death/deterioration[a]		Heart Transplantation[b]	
	sdHR (95% CI)	*p*-value	sdHR (95% CI)	*p*-value
Post vs. Pre (initial Low-priority status)	0.86 (0.73, 1.01)	.07	1.08 (1.02, 1.14)	.007
Post vs. Pre (initial High-priority status)	0.51 (0.41, 0.63)	<.001	2.16 (1.96, 2.38)	<.001
Interaction Term (status × policy)	0.59 (0.45, 0.78)	<.001	2.00 (1.79, 2.23)	<.001

Notes: Each main effect is modeled as a binary covariate: Policy = PRE/POST, Priority Status = LOW/HIGH as defined in the main text. While the interaction term, by itself, is difficult to interpret, the p-value assess whether or not the effect policy (PRE/POST) has on the outcome of interest is dependent on/modified by priority status (Low/High) and vice versa.

Abbreviation: sdHR, sub-distribution hazards ratio.

[a]Adjusted for age, gender, race, blood type, BMI, diabetes mellitus, mechanical ventilation at registration, and prior cardiac surgery after listing.

[b]Adjusted for age, gender, race, blood type, BMI, diabetes mellitus, mechanical ventilation at registration, prior cardiac surgery after listing, ischemic cardiomyopathy, and dialysis after listing (12 observations were omitted due to missing values). The sdHR in the first two rows restricts calculation to either only initial low-priority status at listing patients or initial high-priority status at listing patients, respectively.

percentage of patients being on VA-ECMO at the time of listing (see above), there was a marked increase during the POST era in the percentage of patients that underwent heart transplantation from VA-ECMO (7.3% vs. 1.5%, $p < .001$). Heart transplantation from IABP support was more common in the POST era (41.8% vs. 13.6%, $p < .001$). There was a significant increase in heart transplantation from mechanical ventilation in the POST era (3.1% vs. 0.9%, $p < .001$). This is despite the similar frequency of listing for heart transplantation while on mechanical ventilation between the PRE and POST eras (see above). Not surprisingly, cardiac index ($p < .001$) was significantly lower and pulmonary capillary wedge pressure ($p < .001$) was significantly higher in the POST era.

3.2.2 | Low priority

There was a trend toward fewer patients of the male gender undergoing heart transplants from a low-priority status in the POST versus PRE era (59.2% vs. 64.1%, $p = .059$). Overall, a greater fraction of women underwent heart transplantation at low-priority status compared to high-priority status ($p < .001$).

3.3 | Donor characteristics

See Table 3 for donor characteristics stratified by high-priority and low-priority status and PRE/POST eras.

3.3.1 | High-priority recipients

Donor age was similar between eras ($p = .878$). Male gender donors were more common in the POST era (77.0% vs. 69.7%, $p < .001$) and female donor/recipient male combinations were less common in the POST era (9.4% vs. 14.2%, $p < .001$). As has been shown before, donor ischemic times were longer in the POST era (3.48 vs. 3.10 h, $p < .001$). The predicted heart mass ratio (donor/recipient) was marginally higher in the POST era (1.03 vs. 1.01, $p < .001$).

3.3.2 | Low-priority recipients

Use of male donors was less common in the POST era (51% vs. 59.5%, $p < .001$), while female donor/recipient male combinations in low-priority recipients were similar across eras ($p = .633$). Donor ischemic times in low-priority patients remained higher in POST era patients (3.20 vs. 2.97 h, $p < .001$).

3.4 | Waitlist outcomes

3.4.1 | Death/deterioration

The cumulative incidence plots for the waitlist outcome of death/deterioration stratified by policy era and initial listing priority status are shown in Figure 1. The cumulative incidence of waitlist death/deterioration was lower in the POST era when compared to the PRE era for both low- and high-priority patients ($p = .034$ and $p < .001$, respectively). However, this difference was noticeably larger in the high-priority patients (Figure 1—right panel) than in the low-priority patients (Figure 1—left panel). The results of the Fine-Gray model, adjusted for additional confounders, are shown in Table 4. There was a non-significant trend toward a beneficial effect of PC on the cumulative incidence of waitlist death/deterioration for patients initially listed as low priority (adjusted sdHR: 0.86 [0.73–1.01]; $p = .07$ - see Table 4). Patients who were initially listed at high priority status have a significantly lower cumulative incidence of waitlist death/deterioration in the POST era than those who are in the PRE era (adjusted sdHR: 0.51 [0.41–0.63]; p-value $< .001$ - see Table 4). When looking at the interaction term (Status × Policy), we found a significant dependence between policy era and initial priority status on the cumulative incidence of waitlist death/deterioration (adjusted sdHR: 0.59 [0.45–0.78], p-value < 0.001 - see Table 4). In contrast to the subdistribution hazards results, the cause-specific hazard ratios (see Table 5) examining the effect of the policy era on death/deterioration were not significant for initial high-priority status patients (adjusted cause-specific hazard ratio [csHR]: 1.07 [0.87–1.31], $p = .55$). On the other hand, there was a trend toward a protective effect of policy era on initial low-priority status patients (adjusted csHR: 0.86 [0.73–1.01], $p = .07$), but did not meet significance. We did not observe a dependence (or interaction) between policy era and initial priority status (Status × Policy) on the cause-specific hazard (adjusted csHR: 1.23 [0.95–1.61], $p = .12$). Overall, there was a discrepancy in the sdHR and csHR for the waitlist outcome of death/deterioration.

3.4.2 | Heart transplantation

The cumulative incidence of heart transplantation (Figure 1) was significantly higher in the POST era than in the PRE era for those listed as either high (adjusted sdHR: 2.16 [1.96–2.38], $p < .001$) or low (adjusted sdHR: 1.08 [1.02–1.14], $p = .007$) priority. The

TABLE 5 Multivariable competing risks analysis looking at waitlist outcomes of death/deterioration or heart transplantation using a cause-specific hazards model

	Waitlist death/deterioration[a]		Heart transplantation[b]	
	csHR (95% CI)	*p*-value	csHR (95% CI)	*p*-value
Post vs. Pre (initial Low-priority status at listing)	0.86 (0.73, 1.02)	.09	1.07 (1.00, 1.13)	.046
Post vs. Pre (initial High-priority status at listing)	1.07 (0.87, 1.31)	.55	2.20 (2.04, 2.39)	<.001
Interaction Term (status × policy)	1.23 (0.95, 1.61)	.12	2.07 (1.87, 2.29)	<.001

Notes: Each main effect is modeled as a binary covariate: Policy = PRE/POST, Priority Status = LOW/HIGH as defined in the main text. While the interaction term, by itself, is difficult to interpret, the p-value assess whether or not the effect policy (PRE/POST) has on the outcome of interest is dependent on/modified by priority status (low/high) and vice versa.Abbreviation: csHR, cause-specific hazards ratio.

[a]Adjusted for age, gender, race, blood type, BMI, diabetes mellitus, mechanical ventilation at registration, and prior cardiac surgery after listing.

[b]Adjusted for age, gender, race, blood type, BMI, diabetes mellitus, mechanical ventilation at registration, prior cardiac surgery after listing, ischemic cardiomyopathy, and dialysis after listing (12 observations were omitted due to missing values). The csHR in the first two rows restricts calculation to either only initial low-priority status at listing patients or initial high-priority status at listing patients, respectively.

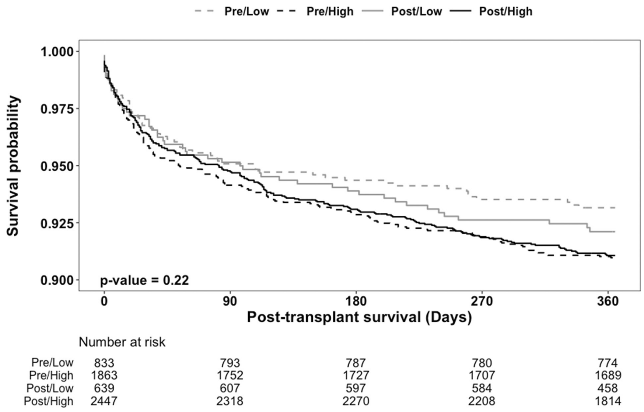

FIGURE 2 Kaplan–Meier plot for 1-year post-transplant survival (freedom from death or graft failure) of the four patient sub-groups based on priority status and policy era. Log-rank *p*-value included in the plot.

TABLE 6 Multivariable Cox's regression (39 observations removed due to missing values)

Variable	Hazard ratio (95% CI)	*p*-value
Policy change	1.03 (0.70, 1.51)	.90
Listing status at transplant	1.26 (0.93, 1.70)	.14
Interaction (Policy × Listing status)	0.85 (0.55, 1.32)	0.50

Notes: Analysis was adjusted for age, gender, race/ethnicity, BMI at transplant, blood type, ischemic cardiomyopathy, prior cardiac surgery, ventilator, dialysis after listing, diabetes mellitus, total bilirubin, creatinine at transplant, and intravenous antibiotics 14 days prior to a heart transplant, ischemic time.

interaction term (Status × Policy) demonstrated a significant dependence of policy era and initial priority status (adjusted sdHR: 2.00 [1.79–2.23], $p < .001$) on heart transplantation (Table 4). The cause-specific hazard ratios (csHR) for the waitlist outcome of heart transplantation were nearly identical to the corresponding sdHRs (see Table 4 and Table 5).

3.5 | One-year post-transplant survival

We also examined the impact of policy era and *final* priority status at transplant on 1-year post-transplant survival. Kaplan–Meier curves of the four subgroups, stratified by policy status and priority status, are shown in Figure 2. We observed that 1-year post-transplant survival did not differ when stratified by policy change and final priority status (log-rank p-value = 0.22). The multivariable Cox model (Table 6) suggests there was no impact of policy change, irrespective of listing status, on 1-year post-transplant survival (HR: 1.03 [0.70–1.51], p-value = .90); see Table 6. Furthermore, there was no significant interaction between policy and listing status on 1-year post-transplant survival (HR: 0.85 [0.55–1.32], $p = .5$; see Table 6).

4 | DISCUSSION

In this analysis of UNOS data pre- and post-policy change, we observed the following: (1) POST era patients had a significant reduction in the cumulative incidence of waitlist death/deterioration and increase in heart transplantation, (2) waitlist outcomes were either the same or improved for low-priority patients, and (3) there was no significant difference in 1-year post-transplant survival across all subgroups. Taken together, adult, first-time, high-priority, POST era patients received a targeted reduction in waitlist death/deterioration, and an increase in access to heart transplantation, without worsening waitlist or survival outcomes in low-priority patients. As such, the overall effects of the UNOS policy change appear to be meeting the intended goal of improving waitlist survival via improved access to donor hearts for the highest urgency patients and does so without harming low-priority patients.

One noteworthy result to focus on is the discrepancy between the subdistribution and cause-specific hazard ratios for the waitlist outcome of death/deterioration. Specifically, there was no decrease in the cause-specific HR for (1) the interaction (Status × Policy) between the policy era and initial priority status or (2) the effect of the policy era on only the initial high-priority status patients. The sdHR on the other hand was reduced (protective) for these two categories (interaction and initial high-priority status patients). We interpret this discrepancy to mean that the decreased cumulative incidence of waitlist death/deterioration is driven primarily by the rapid rate of heart transplantation rather than by the policy change per se. In other words, the primary byproduct of the policy change appears to be more rapid heart transplantation in higher acuity patients, and this secondarily leads to a decreased cumulative incidence of death or deterioration. We base this interpretation[18,19] on the understanding that a cause-specific hazards model provides a causal (or etiologic) interpretation of the effect of policy change on outcomes, whereas the subdistribution hazards model is limited to predicting the outcome of the patient at some time after being listed for a heart transplant. This is consistent with the lack of an effect of policy change on waitlist death/deterioration in our cause-specific hazards analysis. Regardless of the interpretation, the policy change appears to be meeting its overall goal of rapidly providing donor hearts to the highest acuity patients on the waitlist. Moreover, there is no signal for harm to any patient subgroup in our analysis.

Our study adds to the literature by providing an analysis of the interaction, or dependence between, the UNOS policy change of 2018 and patient priority status. Our analysis sought to answer whether the gains seen in hospitalized and mechanically supported patients in the new allocation system came at the expense of worse outcomes in lower priority, ambulatory patients. Based on this analysis, lower priority patients had no observable adverse effects. As alluded to above, one potential mechanism for the observed targeted benefits to high priority, POST era patients is that status upgrades provide a means to "rescue" waitlisted ambulatory patients that suffer from an acute decompensation; we did observe an overall increase in heart transplantation in low-priority patients in the POST era. Similarly, patients with no prior history of cardiomyopathy who present in acute cardiogenic shock also benefit from the "rescue" effect of the policy change. A recent analysis highlighted that one drawback of the rapid time to heart transplantation under the new policy has been an association with a small, but significant reduction in observed myocardial recovery.[20] Additional tools to identify patients that have an increased likelihood of recovery are therefore needed.

Another important observation is that there was a similar proportion of patients on VA-ECMO at the time of listing for both the PRE and POST eras, however, there were approximately 4.9 times more patients transplanted from VA-ECMO in the POST era compared to the PRE era. This further highlights the importance of an allocation policy that prioritizes patients based on clinical acuity. As shown by Gonzalez et al,[3] there was both a substantial waitlist and post-transplant survival benefit in VA-ECMO bridged patients during the POST era. Similarly, we previously observed[12] significant waitlist benefits for POST era IABP-supported (status 2) patients bridged to heart transplantation without any difference in post-transplant survival. Additionally, our analysis identified a nearly 3-fold increase in the number of patients undergoing heart transplantation from mechanical ventilation. This appears to support the idea that in the POST era transplant centers are more inclined to take risks on sicker patients than before; however, an alternative interpretation is that centers are instead prioritizing patients with "sicker therapies." Whether this represents patient advocacy, "gaming" or simply treating patients according to agreed-upon consensus cardiogenic shock criteria is debatable. Nonetheless, future iterations of the organ allocation policy should consider instances where the cardiogenic shock criteria fall short in risk stratification and whether additional markers of end-organ malperfusion should be incorporated.[21]

We deliberately selected our study inclusion time periods to minimize the risk of informative censoring to our post-transplant survival analysis. With this in mind, repeated analysis with more complete follow-up will be important to ensure that reported findings to date regarding the effects of the allocation policy remain accurate.[9,10]

Another notable finding in our analysis is that fewer women donors appear to be selected in high-priority patients. In concert with this, there has been less utilization of female donors for male recipients, especially in high-priority patients. While this change was not found to be a predictor of post-transplant survival, higher status patients are likely seeing more organ offers and thus some programs may have less incentive to accept gender mismatched organs. This finding warrants a dedicated evaluation.

4.1 | Limitations

The major limitations of this study are those imposed by data entry limitations and inconsistencies present in a large registry. Another limitation is that waitlisted patients were stratified based on initial listing status, which is frequently different than the status listing at the time of heart transplantation. With this in mind, many low-priority patients based on their initial listing status were transplanted at a higher priority status, and, therefore, the waitlist outcomes analyzed for the low-priority patients are likely biased by this discrepancy. There were large numbers of missing hemodynamic variables and therefore these parameters were not accounted for in our regression analyses.

5 | CONCLUSIONS

We observed that in the post-policy era that high-priority transplant candidates have a large and targeted reduction in waitlist death/deterioration, while waitlist outcomes for low-priority patients were either improved or no different. One-year post-transplant survival was not affected by policy change or priority status. Taken together, these findings support the conclusion that high-priority patients have benefited from the policy change and low-priority patients have not been harmed. Additional analyses of other patient subgroups are needed to evaluate for potential inequities that may remain despite the recent UNOS policy change.

AUTHOR CONTRIBUTIONS

Study design: AMW, ECD, ESK, ASV. Data analysis: AMW, ECD, ESK, ASV. Writing of the manuscript: AMW, ECD, ESK, SST, MWF, LZ, KP, ASV.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

UNOS registry data is freely available from the OPTN. R code for our analysis is available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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