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ORIGINAL ARTICLE

The heart transplant allocation change attenuates but does not eliminate blood group O waitlist outcome disadvantage

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Abstract

Background: Patients with blood group O have historically been disadvantaged in the United Network for Organ Sharing (UNOS) heart transplant allocation system. We sought to determine whether the new UNOS allocation system implemented in 2018 had an impact on waitlist and post-transplant outcomes among blood groups.

Methods: Using the UNOS database we included all adult patients listed and transplanted with first-time single-organ heart transplant between 10/17/15 and 10/1/21. For post-transplant outcomes, we separately evaluated all adult patients transplanted with the same time-frame. We used exclusion criteria and censoring to limit biases from changing clinical practices around the allocation change (10/18/2018), and from unequal or inadequate follow-up. We compared clinical characteristics and outcomes before and after the allocation change among each blood group. Fine-Gray and Cox regression models were used to estimate the effect of the new allocation system on competing waitlist outcomes- transplantation, death-or-removal from waitlist- and post-transplant survival, respectively.

Results: Of the 21,565 patients listed for transplantation 14,000 met criteria for waitlist analysis (7,035 in the old system vs. 6,965 in the new), and 7,657 met criteria for post-transplant analysis (3,519 in the old system vs. 4,138 in the new). Among each blood group, new allocation change was associated with higher transplantation rates lower waitlist days and lower waitlist mortality (except Group AB). However, despite improvements, Group O was still associated with worse waitlist outcomes for each metric compared to non-O Groups. The new allocation system did not have a significant impact on post-transplant survival among any blood groups.

Conclusion: Changes in heart transplant allocation have attenuated but not eliminated blood group O disadvantage in access to donor hearts.

KEYWORDS
blood group O, heart transplant, UNOS allocation policy

1 | INTRODUCTION

Although a variety of other characteristics impact heart transplant waitlist outcomes including patient body mass index, urgency of transplantation and reactive antibody levels, blood group is unique in that it is an inherited and immutable trait. Due to an absence of erythrocyte antigens and the strict requirement for blood group compatibility, patients with blood group O and end-stage heart failure have been traditionally disadvantaged regarding access to donor hearts. Studies done prior to the new United Network for Organ Sharing (UNOS) heart transplant allocation system implemented in October of 2018 have demonstrated that patients with blood group O have significantly longer waitlist times, higher waitlist death rates and lower transplantation rates.[1–3] Although the introduction of ventricular assist devices as a bridging strategy to transplantation did reduce the likelihood of adverse waitlist events for all blood groups it did not eliminate the relative disadvantage experienced by patients with blood group O.[3]

The new allocation system was devised to address important limitations in the former 3-tiered system that included discrepancies in the assignment of listing priority relative to patient risk characteristics and limitations in the allocation of donor organs based upon the use of the local organ procurement organization as the designated allocator of donor hearts. A major driver of the new allocation system was to improve equitable access to donor organs while maintaining or improving transplant outcomes, and previous studies have confirmed improved waitlist outcomes and increased transplantation rates in the new allocation system.[4] We sought to determine whether the 2018 changes to the allocation system had an impact on the traditional disadvantages experienced by patients with blood group O regarding waitlist and transplantation outcomes.

2 | METHODS

2.1 | Study design

We conducted an analysis of competing waitlist outcomes to test the claim that the new UNOS allocation system improved waitlist times and transplantation rates for patients listed for heart transplantation, both overall and among various blood groups. We also conducted a separate analysis to measure the impact of the new allocation system on post-transplant survival among various blood groups. We obtained UNOS registry data from the Organ Procurement and Transplantation Network on October 1st, 2021. This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the U.S. Government.

2.2 | Participants

We included all adult patients listed and transplanted with first-time, single-organ heart transplant between 10/18/15 and 10/1/21. To avoid biases from changing clinical practices and unequal or inadequate follow-up, we: 1) excluded patients from the old system listed in the year prior to allocation change; 2) censored patients from the old system with more than 1 year follow-up (this was done because as a historical comparator, patients from the old UNOS cohort have significantly longer follow-up than those in the new UNOS cohort. Waitlist and post-transplant follow-up were therefore censored at one year to avoid bias from unequal follow-up between the two groups), and 3) excluded patients from the new system with less than 1 year follow-up. In addition, for post-transplant outcomes, we excluded patients listed in the old system and transplanted in the new (Figure 1). We stratified patients according to blood group: A, B, AB and O. Our study design was submitted to the institutional review board (IRB) at the Loma Linda University Medical Center. The IRB determined that the study did not meet the definition of human subject research because it did not involve identifiable information, no data or specimens were collected, and there was no direct intervention or interaction. Thus, review or approval was waived by the IRB. This work was in strict compliance with the International Society for Heart and Lung Transplantation ethics statement.

2.3 | Clinical characteristics

For each listed patient, we obtained characteristics at the time of transplant listing registration. Demographic characteristics included age, gender, body-mass index (BMI), ethnicity, listing region and education level. Comorbidities included diabetes, dialysis, cerebrovascular accident, prior malignancy, cigarette smoking, prior cardiac surgery and implantable cardiac defibrillator. Additional covariates indicating disease severity included renal function (most recent creatinine), right heart catheterization hemodynamics, use of inotropes, mechanical circulatory support and ventilator support.

For each transplanted patient we obtained characteristics at the time of listing (as above), time of transplantation and characteristics from the donor. Recipient characteristics at the time of transplantation included age, BMI and additional covariates indicating disease severity: ICU status, use of inotropes and mechanical circulatory support, ventilatory support, renal function (most recent creatinine), total bilirubin and right heart catheterization hemodynamics. Donor characteristics included age, gender, recipient-donor mismatch, BMI, blood group, cause of death, diabetes, cocaine use, renal function (most recent creatinine), total bilirubin, left ventricular ejection fraction, ischemic time and distance (miles) from the transplant center.

2.4 | Waitlist and post-transplant outcomes

We followed listed patients to one of three competing waitlist outcomes—transplantation, waitlist death or waitlist removal; patients

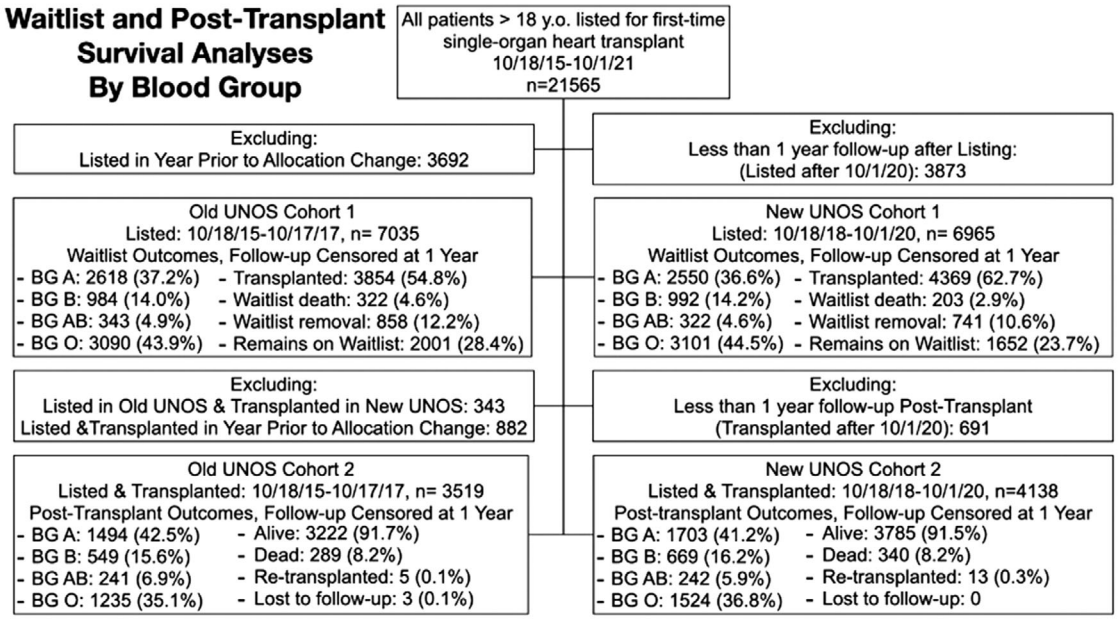

FIGURE 1 Flow diagram

remaining on the waitlist after one year were censored. We followed transplanted patients to determine freedom from death or re-transplantation; patients with follow-up longer than one year were censored. Patients coded as 'lost to follow-up' were also censored.

2.5 | Missing data

There was < 10% missingness for all variables and outcomes included in the analyses (supplemental Tables 6a and 6b). Missing data were imputed to the mean for continuous variables, and to zero for categorical variables (for dichotomous variables, imputation to 0 implies 'not present'. For multi-response variables, imputation to 0 implies 'other').

2.6 | Statistical analyses

Characteristics at listing, transplantation and from the donor were compared before and after the UNOS allocation change, both overall and among blood groups (Tables 1, 3 and 4; Supplemental Tables 1, 3 and 4). A two-sample t test was used to compare continuous variables and chi-square test for categorical variables. Fine-Gray proportional sub-hazard models were used to estimate the effect of allocation change on competing waitlist outcomes—transplantation, death, or removal from waitlist—both overall and among each blood group. Unadjusted and adjusted sub-hazard ratios (SHR) were reported for each competing outcome; multivariable regression models were adjusted for characteristics at listing as outlined above (Tables 2; Supplemental Table 2). A Fine-Gray sub-hazard ratio < 1 or > 1 is interpreted as the covariate (new UNOS allocation system) having an effect on the cumulative incidence function or probability of events occurring over time.[5]

Cox proportional sub-hazard models were used to estimate the effect of allocation change on post-transplant survival- freedom from death or re-transplantation- both overall and among each blood group. Unadjusted and adjusted hazard ratios (HR) were reported; multivariable regression models were adjusted for characteristics at listing, transplantation and from donor as outlined above (Table 5; Supplemental Table 5). A Cox hazard ratio < 1 or > 1 is interpreted as the covariate (new UNOS allocation system) having an effect on the survival function. All analyses were performed using Stata version 17.0 (StataCorp, College Station, Texas 77845 USA). All statistical tests were two-sided and $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Participants

During the study period, 21,565 patients were listed for first time, single-organ heart transplantation. To avoid bias from changing patterns in anticipation of allocation change, 3,692 patients listed in the year prior were excluded. To avoid bias from inadequate follow-up, 3,873 patients with less than one year follow-up after listing were excluded. After exclusions, 14,000 patients were included in analysis of candidate characteristics at listing and waitlist outcomes; Of these 7,035 (50.3%) were listed under the old UNOS system and 6,965 (49.8%) under the new system. Of the listed patients, 8,223 (58.8%) were transplanted, 525 (3.8%) died on the waitlist, 1,599 (11.4%), were removed from the waitlist and 653 (4.7%) remained on the waitlist and

TABLE 1 Comparison of candidate characteristics at listing between Group O and Groups Non-O before and after the allocation change

Old UNOS Cohort Listed: 10/18/15-10/17/17 v. New UNOS Cohort Listed: 10/18/18-10/17/20	Old UNOS			New UNOS		
Candidate Characteristics at Listing Registration	**O**	**Non-O**		**O**	**Non-O**	
n (%) or mean (SD)	**3090**	**3945**	***p-value***	**3101**	**3864**	***p-value***
Age at Listing	52.6 (12.8)	53.8 (12.4)	**<0.001**	52.6 (12.7)	53.3 (12.8)	**0.029**
Male Gender	2242 (72.6)	2950 (74.8)	**0.035**	2267 (73.1)	2847 (73.7)	0.589
Body-mass Index	28.0 (5.0)	27.7 (4.97)	**0.006**	28.2 (5.0)	28.0 (5.0)	**0.038**
Ethnicity			**<0.001**			**<0.001**
White	1818 (58.8)	2618 (66.4)		1754 (56.6)	2501 (64.7)	
Black	826 (26.7)	853 (21.6)		875 (28.2)	877 (22.7)	
Hispanic	337 (10.9)	283 (7.2)		347 (11.2)	310 (8.0)	
Asian	77 (2.5)	150 (3.8)		86 (2.8)	147 (3.8)	
Other	32 (1.0)	41 (1.0)		39 (1.3)	29 (0.8)	
Region			**0.039**			**0.025**
1	155 (5.0)	189 (4.8)		165 (5.3)	200 (5.2)	
2	337 (10.9)	440 (11.2)		303 (9.8)	437 (11.3)	
3	456 (14.8)	507 (12.9)		367 (11.8)	431 (11.2)	
4	360 (11.7)	424 (10.8)		330 (10.6)	321 (8.3)	
5	442 (14.3)	559 (14.2)		429 (13.8)	565 (14.6)	
6	93 (3.0)	145 (3.7)		78 (2.5)	125 (3.2)	
7	262 (8.5)	369 (9.4)		259 (8.4)	327 (8.5)	
8	171 (5.5)	257 (6.5)		215 (6.9)	240 (6.2)	
9	172 (5.6)	259 (6.6)		232 (7.5)	288 (7.5)	
10	258 (8.4)	358 (9.1)		284 (9.2)	376 (9.7)	
11	384 (12.4)	438 (11.1)		439 (14.2)	554 (14.3)	
Education			0.703			**0.029**
Grade School or less	201 (6.5)	231 (5.9)		273 (8.8)	270 (7.0)	
High school or GED	1153 (37.3)	1468 (37.2)		1130 (36.5)	1398 (36.2)	
Some College	833 (27.0)	1069 (27.1)		802 (25.9)	1058 (27.4)	
Graduated College	903 (29.2)	1176 (29.8)		893 (28.8)	1137 (29.4)	
Diabetes	864 (28.0)	1113 (28.2)	0.811	866 (28.0)	1092 (28.3)	0.778
Dialysis	58 (1.9)	50 (1.3)	0.039	63 (2.0)	78 (2.0)	0.965
Prior Stroke	191 (6.2)	236 (6.0)	0.733	221 (7.1)	266 (6.9)	0.684
Prior Malignancy	253 (8.2)	366 (9.3)	0.108	266 (8.6)	344 (8.9)	0.643
History of Cigarette Use	1363 (44.1)	1826 (46.3)	0.067	1287 (41.5)	1726 (44.7)	**0.009**
Prior Cardiac Surgery (non-transplant)	1211 (39.2)	1562 (39.6)	0.718	1256 (40.6)	1459 (37.8)	**0.018**
Implantable Cardiac Defbrillator	2337 (75.6)	3039 (77.1)	0.157	2210 (71.4)	2750 (71.2)	0.875
Creatinine	1.28 (0.77)	1.27 (0.62)	0.339	1.33 (0.95)	1.33 (0.95)	0.811
Cardiac Hemodynamics						
PA Systolic	41.9 (14.2)	41.4 (14.3)	0.152	41.3 (14.7)	41.5 (14.9)	0.466
PA Diastolic	19.9 (8.7)	20.1 (8.6)	0.259	20.0 (8.9)	20.2 (9.0)	0.364
Mean PA	28.1 (10.3)	28.4 (10.1)	0.150	28.0 (10.6)	28.2 (10.7)	0.308
Mean PCWP	18.3 (8.5)	18.7 (8.5)	0.071	18.1 (8.5)	18.5 (8.6)	0.064
CO	4.34 (1.36)	4.31 (1.28)	0.438	4.30 (1.30)	4.29 (1.33)	0.775
No Support	1050 (34.3)	1413 (35.8)	0.187	1086 (35.0)	1460 (37.8)	**0.017**

(Continues)

TABLE 1 (Continued)

Old UNOS Cohort Listed: 10/18/15-10/17/17 v. New UNOS Cohort Listed: 10/18/18-10/17/20	Old UNOS			New UNOS		
Candidate Characteristics at Listing Registration	**O**	**Non-O**		**O**	**Non-O**	
n (%) or mean (SD)	**3090**	**3945**	***p-value***	**3101**	**3864**	***p-value***
Inotropes	971 (31.4)	1316 (33.4)	0.086	957 (30.9)	1210 (31.3)	0.684
IABP	209 (5.3)	167 (5.4)	0.843	528 (13.7)	393 (12.7)	0.225
Durable LVAD	1070 (34.6)	1195 (30.3)	<**0.001**	951 (30.7)	1023 (26.5)	<**0.001**
Temporary LVAD	44 (1.4)	56 (1.4)	0.99	50 (1.6)	58 (1.5)	0.705
ECMO	38 (1.2)	69 (1.8)	0.077	83 (2.7)	129 (3.3)	0.110
Ventilator Support at Listing	54 (1.8)	63 (1.6)	0.624	40 (1.3)	91 (2.4)	**0.001**

TABLE 2 Sub-hazard ratios for competing waitlist outcomes comparing blood group O and Non-O groups before and after the allocation change

Waitlist Outcomes for Listed Patients - Follow-up Censored at 1 year	Old UNOS			New UNOS		
	O	**Non-O**		**O**	**Non-O**	
n (%) or mean (SD)	**3090**	**3945**	***p-value***	**3101**	**3864**	***p-value***
Median Days on Wait List (Wilcoxon Rank-Sum Test)	240 (72-365)	105 (29-310)	<**0.001**	132 (20-365)	39 (10-207)	<**0.001**
Median Days to Transplantation	160 (49-365)	77 (24-220)	<**0.001**	33 (10-153)	23 (7-98)	<**0.001**
Transplanted	1352 (43.8)	2502 (63.4)		1603 (51.7)	2766 (71.6)	
WL Death	157 (5.1)	165 (4.2)		106 (3.4)	97 (2.5)	
Removed from Waitlist	419 (13.6)	439 (11.1)		379 (12.2)	362 (9.4)	
Remains on Waitlist	1162 (37.6)	839 (21.3)		1013 (32.7)	639 (16.5)	
Transplantation rate (per 10000 patient-days), (95 CI)	20.1 (19.0-21.2)	40.8 (39.2-42.4)		29.3 (27.9-30.8)	61.4 (59.2-63.8)	
Transplantation rate ratio, (95 CI)	0.49 (0.46-0.53)		<**0.001**	0.48 (0.45-0.51)		<**0.001**
Death rate (per 10000 patient-days)	2.33 (1.99-2.72)	2.69 (2.31-3.13)		1.94 (1.60-2.34)	2.15 (1.77-2.63)	
Death rate ratio (95 CI)	0.87 (0.69-1.08)		0.198	0.90 (0.68-1.20)		0.450
Competing-risks Regression SHR - Transplantation						
Model 1: unadjusted	0.55 (0.52-0.59)		<**0.001**	0.58 (0.55-0.62)		<**0.001**
Model 2: Age, Gender, BMI, Education, Region	0.55 (0.52-0.59)		<**0.001**	0.59 (0.55-0.62)		<**0.001**
Model 3: Model 2 + Listing Strategy + Co-morbidities + Hemodynamics	0.54 (0.51-0.58)		<**0.001**	0.58 (0.54-0.62)		<**0.001**
Competing-risks Regression SHR - Death						
Model 1: unadjusted	1.22 (0.98-1.51)		0.080	1.37 (1.04-1.80)		**0.027**
Model 2: Age, Gender, BMI, Education, Region	1.24 (1.00-1.55)		0.054	1.37 (1.03-1.81)		**0.028**
Model 3: Model 2 + Listing Strategy + Co-morbidities + Hemodynamics	1.24 (0.99-1.55)		0.065	1.43 (1.08-1.89)		**0.012**
Competing-risks Regression SHR - WL Removal						
Model 1: unadjusted	1.23 (1.07-1.40)		**0.003**	1.31 (1.14-1.52)		<**0.001**
Model 2: Age, Gender, BMI, Education, Region	1.23 (1.08-1.41)		**0.002**	1.28 (1.11-1.48)		**0.001**
Model 3: Model 2 + Listing Strategy + Co-morbidities + Hemodynamics	1.23 (1.08-1.41)		**0.003**	1.29 (1.11-1.49)		**0.001**

TABLE 3 Comparison of recipient characteristics at transplantation between Group O and Groups Non-O before and after the allocation change

Old UNOS Cohort Listed & Transplanted: 10/18/15-10/17/17 v. New UNOS Cohort Listed & Transplanted: 10/18/18-10/17/20	Old UNOS			New UNOS		
Recipient Characteristics at Transplant Registration	O	Non-O		O	Non-O	
n (%) or mean (SD)	1235	2284	*p-value*	1524	2614	*p-value*
Age at Transplantation	53.1 (13.0)	54.3 (12.3)	**0.006**	53.0 (12.9)	53.4 (13.0)	0.286
Body-Mass Index	27.2 (4.8)	27.3 (4.8)	0.336	27.5 (4.9)	27.6 (5.1)	0.500
Hospitalization Status			0.002			<0.001
In Intensive Care Unit	517 (28.1)	850 (29.3)		1108 (62.3)	1511 (51.7)	
Hospitalized - Not in ICU	344 (18.7)	429 (14.8)		252 (14.2)	313 (10.7)	
Not Hospitalized	979 (53.2)	1620 (55.9)		418 (23.5)	1100 (37.6)	
No Support	120 (9.7)	310 (13.6)	**0.001**	182 (11.9)	473 (18.1)	**<0.001**
Inotropes	508 (41.1)	947 (41.5)	0.850	704 (46.2)	1081 (41.4)	**0.002**
IABP	134 (10.9)	203 (8.9)	0.059	569 (37.3)	795 (30.4)	**<0.001**
Durable LVAD	542 (43.9)	931 (40.8)	0.073	438 (28.7)	742 (28.4)	0.808
Temporary LVAD	51 (4.1)	55 (2.4)	**0.004**	58 (3.8)	57 (2.2)	**0.002**
ECMO	12 (1.0)	25 (1.1)	0.733	96 (6.3)	151 (5.8)	0.494
Ventilator Support	14 (1.1)	24 (1.1)	0.821	39 (2.6)	61 (2.3)	0.649
Creatinine	1.25 (0.78)	1.25 (0.99)	0.975	1.21 (0.51)	1.21 (0.65)	0.691
Total Bilirubin	0.95 (1.95)	0.92 (1.13)	0.530	1.06 (2.28)	1.04 (1.96)	0.777
Cardiac Hemodynamics						
PA Systolic	38.8 (13.1)	39.6 (13.7)	0.128	40.8 (13.1)	40.2 (13.5)	0.139
PA Diastolic	18.5 (8.1)	18.9 (8.2)	0.172	20.3 (8.4)	19.6 (8.5)	**0.007**
Mean PA	26.4 (9.5)	26.8 (9.7)	0.311	28.1 (9.6)	27.5 (10.0)	0.069
Mean PCWP	17.0 (8.3)	17.7 (8.6)	**0.037**	18.8 (8.2)	18.1 (8.5)	**0.012**
CO	4.48 (1.44)	4.52 (1.38)	0.344	4.33 (1.39)	4.37 (1.43)	0.335

were censored in the analysis. During the study period 11,992 adult patients were listed and transplanted for first time, single-organ heart transplantation. To avoid bias from changing practice patters around allocation change, 882 patients listed in the year prior were excluded and 343 patients who were listed in the old system and transplanted in the new system were also excluded. To avoid bias from inadequate follow-up, 691 patients with less than one year follow-up after listing were excluded. After exclusions, 7,657 patients were included in analysis of recipient characteristics at listing and transplantation, donor characteristics and post-transplant outcomes. Of these 3,519 (46.0%) were listed and transplanted under the old UNOS system and 4,138 (54.0%) under the new system. At the end of one year follow-up 629 (8.2%) died, 18 (0.2%) were re-transplanted and 7,007 (91.5%) were alive and censored in the analysis (Figure 1).

3.2 | Clinical characteristics

Clinical characteristics at the time of listing were similar before and after the UNOS allocation change both overall and among each blood group (Supplemental Table 1) and when comparing group O with groups Non-O before and after the allocation change (Table 1). Overall use of IABP and ECMO as bridging strategies increased between the old and new systems (Supplemental Table 1) but did not do so disproportionately for Group O vs. Groups Non-O (Table 1). Group O patients were slightly less likely to be managed with no support strategy after the allocation change (35.0 vs. 37.8%, $p = 0.017$) while there was no significant difference prior to the allocation change (34.3 vs. 35.8%, $p = 0.187$). There was no differences in the use of temporary mechanical circulatory support (IABP or ECMO) between Group O patients and non-O patients either before or after the allocation change. Group O patients were slightly more likely to have durable LVADs in both time periods: prior to allocation change 34.6 vs. 30.3 $p < 0.001$ and after the allocation change 30.7 vs. 26.5% $p < 0.001$.

3.3 | Waitlist outcomes

Comparison between the old and new UNOS systems overall and stratified by blood group is presented in Supplemental Table 2. Median days on wait list and median days to transplantation were reduced overall and among each blood group. SHR for waitlist death was < 1 with

TABLE 4 Comparison of donor characteristics at transplantation between Group O and Groups Non-O before and after the allocation change

Old UNOS Cohort Listed & Transplanted: 10/18/15-10/17/17 v.UNOS Cohort Listed & Transplanted: 10/18/18-10/17/20	Old UNOS			New UNOS		
Donor Characteristics	**O**	**Non-O**		**O**	**Non-O**	
n (%) or mean (SD)	**1235**	**2284**	***p-value***	**1524**	**2614**	***p-value***
Donor Age	32.6 (11.0)	31.8 (11.1)	**0.028**	33.2 (10.9)	31.7 (10.3)	**<0.001**
Donor Male Gender	1522 (66.6)	819 (66.3)	0.847	1088 (71.4)	1892 (72.4)	0.50
Recipient-Donor Gender Mismatch	567 (24.8)	289 (23.4)	0.347	580 (22.2)	339 (22.2)	0.967
Donor Body-Mass Index	27.8 (6.6)	27.6 (6.3)	0.368	28.1 (6.4)	27.7 (6.1)	0.071
Donor Blood Group			**<0.001**			**<0.001**
A	0	1369 (59.9)		0	1500 (57.4)	
B	0	404 (17.7)		1 (0.1)	469 (17.9)	
AB	0	94 (4.1)		0	84 (3.2)	
O	1235 (100)	417 (18.3)		1523 (99.9)	561 (21.5)	
			0.042			**0.031**
	702 (38.2)	1073 (37.0)		806 (45.0)	1302 (44.2)	
	308 (16.8)	420 (14.5)		267 (14.9)	368 (12.5)	
	774 (42.1)	1329 (45.8)		662 (37.0)	1186 (40.2)	
	6 (0.3)	17 (0.6)		9 (0.5)	7 (0.2)	
	48 (2.6)	65 (2.2)		47 (2.6)	84 (2.9)	
Diabetes	70 (3.8)	95 (3.3)	0.325	66 (3.7)	106 (3.6)	0.875
History of Cocaine Use	445 (24.2)	711 (24.6)	0.794	502 (28.1)	780 (26.6)	0.250
Creatinine	1.55 (1.61)	1.50 (1.57)	0.416	1.67 (1.76)	1.67 (1.79)	0.995
Total Bilirubin	1.02 (1.31)	1.03 (1.14)	0.813	1.03 (1.52)	1.05 (1.42)	0.761
LV Ejection Fraction	61.2 (6.6)	61.9 (6.5)	**0.004**	61.3 (7.0)	61.6 (6.6)	0.173
Ischemic Time	2.99 (1.09)	3.09 (1.03)	**0.011**	3.49 (1.10)	3.43 (1.05)	0.078
Distance (miles) from Tx Center - median (IQR)	59 (8-206)	81 (13-272)	**<0.001**	222 (89-392)	237 (86-415)	0.144

significant p values for all groups except for Group AB, indicating significantly improved waitlist survival. SHR for transplantation was > 1 with significant p values for all groups, indicating greater rates of transplantation for each blood group. These findings were consistent after adjustment for demographic and comorbid covariates.

Comparison of Group O with Non-O Groups under the old and new allocation systems is presented in Table 2. Group O patients had a lower likelihood of transplantation in both systems, (SHR < 1 both before and after the allocation change, $p < 0.001$ for each). Similarly, compared to non-O, the likelihood of waitlist removal for Group O was higher) in both the old and new UNOS systems (SHR > 1 before and after the allocation change, $p < 0.001$ for each. These findings were consistent after adjustment for demographic and comorbid covariates.

Cumulative incidence of competing waitlist outcomes between Group O and non-O in the new allocation system is shown in Figure 2.

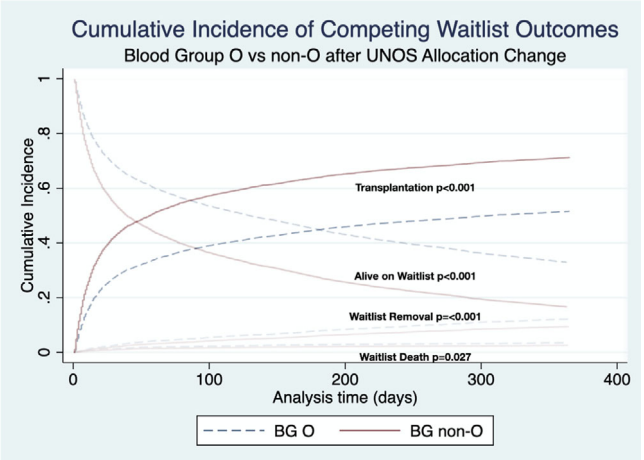

FIGURE 2 Cumulative incidence estimates of waitlist outcomes for blood group O vs Non-O Groups before and after the allocation change

3.4 | Transplant outcomes

Donor characteristics were not clinically different between the old and the new allocation system, Table 4 and Supplemental Table 4, except for longer ischemic time and travel distance in the new allocation system. Post-transplant outcomes are listed in Table 5 and Supplementary Table 5, showing no difference in post-transplant outcomes under the

TABLE 5 Hazard ratios for post-transplant death or re-transplantation comparing blood group O and Non-O groups before and after the allocation change

Outcomes for Transplanted Patients - Follow-up Censored at 1 year	Old UNOS			New UNOS		
	O	Non-O		O	Non-O	
n (%) or mean (SD)	1235	2284	*p-value*	1524	2614	*p-value*
Alive	1131 (91.6)	2091 (91.6)		1383 (90.8)	2402 (91.9)	
Dead	101 (8.2)	188 (8.2)		137 (9.0)	203 (7.8)	
Re-transplant	1 (0.1)	4 (0.2)		4 (0.27)	9 (0.3)	
Lost to Follow up	2 (0.2)	1 (< 0.1)		0	0	
Death or Re-Transplantation Incidence Rate						
N/total	102/1235	192/2284		141/1524	212/2614	0.491
Median Follow-up days	365	365	0.883	365 (356-365)	365 (357-365)	
Rate per 10,000 person-days (95 CI)	2.43 (2.00-2.95)	2.47 (2.15-2.85)		2.82 (2.39-3.32)	2.44 (2.14-2.80)	
Incidence rate ratio (95 CI)	0.98 (0.76-1.25)		0.886	1.15 (0.92-1.43)		0.193
Cox proportional-hazards model						
HR (95 CI)						
Model 1: unadjusted	0.98 (0.77-1.25)		0.884	1.15 (0.93-1.42)		0.202
Model 2: Recipient and Donor Demographics	0.88 (0.62-1.26)		0.492	1.28 (0.92-1.78)		0.142
Model 3: Model 2 + Recipient and Donor Markers of disease severity Demographics	0.80 (0.56-1.14		0.219	1.30 (0.93-1.81)		0.122

new allocation system among the whole cohort, as well as based on blood group.

4 | DISCUSSION

The salient features of our analysis are that the new UNOS allocation system is associated with lower median days to transplantation, lower waitlist death rate for all blood groups (except potentially for the rarer Group AB cohort which may have been underpowered to demonstrate significant differences) and higher transplantation rates for all blood groups. Although disparities in median days on the waitlist and median days to transplantation between Group O and Non-O Groups have been reduced, compared to Non-O Groups, Group O remains associated with higher waitlist death rates, lower transplantation rates and higher waitlist removal rates in both the old and new UNOS systems. Post-transplant outcomes were unchanged for all blood groups under the new allocation system. These results may lead to important considerations for the management of advanced heart failure patients with blood group O.

Blood group is an important non-modifiable variable in advanced heart failure patients being listed for heart transplantation. Under the new allocation system, patients with Group O were less likely to be listed with inotropes alone and more likely to have a durable LVAD at the time of listing compared to non-Group O patients, a strategy that may be beneficial in Group O patients.[3] While individual transplant programs may alter listing strategy to favor temporary LVAD, IABP, ECMO or other listing strategies that increase transplant priority, there is no evidence in the current study that this is a common practice among the whole UNOS cohort. After adjusting for the small differences in waitlist strategy, Group O patients remain disadvantaged on the waitlist compared to other blood groups. Additionally, the current analysis cannot account for patients whose management is altered by their blood group prior to transplant listing, i.e. older patients with Group O who may be offered destination therapy LVAD instead of transplant listing due to perceived longer wait times. Therefore, consideration for prioritizing Group O patients listed for transplant could be considered as part of future changes to the UNOS allocation system to both minimize potential incentives for different waitlist management of Group O patients as well as to reduce the adverse waitlist events currently associated with Group O patients. Potential strategies to address waitlist disadvantage for Group O patients include decreasing the percent of O donors going to non-O recipients[6] or potentially allowing Group O patients to accumulate more time per listed time compared to other groups which would move them up the list relatively more quickly. The findings of the current manuscript may warrant a formal review of the current waitlist disparities for blood group O patients. Prioritizing Group O patients listed for transplant could be considered as part of future changes to the UNOS allocation system to both minimize potential incentives for different waitlist management of Group O patients as well as to reduce the adverse waitlist events currently associated with Group O patients. Whether other non-modifiable or less modifiable factors influencing weight list times such as weight, height and antibody status may deserve extra focus to improve equity under the allocation system also deserves further investigation.

Although the effect of race on waitlist outcomes was not evaluated in the current analysis, because Hispanic and African American patients have the highest rates of blood group O transplant equity may be more impacted in these cohorts. Indeed, although confounders abound such as a higher proportion of patients with Medicaid insurance, higher presence of reactive antibodies and higher likelihood of being listed at low-volume transplant centers compared to Caucasian patients,[7,8] the effects of ethnicity on outcomes in the new allocation system merit further evaluation.

Prior studies have demonstrated variable results on post-transplant outcomes under the new allocation system.[9,10] Additionally, recent work has demonstrated the importance of evaluating adequate follow-up between the old and new allocation system, and demonstrated no difference in one-year post-transplant survival under the new allocation system.[11]

This study has limitations that are common to retrospective database evaluation. The UNOS dataset is populated by transplant centers and lacks important variables which may affect decisions regarding transplant listing and waitlist management. The use of certain mechanical support, such as Impella, is not well-characterized in UNOS, yet may be an important listing strategy thereby confounding results.

In conclusion, patients with Group O listed for heart transplant in the new UNOS allocation system have improved wait times and transplant rates compared to the prior allocation system but, nevertheless, experienced worse waitlist outcomes when compared to non-Group O patients. Prioritization of Group O patients should be considered in future changes to the UNOS allocation system.

CONFLICT OF INTEREST

Dr. Fudim receives consulting fees from AxonTherapies, Bodyport, Boston Scientific, CVRx, Daxor, Edwards LifeSciences, Fire1, Inovise, NXT Biomedical, Viscardia and Zoll. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or any other conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Dr. Jay Patel was involved in statistical analysis, study design, data analysis and revising the manuscript.

Dr. Dmitry Abramov was involved in study design, data analysis, writing the manuscript and the revisions.

Dr. Marat Fudim was involved in data analysis and revising the manuscript.

Dr. Ike S. Okwuosa was involved in data analysis and revising the manuscript.

Dr. David G. Rabkin was involved in study design, data analysis, writing the manuscript and the revisions.

Dr. Josh Chung was involved in study design, data analysis and writing the manuscript.

DATA AVAILABILITY STATEMENT

Data are available from the UNOS dataset.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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