Current Cardiovascular Risk Reports
https://doi.org/10.1007/s12170-019-0629-6

RACE AND ETHNICITY DISPARITIES (M. ALBERT, SECTION EDITOR)

Race/Ethnic Disparities in Cardiac Transplantation

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Abstract

Purpose of Review Heart transplant (HT) is the therapy of choice for patients with end-stage heart failure (HF), leading to substantial improvements in quality of life, functional status, and longevity compared to optimal medical therapy for end-stage HF. However, race/ethnic disparities in post-HT survival persist and remain a major concern. The purpose of this review is to describe differences in post-transplant outcomes based on race/ethnicity and to highlight evolving knowledge of the reasons for these persistent disparate outcomes.

Recent Findings Black HT recipients have the highest risk for allograft failure and the worst survival post-HT compared to other race/ethnic groups. Although differences in socioeconomic status, access to medical care, and medical compliance have been cited in the past as reasons for these disparate outcomes, recent research highlights the importance of heightened immune reactivity in black HT recipients as a major cause of allograft loss and death. Novel techniques such as gene expression profiling, detection of donor specific antibodies, and detection of genotypes associated with increased metabolism of immunosuppressive medications highlight the role of immune and inflammatory dysregulation and reduced immunosuppressive drug efficacy as significant contributors to post-HT outcomes.

Summary Race/ethnic disparities in post-HT outcomes are due to a complex interplay of immunologic, clinical, and socioeconomic factors. However, multiple reports that demonstrate that black race confers a survival disadvantage post-HT that is independent of differences in access to care or socioeconomic status highlight the need for more research to understand racial differences in biological and genetic responses to immunosuppressive therapy.

Keywords Race/ethnic disparities · Heart transplantation · Transplant outcomes · Transplant disparities

Introduction

Heart transplant (HT) is the therapy of choice for patients with end-stage heart failure (HF), leading to substantial improvements in quality of life, functional status, and longevity compared to optimal medical therapy for end-stage HF [1]. Advances in surgical technique, organ preservation, mechanical circulatory support, and maintenance immunosuppression over the last 50 years have dramatically improved outcomes, with 1-year post-transplant survival of > 90% and a median conditional survival now exceeding 13 years [2]. Although post-transplant survival has improved for all race/ethnic groups [3], race/ethnic disparities persist and remain a major concern. Many reasons have been offered to explain race/ethnic disparities in post-transplant outcomes, including socioeconomic status (SES) and access to medical care, compliance with medical regimens, differences in prevalence of comorbidities including hypertension and diabetes, and differences in immunologic phenomena. The purpose of this review is to describe differences in post-transplant outcomes based on race/ethnicity and to highlight evolving knowledge of the reasons for these persistent disparate outcomes. The vast majority of published data describe differences in outcomes between black and white patients; however, data on Hispanics is presented where available. Data about Asian patients is lacking and represents an area where research is sorely needed.

This article is part of the Topical Collection on *Race and Ethnicity Disparities*

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Racial Differences in the Etiology of HF

The prevalence of HF in the USA is expected to rise from 2.42% in 2012 to almost 3% by 2030, primarily due to the aging of the population. However, black patients have the highest risk for HF compared to other race/ethnic groups, with 3.6% of black patients affected by 2030 [4]. Black patients are more likely to develop HF at younger age, have a greater prevalence of nonischemic HF [5, 6], and experience higher rates of hospitalization and death [7–10]. The higher burden of traditional cardiovascular (CV) risk factors, particularly hypertension, among black patients explains a large degree of the higher burden of HF in this population [11••]. However, the morbidity and mortality from HF in black patients exceed what would be expected solely based on differences in traditional CV risk factor burden [10]. Although Hispanics also have a high burden of traditional CV risk factors, particularly obesity, physical inactivity, and diabetes, their overall risk for CVD (including HF) is lower than expected, a phenomenon often referred to as the "Hispanic paradox" [4, 12••]. Although Hispanics are estimated to have the lowest prevalence of HF [4], their risk of HF hospitalization remains higher than their white counterparts [13••].

The most common underlying etiology for end-stage HF is dilated cardiomyopathy (DCM) in the majority of black patients, compared to ischemic cardiomyopathy in white patients [14, 15••]. Black patients have a 3-fold increased risk for developing DCM even after adjusting for confounders such as traditional CV risk factors (i.e. hypertension, diabetes) and socioeconomic status [9, 16••]. Additionally, once they develop DCM, black patients are twice as likely to die as their white counterparts with DCM [16••, 17]. Recent data suggest that genetic polymorphisms that are unique to, and or more common in black patients, contribute strongly to the increased risk of DCM in this group. A genome-wide association study (GWAS) performed in a cohort of black patients estimated the heritability of DCM to be 33% (compared to 18% for HF in data from the Framingham cohort) [18], and identified a novel intronic locus in the *CACNB4* gene which encodes a calcium channel subunit that is important for cardiac muscle contraction [19••]. In addition, Myers et al. utilized data from 3 cohorts of black subjects with DCM and determined that the carriers of certain *BAG3* variants had a nearly 2-fold increased risk of cardiac events compared with noncarriers [20••]. Importantly, the four variants seen associated with increased risk in this cohort were not seen in a reference population of European ancestry. Similarly, black women have an increased incidence of peripartum cardiomyopathy (PPCM) and a poorer prognosis once diagnosed compared to whites [21]. Ware and colleagues recently studied the burden of genetic variants in patients with DCM and PPCM, showing a similar prevalence of truncating variants in eight unique genes, suggesting that a shared mechanism may be responsible for both conditions [22]. *TTN* truncating variants were the most common variants and were more common in women of African descent compared to women of European descent (13% vs. 8%). The higher prevalence of these and other unique genetic variants may explain the higher incidence of DCM in black patients, and the higher likelihood of progression to end-stage HF once DCM is diagnosed.

Racial Differences in Wait List Characteristics

The number of persons with HF listed for HT continues to rise each year. Moreover, the proportion of black HT candidates has increased to 25.5% over the past decade, with 23.8% of organs being transplanted into black patients in 2017 [23]. The proportion of Hispanic HT candidates has also risen somewhat over the past decade, from 7.3% in 2007 to 8.9% in 2017 [23]. Although prior reports suggest that Hispanics with end-stage HF do not present with as severe a level of illness [12••, 24••], underinsurance is more common in Hispanics than other race/ethnic groups [25], and may be a barrier to listing for HT.

Multiple phenomena likely contribute to the increasing proportion of black patients on the HT waiting list. As mentioned previously, DCM is the most common cause of HF in black patients and has an earlier age of onset in this group. Recent changes in public policy have also improved access to advanced HF therapies for race/ethnic minorities [14, 24••]. The Patient Protection and Affordable Care Act (ACA) sought to increase the number of Americans with health insurance by expanding adult eligibility for Medicaid, providing tax credits for the purchase of private insurance, and establishing annual limits on out-of-pocket costs and other innovative reforms [26]. After the main ACA provisions went into effect in 2014, the percentage of adults who were uninsured decreased by 7.1% for Hispanics, 5.1% for black patients, and 3% for white patients, with greater coverage gains in states that expanded Medicaid [25]. Breathett et al. analyzed more than 10,000 patients in the Scientific Registry of Transplant Recipients (SRTR) database to show that rates of listing for HT increased by 30% for black patients in states that were "early adopters" of Medicaid expansion under the ACA, while rates of listing for HT for black patients remained constant in non-adopter states [24••]. The same study found that Hispanics experienced the opposite, with no significant changes in "early adopter" states, but a significant increase in non-adopter states [24••]. Breathett et al. hypothesized that this could be due to the ineligibility for ACA insurance coverage for undocumented immigrants, since California, Texas, and Florida, states with the highest number of undocumented individuals, accounted for the most variability of results [24••]. Similarly, a large Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) study showed an increase in left ventricular assist device

(LVAD) implantation in black patients from 2012 to 2015, with 54.9% of these devices being implanted with a bridge-to-transplant (BTT) strategy [14]. The rate of LVAD utilization in Hispanics remained constant during the same time period, with 60.3% of these being implanted as BTT. black and Hispanic patients were less likely to receive LVAD implant at more hemodynamically stable INTERMACS profiles 4–7, suggesting that race/ethnic minorities are sicker at the time of LVAD implantation [14]. Fortunately, mortality on the HT waitlist has declined substantially since the mid-2000s, with the most notable declines for black and Hispanic HT candidates, such that their waitlist mortality is now comparable to other racial/ethnic groups [23].

Racial Differences in Outcomes After Heart Transplant

While post-transplant survival has progressively improved in white patients over the past two decades, this trend has not been seen in black HT recipients [3]. Hispanic patients experience post-transplant outcomes similar to that for their white counterparts [27, 28]. Several studies have demonstrated that black race is a risk factor for allograft failure [15••] and post-transplant mortality [23, 27–31], but protective for the risk of post-transplant malignancy and infection [27]. An analysis of over 20,000 HT recipients over 10 years demonstrated that blacks had a 46% increase in adjusted cumulative mortality risk after HT compared to white recipients [28]. In fact, black race is considered to be an independent risk factor for mortality post-HT, conferring 3 out of a total possible 50 points in the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) risk score [29, 32]. The reasons for the disparity in long-term survival for black HT recipients are multifactorial and likely represent a constellation of clinical, immunological, psychosocial, and socioeconomic factors [15••].

Clinical and Sociodemographic Factors Several clinical characteristics known to be associated with poor post-HT survival are more prevalent in race/ethnic minorities compared to white HT recipients [3, 29, 30, 33–36]: Black HT recipients are younger, more likely to be women [36], obese [36], have pre- and post-transplant hypertension [28], and worse renal function [3, 15••, 27, 30, 35, 36] than their white and Hispanic counterparts. Hispanic HT recipients are more likely to have diabetes than white or black patients [1]. Black patients are more likely to be transplanted from the ICU as a high priority UNOS status, from higher risk donors, and in centers with lower annual volumes and higher-than-expected mortality than white and Hispanic patients, even after adjusting for recipient insurance type and education level [30]. Black and Hispanic recipients are more likely to have had multiple pregnancies, but less likely to have had prior blood transfusions [36]. Black and Hispanics patients are more likely to have public insurance [36], which has consistently been shown to be associated with inferior post-HT outcomes [37]. However, adjusting for these clinical and sociodemographic confounders in several large databases attenuates but does not eliminate racial disparities in post-HT survival [15••, 30, 35, 36].

Genomic Factors The era of precision medicine has enhanced our ability to define genomic variants that influence response to maintenance immunosuppression post-HT. In a study of pediatric HT recipients, Girnita et al. showed that black patients more frequently possessed genotypes associated with dysregulated inflammation and reduced immunosuppressive drug efficacy [38, 39]. They found that black and Hispanics patients were more likely to carry single nucleotide polymorphisms (SNP) conferring higher expression of proinflammatory cytokines such as interleukin-6 (IL-6) [40, 41] and a lower expression of regulatory cytokines such as IL-10 [40–42], all of which have been associated with poor graft survival post-HT [38, 39, 43]. Black patients were more likely to carry a high VEGF haplotype, implicated in the pathogenesis of cardiac allograft vasculopathy [38, 44]. Additionally, a SNP associated with the ABCB1 gene, which encodes for the P-glycoprotein membrane pump responsible for immunosuppressive drug efflux into the intestinal lumen [45], had a 78.6% prevalence in black patients versus 50% in Hispanics and 33.7% in white patients [38], and is predictive of prolonged corticosteroid requirement post-HT in pediatric patients [46]. Green et al. examined 33 allelic variants for 20 genes involved in the immune response or the transport and metabolism of immunosuppressive medications in 530 pediatric HT recipients at 6 centers [47]. Variant distribution in genes encoding cytokines, growth factors, effector molecules, and genes involved in drug disposition differed between black and non-black patients in 22 of the 33 variants examined. The investigators determined that demographic, clinical, and genetic factors explained approximately 8% of the observed excess risk for death and 13% of the observed excess risk for graft loss in black HT recipients.

Other analyses have identified important race/ethnic differences in metabolism of the calcineurin inhibitor tacrolimus. Tacrolimus is the modern-day calcineurin inhibitor of choice, largely replacing the use of cyclosporine post-HT [2]. Moreover, use of tacrolimus has increased in all patients over time regardless of race/ethnicity [48]. However, black and Hispanic patients are more likely to be “rapid metabolizers” of tacrolimus [49], such that significantly higher tacrolimus doses are required in black and Hispanic patients than white patients to achieve similar trough levels [50]. Tacrolimus is dependent on the CYP3A5 enzyme for metabolism, and expression of the enzyme is controlled by several alleles [51,

52]. At least one fully functional rs776746-A allele (commonly referred to as CYP3A5*1) is present in about 90% of black patients, leading to lower bioavailability, higher clearance, and lower blood concentrations of tacrolimus as compared to white patients [49, 53••]. Conversely, the non-functional CYP3A5*3 variant, associated with lower tacrolimus clearance, has a minor allele frequency of 18–35% in black patients and 88–95% in white patients [53••, 54, 55]. Khangavi et al. developed a genotype-guided dosing model for use of tacrolimus in black patients, incorporating race-specific genotypes as well as clinical factors including age, time posttransplant, and steroid and antiviral use [53••]. More widespread use of precision algorithms such as this one in heart, kidney, and other solid organ transplants could be used to predict the high pharmacokinetic variability in immunosuppression in patients with high risk genotypes, reducing the need for frequent dose changes and longer periods of time out of the therapeutic range that may contribute to worse outcomes in black patients post-transplant.

Novel tests of immune function have demonstrated that immunologic responses of HT recipients of different race/ethnic groups may play an important role in response to maintenance immunosuppression. Gene expression profiling (GEP) of peripheral blood mononuclear cells is a novel method that evaluates expression of 11 informative genes with high discrimination between the presence and absence of moderate/severe cellular rejection [56]. An analysis of data from the multi-center Invasive Monitoring Attenuation through Gene Expression (IMAGE) study found that black patients treated with cyclosporine had higher gene expression profiling (GEP) scores than white and non-white patients treated with cyclosporine [57••]. Among patients treated with tacrolimus, other non-white patients had significantly higher GEP scores than blacks or white patients. In white patients, increasing levels of tacrolimus were associated with downregulation of MARCH8 and WDR40A, genes known to mediate hematopoiesis, and upregulation of ITGAM, a gene expressed by monocytes that mediates responsiveness to corticosteroids. However, increasing levels of tacrolimus were associated with decreased expression of FLT3 in black patients, a gene that promotes B cell and NK-cell proliferation. Importantly, FLT3 and MARCH8 expressions were significant predictors of clinical events in black subjects, showing that unique racial differences in immune responsiveness to immunosuppression are associated with clinical outcomes.

Immunologic Factors That Contribute to Differences in Rates of Cellular Rejection Acute cellular rejection is an important cause of morbidity and mortality after HT, as episodes of rejection are associated with higher risk of allograft dysfunction and loss. Multiple prior studies have documented higher rates of cellular rejection post-HT in race/ethnic minorities [15••, 47, 58]. These observations may be due to a more robust immune response in black HT recipients. A small study by Hutchings and colleagues found that black patients have increased expression of B7 costimulatory molecules on peripheral blood antigen presenting cells, translating into a more robust T cell response to mitogens [59]. Blockade of B7 costimulation has previously been shown to prevent experimental allograft rejection [60]. Greene et al. noted black race to be a significant predictor of multiple types of rejection, including rejection with hemodynamic compromise requiring inotropes, late rejection (beyond the first year post-HT), and late rejection with hemodynamic compromise [47]. There were no significant differences in rates of rejection between Hispanic and non-Hispanic white populations. The use of induction therapy has been shown to reduce the incidence of acute rejection post-HT, particularly in young black HT recipients [61–63]. Higgins et al. demonstrated that induction with anti-thymocyte globulin (ATG) conferred a survival benefit in high risk black HT recipients who were less than 25 years old and with > 4 HLA mismatches [63]. Similarly, Coleman and colleagues found that younger black HT recipients (21–39 years) had improved survival after induction with ATG [62]. In black renal transplant recipients, quadruple induction immunosuppression with both monoclonal and polyclonal antibodies eliminated racial differences in allograft survival [64]. However, the use of induction therapy varies highly between HT centers. In the IMAGE study, despite the inclusion of low-risk, clinically stable patients with normal allograft function, the overall rates of rejection with hemodynamic compromise, allograft dysfunction, and mortality were noted to be higher in black and other non-white groups compared to white HT recipients [57••]. These findings are quite remarkable, since all patients were treated at major academic medical centers, with close monitoring of compliance and maintenance immunosuppression levels by study coordinators. Indeed, immunosuppressive drug levels were similar between racial groups throughout the study. Notably, black patients treated with cyclosporine had higher GEP scores and higher rates of rejection, supporting prior data showing that use of tacrolimus is the superior calcineurin inhibitor [50].

Immunologic Factors That Contribute to Differences in Rates of Humoral Rejection An analysis of more than 19,000 patients in the Organ Procurement and Transplantation Network database found that black patients listed for HT have higher peak panel reactive antibodies (PRA) and are more likely to be sensitized than all other racial/ethnic groups [36]. Genetic diversity of human leukocyte antigens (HLA) is the highest among black patients [65, 66]. Not surprisingly, several prior studies have confirmed that black patients have higher rates of donor-recipient HLA mismatch than their white counterparts [15••, 30, 36, 67]. There are conflicting data on HLA matching as an effector of allograft survival, with some studies suggesting no effect on incidence of

rejection [68, 69], and others finding that high degrees of mismatch are related to worse outcomes [36, 67]. The development of de novo donor-specific antibodies (dnDSA) leading to antibody-mediated, or humoral rejection, is a well-recognized risk factor for mortality after HT [70]. Cole et al. found that black patients had a nearly 4-fold higher risk of dnDSA compared to non-black patients following HT, leading to a nearly 5-fold higher risk of treated antibody-mediated rejection [71••]. Although there was a higher risk of death and allograft dysfunction in black patients, the effect of black race was no longer significant in a multivariable model that included dnDSA. Higher levels of allosensitization in black patients pre-HT may contribute to a higher risk of dnDSA formation post-HT. Importantly, the median time to development of dnDSA is 1.8 (0.8 to 2.8) years, which is relevant considering that current guidelines recommend only annual testing for DSA after the first year post-HT [72]. Though not definitive, these findings suggest the higher propensity for black patients to generate a humoral response to foreign HLA antigens, leading to the development of dnDSA, may play an important role in the worse clinical outcomes in this population.

Social Determinants of Health Prior studies have shown socioeconomic factors such as lower household income, Medicare and Medicaid insurance, and lower education are associated with allograft failure and lower post-transplant survival [37, 73–75]. These socioeconomic risk factors are more prevalent among black and Hispanic HT recipients, making it quite difficult to disentangle the independent effects of socioeconomic status (SES) from race/ethnicity in large registry studies. Moreover, many large transplant registries do not collect detailed SES data including individual income, individual copays for post-HT medications, social support, health literacy, psychosocial factors, or other factors that may affect post-HT outcomes. Smaller studies that have examined race in conjunction with detailed assessments of SES have confirmed the independent risk associated with these variables. Singh et al. examined the association of a composite socioeconomic risk score (constructed from 6 proxies of wealth and income, education and occupation) with clinical outcomes in 520 HT recipients [73]. Adjustment for the SES score only partially mediated the association of race/ethnicity with the risk for rejection episodes and allograft loss, demonstrating that non-white race/ethnicity and low SES are independently associated with the risk for adverse outcomes. Wayda et al. examined individual level SES indicators, including insurance and education, and neighborhood SES in 33,893 adult HT recipients from the UNOS registry [76]. Black race and low SES indicators were associated with the risk of death or re-transplant in fully adjusted models. Interestingly, disparities associated with low SES appeared to be diminishing over time, while black–white disparities in outcomes remained unchanged. While Hispanic HT recipients tend to have SES indicators that are very similar to black HT recipients [12••], their risk of post-transplant mortality is typically found to be similar to white HT recipients [27]. Interestingly, multiple analyses have documented that low SES may have a greater impact on post-HT outcomes in white compared to black HT recipients [15••, 37, 77]. Finally, although SES drives outcomes after HT and other conditions, universal access to medical care has not been found to eliminate racial disparities in renal transplant outcomes [78, 79].

Psychosocial Factors There is an increasing recognition that psychosocial factors play an important role in post-transplant outcomes [80, 81]. Higher social and economic satisfactions measured by quality of life indices are associated with improved survival after HT [74]. A small study of pre-HT psychosocial risk, as assessed by the validated Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) tool that is predictive of non-adherence to clinic visits, did not demonstrate significant racial differences in SIPAT scores [82]. Non-adherence with immunosuppressant medications is more common among non-white transplant recipients and associated with worse post-transplant outcomes [83]. However, it is unclear if the higher prevalence of genotypes that lead to increased clearance of tacrolimus in black and Hispanic patients causes lower troughs that are falsely interpreted as noncompliance with medical therapy. Familism, defined as viewing family members as primary financial and emotional support, is an important part of Hispanic culture and may play a role in their outcomes which are "better-than-expected" based on clinical and SES risk factors [12••].

Conclusions

HT represents a medical marvel that restores longevity and functional status in patients with end-stage HF, requiring enormous investment on the part of the donors and recipients themselves, donor and recipient families, hospital systems, and society as a whole. As such, the commitment of transplant programs to improving outcomes for all HT recipients should remain steadfast and unwavering. Despite this commitment, race/ethnic disparities in post-HT outcomes persist. In order to eliminate these disparities, any approaches to intervention must recognize the complexity of the contributing immunologic, clinical, and socioeconomic factors that influence the gap in post-HT outcomes. Multiple reports suggest black race confers a survival disadvantage post-HT that is independent of differences in access to care or SES. Thus, race-based differences in outcomes may be in part due to the genetic predisposition that renders a "pro-inflammatory, low regulatory immunological environment" and decreased efficacy of

immunosuppressive drugs due to reduced drug exposure that is more commonly found in black HT recipients [47]. More research is required that will comprehensively characterize racial differences in biological and genetic responses to immunosuppressive therapy against the backdrop of psychosocial and sociodemographic factors, in addition to ongoing public policy efforts that will increase access to advanced HF therapies for all persons with HF regardless of SES or race/ethnicity. Finally, more research is needed about Asian HT patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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