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## Ethnic advantages in kidney transplant outcomes: the Hispanic Paradox at work?

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## Introduction

Kidney graft loss in the first 10 years following transplantation is a significant problem despite tremendous scientific advances in treating acute and chronic rejection. While short-term acute rejection has come under control with 1-year survival rates surpassing 91%, long-term graft survival remains inadequate [1]. The 3-year, 5-year and 10-year deceased donor unadjusted graft survival rates are 78.6%, 67.1% and 40.8%, respectively, among all kidney recipients in the United States (USA) [2].

The loss of transplanted grafts is a major public health problem. Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD) since it provides a longer length of life, better quality of life [3,4] and is more cost-effective than dialysis [5,6]. When kidney grafts fail, patients return to dialysis, creating an even greater demand for scarce kidney (re-)transplants and further burdening society with greater costs [7–9]. Mortality rates on dialysis following a failed kidney transplant are significantly higher than those prior to transplant [10]. The shortage of donated kidneys provides a moral and societal imperative to optimize their use. These concerns underscore the need to maximize long-term graft survival [11]. Understanding factors that contribute to long-term graft survival is critical to public health and its expectation that scarce resources be utilized efficiently. This paper examines the possible underlying demographic and socioeconomic factors associated with better graft survival among Hispanic kidney transplant recipients.

The presence of sociodemographic and socioeconomic disparities in graft survival rates compounds the problem of inadequate long-term graft survival. Health disparities can be defined as 'potentially avoidable differences in health (or in health risks that policy can influence) between groups of people who are more or less advantaged socially; these differences systematically place socially disadvantaged groups at further disadvantage on health' [12]. Most research on disparities in transplant outcomes has focused on African Americans who experience higher rates of chronic allograft nephropathy (CAN) compared to whites and other minorities. The mean time to CAN is shorter in African American recipients than in white recipients (18 versus 37 months), although the incidence of CAN is comparable [13]. African Americans also experience lower graft survival [14,15]. Beyond 3 years, African American recipients experience a 5-15% lower graft survival rate than that in whites [16,17]. The conditional half-lives for deceased donor kidneys in adult African American and white recipients are 8 years and 14 years, respectively [18]. Compared to whites, minorities receive poorer quality

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	(Tx 2003–2004)		(Tx 2001–2004)		(Tx 1999–2004)	
	1-year DD	1-year LD	3-years DD	3-years LD	5-years DD	5-years LD
Hispanic/Latino	92.7%	96.0%	84.6%	90.8%	74.2%	83.8%
Asian	94.2%	98.1%	85.9%	93.3%	77.5%	86.6%
White	91.3%	95.1%	82.0%	88.8%	72.1%	81.1%
African American	88.8%	94.3%	75.1%	83.3%	61.0%	71.5%
Multi-race/other	95.6%	92.6%	84.2%	88.3%	74.3%	84.5%

deceased donor kidneys [19] suggesting an even greater likelihood of shorter graft survival. Even after controlling for non-immunologic and immunologic factors, African Americans are 1.7 times as likely as whites to suffer graft failure >9 years, which suggests that socioeconomic or behavioural factors contribute to racial/ethnic disparities in outcomes [15].

Unlike other ethnic groups, there are heterogeneous reports in the literature regarding outcomes after kidney transplantation in Hispanics. Early studies show that Hispanic patients experience significantly higher rates of kidney graft survival than those in non-Hispanic whites, African Americans and others 1 year, 3 years and 5 years post-transplant [2,20,21]. The rate of deceased donor graft failure in Hispanics is 75% of the rate observed in non-Hispanics between 1998 and 2003 [22]. See Table 1. Saunders and colleagues found similar results in that immunologic factors, i.e. donor-recipient human leukocyte antigen matching, donor ethnic origin, recipient age, splenectomy, transfusion status and patient serum panel reactivity, could not explain this finding [23]. They suggested that non-immunologic factors (i.e. social, economic factors) may contribute to Hispanic patients' superior graft survival rates [23]. Alternatively, a retrospective cohort study of adults receiving renal transplants in 1990 (n = 4471) based on the United Network for Organ Sharing (UNOS) database found that Hispanics have higher rates of graft failure compared to whites after controlling for poverty level [24]. However, findings by Press and colleagues must be interpreted with caution as their study was conducted in 1990, during which time the era of immunosuppression differed and had worse outcomes, and no differences in graft survival between Hispanics and whites emerged when controlling for socioeconomic status (SES) [24]. Other studies have shown similar renal graft survival and mortality between Hispanics and whites [25,26]. More recent studies have shown better patient and graft survival in Hispanics compared to non-Hispanics [27,28]. Caicedo and colleagues examined a national sample of adult and paediatric patients receiving renal transplants in 1994 who were followed for 13 years [n = 111 833, of whom 19 952 (17%) were Hispanic][28]. The 1-, 5- and 10-year patient and graft survival rates were evaluated controlling for potential covariates including age, payer, educational level and comorbid conditions. They found that compared to white recipients. Hispanic adult recipients had better graft survival (HR = 0.91, 95%CI: 0.88-0.94, P < 0.001) and patient survival (HR = 0.72, 95% CI: 0.76–0.86, P < 0.001) [28]. That the literature

shows some contradictory findings on this topic suggests that further analysis is needed to understand factors contributing to these trends.

Patient survival rates for Hispanic renal recipients have also been found to be equivalent to or better than those in non-Hispanic whites [15,23]. This trend has been identified in haemodialysis patients whereby Hispanics experience equivalent or better intermediate survival and health outcomes of dialytic care than those in non-Hispanics [29– 31], in part, due to being healthier at ESRD onset [32]. Even Hispanic adults with chronic kidney disease have a lower risk of death and cardiovascular events than that in non-Hispanics [33]. Such studies lend further support to Hispanic patients' observed advantage in transplantation.

Better graft survival rates among Hispanics are noteworthy because they persist despite numerous odds against them. Compared to non-Hispanic whites in the USA, Hispanics suffer from disproportionately high rates of ESRD [34] and risk factors for ESRD [35,36]. Specifically, Hispanics are twice as likely as non-Hispanic whites to develop kidney failure [35]. The prevalence of ESRD among Hispanics in 2005 was 47% higher than that found in non-Hispanics. The prevalence of ESRD for Hispanics increased 40% between 1996 and 2005 compared to an increase of 34% in the non-Hispanic population [20]. Additionally, the prevalence of type 2 diabetes, the main cause of ESRD in Hispanics [37], is two to five times higher in Hispanics than in non-Hispanic whites [14,35]. Hispanics also have higher rates of direct contributing factors to chronic kidney disease, including obesity, high blood pressure and low SES [37]. Socioeconomic factors, including low income, poor education, residence in a low-income area and poor access to health care, are strong predictors of the development and progression of chronic kidney disease among Hispanics [34]. Moreover, Hispanics are less likely to initiate dialysis early [38], be hospitalized from dialysis complications [39], have pre-emptive transplantation [40], or be placed on a transplant waiting list or receive a transplant [41,42].

The superior Hispanic transplant outcomes can be understood within a general pattern of 'Hispanic Paradox' [43– 55]. The 'Hispanic Paradox' is the phenomenon whereby Hispanics, as a group, have comparable or even lower allcause and infant mortality rates than those in non-Hispanic whites in the USA (as documented in national vital statistics), even though they rank low in socioeconomic indicators [43–48]. This phenomenon is construed as a paradox given the correlation between social characteristics (i.e. race/ethnicity, SES, education, income) and mortality and morbidity rates in the USA [48,49]. The Hispanic Paradox has emerged within the last 20 years and applies predominantly to older Hispanics, Mexican Americans, Hispanic immigrants including Central and South Americans and to Hispanics with lower levels of acculturation [50]. Limited research to date shows that the Hispanic Paradox may apply to a lesser extent to Puerto Ricans and other Hispanic subgroups [51,52]. Hispanics begin to benefit from the Hispanic Paradox in the middle and older ages (age 45+) [43,50], which coincide with the average age of the ESRD population (59 years) [20]. No studies have previously documented or empirically examined this remarkable phenomenon as a paradox within transplantation. Accordingly, little is known about factors contributing to Hispanics' graft and patient survival advantage.

The fact that the Hispanic Paradox is related to age may explain why Hispanic paediatric recipients do not fare better than non-Hispanic whites. Another possible consideration is that paediatric Hispanic recipients have a different aetiology of renal disease compared to adults. Paediatric recipients' aetiology is typically associated with diabetes mellitus, arterial hypertension, obesity and metabolic syndrome, which may have a greater impact on outcomes than non-immune or socioeconomic factors. Alternatively, as social and environmental factors are more likely to drive the Hispanic Paradox than immune or genetic factors, paediatric patients may simply be too young to experience the positive or negative effects of social factors. Moreover, paediatric patients exhibit poor adherence compared to adults, which is not unique to the Hispanic population, but cuts across all paediatric groups.

Multiple biological explanations have been proposed for observed, purported racial differences in transplant outcomes. Most of the biological reasons have been described in African Americans, and few references are published in Hispanics. Some investigators have suggested that African Americans have worse outcomes related to differences in genetic, immune, metabolic and pharmacokinetic factors. Worse outcomes in African Americans compared to whites have been attributed to having more comorbid conditions [56], higher immunological risk due to greater variation in human leukocyte antigen polymorphisms [57-60], poorer control of hypertension [56,61]; requiring higher doses of immunosuppressive drugs [62-64] and variability in the pharmacokinetics of immunosuppressive drugs [65,66]. In Hispanics, there are few reports: the 1-year graft survival in Hispanics was not affected by broad sensitization compared with African Americans [67], and they need less immunosuppression [68,69]. Thus, it is unclear whether biological mechanisms adequately explain variations in transplant outcomes for Hispanics. However, as Hispanics are a heterogeneous population, including those of African and European descent, genetic explanations are less likely to explain the Hispanic Paradox.

A number of interrelated clinical and sociocultural factors proposed herein may confer graft survival advantage to Hispanics. It may be the case that selection bias plays a role whereby Hispanics who reach transplantation represent a more selective group than other populations. Analysis of UNOS data reveals several factors that support this hypothesis. Compared to other minorities, Hispanic kidney transplant recipients are more likely to have characteristics associated with better graft survival: younger age at transplantation, receiving more living donors, receiving more standard criteria donor kidneys rather than expanded criteria donors, and undergoing more primary transplantation than re-transplantation [53].

Firstly, there is a higher proportion of Hispanics ages 18-34 (19.0%) compared to Whites (11.9%), Blacks (14.6%) and Asians (12.8%) in that age range in 2007 [54]. Conversely, there are lower proportions of Hispanics ages 50-64 and 65 years and older (33.7% & 10.7%, respectively) than Whites (41.0% & 16.5%), Blacks (37.9% & 11.3%) and Asians (38.7% & 15.7%), in those age ranges in 2007 [54]. Since Hispanics tend to be younger than other ethnic/racial groups when they receive a transplant, they may be less likely than other groups to have comorbidities (besides diabetes). That Hispanics experience reduced risk of post-kidney transplantation myocardial infarction than that in whites [55] supports this point. Having fewer comorbidities would suggest that Hispanics are relatively healthier than other groups when they reach ESRD and/or at the time of the transplant. This explanation has likewise been suggested to explain higher patient survival of African Americans on dialysis [20].

Secondly, Hispanics have a higher proportion of living donors than deceased donors (33.7% versus 66.3%) compared to Blacks (20.3% versus 79.7%) and Asians (29.5% versus 70.5%), but a lower proportion compared to Whites (45.0% versus 55.0%) in 2007 [54]. The decision to seek and accept a living donor kidney offer is shaped largely by cultural values [70,71]. Certainly, patients' decision making bears upon health outcomes, as recipients of living donor kidneys experience better graft survival than that in recipients of deceased donor kidneys [20].

Thirdly, Hispanic deceased donor kidney recipients have a higher proportion of standard criteria donors than expanded criteria donors (78.5% versus 13.5%) compared to Whites (73.2% versus 16.0%), Blacks (71.9% versus 16.1%) and Asians (69.6% versus 19.5%) in 2007 [54]. The decision to receive expanded criteria donor kidneys versus standard criteria donor kidneys is again a matter of patient choice that is likely informed by cultural values and notions of risk.

Fourthly, Hispanics have a higher proportion of primary transplants than repeat transplants (92.6% versus 7.4%) compared to Whites (87.0% versus 13.0%) and Blacks (91.2% versus 9.6%), but not compared to Asians (93.9% versus 6.1%) in 2007 [54]. It is unknown whether these four factors represent statistically significant differences between ethnic/racial groups. These factors therefore remain to be empirically investigated, and indicate possible mechanisms explaining the Hispanic advantage in graft survival.

There are some reports that suggest similar extra-renal transplant outcomes in Hispanics compared with non-Hispanic whites for liver [72,73] and pancreas [74], but not for heart, lung or small bowel transplants [73,75]. There is no clear explanation for these outcomes, but the Hispanic Paradox may contribute in part to these findings.

The causes of the Hispanic Paradox in other conditions are largely unknown [46,50]. Various hypotheses have been proposed to explain this phenomenon. The 'salmon bias hypothesis' refers to the pattern where the sickest or elderly people migrate to their place of origin to retire or die. In the 'healthy migrant hypothesis', the healthiest members of a population migrate, thereby biasing mortality rates for the entire Hispanic population [50,76]. Neither hypothesis fully explains the pattern of findings [50,76]. Risk factors within Hispanic ethnicity, i.e. lower rates of cigarette smoking and high fibre diets, may also account for the phenomenon, but their degree of influence remains to be determined.

The primary reasons for the paradox are likely to be social and cultural in origin and multifactorial [50,76]. Relevant social and cultural factors include positive identification with a cultural identity, immigrant status and acculturation in health behaviours. These factors have not been examined in Hispanic kidney transplant recipients. One possible hypothesis is that the Hispanic cultural value of 'familismo' is associated with better outcomes. Familismo refers to individuals' strong identification with and attachment to their nuclear and extended families, and entails perceived obligations to provide material and emotional support to family members [77]. Social support is associated with greater survival among haemodialysis patients and better health outcomes for other diseases [78]. Additionally, Hispanic cultural values and beliefs regarding chronic illness, as expressed through a framework of representations relating to illness identity, cause, timeline, consequences and cure/control [79], may play a role. Illness representations are related to health outcomes for chronic diseases [80,81]. Another hypothesis is that Hispanics with lower levels of acculturation may retain healthful dietary behaviours that do not result in weight gain. Acculturation can have adverse [82,83] and beneficial effects [82,84] on health behaviors and outcomes, through numerous pathways [50]. One pathway by which these factors may affect graft survival is through enhancing self-care management (dietary, exercise, symptom management). These explanations correspond with non-immunological, notably, behavioural factors contributing to long-term graft survival.

Further investigation is needed to understand why this pattern emerges. Yet there are several caveats that make understanding and investigation into the Hispanic Paradox in kidney transplantation difficult. These caveats largely pertain to the social and cultural categories used to measure disparities, such as 'race', 'ethnicity' and 'minority status'. Distinguishing these terms is necessary to clarify the caveats, and to accurately identify and aid groups facing health disparities, since graft outcomes are usually evaluated in terms of race.

*Race* is typically used as an indicator of biological differences among human groups. Biomedical research, including transplant research, generally treats 'race' as a biological marker when examining health disparities, rather than addressing the social aspects of racial or ethnic identity [85]. There has been and continues to be intermixing among ethnic minority populations in the USA. However, racial categories can overlap with ethnic-group categories. Thus, biological distinctions between racial and/or ethnic groups cannot be made. As a social construction, 'race' refers to social relations among ethnic and minority groups shaped by historical and current patterns of discrimination and exploitation [86]. Nonetheless, race remains a valuable variable because it tracks health disparities resulting from perceived discrimination [87].

*Ethnicity* refers to cultural or group identity [86]. An 'ethnic group' can be defined as 'a self-perceived inclusion of those who hold in common a set of traditions not shared by others with whom they are in contact'. Such traditions typically include 'folk' religious beliefs and practices, language, a sense of historical continuity, and common ancestry or place of origin' [88]. Ethnic groups maintain a common cultural identity, but there is heterogeneity within them [89,90]. For example, Hispanics, as an ethnic group, include Hispanics of Mexican, Puerto Rican, Cuban, Spanish, South and Central American and other Spanish-speaking countries [91]. *Minority status* refers to experiences of prejudice and discrimination among ethnic groups in relationships with mainstream groups [86].

Health disparities rooted in racial/ethnic relations include factors reflecting majority/minority relations, i.e. perceived discrimination, residential segregation, social class and poverty. In contrast, disparities stemming from ethnic/ cultural differences include beliefs, attitudes, and values about self-care management and medication adherence [86]. Both types of factors associated with disparities may be contributing to the Hispanic Paradox. It may be the case, for instance, that residential segregation for Hispanics, or that cultural beliefs and practices pertaining to self-care management, is protective of health [92].

The first caveat to researching the Hispanic Paradox is that it applies predominantly to Mexican Americans. Mexican Americans are the largest Hispanic subgroup in the USA. However, very little research on the Hispanic Paradox in general has been conducted on other Hispanic groups such as Cubans, Puerto Ricans and others. Therefore, it is unclear to what extent the Hispanic Paradox applies to all Hispanic groups. With regard to transplantation, further investigation should determine whether all Hispanic kidney recipients necessarily experience the same levels of advantage in graft and patient survival.

A common problem in the examination of ethnic factors associated with graft survival is that demographic details tracked by the UNOS and the United States Renal Disease System (USRDS) are limited. Neither organization tracks different ethnic subgroups, i.e. Mexican American, Puerto Rican, South American etc. In fact, USRDS recently eliminated the category of 'Hispanic Mexican' (likely to be more inclusive of all Hispanic subgroups) [20]. Instead, 'Hispanic' is the only ethnic group under surveillance. Additionally, UNOS and USRDS do not combine ethnic and racial groups, i.e. Hispanic Black and Hispanic white, in its analyses, as does the US Census. As a result, the available UNOS and USRDS surveillance categories limit the analysis of demographic characteristics associated with the Hispanic Paradox phenomenon. That is, it remains to be determined whether the Hispanic Paradox applies to all Hispanic kidney transplant recipients or to only Mexican Americans and/or other subgroups. Knowing which subgroups experience better transplant outcomes is important for identifying factors contributing to their advantage.

The paucity of information on Hispanics, who constituted 13.6% of the kidney transplant population from 1996 to 2006 [93], may be due to other issues beyond surveillance strategies offered by UNOS and USRDS. Information on the health status for Hispanic Americans in general is not as complete as the data for the white, non-Hispanic population or for other minority groups [37,94]. Similarly, most empirical research on factors contributing to health disparities has been conducted on African Americans and not on Hispanics [95,96]. Consequently, 40% of the populationbased objectives for the Healthy People 2010 initiative lack baseline Hispanic data, thereby inhibiting progress on measuring objectives for Hispanic communities [97].

Another concern with identifying factors associated with the Hispanic Paradox in the context of kidney transplantation is that Asians, classified as a 'racial group', have greater graft survival rates than those in Hispanics. But this does not mean that a paradox applies to them as well. It is not accurate to refer to Asians as an ethnic or cultural group (let alone a racial group) as the definitions of these terms noted above do not apply. The term 'Asian' subsumes a broad range of groups with vastly different cultures, languages and social structures, e.g. Japanese, Vietnamese, Indians [98]. Thus, finding any commonly shared cultural or behavioural basis for graft survival among Asians would be unlikely. Moreover, many Asian subgroups experience higher education and/or income levels than those in Hispanics [99]. By these tokens, while Asian populations experience better graft survival, their advantage cannot be explained within a paradox framework.

In sum, evidence suggests that the Hispanic Paradox applies to the case of better transplant outcomes among Hispanic kidney recipients. To date, this is the first documentation of this phenomenon in transplantation. Further research is needed to determine precisely which Hispanic subgroups experience the best transplant outcomes and to investigate why the Hispanic Paradox occurs. Identifying factors conferring advantage in Hispanic kidney recipients can help to reduce poor transplant outcomes among other groups. Future research should determine the protective effects of positive identification with Hispanic ethnicity on transplant-related health behaviours, specifically, selfcare management, that may contribute to graft survival, as recommended [50]. Thus, further investigation can help to explain disparities in graft function and patient survival.

Finding ways to reduce disparities in transplant graft survival will contribute to social justice. Fostering equity in health is necessary to promote well-being among the disadvantaged and enable the escape from social disadvantage [12]. By addressing disparities in transplantation, health professionals and policy makers can improve and foster equity in transplant access and outcomes [9].

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