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Geographic Variation in Organ Availability Is Responsible for Disparities in Liver Transplantation between Hispanics and Caucasians

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The aims of this study were to determine whether disparities in waiting list outcomes exist for Hispanics and African Americans during the post-MELD era, and to investigate interactions between disparities and geography. Scientific Registry of Transplant Recipients data were used to compare Hispanics and African Americans to Caucasians listed between 2003 and 2008. Endpoints included (i) receipt of a liver transplant and (ii) death or removal from the waiting list for being too sick or medically unsuitable. Adjustment for possible confounders was performed using multivariate Cox regression, with adjustment for geographic variation using a fixed-effects multilevel model. In multivariate analysis, African Americans have similar hazard of transplantation and death/removal as Caucasians during the post-MELD era. However, Hispanics are less likely to receive a transplant than Caucasians despite adjustment for potential confounders (HR 0.80, 95% CI 0.77–0.83), while having a similar hazard of death/removal. This effect disappeared after adjusting for unequal regional distribution of Hispanics, who represent 8% of patients in donation service areas (DSAs) having median waiting times of $\leq$155 days versus 19% in DSAs with median waiting times of $>$155 days. In conclusion, disparities in liver transplantation exist for Hispanics during the post-MELD era, caused by geographic variation in organ availability.

Key words: Clinical liver transplantation, racial and ethnic disparities, regional sharing, waiting time

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Introduction

Since the supply of organs available for liver transplantation is limited, equitable allocation of these organs represents a major concern for the transplant community and society as a whole. Unfortunately, significant racial and ethnic disparities in access to liver transplantation have been well documented at every stage of the liver transplant process: referral for medical evaluation for transplant (1), placement on the transplant list (2) and actual receipt of a transplant once listed (3–5). For example, one study which analyzed data from 1994 to 1998 found that African Americans were 33% less likely to receive a transplant than Caucasians once placed on the waiting list (2). These disparities may have been partially caused by the organ allocation policies during that period, which emphasized time spent on the waiting list and subjective measures of disease severity such as degree of encephalopathy and ascites, or need for inpatient care (6).

Because of these concerns, the Institute of Medicine released a report in 2000 calling for organs to be allocated on the basis of objective measures of disease severity (7). This led to implementation of the model for end-stage liver disease (MELD) allocation policy in 2002 for deceased donor liver transplantation among adults in the United States. The MELD system is based entirely on laboratory data to accurately predict the probability of death within 3 months. While this system provides a completely objective means for prioritizing patients on the waiting list for liver transplantation (8), the distribution and availability of organs is still subject to geographic variation (9), which could contribute to racial and ethnic disparities. A recent study analyzing data from 2002 to 2006 found equal rates of transplantation between African Americans and Caucasians, and concluded that implementation of the MELD allocation system was associated with improvements in racial disparities (10). However, this study did not include Hispanics, who are the largest and fastest growing minority group in the United States (11) and have higher rates of hepatitis C than Caucasians or African Americans (12). Therefore, the aim of this study was to determine whether disparities in waiting list outcomes exist for Hispanics during the post-MELD era, and to investigate interactions between disparities and geographic location.

Methods

The data source was the Scientific Registry of Transplant Recipients (SRTR) Standard Analysis File as of February 2, 2009, of all adults ($\geq$18) placed on the waiting list for liver transplantation in the United States (US) between

January 2003 and January 2008. These dates were chosen to allow 5 years of analysis data during the post-MELD era. Race and ethnicity were determined by the individual transplant centers, with the largest categories being White (74%), Hispanic (13%) and African American (8%). Waiting list outcomes for African Americans and Hispanics were compared to Caucasians among 47 363 subjects; Missing data for some variables resulted in a final sample size of 47 070.

The primary endpoints of this study were (i) transplantation and (ii) removal from the waiting list because of death, being too sick or being medically unsuitable for a transplant. Patients removed from the waiting list for other reasons, such as being too well or transfer to another center, were censored at the time of removal. The two endpoints of interest, transplant and death/removal, represent competing risks which can confound survival analysis (13). However, it is unknown whether these competing risks might affect the analysis of disparities by race and ethnicity. In order to evaluate this, we constructed several competing risk models which varied the assumptions about baseline hazard functions and differences in hazard ratios by outcome type (14). In addition, cumulative incidence plots were generated using nonparametric competing risk methods (15). None of these models showed significant differences in disparities compared with simple Cox regression. Therefore, Cox regression was used for the remainder of the comparative analyses.

Clinical and demographic characteristics were compared between Caucasians versus African Americans, and Caucasians versus Hispanics. The chi-square test was used for categorical data and *t*-test was used for continuous data. Variables included age at listing, gender, blood type, etiology of liver disease (viral, alcohol, hepatocellular carcinoma or other) and available comorbidities which have been shown to affect posttransplant survival (16). Severity of liver disease was determined by the laboratory MELD score, which was treated as a time-varying covariate to reflect changing MELD scores while on the waiting list. Multivariate Cox regression was then used to adjust for these variables in the analysis of differences in waiting list outcomes between African Americans and Hispanics versus Caucasians.

We hypothesized that geographic variability may contribute to disparities, since African Americans and Hispanics may be more likely to live in donation service areas (DSAs) with more severe organ shortage. In order to test this hypothesis, we considered median waiting time in each DSA as a surrogate measure of organ shortage. DSAs were ranked by their median waiting time and divided at the midpoint into two categories labeled 'Median wait-time >155 days' and 'Median wait-time ≤155 days. The proportion of patients identified as African American and Hispanic was calculated for each DSA category, and the chi-square test was used to determine statistically significant differences relative to Caucasians. Finally, the multivariate Cox regression on waiting list outcomes was repeated, adjusting for geographic variability in organ shortage using a multilevel model. The Hausman specification test for appropriateness of a random-effects estimator was statistically significant, so results are presented using a fixed-effects model (stratified by DSA) with robust standard errors (17).

Results

During the post-MELD era (January 2003–January 2008), there were 50 047 adults listed for liver transplantation, of whom 4195 (8%) were African American, 6854 (13%) were Hispanic and 36 314 (73%) were Caucasian.

The unadjusted hazard ratios (HR) of transplantation and death/removal for African Americans and Hispanics compared to Caucasians are shown in Table 1. African Americans were more likely than Caucasians to receive a transplant and more likely to die/be removed (HR 1.32, $p < 0.001$ and 1.30, $p < 0.001$ respectively), while Hispanics were less likely than Caucasians to receive a transplant but equally likely to die/be removed (HR 0.82, $p < 0.001$ and 1.03, $p = 0.32$ respectively). Cumulative incidence plots for the two endpoints are shown in Figure 1.

Table 1: Unadjusted analysis of waiting list outcomes for African Americans and Hispanics, compared to Caucasians during the post-MELD era

	Post-MELD n = 47 070	
	HR	95% CI
African American		
Transplant	1.32	1.26–1.37
Death/removal	1.30	1.21–1.40
Hispanic	0.82	0.79–0.86
Transplant		
Death/removal	1.03	0.97–1.09

HR = hazard ratio; CI = confidence interval; MELD = model for end-stage liver disease.

Clinical and demographic differences between the racial and ethnic groups are shown in Table 2. African Americans had more severe liver disease than Caucasians, with median listing MELD scores of 18 versus 15, respectively. African Americans also tended to be younger, were less commonly male and had differing distributions of blood type and etiology of liver disease compared to Caucasians. When adjusting for these differences in multivariate analysis, the hazard of transplantation and death/removal for African Americans was no longer significantly different from that of Caucasians, as shown in Table 3. Hispanics during the post-MELD era were similar in age and severity of liver disease compared to Caucasians, as shown in Table 2. However, Hispanics were less commonly male, were more likely to have comorbidities and had differing distributions of blood type and etiology of liver disease compared to Caucasians. Despite adjustment for all of these variables, Hispanics still appear less likely to receive a transplant (HR 0.80, $p < 0.001$) during the post-MELD era, while their hazard of death/removal was no longer statistically different from that of Caucasians as shown in Table 3.

Comparison of geographic differences between the groups revealed that Hispanics make up a much larger proportion of the waiting list in DSAs with median wait-time >155 days compared to those with median wait-time ≤155 days, as shown in Figure 2. Results from the multilevel Cox regression indicate that there was significant correlation in waitlist outcomes according to DSA (likelihood ratio = 5110 for transplantation and 299 for removal, $p < 0.001$ for both). This indicates that the DSA a patient was listed in contributed significantly to the probability of these outcomes, despite adjustment for multiple potential confounders.

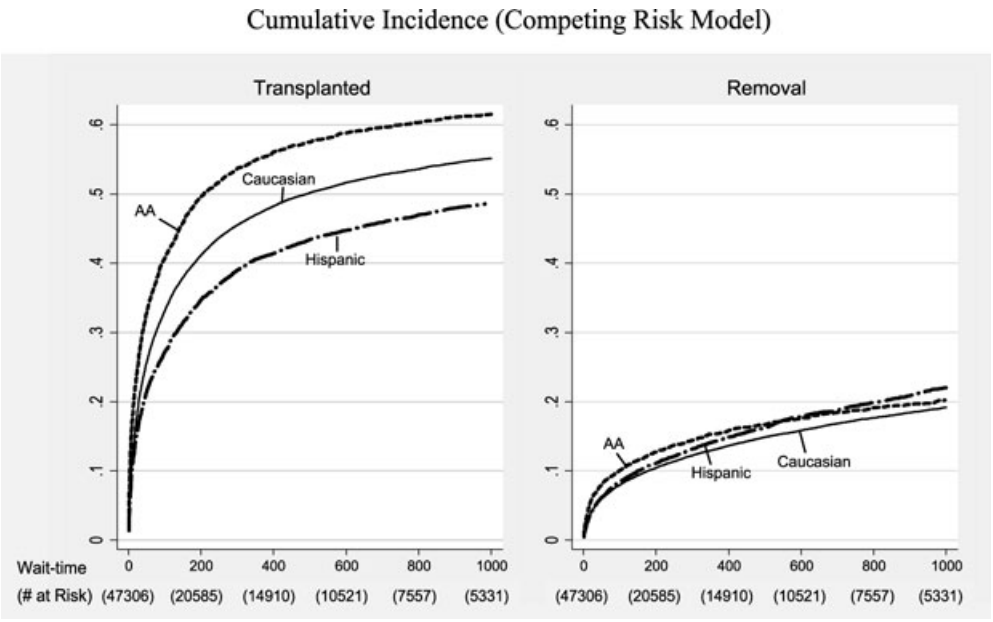

Figure 1: Cumulative incidence of primary endpoints: (A) transplantation, and (B) death or removal for being too ill or medically unsuitable. Cumulative incidence calculated using the nonparametric competing risk method.

After adjusting for these DSA-level effects in the multilevel model, the hazards of transplantation and death/removal for Hispanics were no longer significantly different from those of Caucasians, as shown in Table 4. African

Table 2: Clinical and demographic characteristics according to racial and ethnic group during the post-MELD era

	Caucasian n = 36314	African American n = 4195	Hispanic n = 6854
Initial MELD score, median	15	18*	15
Final MELD score, median	17	21*	18
1° Diagnosis			
Hepatitis C	37%	41%*	44%*
Alcohol	16%	5%*	16%
HCC	4%	5%#	4%
Other	43%	49%*	36%
Comorbidities	9%	8%#	8%#
Blood group			
A	40%	28%*	31%*
B	11%	18%*	9%#
AB	4%	3%*	1%#
O	45%	51%*	59%*
Median age at listing	53	52*	53
Gender (% male)	66%	58%*	62%*

#p < 0.05 versus Caucasians.
*p < 0.001 versus Caucasians.
HCC = hepatocellular carcinoma.
Comorbidities include chronic obstructive pulmonary disease, diabetes and coronary artery disease. Initial MELD score is at listing, while final MELD score is the most recent value prior to transplant, removal or end of the analysis period.

Table 3: Predictors of waiting list outcomes during the post-MELD era, multivariate analysis

		HR	95% CI
Transplant	African American	0.99	0.93–1.04
	Hispanic	**0.80**	**0.77–0.83**
	MELD score (per unit)[1]	**1.13**	**1.13–1.14**
	Primary diagnosis		
	Hepatitis C (vs. other)	**0.96**	**0.93–0.99**
	Alcohol (vs. other)	**0.85**	**0.81–0.89**
	HCC (vs. other)	**3.36**	**3.14–3.59**
	Comorbidity	1.01	0.96–1.06
	Blood group		
	B (vs. A)	**1.20**	**1.14–1.25**
	AB (vs. A)	**1.90**	**1.74–2.07**
	O (vs. A)	**0.93**	**0.90–0.96**
	Age (per 10 years)	**1.08**	**1.06–1.10**
	Male gender	**1.20**	**1.16–1.24**
Death/removal	African American	0.85	0.71–1.01
	Hispanic	0.92	0.84–1.01
	MELD score (per unit)[1]	**1.22**	**1.21–1.23**
	Primary diagnosis		
	Hepatitis C (vs. other)	**1.18**	**1.08–1.28**
	Alcohol (vs. other)	0.99	0.90–1.08
	HCC (vs. other)	**2.07**	**1.74–2.47**
	Comorbidity	**1.16**	**1.02–1.32**
	Blood group		
	B (vs. A)	**1.19**	**1.07–1.32**
	AB (vs. A)	1.02	0.80–1.31
	O (vs. A)	**1.12**	**1.03–1.22**
	Age (per 10 years)	**1.44**	**1.38–1.51**
	Male gender	**0.92**	**0.86–0.99**

[1]MELD score treated as a time-varying covariate, reflecting changes in MELD score over time.
Values in bold have a p-value <0.05.

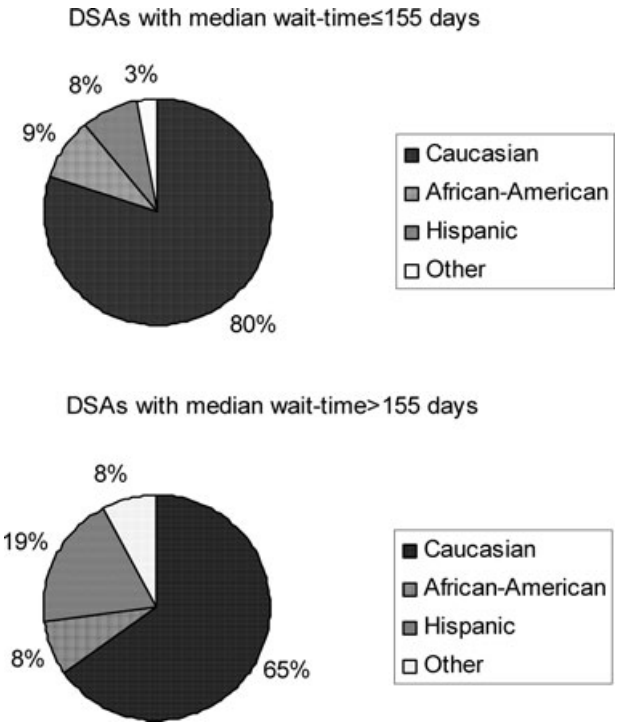

Figure 2: Racial and ethnic distribution of donation service areas (DSAs) with median waiting times of ≤155 days versus >155 days. Difference in proportion of Hispanics between the DSA categories is statistically significant ($p < 0.001$).

Americans appear less likely to die/be removed from the waiting list after adjusting for DSA-level effects (HR 0.81, $p = 0.001$), while their hazard of transplantation remained statistically not different from that of Caucasians as shown in Table 4.

Discussion

This study has demonstrated that disparities in waitlist outcomes exist for Hispanics during the post-MELD era, but not for African Americans. After adjusting for differences in severity of liver disease, African Americans appear to have equal or better waitlist outcomes than Caucasians during the post-MELD era. These findings are similar to those of a recently published study by Moylan et al. (10) who despite using different methodology and subject inclusion criteria also found no significant disparities for African Americans during the post-MELD era. The study by Moylan et al. did not analyze outcomes for Hispanics, who represent the largest minority group in the United States, nor did it adequately adjust for geographic variations in organ supply.

Unfortunately, Hispanics have not fared as well during the post-MELD era, and are less likely than Caucasians to receive a transplant despite adjustment for multiple potential confounders. We found that all of the remaining disparities

Table 4: Predictors of waiting list outcomes during the post-MELD era, adjusted for DSA-level effects

		HR	95% CI
Transplant	African American	1.01	0.97–1.06
	Hispanic	1.00	0.96–1.05
	MELD score (per unit)[1]	**1.14**	**1.13–1.14**
	Primary diagnosis		
	Hepatitis C (vs. other)	0.99	0.96–1.03
	Alcohol (vs. other)	**0.90**	**0.86–0.94**
	HCC (vs. other)	**3.86**	**3.60–4.15**
	Comorbidity	0.96	0.91–1.01
	Blood group		
	B (vs. A)	**1.20**	**1.15–1.26**
	AB (vs. A)	**2.07**	**1.89–2.27**
	O (vs. A)	**0.93**	**0.90–0.96**
	Age (per 10 years)	**1.05**	**1.03–1.07**
	Male gender	**1.23**	**1.19–1.27**
Death/removal	African American	**0.81**	**0.72–0.92**
	Hispanic	0.97	0.89–1.05
	MELD score (per unit)[1]	**1.22**	**1.22–1.23**
	Primary diagnosis		
	Hepatitis C (vs. other)	**1.20**	**1.12–1.28**
	Alcohol (vs. other)	0.99	0.91–1.08
	HCC (vs. other)	**2.20**	**1.84–2.62**
	Comorbidity	**1.18**	**1.07–1.30**
	Blood group		
	B (vs. A)	**1.17**	**1.07–1.29**
	AB (vs. A)	1.03	0.83–1.27
	O (vs. A)	**1.11**	**1.04–1.19**
	Age (per 10 years)	**1.32**	**1.28–1.36**
	Male gender	**0.93**	**0.87–0.99**

[1]MELD score treated as a time-varying covariate, reflecting changes in MELD score over time.
Values in bold have a p-value <0.05.
Results are from a fixed-effects multilevel model stratified by DSA.

for Hispanics could be explained by the fact that they live in transplant regions with more severe organ shortage, as measured by average time on the waiting list. Geographic differences in availability of organs for transplantation have been demonstrated in a number of other studies (9,18) and may be partially due to clustering of transplant centers in urban locations (19). To our knowledge, this is the first study demonstrating that these geographic differences exacerbate racial/ethnic disparities.

Several other findings in this study deserve mention. First, we consistently identified that women are less likely to receive a transplant and more likely to die/be removed from the waiting list. This finding has been reported in previous studies (10), but the reason for this disparity is unknown. Secondly, we identified that African Americans tend to have higher MELD scores than other racial/ethnic groups, which may reflect later referral to transplant centers (1). After adjustment for MELD score and other confounders, African Americans appear less likely to die/be removed than Caucasians; this difference became statistically significant after additional adjustment for DSA-level effects. We hypothesize that some of these findings for

women and African Americans can be at least partially explained by the relative weight of creatinine in calculation of the MELD score (20). It is known that women tend to have worse renal function for a given creatinine, while African Americans tend to have better renal function for a given creatinine (21), so the mortality risk at a given MELD score may not be equivalent across racial and gender groups. This hypothesis should be formally tested in future studies.

This study was limited by its observational nature, which means that we cannot be certain that associations between geography and disparities are causative. Additionally, patients' race and ethnicity are designated by each individual transplant center in a nonsystematic fashion, and the reliability of these designations is unknown. Finally, we have only analyzed one stage of access to liver transplantation, and cannot comment on disparities in referral and listing. Since there are 40 000 deaths per year due to liver disease in the United States (22) but only 6500 liver transplants (23) performed, the referral and listing stages of the liver transplant process are likely to be of equal or greater importance than receipt of a liver transplant once on the waiting list. Despite these limitations, this study provides an understanding of the interactions between geographic variations in organ supply and racial/ethnic disparities.

In conclusion, significant disparities in wait-list outcomes exist for Hispanics during the post-MELD era, and these disparities are attributable to geographic differences in organ availability. These findings should serve to call attention to the fact that where one happens to live plays a large role in the likelihood of receiving a transplant. Indeed, these geographic variations are unjust for all patients, not only Hispanics. Further research is needed to determine whether these variations could be eliminated by changing the allocation rules to foster increased interregional sharing of organs, or whether a complete reorganization of transplant regions is indicated (24).

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Conflict of Interest Statement

None

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