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Original article

Waitlist mortality and transplant free survival in Hispanic patients listed for liver transplant using the UNOS database

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ABSTRACT

Introduction and objectives: After the implementation of "Share 35", several concerns arose such as the potential to increase travel distance, costs, and decreased liver availability. These elements could have a negative impact on waitlist outcomes among ethnic minorities. We aimed to determine waitlist survival after the implementation of the Share 35 policy in non-Hispanic white and Hispanic patients.
Materials and methods: We identified non-Hispanic whites and Hispanics who were listed for liver transplantation from June 18th, 2013 to June 18, 2018. We excluded pediatric patients, patients with acute hepatic necrosis, re-transplants, multiorgan transplant, living donor, and exception cases. The primary outcome was death or removal from the waitlist due to clinical deterioration. We used competing risk analysis to compare waitlist survival between the two groups.
Results: There were 23,340 non-Hispanic whites and 4938 Hispanics listed for transplant. On competing risk analysis, Hispanic patients had a higher risk of being removed from the waitlist for death or clinical deterioration compared to their counterpart (SHR 1.23, 95% CI 1.13–1.34; P < 0.001).
Conclusion: After the implementation of Share 35, disparities are still present and continue to negatively impact outcomes in minority populations especially Hispanic patients.

1. Introduction

Liver transplant (LT) remains the definitive treatment for patients with end-stage liver disease and it is the second most common solid organ transplantation after kidney transplant worldwide [1]. Whereas the number of patients with irreversible liver injury has increased, the number of available organs has remained comparatively low creating a shortage of organs for transplantation [2]. This imbalance emphasizes the need for systems of equitable organ allocation. In 2002, the Organ Procurement and Transplantation Network (OPTN) adopted the model for end-stage liver disease (MELD) score, both for listing and recipient selection, changing the policy of organ allocation [3]. This new allocation system was aimed to ensure that patients at greatest risk for mortality are given the highest priority for transplantation [4]. Unfortunately, significant racial and ethnic disparities in waitlist outcomes have been documented during the post-MELD era and some of these disparities have been attributed to geographic differences in organ availability [5].

On June 18th, 2013, the OPTN implemented a new policy, known as "Share 35", to reduce the number of deaths on the waitlist by increasing regional sharing of livers for patients with a MELD score ≥35 [6]. However, concerns such as the potential to increase travel distance, increased costs, and lowered liver availability in some areas of the country arose [7]. These elements could potentially negatively impact waitlist outcomes among ethnic minorities, especially Hispanics.

Therefore, we aimed to determine waitlist survival after the implementation of the Share 35 policy in non-Hispanic white and Hispanic patients. Identification of potential disparities is an important first step in developing interventions to reduce these inequalities and allows public health professionals to target populations at particular risk.

2. Methods

2.1. Study population

The UNOS Standard Transplant Analysis and Research (STAR) file was used to identify all patients who underwent LT from June

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18th, 2013 to June 18, 2018. These dates were chosen to allow 5 years of analysis data after the implementation of Share 35 policy. We excluded pediatric patients (age <18 years), ethnicity other than Hispanic or non-Hispanic white, patients listed as status 1, re-transplants, multiorgan transplant, living donor transplant, and those receiving MELD exception points. The study population was divided into Hispanic and non-Hispanic white based on the ethnic group provided by patients when registering on the waiting list. Our final study population included 28,278 patients. Using the same exclusion criteria, a cohort of 31,967 patients from June 18th, 2008 to June 17th, 2013, was selected in order to compare 5 years prior the implementation of Share 35. This study was exempt from institutional review board approval as it was based on an already existing dataset of deidentified information.

2.2. Study variables and definitions

Demographics, including gender, age, payment source, highest educational achievement, and citizenship were compared between groups. Clinical characteristics at listing such as body mass index (BMI), blood type, primary diagnosis, history of diabetes or hepatocellular carcinoma (HCC), presence of encephalopathy, ascites, muscle wasting or spontaneous bacterial peritonitis (SBP), MELD score, and functional status were also collected. Characteristics at the time of transplant such as level of care, MELD score, time spent on the waitlist, removal from the waitlist, and distribution MELD regions were also compared between groups.

The etiology of liver disease was extracted from the primary diagnosis codes in the Scientific Registry of Transplant Recipient (SRTR) dictionary. Our study focused on the following liver disease etiologies: non-alcoholic steatohepatitis (NASH), alcohol-related liver disease (ALD), hepatitis B (HBV), hepatitis C (HCV), cholestatic liver disease, and autoimmune hepatitis (AIH). All other diagnoses were combined into the category of "Other". As described in previous studies, we included obese patients (body mass index $\geq$30 kg/m [2]) with cryptogenic cirrhosis in NASH cirrhosis [8]. Similarly, patients with HCV and ALD were categorized as HCV [9]. Patients with primary biliary cholangitis, secondary biliary cirrhosis, and primary sclerosing cholangitis were recategorized as cholestatic liver disease [10]. Among patients with HCC, the underlying liver disease was determined based on the secondary disease diagnosis codes provided to estimate the contribution of each underlying etiology to the overall LT population [11].

The primary source of payment was classified as private insurance, public insurance, and other (self, donation, free care, pending, foreign government and US/State Government Agency). Education level was divided into college degree or above, and less than college degree (included non-formal education). Citizenship status was considered as US and non-US citizen (included resident alien and non-resident alien). Since geographic racial and ethnic disparities in access to liver transplantation have been documented [12] we considered the median MELD score in each UNOS region as a surrogate measure of organ shortage. Regions were categorized depending on the median national MELD score at listing as either low MELD < 19 (noted on regions 1, 8, 9, and 10), or high MELD $\geq$19 (as seen in regions 2, 3, 4, 5, 6, 7, and 11) [13].

2.3. Statistical analysis

The primary outcome was waitlist survival using the composite outcome of death or removal for clinical deterioration (United Network of Organ Sharing [UNOS] removal codes 5, 8, and 13). We compared waitlist survival among groups using competing risk analysis with liver transplantation as a competing risk.

Recipient ethnicity was used to stratify the demographics and clinical characteristics of patients listed for LT. Categorical variables were presented as frequencies and percentages and were compared using the Pearson's chi-squared test (χ^2). Continuous variables that were not normally distributed were reported as medians and interquartile range (IQR) and were analyzed with the Kruskal-Wallis test.

Our outcomes of interest, death/delisting and transplant represented competing risks. Therefore, we built competing risk models to evaluate the cumulative incidence of death/delisting. We adjusted for recipient characteristics including age, sex, education, payment source, citizenship, comorbidities (diabetes), blood type, primary diagnosis, MELD region in which the patient was listed and MELD score at listing. The competing risk model was also used to conduct a subgroup analysis excluding those patients with MELD score < 35. All covariates had less than 5% of missing data. All statistical analyses were conducted using Stata version 14.0 (College Station, TX StataCorp LP).

3. Results

3.1. Characteristics of the population

Clinical and demographic differences between groups are displayed in Table 1. In both the pre and post-Share 35 era, non-Hispanic white recipients accounted for the majority (83%) of the population. A greater proportion of Hispanics were female and were younger at the time of listing when compared to non-Hispanic whites. Hispanic patients also had less college education and more public insurance. They also had characteristics of more severe disease such as a greater proportion of comorbidities including diabetes (34%) and HCC (6.2%).

Patients with ALD, NASH, and HCV formed a larger proportion of the subjects undergoing liver transplantation in both eras across the two ethnic groups. In accordance with regional demographics, a greater proportion of Hispanic patients were transplanted at high MELD regions (83% vs 72%; P < 0.001) in the post-share 35, a slight increase from pre-share 35 (81% vs 72%). Finally, Hispanic recipients experienced longer median waitlist times for transplant 237 days [IQR 44-813] in the pre-share 35 era and 152 days [IQR 22-643] in the post-share 35 era when compared to their counterparts.

3.2. Waitlist survival

On competing risk analysis with transplant as a competing risk, Hispanic patients also had a higher risk of being removed from the waitlist for death or clinical deterioration compared to non-Hispanic whites in the pre-share 35 era (SHR 1.12, 95% CI 1.05–1.18; P < 0.001) (Fig. 1) and in the post-share 35 era (subdistribution hazard ratio [SHR] 1.23, 95% CI 1.13–1.34; P < 0.001) (Table 2, Fig. 2). Other variables associated with higher risk of the waitlist mortality on the competing risk analysis were age, diabetes, having public insurance, no-college education and a high MELD score whereas being male, having blood type B and AB were associated with lower risk of being removed from the waitlist (Table 2). Regarding geography, there was no statically significant difference in the waitlist mortality between high and low MELD score regions in the post-share 35 era. In the subgroup analysis of patients with MELD > 35, Hispanics also had a higher risk of delisting from the waitlist due to death or clinical deterioration. (SHR 1.28, 95% CI 1.01–1.61; P = 0.037) (Fig. 3, Table 3).

4. Discussion

Our study has demonstrated that racial/ethnic disparities in waitlist outcomes are still present and remain an area of concern in the post-Share 35 era. These disparities extend to Hispanics who are

Table 1
Baseline characteristics.

	Pre-share 35			Post-share 35		
	Non-Hispanic white n = 26,424 (83)	Hispanic n = 5543(17)	*p* value	Non-Hispanic white n = 23,340 (83)	Hispanic n = 4938 (17.4)	*p* Value
Gender (female), n (%)	8924 (34)	2011 (36)	<0.001	8761 (38)	1991 (40.3)	<0.001
Age, median (IQR)	56 (51–61)	55 (49–60)	<0.001	57 (50–63)	56 (48–62)	<0.001
BMI, median (IQR)	28 (25–33)	29 (25–33)	<0.001	29 (25–33)	29 (25–33)	0.0077
BMI ≥ 30, n (%)	10,252 (39)	2268 (41)	0.003	9525 (41)	2066 (42)	0.182
Blood type, n (%)			<0.001			<0.001
A	10,852 (41)	1739 (31)		9572 (41)	1491 (30.1)	
B	2805 (11)	554 (10)		2526 (11)	513 (10.3)	
AB	1053 (4)	113 (2)		908 (4)	96 (2)	
O	11,714 (44)	3137 (57)		10,334 (44.2)	2838 (57.4)	
Public insurance, n (%)	10,093 (38)	2983 (54)	<0.001	9906 (42.4)	2908 (59)	<0.001
College education, n (%)	12,513 (53)	1457 (29)	<0.001	12,656 (54.2)	1475 (30)	<0.001
Citizenship Non-US, n (%)	380 (1)	721 (13)	<0.001	453 (2)	868 (18)	<0.001
Comorbidities at listing, n (%)						
Diabetes	6442 (24)	1748 (32)	<0.001	6179 (26.4)	1673 (34)	<0.001
Encephalopathy	16,746 (63)	3555 (64)	0.135	16,332 (70)	3256 (66)	<0.001
Ascites	20,573 (78)	4352 (79)	0.132	19,622 (84)	4006 (81)	<0.001
SBP	1667 (6)	424 (8)	<0.001	2403 (10.3)	527 (11)	0.007
HCC diagnosis ever, n (%)	1060 (4)	202 (4)		1024 (4.3)	309 (6.2)	<0.001
Functional status at listing, n (%)			<0.001			<0.001
No assistance	9830 (37)	1778 (32)		5127 (22)	983 (20)	
Some assistance	11,278 (42)	2399 (43)		11,132 (48)	2471 (50)	
Total assistance	4505 (17)	1300 (23)		6717 (29)	1464 (30)	
Missing	811 (3)	66 (1)		364 (1.5)	20 (0.4)	
Level of care at transplant, n (%)			<0.001			<0.001
Outpatient	8455 (32)	1297 (23)		6395 (27.4)	879 (18)	
Inpatient non-ICU	2678 (10)	608 (11)		2982 (13)	603 (12.2)	
Inpatient ICU	1356 (5)	363 (7)		1935 (8.2)	600 (12.1)	
Missing	13,935 (52)	3275 (59)		12,028 (52)	2856 (58)	
Primary diagnosis, n (%)						
NASH	41,152 (16)	773 (14)	<0.001	5639 (24.1)	1105 (22.3)	0.008
ALD	5711 (22)	1222 (22)	0.477	8099 (35)	1614 (33)	0.007
HBV	318 (1)	50 (1)	0.056	201 (1)	44 (1)	0.837
HCV	11,053 (42)	2527 (46)	<0.001	4528 (19.4)	1124 (23)	<0.001
AIH	742 (3)	225 (4)	<0.001	760 (3.2)	257 (5.2)	<0.001
Cholestatic liver disease	2138 (8)	282 (5)	<0.001	1879 (8)	324 (7)	<0.001
Other	2310 (9)	464 (8)	0.372	2234 (10)	470 (10)	0.907
MELD score at listing, median (IQR)	16 (12–22)	16 (12–23)	<0.001	19 (14–27)	20 (15–29)	<0.001
Days on waitlist, median (IQR)	191 (39–672)	237 (44–813)	<0.001	132 (21–551)	152 (22–643)	0.0019
MELD regions, n (%)			<0.001			<0.001
Low MELD region (1, 8, 9, 10)	7408 (28)	1060 (19)		6487 (28)	845 (17.1)	
High MELD region (2, 3, 4, 5, 6, 7, 11)	19,016 (72)	4483 (81)		16,853 (72.2)	4093 (83)	
MELD score at transplant, median (IQR)	20 (13–29)	21 (14–33)	<0.001	23 (16–33)	25 (16–36)	<0.001
Transplanted, n (%)	12,492 (47)	2269 (41)	<0.001	11,336 (49)	2091 (42)	<0.001
Removed from waitlist for being too sick or death, n (%)	7444 (28)	1823 (33)	<0.001	5320 (23)	1378 (28)	<0.001

SBP, spontaneous bacterial peritonitis. ICU, Intensive Care Unit. NASH, non-alcoholic steatohepatitis. ALD, alcohol related liver disease. HBV. hepatitis B. HCV, hepatitis C. AIH, autoimmune hepatitis. MELD, model for end-stage liver disease. IQR, interquartile range.

both more likely to be removed from the waitlist and less likely to receive a transplant than their non-Hispanic white counterparts. Although previous studies have shown that Hispanic candidates appeared to fare slightly better under Share 35, their mortality was not significantly different across eras [14].

Within the constraints of a retrospective study using a large database without granular data, we provide several hypotheses for these disparities. First, Hispanic patients were listed with a higher MELD score compared to non-Hispanic whites, potentially indicating a delay in referral of these patients for transplant which may play a role in their higher rate of adverse waitlist outcomes. Such delays may be due to socioeconomic disparities like educational level or source of health care payment insurance status playing a larger role [15]. Second, we may intuitively attribute such observations to language barriers, which may impair Hispanic patients' ability to better understand their conditions, thus making them

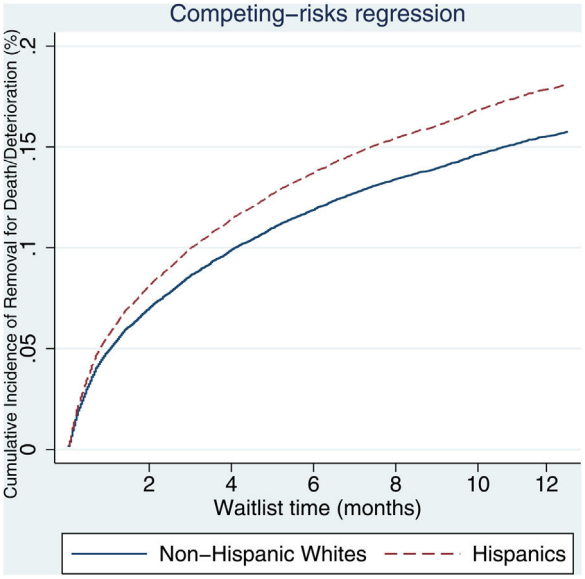

Fig. 1. Post-Share 35: 1 year competing risk regression of non-Hispanic whites and Hispanics demonstrating relative removal from waitlist for death or clinical deterioration.

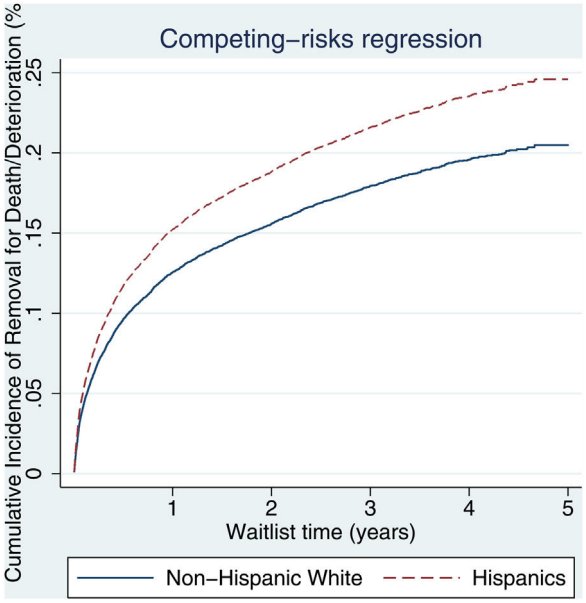

Fig. 2. Post-Share 35: 5 year competing risk regression of non-Hispanic whites and Hispanics demonstrating relative removal from waitlist for death or clinical deterioration.

less likely to seek medical care earlier in disease course. Third, differences in literacy and numeric skills have shown to affect individuals' ability to obtain relevant information and their opportunity to apply that information in communications with health professionals [16]. The complexity of liver cirrhosis requires extensive self-care management that also increases the demands on patients to understand, and utilize health information [17].

Nonetheless, after accounting for these covariates, Hispanic patients remained at higher risk compared to non-Hispanic white patients by the nature of ethnicity alone. Pingitore et al. have described that a variant of the human patatin-like phospholipase domain-containing 3 (PNPLA3) gene, which encodes for a protein of 481 amino-acids, is highly expressed in the liver and strongly associated with entire spectrum of liver diseases [18]. Its mutant protein has a negative effect on triglycerides mobilization from liver droplets that leads to inflammatory infiltrate and the initial presence of fibrotic lesions [19,20]. The frequency

Table 2
Competing risk analysis of time to death or waitlist removal for clinical deterioration with transplant as competing risk.

Variables	Pre-share 35			Post-share 35		
	SHR	95% CI	P value	SHR	95% CI	P value
Age	1.02	1.02–1.03	<0.001	1.03	1.03–1.04	<0.001
Gender (male)	0.82	0.79–0.87	<0.001	0.81	0.76–0.86	<0.001
Comorbidities						
Diabetes	1.22	1.16–1.28	<0.001	1.32	1.23–1.42	<0.001
No-college education	0.93	0.89–0.97	0.005	1.10	1.03–1.18	0.005
Payment source						
Private	Ref			Ref		
Public	1.21	1.15–1.26	<0.001	1.21	1.13–1.30	<0.001
Other	1.14	0.85–1.53	0.359	0.91	0.58–1.42	0.678
Citizenship (Non-US)	1.04	0.92–1.16	0.533	1.03	0.88–1.20	0.668
MELD score at listing	1.03	1.02–1.03	<0.001	1.02	1.01–1.03	<0.001
MELD Region (Low)	1.02	1.05–1.15	<0.001	1.03	0.96–1.11	0.439
Blood type						
A	Ref			Ref		
B	0.81	0.75–0.88	<0.001	0.71	0.64–0.81	<0.001
AB	0.47	0.40–0.55	<0.001	0.53	0.42–0.66	<0.001
O	0.97	0.93–1.02	0.322	0.96	0.89–1.03	0.257
Primary diagnosis						
NASH	Ref			Ref		
ALD	0.98	0.91–1.06	0.765	0.97	0.88–1.06	0.493
HBV	0.84	0.66–1.06	0.156	0.79	0.52–1.19	0.268
HCV	1.15	1.07–1.22	<0.001	0.99	0.89–1.10	0.866
AIH	1.07	0.93–1.23	0.312	1.21	1.01–1.44	0.030
Cholestatic liver disease	1.07	0.97–1.18	0.163	1.03	0.90–1.18	0.616
Other	1.08	0.98–1.18	0.099	1.44	1.28–1.61	<0.001
Ethnicity (Hispanics)	1.12	1.05–1.18	<0.001	1.23	1.13–1.34	<0.001

MELD, model for end-stage liver disease. HCC, Hepatocellular carcinoma. NASH, non-alcoholic steatohepatitis. ALD, alcohol related liver disease. HBV. hepatitis B. HCV, hepatitis C. AIH, autoimmune hepatitis. SHR, subdistribution hazard ratio.CI, confidence interval. REF, reference.

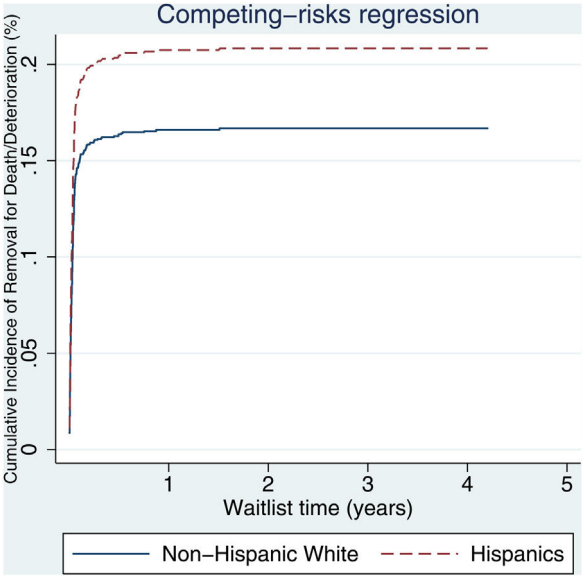

Fig. 3. Competing risk regression of non-Hispanic whites and Hispanics demonstrating relative removal from waitlist for death or clinical deterioration in the population with MELD score ≥ 35.

Table 3
Subgroup competing risk analysis of time to death or waitlist removal for clinical deterioration with transplant as competing risk: population with MELD score ≥ 35.

Variables	SHR	95% CI	P value
Age	1.04	1.03–1.05	<0.001
Gender (male)	1.02	0.84–1.24	0.837
Comorbidities			
Diabetes	1.54	1.23–1.92	<0.001
No-college education	0.96	0.78–1.17	0.675
Payment source			
Private			
Public	1.03	0.84–1.25	0.788
Other	0.32	0.75–1.34	0.120
Citizenship (Non-US)	1	0.67–1.47	0.996
MELD score at listing	1.07	1.05–1.10	<0.001
MELD Region (Low)	1.37	1.09–1.72	0.006
Blood type			
A			
B	0.77	0.55–1.09	0.145
AB	0.60	0.31–1.13	0.116
O	0.90	0.74–1.10	0.318
Primary diagnosis			
NASH			
ALD	1.08	0.80–1.44	0.599
HBV	0.92	0.35–2.42	0.871
HCV	1.04	0.74–1.48	0.786
AIH	1.17	0.69–1.97	0.551
Cholestatic liver disease	1.14	0.72–1.82	0.562
Other	1.84	1.29–2.64	<0.001
Ethnicity (Hispanics)	1.28	1.01–1.61	0.037

MELD, model for end-stage liver disease. HCC, Hepatocellular carcinoma. NASH, non-alcoholic steatohepatitis. ALD, alcohol related liver disease. HBV. hepatitis B. HCV, hepatitis C. AIH, autoimmune hepatitis. SHR, subdistribution hazard ratio.CI, confidence interval. REF, reference.

of this variant is higher in the Hispanic population and accounts for an elevated risk for hepatic injury compared to individuals of other ethnicities [21,22]. Consequently, these inherent biologic factors could serve as an explanation of their higher waitlist mortality.

In contrast to our study, a recent study by Kaswala et al. found a lower risk of waitlist death in Hispanics compared to non-Hispanic whites (HR 0.84, 95% CI 0.79–0.90, P < 0.001) [23]. In their analysis, they used only waitlist death and not removal for clinical deterioration which generally also results in death. In addition, they used only Cox regression in their analysis and not competing risk regression which treats those who are transplanted (generally higher MELD and also higher risk of death) the same as those who are censored and does not accurately reflect the survival probability [24].

Our study also shows that a greater proportion of Hispanics are transplanted at high MELD score regions and experience longer waitlist time. However, on a competing risk analysis we found no differences in waitlist mortality between high and low MELD regions in the post-share 35 era. These results are in contrast to that of Volk et al. who found that Hispanics have not fared as well during the post-MELD era and are less likely than Caucasians to receive a transplant given that they live in transplant regions with more severe organ shortage [5]. Even though the implementation of share 35 has resulted in liver transplant being more equitable across regions, it has not addressed racial/ethnic disparities that are still present.

The strength of this study is the utilization of the competing risk analysis method, which allows the simultaneous assessment of the effects of competing risks such as waitlist removal for death or deterioration and transplant on the survival probability for each failure type. In addition, the utilization of a large database and the large scale of the study allows for a better reflection and assessment of the disparities that are currently present in the allocation of liver transplants in Hispanic populations. However, like all similar studies, this study is limited by the retrospective nature of the analysis that is limited by the available data in the UNOS database. For example, there was not available data on patient's occupation, psychosocial characteristics or proximity to transplant centers, which have been shown in small single center studies to impact access to liver transplantation [16]. In addition, Hispanic ethnicity in our data was self-reported and may represent a heterogeneous mix of races. Given the strong effect of race on many health outcomes, there is a risk of misclassification bias. Although the multivariate model attempts to include adjustments for potential confounders, it should be acknowledged that our study was only able to include variables that were available in SRTR and thus there remains the potential for unmeasured confounders. Finally, the SRTR database presents challenges related to accurate coding and data availability.

5. Conclusions

Our study demonstrates that despite the improvement of geographic disparities with the new Share 35 policy, racial/ethnic disparities remain an area of concern. A combination of factors such as differences in socioeconomic status, health literacy, or even genetic factors potentially play an important role. Clinicians should continue to ensure patients have access to readily available translators, health care information in their native language, and social workers with experience in ethnic minorities in order to detect and avoid inequalities in the fair allocation of scarce life-saving organs.

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Disclosure

The authors declare no conflicts of interest.

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