Assessment of U.S. heart transplantation equity as a function of race: Observational analyses of the OPTN database

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Summary

Background Racial disparities in heart transplantation (HT) outcomes are suspected but uncertain. The additional impact of a recent change in donor allocation on disparities in HT in the United States (US) is unknown. We hypothesize racial disparities in HT are present and may be worsened by new allocation practices.

Methods Cohort: Adults listed for HT before and after a heart allocation policy change (Era 1: Oct 18th, 2015 - Oct 18th, 2018, Era 2: Oct 18th, 2018-June 30, 2021). The primary outcome was the rate of HT by race (Black vs. White), assessed using multivariable competing risk analysis (compete: waitlist removal for death or clinical deterioration). Final adjusted models included co-morbidities, SES and community-level Social Determinants of Health. The secondary outcome was waitlist removal for death or clinical deterioration.

Results Of 17,384 waitlist candidates (Era 1: 9,150, Era 2: 8,234), Black waitlist candidates had a lower rate of HT compared to White waitlist candidates in Era 1 (adjusted HR 0·90, 95 % CI 0·84-0·97, p = 0·0053) and in Era 2 (adjusted HR 0·81, 95 % CI 0·75-0·88, p <0·0001, era race interaction p=0·056). The rate of waitlist removal for death or deterioration was similar between races in Era 1 (adjusted HR 0·92, 95 % 0·77-1·1, p = 0·38), but increased for Black candidates in Era 2 (adjusted HR 1·34, 95 % CI 1·09-1·65, p = 0·0054, era race interaction p = 0·0051).

Interpretation Both the measured rate of transplantation and rate of delisting for death or clinical deterioration have worsened for Black compared to White waitlist candidates under the new allocation system. Causes for these disparities require further study.

Funding University of Minnesota Department of Cardiology funds.

Keywords: Disparities; Heart Transplantation

Introduction

Heart failure and heart transplantation (HT) outcomes are known to vary by race.[1-3] A recent major change in the United States (US) heart donor allocation system took place in 2018. This change separated the previous 3 tier system into 6 tiers, a stratification designed to provide more rapid transplantation of the sickest waitlist candidates. The implementation of a new policy allows for a comparative race-based analysis of access to HT both before and after this change. In this analysis, we utilized the Organ Procurement and Transplantation Network (OPTN), a database of all organ transplantations

Abbreviations: BMI, body mass index; HT, Heart transplantation; LVAD, Left ventricular assist device; MCS, Mechanical Circulatory Support; SES, socioeconomic status; SDOH, social determinants of health; SRTR, Scientific Registry of Transplant Recipient; SVI, social vulnerability index; OPTN, Organ Procurement and Transplantation Network

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Research in context

Evidence before this study

Despite many reports in the literature documenting health disparities as a function of race, few analyses offer sufficient adjustments to address the obvious confounder, specifically the Social Determinants of Health (SDOH). In the present analysis, we investigated the association of Black race and waitlist outcomes both before and after implementation of a new heart transplant allocation policy in 2018. This study utilized data from the Organ Procurement and Transplantation Network and was adjusted for social vulnerability index using candidate zip codes to approximate SDOH.

Added value of this study

This analysis demonstrated that both the measured rate of transplantation and rate of delisting for death of clinical deterioration have worsened for Black compared to White waitlist candidates under the new allocation system. Importantly, these findings persisted after adjustment for co-morbidities, individual socio-economic status, and the social vulnerability index. As we and others work to unravel race-based health inequities, this paper introduces new methodology allowing for more precision in future analyses and more certainty with the findings.

Implications of all the available evidence

The results of this analysis call for further analyses and prompt discussions to address policy change with the intent to ensure equity in organ distribution.

within the United States, to evaluate the impact of the allocation system change on the rate of both transplantation and delisting for death or clinical deterioration between Black and White waitlist candidates. We hypothesize the existence of racial disparities in HT due to deeply embedded and likely subconscious bias leading to inequitable subjective decision making.[4,5] We further hypothesize that despite a more objective allocation scheme, decision-making influenced by race and racial bias remains embedded in heart transplantation. To study this important question, we recognized the need to fully account for the totality of associated characteristics for which race may serve as a surrogate. These include co-morbidities, use of mechanical circulatory support, immunological status, socioeconomic status and indices of community vulnerability, i.e., Adverse Social Determinants of Health, as aggregated by the United States (US) Census Social Vulnerability Index. If race is a placeholder for the social construct, then such a community-based assessment of vulnerability should supplant the use of race as a risk factor. A pre- and post-analysis driven by the change in the OPTN allocation scheme also allows an assessment of a new allocation model on either the persistence of race-based differences, if any, or a narrowing of race-based differences given the more rigorous objective criteria that qualify for urgent transplantation status. Residual race-based differences in the rate of HT found after extensive adjustment for co-morbidities, SES and social determinants of health, suggest either persistent unmeasured confounders or the influence of bias. If disparities are present, an in-depth analysis of which status-level designations are most affected and the timing of the highest risk is necessary to improve equitable care of Black waitlist candidates. These analyses inclusive of the social construct not only address race-based differences in HT but may serve as a model to study race-based differences for many other conditions.

Methods

Cohort

The data for this analysis were acquired from the publicly available OPTN database. To obtain candidate zip codes for geocoding, a waiver from the University of Minnesota IRB was obtained and a separate OPTN data request was granted. The analysis was limited to adult patients (age ≥ 18 years) listed for single organ HT in 2 time periods: patients listed in the 3 years prior to the OPTN allocation change (Era 1: Oct 18th, 2015 - Oct 18th, 2018) and those listed after the allocation change (Era 2, after Oct 18th, 2018 – June 30, 2021). A summary of the changes to the allocation system is outlined in the *Supplementary Appendix*; this change allowed further stratification of the previous highest urgency status (1A) into 3 separately ranked statuses (statuses 1, 2 and 3), with the goal of reducing wait times for the sickest waitlist candidates. Objective hemodynamic criteria are now required to meet the highest tiers and the majority of hearts are now allocated to these top strata [6]. Race is reported to OPTN by transplant centres and defined according to the OPTN "ETHCAT" variable, which is divided into White, Black, Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, multiracial or unknown reflecting the categories of race-ethnicity as a social construct utilized by the US Office of Management and Budget. Ethnicity was defined according to the ETHNICITY variable, which is divided into Hispanic/Latino, Non-Hispanic/Latino, or unknown. As there were no White or Black patients coded as Hispanic/Latino ethnicity in OPTN, the final analytic cohort was limited to White and Black non-Hispanic/Latino patients (Era 1 n=9,150 Era 2 n= 8,234). The other race categories did not have enough of a sample size to allow adjustment for the social determinants of health.

Clinical Outcomes

The primary outcome was the rate of HT, with delisting due to death or clinical deterioration as competing

clinical outcomes. Patients were labelled as delisted for medical deterioration if they were coded as "medically unsuitable or "candidate condition deteriorated, too sick to transplant" at the time of delisting. The secondary outcome was the rate of waitlist removal for death or clinical deterioration using transplant as a competing outcome. Outcomes of waitlisted patients were available until June 2, 2021. For Era 1, time on the waitlist was censored on Oct 18, 2018, if patients had not undergone HT.

Statistical analysis

Continuous baseline characteristics were assessed for normality of distribution using histograms. Normally distributed baseline characteristics among Black vs. White listed candidates in each Era were compared with student's t-tests and non-normally distributed variables were compared with Wilcoxon-Mann-Whitney test. Chi-square tests were used for the comparison of categorical variables. To visually compare the unadjusted rates of HT according to race, cumulative incidence plots were created for Black and White patients displaying the incidence of both transplant and waitlist removal for death or clinical deterioration. Cumulative incidence plots were repeated by initial listing status in both eras matching by status acuity (highest, middle and lowest). To assess the rate of HT by race, sub-distribution hazard ratios were obtained from a Fine-Grey competing risk Cox proportional hazards regression, using delisting due to death or clinical deterioration as the competing outcomes (model 1). This was repeated by each initial listing status in each era. Proportional hazards assumption was checked for all key variables via visually assessing plots of Schoenfeld residuals. To assess the adjusted rate of HT by race, we created the following additional models: Model 2 incorporated recipient medical variables from the time of listing (age, gender, ABO blood group, body mass index (BMI), listing status (matched for high, middle, lowest acuity), serum creatinine, left ventricular assist device (LVAD) support, ischemic heart failure aetiology, presence of diabetes, pulmonary artery pressure, dialysis, extracorporeal membrane oxygenation support, OPTN region, or prior cardiothoracic surgery). The methodology for identifying LVAD support is outlined in the *Supplementary Appendix*. Model 3 included model 2 plus patient-level socioeconomic variables present within the OPTN database (insurance type, level of education). To approximate Social Determinants of Health, Model 4 added social vulnerability index (SVI) scores. To perform this adjustment, data were retrieved at the Census tract level. The United States Postal Service zip code crosswalk file from quarter 4 of 2018 was pulled from the United States Department of Housing and Urban Development to find the most common zip code associated with each census tract. Each theme within the SVI (Socioeconomic Status, Housing Composition and Disability, Minority Status and Language, and Housing Type and Transportation) was estimated for a given zip code by weighted average for all census tracts within that zip code based on residential ratio. Model 4 included the following themes: Socioeconomic Status, Housing Composition and Disability, and Housing Type and Transportation by patient zip code (*Supplementary Appendix*). As the patient location was already in Model 4, OPTN region was removed from this model. For each model, we performed a complete case analysis as missingness was rare (Era 1: <5%, Era 2: <6%). We then performed cause-specific Cox proportional hazards regression censoring at death or removal from the list due to clinical deterioration. To assess the rate of delisting for death or clinical deterioration by race, the above models were repeated using delisting for death or clinical deterioration as the outcome variable and transplant as a competing risk. These models were then repeated by performing cause-specific Cox proportional hazards regression censoring at the time of HT. To assess the statistical significance of the difference between eras for both outcomes, an interaction term was tested between race and era for all patients listed between Oct 18th, 2015 and June 30, 2021 (*Supplementary Appendix*). Lastly, to ensure that the timing of the change in hazard ratios was associated with the policy change and was not a preexisting trend nor a function of the pandemic, we assessed the fully adjusted (model 4, Fine Gray) hazard ratios for the primary and secondary outcome by year of listing. Era 2 was divided into before and after the start of the COVID-19 pandemic. Patients listed in Era 1 who had not received a transplant were not censored at the allocation change.

Sensitivity analyses

We performed several sensitivity analyses to ensure the robustness of the primary results assessing the rate of HT by race. The first assessed the impact of panel reactive antibody (PRA), the second employed a prevalent patient cohort selection technique, and in the third we performed coarsened exact matched cohort analysis based on race.

All analyses were performed using R Version 4.0.2. All comparisons were two-sided and a p-value < 0·05 was considered significant. University of Minnesota departmental Funds were utilized for data analysis.

Role of the funding source

No external funders had any role in the study design, data collection, data analysis, interpretation, writing of the report or decision to submit.

Results

Baseline characteristics

The study cohorts included 9,150 patients who were listed for HT in Era 1 and 8,234 in Era 2. Baseline characteristics by race are presented in Table 1A-D. Compared to White candidates in both eras, Black waitlist candidates were younger, more likely to be female, less likely to have diabetes, had a slightly higher BMI, and were more likely to have an LVAD at listing. White patients were more likely to have previous cardiothoracic surgery prior to listing. Educational attainment, waitlist status, and PRA category varied significantly by race. Black patients had greater social vulnerability based on SVI scores.

Unadjusted Assessment of Outcomes

The unadjusted cumulative incidence of HT in either Era by race across the cohort and by listing status acuity is displayed in Figure 1. At 365 days in Era 1, 53% per cent of Black and 59% per cent of White waitlist candidates were transplanted (unadjusted HR Black vs. White 0·88, 95 % CI 0·83- 0·94, p <0·001). In Era 2 at 365 days, 61% of Black and 68% of White candidates were transplanted (unadjusted HR 0·83, 95 %

	White n = 6,705	Black n = 2,445	*p* value
Age at listing (years) (mean (SD))	54·6 (12·4)	51·1 (12·3)	<0.0001
Male (%)	5,095 (76·0)	1,652 (67·6)	<0.0001
Body Mass Index (kg/m2) (mean (SD))	27·9 (4·8)	28·4 (5·1)	<0.0001
ABO (%)			<0.0001
A	2,862 (42·7)	638 (26·1)	
B	765 (11·4)	509 (20·8)	
AB	317 (4·7)	124 (5·1)	
O	2,761 (41·2)	1,174 (48·0)	
Initial listing status (%)			<0.0001
1A	1,596 (23·8)	613 (25·1)	
1B	3,138 (46·8)	1,321 (54·0)	
2	1,971 (29·4)	511 (20·9)	
Ischemic cardiomyopathy (%)	2,450 (36·5)	390 (16·0)	<0.0001
LVAD at listing (%)	1,998 (29·8)	864 (35·3)	<0.0001
Any LVAD while listed (%)	3,113 (46·4)	1,334 (54·6)	<0.0001
Creatinine (mg/dL) (median [IQR])	1·14 [0·93, 1·40]	1·25 [1·00, 1·57]	<0.0001*
ECMO while listed (%)	249 (3·7)	66 (2·7)	0.022
Dialysis at listing (%)	97 (1·4)	50 (2·0)	0.055
Ventilator at listing (%)	104 (1·6)	19 (0·8)	0.0061
PA systolic pressure (mmHg) (mean (SD))	40·6 (14·6)	43·0 (13·6)	<0.0001
Diabetes (%)	1,667 (24·9)	685 (28·0)	0.0026
PRA category (%)			<0.0001[t]
0	2,537 (37·8)	777 (31·8)	
0-10	317 (4·7)	130 (5·3)	
10-20	143 (2·1)	56 (2·3)	
>20	621 (9·3)	303 (12·4)	
Missing	3,124 (46·6)	1,179 (48·2)	
Prior cardiothoracic surgery (%)	2,851 (42·5)	828 (33·9)	<0.0001
OPTN region (%)			
Northeast (1/2/9)	1516 (22·6)	588 (24·0)	<0.0001
South (3/4/11)	2,148 (32·0)	1,174(48·0)	
West (5/6)	1099 (16·4)	243 (9·9)	
Midwest (7/10/8)	1944 (27·0)	441(18·0)	

***Table 1A*: Baseline medical characteristics of heart waitlist candidates, by race, allocation era 1.**
Normally distributed baseline characteristics were compared with student's t-tests and non-normally distributed variables were compared with Wilcoxon-Mann-Whitney test. Chi-square tests were used for comparison of categorical variables.

* non-normally distributed variables.

[t] variable only available for transplanted candidates. PRA: panel reactive antibody, ECMO: extra corporal membrane oxygenation, OPTN: Organ Procurement and Transplantation Network, PA: pulmonary artery.

	White n = 5,792	Black n= 2,442	*p* value
Age at listing (years) [mean (SD)]	54·7 (12·4)	50· 9(12·7)	<0.0001
Male (%)	4,377 (75·6)	1,682 (68·9)	<0.0001
Body Mass Index (kg/m2) [mean (SD)]	28·2 (4·9)	28·7 (5·2)	<0.0001
ABO (%)			<0.0001
A	2,488 (43·0)	613 (25·1)	
B	654 (11·3)	524 (21·5)	
AB	267 (4·6)	101 (4·1)	
O	2,383(41·1)	1204 (49·3)	
Status at listing (%)			<0.0001
1	267 (4·6)	73 (3·0)	
2	1,184 (20·4)	547 (22·4)	
3	603 (10·4)	322 (13·2)	
4	2,245 (38·8)	1,011 (41·4)	
6	1,493 (25·8)	489 (20·0)	
Ischemic Cardiomyopathy (%)	2,008 (34·7)	340 (13·9)	<0.0001
LVAD at listing (%)	863 (14·9)	425 (17·4)	0.0047
Any LVAD while listed (%)	1,494 (25·8)	824 (33·7)	<0.0001
Creatinine (mg/dL) (median [IQR])	1·16 [0·94, 1·42]	1·26 [1·01, 1·56]	<0.0001*
ECMO while listed (%)	362 (6·2)	127 (5·2)	0.074
Dialysis at listing (%)	67 (1·2)	53 (2·2)	0.0006
Ventilator at listing (%)	109 (2·0)	25 (1·0)	0.0066
PA systolic pressure (mmHg) (mean (SD))	40·1 (14·7)	42·7 (14·1)	<0.0001
Diabetes (%)	1,427 (25·1)	666 (27·9)	0.0077
PRA category (%)			<0.0001[t]
0	1,995 (34·4)	654 (27)	
0-10	214 (3·7)	104 (4·3)	
10-20	67 (1·4)	52 (2·1)	
>20	387 (6·7)	228 (9·3)	
Missing	2,511 (53·7)	1,404 (57·5)	
Prior cardiothoracic surgery (%)	2,397 (41·4)	839 (34·5)	<0.0001
OPTN region (%)			<0.0001
Northeast (1/2/9)	1,516 (23·3)	578 (23·7)	
South (3/4/11)	2,148(31·7)	1182 (48·4)	
West (5/6)	1,099 (16·5)	210 (8·6)	
Midwest (7/10/8)	1,810 (28·5)	472 (19·3)	

***Table 1B*: Baseline medical characteristics of heart waitlist candidates, by race, allocation era 2.**
Normally distributed baseline characteristics were compared with student's t-tests and non-normally distributed variables were compared with Wilcoxon-Mann-Whitney test. Chi-square tests were used for comparison of categorical variables.

* non-normally distributed variables.

[t] variable only available for transplanted candidates. PRA: panel reactive antibody, ECMO: extra corporal membrane oxygenation, OPTN: Organ Procurement and Transplantation Network, PA: pulmonary artery.

CI 0·78- 0·89, p <0·0001). The rate of transplantation is overall higher in Era 2, however, the rate of transplant is lower for Black waitlist candidates regardless of Era. Under the prior allocation system (Era 1), the rate of transplant did not differ by race for patients at the highest acuity status 1A (HR 0·97, 95 % CI 0·87-1·08, p = 0·60) (Table 2**).** The observed disparity appeared to be driven by a lower rate of transplantation for Black patients listed in the lower acuity status categories, including Status 1B (HR 0·80, 95 % CI 0·73-0·87, p <0·0001) and Status 2 waitlist candidates (HR 0·73, 95 % CI 0·62-0·85, p <0·0001). Under the new allocation system (Era 2), the measured rate of transplantation in the unadjusted analyses was lower among Black compared to White waitlist candidates, regardless of listing status **(**Figure 1, Table 2**).**

The unadjusted cumulative incidence of delisting for death or clinical deterioration in either Era is displayed in Figure 2**.** Under the prior allocation system (Era 1) White and Black waitlist candidates had similar rates of delisting due to death or clinical deterioration (HR 0·95, 95 % CI 0·82-1·10). Under the new system, Black waitlist candidates have a higher rate of delisting due to death or clinical deterioration (HR 1·42, 95 %CI 1·19-

	White n = 6,705	Black n = 2,445	*p* value
Private insurance (%)	3,523 (52·5)	974 (39·8)	<0·0001
Education Category (%)			<0·0001
College	4,078 (60·8)	1,276 (52·2)	
High school	2,352 (35·1)	1,047 (42·8)	
Less than high school	102 (1·5)	53 (2·2)	
Missing	173 (2·6)	69 (2·8)	
Social Vulnerability Index [mean (SD)]	0·43 (0·21)	0·60 (0·22)	<0·0001
Socioeconomic Status	0·42 (0·22)	0·59 (0·23)	<0·0001
Housing Composition and Disability	0·48 (0·21)	0·56 (0·22)	<0·0001
Minority Status and Language	0·42 (0·23)	0·63 (0·19)	<0·0001
Housing Type and Transportation	0·47 (0·20)	0·53 (0·19)	<0·0001

***Table 1C*: Baseline psychosocial characteristics of heart waitlist candidates, by race, allocation era 1.**
Normally distributed baseline characteristics were compared with student's t-tests and non-normally distributed variables were compared with Wilcoxon-Mann-Whitney test. Chi-square tests were used for comparison of categorical variables.

1·68). The cumulative incidence plots by initial listing acuity are also displayed. Under the new system (Era 2), the measured rate of delisting due to death or clinical deterioration in the unadjusted analyses was higher among Black waitlist candidates, regardless of listing status (Figure 2, Table 2).

Adjusted Analyses of the Rates of HT by Era and Race

A summary of the adjusted models depicting the association between race and the rate of HT in each allocation era is displayed in Figure 3A. The disparity observed in the unadjusted analysis for Era 1 attenuated slightly but remained largely unchanged with sequential adjustment for medical (Model 2: HR 0·87, 95 % CI 0·81-0·94, p=0.0002), socioeconomic (Model 3: HR 0·88, 95 % CI 0·81-0·94, p=0.0004), and SVI scores by zip code (Model 4: HR 0·90, 95 % CI 0·84-0·97, p=0·0053). In Era 2 under the new allocation system, the lower rate of transplantation for Black patients persisted despite sequential adjustment for medical (model 2: HR 0·79, 95 % CI 0·73-0·85, p < 0·0001), socioeconomic (model 3: HR 0·80, 95 % CI 0·74-0·86, p < 0·0001) and SVI scores by zip code (model 4: HR 0·81, 95 % CI 0·75-0·88, p < 0·0001). In the cause-specific Cox regression models, Black race was associated with a 15% lower rate of HT in waitlisted candidates who were currently alive and waiting in Era 1 (model 4: HR 0·85, 95 % CI 0·79-0·91, p<0·0001, and a 20 % lower rate in Era 2 (model 4: HR 0·81, 95 % CI 0·75-0·87, p <0·0001). The rate of transplantation was lower among Black candidates in both the competing risk and cause-specific models, suggesting that the decreased rate of transplantation was not driven by increased rates of death or delisting due to deteriorating clinical status. All sensitivity analyses confirmed the direction, and strength of the primary

	White n = 5,792	Black n= 2,442	*p* value
Private insurance (%)	3,029 (52·3)	948 (38·8)	<0·0001
Education Category (%)			<0·0001
College	3,548 (59·7)	1221 (50·0)	
High school	1,889 (32·6)	992 (40·6)	
Less than high school	87 (1·5)	47 (1·9)	
Missing	358 (6·2)	182 (7·5)	
Social Vulnerability Index [mean (SD)]	0·42 (0·21)	0·60 (0·21)	<0·0001
Socioeconomic Status	0·42 (0·21)	0·60 (0·23)	<0·0001
Housing Composition and Disability	0·48 (0·21)	0·56 (0·22)	<0·0001
Minority Status and Language	0·42 (0·23)	0·63 (0·20)	<0·0001
Housing Type and Transportation	0·46 (0·20)	0·53 (0·19)	<0·0001

***Table 1D*: Baseline psychosocial characteristics of heart waitlist candidates, by race, allocation era 2.**
Normally distributed baseline characteristics were compared with student's t-tests and non-normally distributed variables were compared with Wilcoxon-Mann-Whitney test. Chi-square tests were used for comparison of categorical variables.

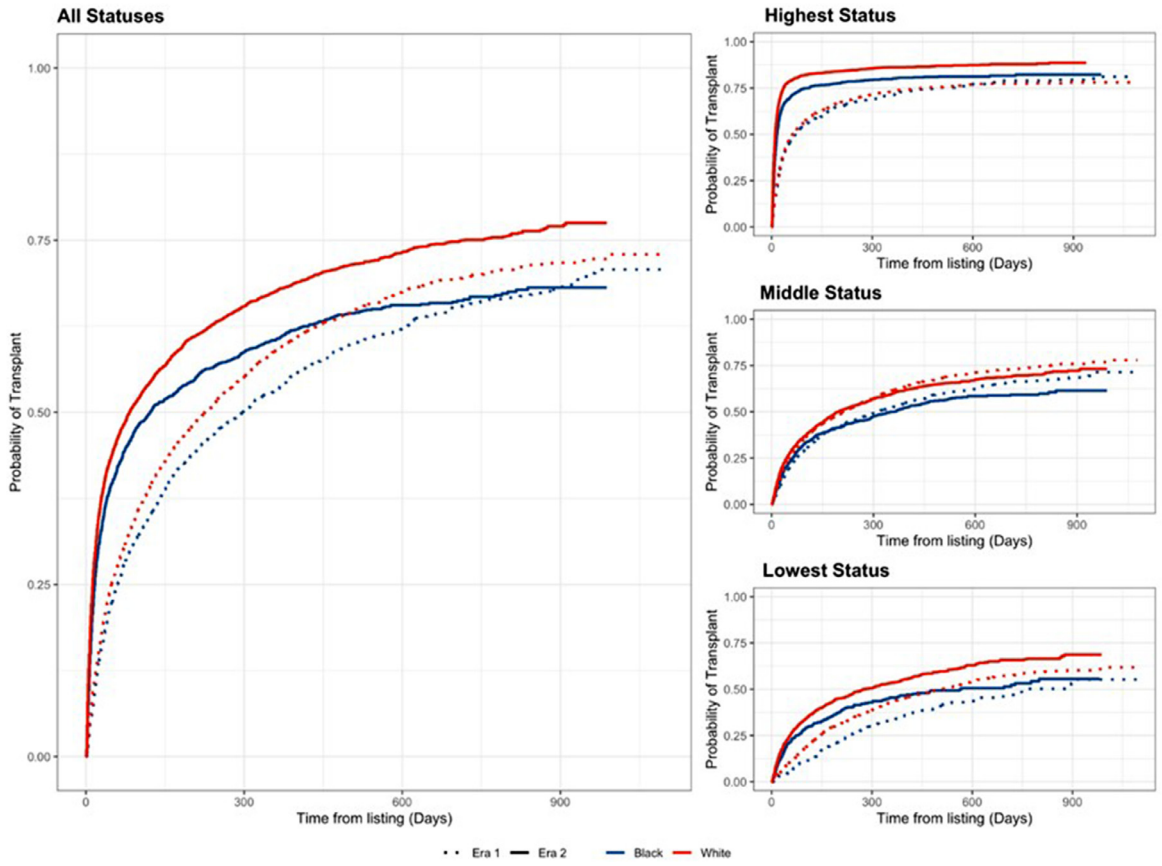


Figure 1. Unadjusted cumulative incidence of heart transplantation by allocation era.

The lines graphically displays the probability of undergoing heart transplant after listing by race over time. The dotted lines represent Era 1 and the sold lines represent Era 2. Black waitlist candidates (Blue) have a lower rate of transplantation than White waitlist candidates (Red) under both allocation systems. While there is an early increase in the rate of transplant in Era 2 (solid lines) for both races, Black waitlist candidates over time have a probability of transplantation that mirrors Era 1. Under the new allocation system, the measured rate of transplantation system is lower regardless of initial listing status.

results. The interaction of race and era and 95 % confidence interval is visually displayed in *Supplementary Figure* S2. All measured interaction terms for the rate of transplantation suggest a widening of the racial disparity between Black and White patients under the new system, however, this did not reach statistical significance in the fully adjusted model (model 4 HR 0·91, 95 % CI 0·83-1·002, p = 0·056).

Adjusted analyses of the rates of delisting due to death or clinical deterioration

The models depicting the association between race and rate of delisting due to death or clinical deterioration are displayed in Figure 3B. Under the prior allocation system (Era 1), there was no difference by race in waitlist mortality or delisting due to clinical deterioration in the unadjusted (HR 0·95, 95 % CI 0·82-1·10, p = 0·49) or fully adjusted (model 4 HR 0·92, 95 % 0·77-1·11, p = 0·38) models. Under the new allocation system, the rate of death or delisting was 42 % higher for Black patients in the unadjusted (unadjusted HR 1·42, 95 % CI 1·19-1·60, p<0·0001) and 34 % higher in the fully adjusted models (model 4 HR 1·34, 95 % CI 1·09-1·65, p = 0·0054). In the cause-specific models, the rate of death or delisting was higher for Black waitlist candidates in the new system. This was significant in the unadjusted but not in the fully adjusted models (unadjusted HR 1·28, 95 % CI 1·08-1·53, p =0·004, model 4: HR 1·18, 95 % CI 0·95-1·45, p =0·13). The interaction terms between race and era and 95 % confidence intervals for the rate of delisting for death or clinical deterioration are visually displayed in *Supplementary Figure* S3. The interaction term was significant in all 4 models (model 4: HR 1·36, 95 % CI 1·1-1·7, p =0·005). This indicates a significant widening of the racial disparity in the rate of death and delisting since the allocation change. Lastly, a visual assessment of the fully adjusted (model 4) hazard ratios demonstrates that the timing of the widening racial disparity for both the primary and

Event = Transplant	Era 1		Era 2	
Initial Status	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
All	0.88 (0.83,0.94)	<.0001	0.83 (0.78,0.89)	<.0001
Highest	0.97 (0.87,1.08)	0.60	0.78 (0.72,0.85)	<.0001
Middle	0.80 (0.73,0.87)	<.0001	0.78 (0.70,0.87)	<.0001
Lowest	0.73 (0.62,0.85)	<.0001	0.76 (0.65,0.89)	0.00048
Event = Delisting for Death or Deterioration				
	Era 1		**Era 2**	
Initial Status	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
All	0.95 (0.82,1.10)	0.49	1.42 (1.19,1.68)	<.0001
Highest	0.79 (0.60,1.03)	0.080	1.45 (1.116,1.89)	0.0050
Middle	0.96 (0.76,1.20)	0.70	1.15 (0.87,1.53)	0.33
Lowest	1.21 (0.90,1.65)	0.21	1.87 (1.29,2.70)	0.0010

***Table 2*: Rate of transplant or delisting due to death or clinical deterioration by initial listing status, unadjusted.**
Highest: Era 1: 1A, Era 2: 1,2,3. Middle: Era 1: 1B, Era 2: 4, Lowest: Era 1: 2, Era2: 6. The unadjusted hazard ratios show reduced rates of transplant in Era 2 across all listing statuses.

secondary outcome was not a preexisting trend or associated with the pandemic (Figure 4). but occurred at the time of the policy change.

Discussion

In this analysis of OPTN data, Black patients had a lower rate of HT. This disparity persisted after adjustment for known co-morbidities, immunological status, use of mechanical circulatory support, SES and a social construct measurement tool - the SVI. Further, when comparing the rates of HT under the old and new allocation systems, race-based disparities persisted despite the more rigorous criteria present under the new allocation system. Multiple analyses evaluating the impact of the new allocation scheme based on a new hierarchal algorithm yielded reduced rates of HT among Black waitlist candidates. The timing of this change corresponded with the onset of the policy change and was not a preexisting trend or due to the COVID-19 pandemic. While the rate of transplantation did improve for the sickest waitlist candidates under the new policy as intended, this benefit was not equally shared. Our data demonstrate potential unforeseen consequences of the new allocation scheme given an increase in the rate of delisting for death or clinical deterioration among Black compared to White waitlist candidates under the new system. These findings not apparent under the old allocation system.

Healthcare disparities based on race are typically multifactorial, and elucidating the underlying root cause requires study of clinically important variables, access to care, healthcare decision making and the social construct. Any argument that race per se is the cause of race-based disparities requires a careful assessment of all possible confounders and concurrent conditions. Hence, we intentionally incorporated a comprehensive set of medical and SES variables to both ensure the validity of our findings and to search for potential mediators. With respect to the medical variables, prior studies document that LVAD implantation is more common at listing among Black waitlist candidates, and hemodynamically stable patients with LVADs are given lower priority under the new allocation system. However, the lower rate of transplantation among Black HT candidates occurred at every status under the new system and persisted after adjustment for LVAD use. Patients with severe allosensitization have longer wait times for solid organ transplantation, and prior studies document that allosensitization is more common among Black HT candidates. Yet, despite incorporation of imputed PRA, the strength and significance of the measured disparity persisted. Blood group O is also more common in Black waitlist candidates and can lead to delays in matching organs. This variable, however, was included in all adjusted models and the disparity persisted in the matched cohort analysis, which was matched on blood group.

Disentangling race from associated SES barriers is a complex problem. No perfect model exists for this type of adjustment, in part because the social construct has not traditionally accommodated quantitative assessments. Race is often, and incorrectly, viewed as a biological determinant responsible for race-based differences. It is more likely the social construct, as influenced by structural racism, that drives inequities in the U.S. Black communities.[7] The OPTN registry collects limited information on SES, namely insurance and educational attainment. For the present analysis, we recognized the need for more precision and further evaluated an

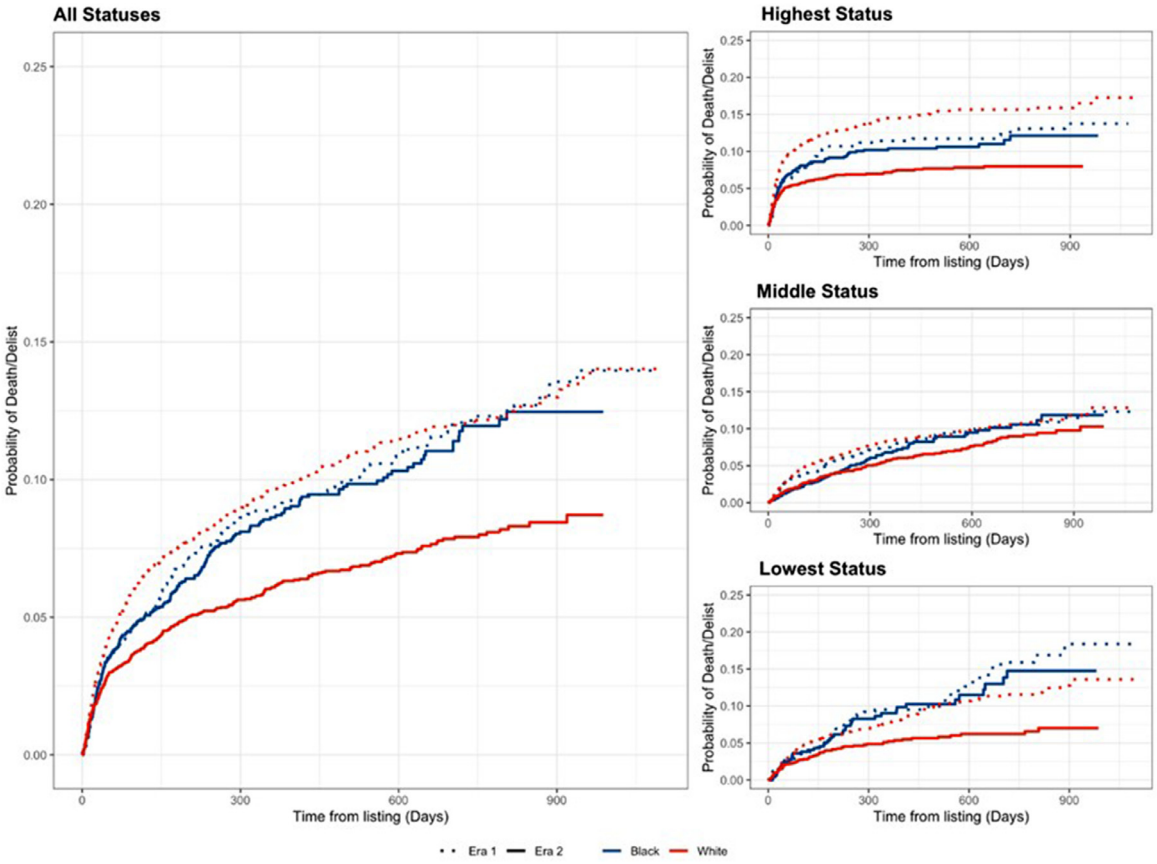


Figure 2. Unadjusted cumulative delisting for death or clinical deterioration by allocation era.

The dotted lines represent Era 1 and the sold lines represent Era 2. The lines graphically represent the probability of delisting for death or clinical deterioration by race. Under the prior allocation system (Era 1) white and Black waitlist candidates has a similar rate of delisting due to death or clinical deterioration. Under the new system, White waitlist candidates experienced reduced rates of delisting for death or clinical deterioration and Black waitlist candidates did not. Under the new allocation system, the measured rate of delisting for death or clinical deterioration is higher for Black vs. White waitlist candidates, initial listing acuity.

approximation of the Social Determinants of Health: the social vulnerability index (SVI). The SVI was first developed for disaster planning to identify communities that would be more vulnerable in the setting of a major crisis, e.g., COVID19. Components include Socioeconomic Status, Housing Composition and Disability, and Housing Type and Transportation (*Supplementary Appendix*). The SVI captures additional aspects of the complex social construct beyond SES and allows for an approximation of otherwise unaccounted race-related life and living circumstances. Moreover, the SVI is validated as a predictive measure of health-related outcomes. Despite extensive adjustment for SES and SVI, the residual independent association of race with lower rates of HT in the new allocation scheme identifies an evident disparity.

Our results identifying rate of transplantation among Black waitlist candidates is consistent with estimates by the Scientific Registry of Transplant Recipients (SRTR), however, the SRTR model does not account for listing status or competing risk. In addition, sensitivity and matched cohort analyses are not performed by SRTR to specifically address this question. Yet, a prior (2006 – 2010) OPTN analysis did not reveal a disparity in the rate of HT in Black candidates.[8] A recently published analysis of the rate of transplantation in the United States by race spanning 2011-2020 demonstrated a lower rate of transplantation among Black waitlist candidates, however, this analysis suggested the disparity may be decreasing under the new allocation system. This analysis included data to June of 2020 (vs. June 2021 in the present analysis) and excluded patients with less than 30 days of follow up (which is where the bulk of waitlist outcomes occur). The multivariable models utilized included at least one variable that is only available on patients who underwent cardiac transplant nor does the model address imputation or the handling of missing data, which would lead to significant bias and problems with convergence in estimates. Thus, the findings as analyzed suggest the disparity is

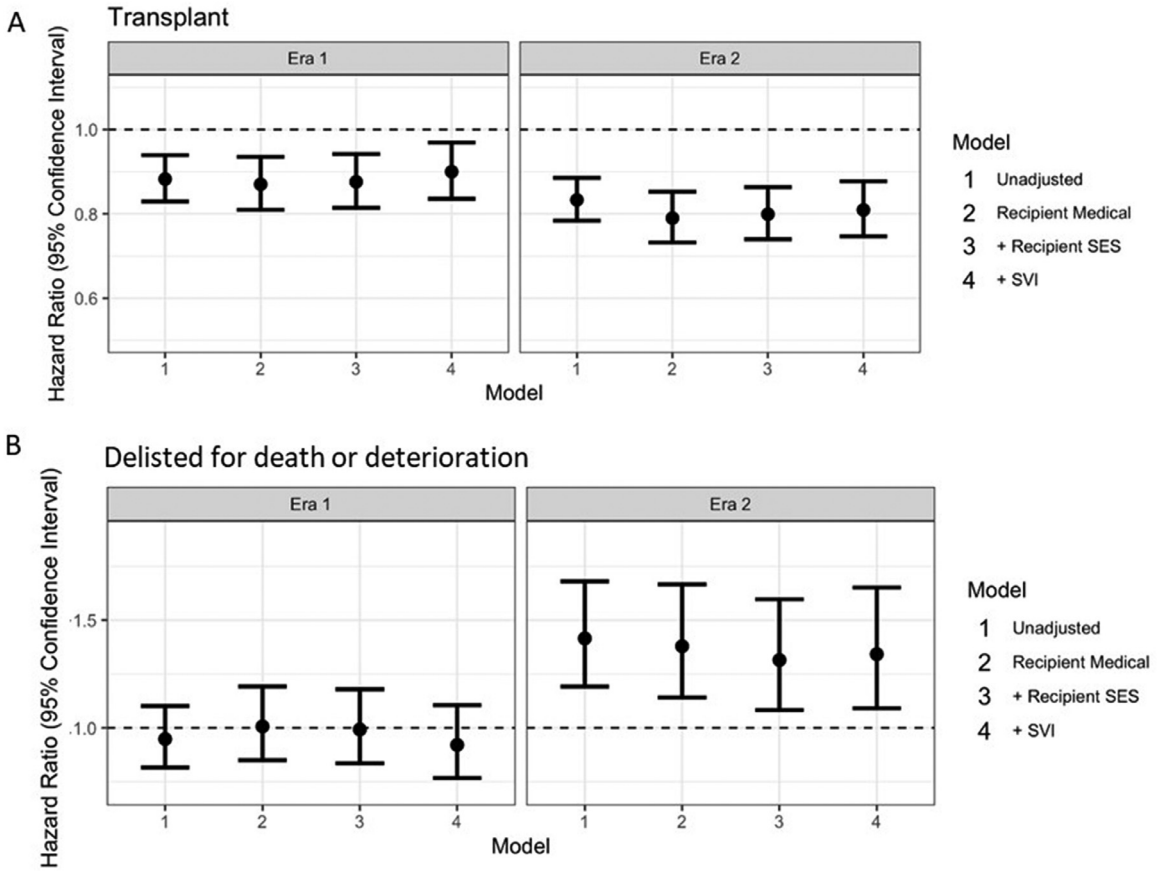
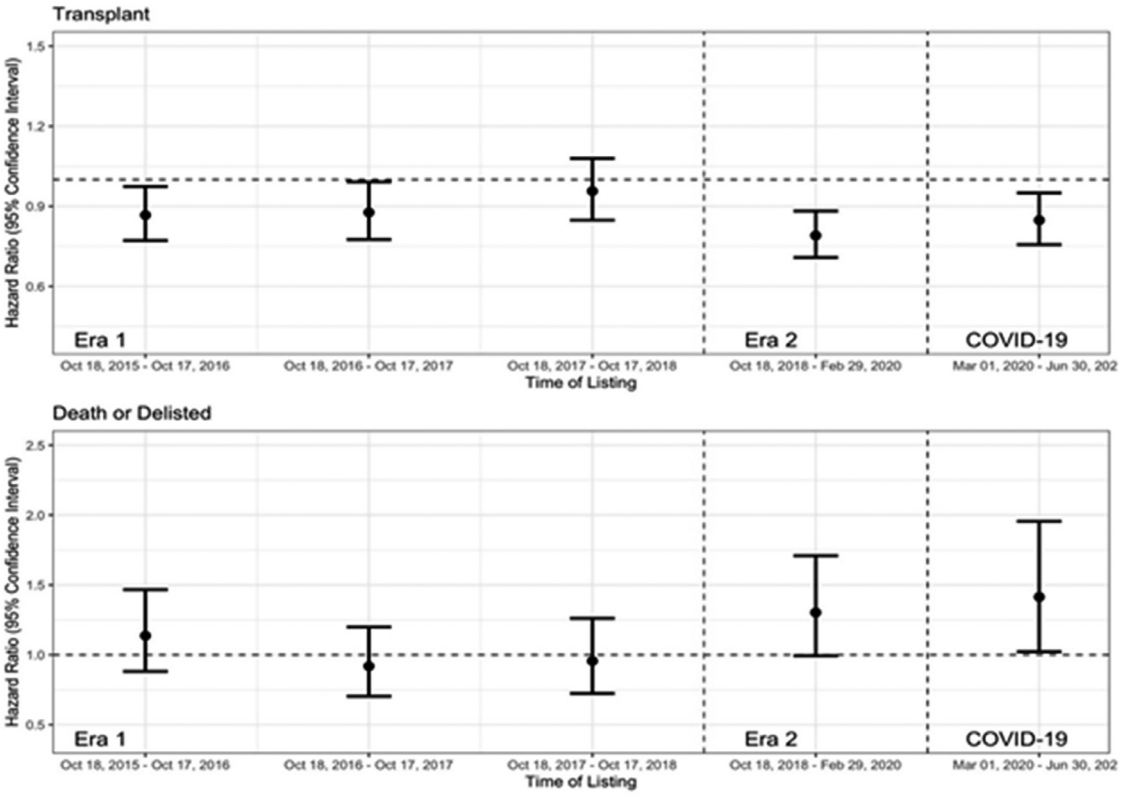


Figure 3. (A): Unadjusted and adjusted hazard ratios assessing rate of heart transplant for Black vs. White waitlist candidates by allocation era and model. **(B):** Unadjusted and adjusted HRs assessing rate of delisting for death or clinical deterioration for Black vs. White waitlist candidates by allocation era and model.

Model 1: unadjusted, model 2: + medical adjustment (age, gender, ABO blood group, body mass index (BMI), listing status, serum creatinine, left ventricular assist device support, ischemic heart failure etiology, presence of diabetes, pulmonary artery pressure, dialysis, extracorporeal membrane oxygenation support, OPTN region, or prior cardiothoracic surgery), model 3: + patient level socioeconomic variables, model 4: + social vulnerability index scores. Dotted line indicates no effect of being Black as compared to white (HR=1.0).

shrinking under the new allocation system, but provide no statistical evidence of this. In the present analysis, the hazard ratios associated with race-based inequities in heart transplantation under the new allocation system remained despite adjustment for SDOH, PRA, and after several additional sensitivity analyses. Our analyses demonstrate evidence of race-based inequity as measurable since 2015; moreover, under the new allocation system, the measured disparity is worsening. The new system is ostensibly based on more overt and objective criteria which should have reduced any subjective decision making yet the evidence of a measurable and widening gap between Black and White waitlist candidates is probable. Similar to our findings, prior analyses of post-HT outcomes have demonstrated that adjustment for SES variables does not explain the inferior clinical outcomes observed for Black patients. More extensive adjustment with SVI has not occurred.

A full explanation for the persistent and increasing evidence of disparity under the new allocation system is not clear. The expectation of narrowing disparities based on a shift to more objective criteria was not realized. This observation may attest to the extent to which subconscious or implicit bias is embedded in clinical decision making.[4,9] While the measured disparity in the rate of heart transplantation was present prior to the allocation system change, it was not driven by the rate of transplantation at the top of the list (previous 1A). Under the prior system, waitlist candidates became most eligible by accruing time at the top status, a measure not impacted by race. Under the current system, the development of more waitlist strata de-emphasizes wait time and may allow for more subjectivity in the allocation of donors. The unintended consequence of high rates of delisting due to death or clinical



Era 1				
	Event = Transplant		Event = Death/Delisting	
Time of Listing	HR (95% CI)	p	HR (95% CI)	p
Oct 18,2015 - Oct 17, 2016	0.87 (0.77,0.97)	0.016	1.10 (0.88,1.5)	0.32
Oct 18,2016 - Oct 17, 2017	0.88 (0.78,0.99)	0.035	0.92 (0.7,1.2)	0.53
Oct 18,2017 - Oct 17, 2018	0.96 (0.85,1.1)	0.47	0.96 (0.72,1.3)	0.75
Era 2				
	Event = Transplant		Event = Death/Delisting	
Time of Listing	HR (95% CI)	p	HR (95% CI)	p
Oct 18,2018 - Feb 29, 2020	0.79 (0.71,0.88)	<0.001	1.30 (0.99,1.7)	0.056
Mar 01, 2020 - June 30, 2021	0.85 (0.76,0.95)	0.0044	1.40 (1,2)	0.036

Figure 4. Adjusted models assessing the rate of heart transplant and delisting for death or clinical deterioration for Black vs. White waitlist candidates, by year of listing.

Each dot represents the HR of being Black as compared to White in the fully adjusted models for patients listed in each time period. The bars display 95% confidence intervals for the HR. The red dotted line shows the timing of the allocation system policy change. The blue dotted line indicates the beginning of the COVID-19 pandemic (Mar 1, 2020). The black dotted line indicates no effect of being Black compared to white race. Era 1 is divided into three year long periods. Era 2 is split into two roughly equal time periods before and after the onset of the COVID-19 pandemic. The decrease in the hazards rate of heart transplant and the increase in the hazards rate of delisting for death or clinical deterioration was not a pre-existing trend and was not impacted by the COVID-19 pandemic.

deterioration greater among Black compared to White waitlist candidates is a concern that requires further study. But the evidence of potential harm cannot be overlooked.

Limitations

There are several limitations to the current analysis. The use of observational data does not allow causal inferences. Other unmeasured variables may be at play including

psychosocial status, caregiver support, stability of housing and compliance. However, these are typically pre-requisites prior to listing for HT. The coding of ethnicity under race in the OPTN dataset suggests misclassification within the dataset. The impact of the higher prevalence of LVAD support among Black patients, including LVAD complications, may have exceeded the adjustments in our models. LVAD complications are managed locally and decisions to proceed with HT require clinical judgment under the duress of limited access to donor organs and a critical need to make timely decisions. There are differences between the Era 1 and Era 2 listing criteria that cannot be fully accounted for in the models. For example, LVAD patients in Era1 were given elective time at the top tier status (1A). Our adjustment for SVI is limited to the use of 5-digit zip codes. More precision in social vulnerability score assignment would have been possible with the use of 9-digit zip codes, but these data were not available. Race is not defined by the social vulnerability index alone. The SVI approximates the social construct but is incomplete. The PRA variable was not consistently available however extensive modelling including imputation did not impact our results. The higher prevalence of blood group O among Black waitlist candidates can lead to delay in transplantation, however, this was accounted for in all adjusted models and the findings persisted in the matched cohort analysis which included matching on blood group.

Conclusions

These data raise concerns that an important race-based healthcare disparity is apparent in HT; a disparity now worsened after the incorporation of a new OPTN organ allocation scheme. Further study is warranted to confirm our findings and elucidate other variables associated with these described disparities. Consistent inclusion of neighbourhood level estimates of the Social Determinants of Health and the SVI is recommended to support further study of these associations not just for heart transplantation but in other conditions where a question of race-based differences is plausible. The new allocation system for HT is associated with shorter wait times but has also led to high use of temporary mechanical support and fewer transplants for patients on durable left ventricular assist devices. We add the concern of worsening race-based disparities under the new allocation system, which heightens the urgency for a deeper evaluation and potential modification. Centres should evaluate their own data to determine the absence or presence of transplant equity. An in-depth analysis of acceptance patterns of center by race will be an important next step in understanding the mechanism of this disparity. As the community moves toward an allocation score for heart transplantation, our analysis suggests protections will be needed for Black waitlist candidates. In closure, a transplanted heart is a life saved; there is no room for inequity in the restoration of life.

Contributors

Rebecca Cogswell: conception and design, analysis and interpretation of data, drafting the manuscript, revisions, leader of the project overall. Dr. Cogswell had compete access to the data and can verify the data as reported in the manuscript.

Maria Masotti: statistical analysis, conception and design, analysis and interpretation of data, drafting pf the manuscript. figure and table creation. Ms. Masotti had compete access to the data and can verify the data as reported in the manuscript.

Alanna Morris: analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript on subsequent drafts.

Allyson Hart: analysis and interpretation of the data. As a content expert on disparities in transplantation provided critical context and direction for analyses. Drafted and participated in editing and revisions of the manuscript.

Tom Murray: senior statistician for this work. Helped with conception and design, analysis and interpretation of data. Participated in calls around statistical methodology and checked all work and statistical code for this manuscript. Participated in editing and revisions of the manuscript.

Clyde Yancy: analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript. A project leader with Dr. Cogswell.

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Tom Murray: none.

Clyde Yancy: Abbott Lab: spousal employment.

Data sharing statement

The majority of data utilized for this analysis are publically available and can be requested at https://optn.transplant.hrsa.gov/data/view-data-reports/request-data/. The zip codes utilized in this analysis required IRB approval and an application to UNOS.

Declaration of interests

Rebecca Cogswell: Abbott Lab: Speaker, HeartMate 3 Advisory Board, Medtronic: Heart Failure Advisory Board, spousal employment.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100290.

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