Original Research

Robust Outcomes for Hispanic Lung Transplant Recipients in the United States

Michelle N. Bremer [1], Garrick J. Gama [1], Omkar Rao [2], Eugene Golts [3], Deepa Kurup [2], Aarya Kafi [4], Christine M. Lin [4], Gordon Yung [4], Kamyar Afshar [4, *]

1. University of Iowa Carver College of Medicine, US; E-Mails: michelle-bremer@uiowa.edu; garrick-gama@uiowa.edu
2. University of California San Diego Health, Department of Lung Transplantation, US; E-Mail: onrao@ucsd.edu; dkurup@health.ucsd.edu
3. UC San Diego School of Medicine, Department of Cardiovascular Surgery, US; E-Mail: egolts@health.ucsd.edu
4. UC San Diego School of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, US; E-Mails: akafi@health.ucsd.edu; cml008@health.ucsd.edu; gyung@health.ucsd.edu; Kaafshar@health.ucsd.edu

* **Correspondence:** Kamyar Afshar; E-Mail: Kaafshar@health.ucsd.edu

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Abstract

Race, while a social construct, has a strong effect on a person's health. There is limited data on racial disparities within lung transplantation (LTx), especially for Hispanic recipients. Therefore, the aim of this study was to identify inequalities that may involve this population. We analyzed historical data from the Organ Procurement and Transplantation Network (OPTN) and performed a retrospective review of Hispanic and Caucasian patients who underwent lung transplantation in the United States between May 4, 2005 and October 31, 2019. We compared pre-transplant health status to that of survival outcomes for both Caucasians and Hispanics using Kaplan-Meier survival analyses and Cox proportional hazards modeling to controlling for age, gender, pre-LTx diagnosis, and type of LTx. During this timeframe, 1,934 Hispanics and 22,767 Caucasians underwent lung transplantation. A statistically significant

difference was seen between the two groups regarding age (p < 0.0001), body mass index (BMI) (p < 0.0001), type of lung transplant (bilateral versus single, p < 0.0001), and pre-transplant diagnoses (p < 0.0001). In all included pre-LTx health measures, Hispanics were significantly worse (p ≤ 0.0001-0.0410). Interestingly, it was found that Hispanics have better survival rates at 1 year and 3 years (p < 0.0001) with an associated hazards ratio of 0.927[0.868, 0.991] in comparison to Caucasians. Hispanics are underrepresented among LTx recipients, transplanted in worse health, and for diseases that have been noted to have the worst long-term survival outcomes. Despite these factors, Hispanics have a better long-term survival rate post-LTx.

Keywords
Hispanics; lung transplantation; health disparities

1. Introduction

The World Health Organization (WHO) defines disparities as "differences in health that are not only unnecessary and avoidable, but in addition, are considered unfair and unjust [1]." Health disparities often adversely affect access to high-quality health care, increase the burden of disease, and directly affect mortality. As a social construct, race underlies the biases that influence the ability for patients to receive appropriate and timely medical treatment. Health data from the United States clearly indicates that an individual's race strongly correlates with morbidity and mortality [2-4].

A high morbidity and mortality due to end-stage lung disease is observed in all races and ethnicities. However, the exact prevalence (and effect) of disparities post-lung transplant (LTx) is less clear. Disparities are often dismissed as the result of minority patients experiencing limited access to healthcare. However, controlling for lack of access does not eliminate disparities in health outcomes [3]. Studies investigating racial disparities in solid organ transplantation have primarily focused on African Americans [5-9]. Specifically within lung transplantation, it was observed that prior to the adoption of the current United Network for Organ Sharing (UNOS) lung allocation system (LAS), Black LTx candidates had a higher mortality rate while waiting for lung transplantation [9-11]. Following the implementation of the LAS, however, no difference was observed for Black candidates [9, 12], rather the difference in mortality rates was based upon pre-LTx illness severity [13, 14]. For reference, the LAS is a calculated score based on various pre-LTx health parameters to help prioritize the waitlist with the primary goal of decreasing waitlist mortality.

Although not focused only on lung transplant recipients, one study did evaluate survival outcomes of solid organ (kidney, liver, heart, and lung) transplant recipients by race/ethnicity [15]. This study used data comprising patients transplanted between 1999-2008 found that adjusted patient survival at one-year post-lung transplant was highest for Caucasians and African Americans (84%), followed by Hispanics/Latinos (82%), and Asians (78%) [15]. Five-year survival, however, demonstrated a different demographic trend with the highest survival noted in Asians (61.4%), followed by African Americans (57%), and Caucasians (53.2%). Hispanics/Latinos had the worst five-year survival rate at 49.4% [15]. Given the existing data, the goal of this study is to identify whether

or not Hispanic post-lung transplant outcomes differ from Caucasian recipients and what factor(s) may influence these results.

2. Methods

Using historical data from the Organ Procurement and Transplantation Network (OPTN), we performed a retrospective review of Hispanic (n = 1,934) and Caucasian (n = 22,767) patients who underwent lung transplantation between May 4, 2005 and October 31, 2019. The date range was selected to start at the time when the LAS scores were implemented and ended with the most recent data that would include 3 year survival rates. OPTN gathers data from all transplant centers in the United States, organ procurement organizations (OPOs), and histocompatibility laboratories. Recipients under the age of 18 years, those undergoing re-transplantation, multi-organ transplants, and those missing data on race/ethnicity were excluded. Race/ethnicity was classified according to the reported data fields entered by the transplant center. Individuals who selected multiple races/ethnicities were not included in this study as they were categorized as "Multiracial". Approval to conduct this study was obtained from UC San Diego Institutional Review Board.

Demographic variables used to compare the two groups included age, gender, body mass index (BMI), and type of lung transplant (single versus bilateral). The variables used to delineate recipients' pre-transplant health status were the LAS, supplemental oxygen requirements (includes oxygen at rest, at night, and with exercise only), forced expiratory volume (FEV1), forced vital capacity (FVC), cardiac output, pulmonary artery pressure, and history of diabetes mellitus. Recipients' pre-transplant pulmonary diagnoses were grouped into four main categories: Group A – obstructive lung diseases, Group B – pulmonary vascular diseases, Group C-cystic fibrosis (CF) and immunodeficiency disorders, and Group D – restrictive lung diseases. Patients with diagnoses not explicitly listed under the current UNOS LAS guidelines were grouped as "Other" [16]. These diagnoses included Swyer James Syndrome and Other-Specify.

The primary outcomes of the study were the LTx index hospitalization length-of-stay and survival at 30 days, one year, and three years post-LTx. The post-LTx survival outcomes at 30 days, one year, and three years were calculated by OPTN from Kaplan-Meier curves with a 95% confidence interval reported for each data point. The Kaplan-Meier curve was plotted in 'R' version 4.2.2 [17]. To ensure adequate follow-up data to assess for post-transplant survival, the end of the study period analyzed was set to October 31, 2019.

The secondary outcomes of the study included acute rejection episodes, total deaths reported, deaths due to infection, and deaths due to rejection at the time of hospital discharge following LTx, at 6 month follow-up, 1 year follow-up, 2 year follow-up, and 3 year follow-up as reported to OPTN. These data points were based on OPTN data as of March 10, 2023 which includes data from follow-ups for death, graft failure, or lost to follow-up in the follow-up periods when they occurred. The deaths reported as "due to infection" includes deaths for graft failure secondary to graft infection or any cause of death beginning with infection. Deaths reported as "due to rejection" includes deaths for graft failure secondary to hyperacute, acute, or chronic rejection. The goal of including these secondary outcomes was to help further delineate possible etiologies of survival outcome differences between Hispanics and Caucasians.

Statistical analyses were performed utilizing MedCalc to calculate p values by comparing proportions using the "N-1" Chi-squared test and comparing means using two-tailed T-testing [18,

19]. The Cox proportional hazard ratio was calculated in 'R' version 4.2.2 to estimate the independent effects of being Hispanic on post-LTx survival outcomes in comparison to Caucasians [17]. Our Cox proportional hazard model included the potential confounding variables of age at the time of transplantation, gender, pre-LTx diagnosis, and type of LTx (single vs. double). A type 1 error rate of $\alpha = 0.05$ was utilized and thus $p < 0.05$ is considered a significant difference between Caucasians and Hispanics.

3. Results

Between May 4, 2005 and October 31, 2019, a total of 1,934 Hispanics and 22,767 Caucasians underwent lung transplantation in the United States. A statistically significant difference was seen between the two groups in terms of age, body mass index (BMI), type of lung transplant (bilateral versus single), and pre-LTx diagnoses, Table 1. Hispanics were younger at the time of transplant (50.3 years vs 55.1 years, $p < 0.0001$), but had a higher BMI (25.4 vs 24.9, $p < 0.0001$). Additionally, in comparison to Caucasians, a higher percentage of Hispanics (73.6% vs 68.7%, $p < 0.0001$) received a bilateral lung transplantation as opposed to a single lung transplant. Hispanic lung transplant recipients had a significantly higher rate of comorbid diabetes mellitus at the time of transplant (22.6% vs. 14.8%, $p < 0.0001$). The majority of Hispanic recipients underwent lung transplantation due to a diagnosis of restrictive lung disease (73.7%); they also had a higher percentage of recipients in which pulmonary vascular disease was the primary indication for transplantation ($p < 0.0001$). Caucasians demonstrated a higher percentage of diagnosis of recipients with obstructive lung disease and cystic fibrosis/immunodeficiency disorders ($p < 0.0001$), Table 1.

Table 1 Baseline demographic characteristics and pulmonary disease diagnoses at the time of transplantation.

	Hispanic (n = 1,934)	Caucasian (n = 22,767)	P Value
Demographics:			
Age, mean [SD]	50.3[16.8]	55.1[15.9]	<0.0001
Female Sex (%)	821(42.4%)	8998(39.5%)	0.0123
BMI, mean [SD]	25.36[4.83]	24.93[4.73]	0.0001
Diagnosis (%)*			
Group A	178(9.2%)	7203(31.6%)	<0.0001
Group B	140(7.2%)	828(3.6%)	<0.0001
Group C	180(9.3%)	3128(13.7%)	<0.0001
Group D	1425(73.7%)	11435(50.2%)	<0.0001
Other	11(0.6%)	173(0.8%)	0.3385
Comorbidities			
Diabetes mellitus	438(22.6%)	3371(14.8%)	<0.0001

* Diagnosis groups defined as the following:

Group A: Obstructive lung disease (e.g., emphysema);

Group B: Pulmonary vascular disease (e.g., primary pulmonary hypertension);

Group C: Cystic fibrosis or immunodeficiency disorder;

Group D: Restrictive lung disease (e.g., idiopathic pulmonary fibrosis);

Other: Diagnoses not listed under UNOS lung allocation score (LAS) diagnostic guidelines.

Based on clinical and physiologic variables, Hispanics had worse overall health prior to transplantation, Table 2. These recipients had a significantly lower pre-transplant FEV_1, FVC, and 6-minute walk distance. From a cardiac standpoint, Hispanics also had a significantly higher mean pulmonary arterial pressure (28.4 mmHg vs 26.9 mmHg, p < 0.0001) and associated lower cardiac output, (5.27 L/min vs 5.34 L/min, p = 0.0410), Table 2. LAS at the time of removal from the waitlist was significantly higher for Hispanics (53.1 vs 46.6, p < 0.0001) and a greater percentage of these patients required mechanical ventilatory support prior to lung transplantation (p < 0.0001), Table 2.

Table 2 Physiologic parameters at the time of lung transplantation.

	Hispanic (n = 1,934)	Caucasian (n = 22,767)	P Value
Lung Allocation Scores			
LAS, mean [SD]	53.08[18.95]	46.58[17.39]	<0.0001
Cardiopulmonary Function			
FVC (% Predicted), mean [SD]	42.37[16.51]	49.5[17.73]	<0.0001
FEV_1 (% Predicted), mean [SD]	40.72[18.47]	38.82[21.3]	0.0001
PASP (mmHg), mean [SD]	44.93[19.81]	41.61[16.04]	<0.0001
PADP (mmHg), mean [SD]	18.2[10.74]	17.69[9.02]	0.0188
mPAP (mmHg), mean [SD]	28.42[12.96]	26.89[10.64]	<0.0001
PCWP (mmHg), mean [SD]	10.27[5.83]	10.67[5.36]	0.0018
CO (L/min), mean [SD]	5.27[1.52]	5.34[1.44]	0.0410
6-MWD (feet), mean [SD]	633.47[427.99]	777.15[439.28]	<0.0001
Respiratory Support			
Requiring Supplemental Oxygen	473(24.5%)	7405(32.5%)	<0.0001
Receiving Mechanical Ventilation	175(9.0%)	1503(6.6%)	0.0001

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; 6-MWD, six-minute walk distance.

Post-transplant, Hispanics demonstrated superior long-term post-LTx survival outcomes with no difference in immediate survival outcomes. Immediately post-LTx, there was no difference in the length of hospital between Hispanics (median: 16 days, IQR: 15) and Caucasians (median: 16 days, IQR: 16). At 30 days post-LTx, Caucasians have a higher survival probability at 97.08%, whereas Hispanics had a survival probability of 96.77% (p < 0.0001). However, at one and three years post-LTx, Hispanics had a higher rate of survival (<0.0001), Table 3. After plotting the Kaplan-Meier survival curve, it is apparent that the Hispanics have better long-term post-LTx survival, Figure 1.

Table 3 Kaplan-Meier survival rates at 30 days, one year, and three years post-LTx excluding multi-organ and repeat transplants.

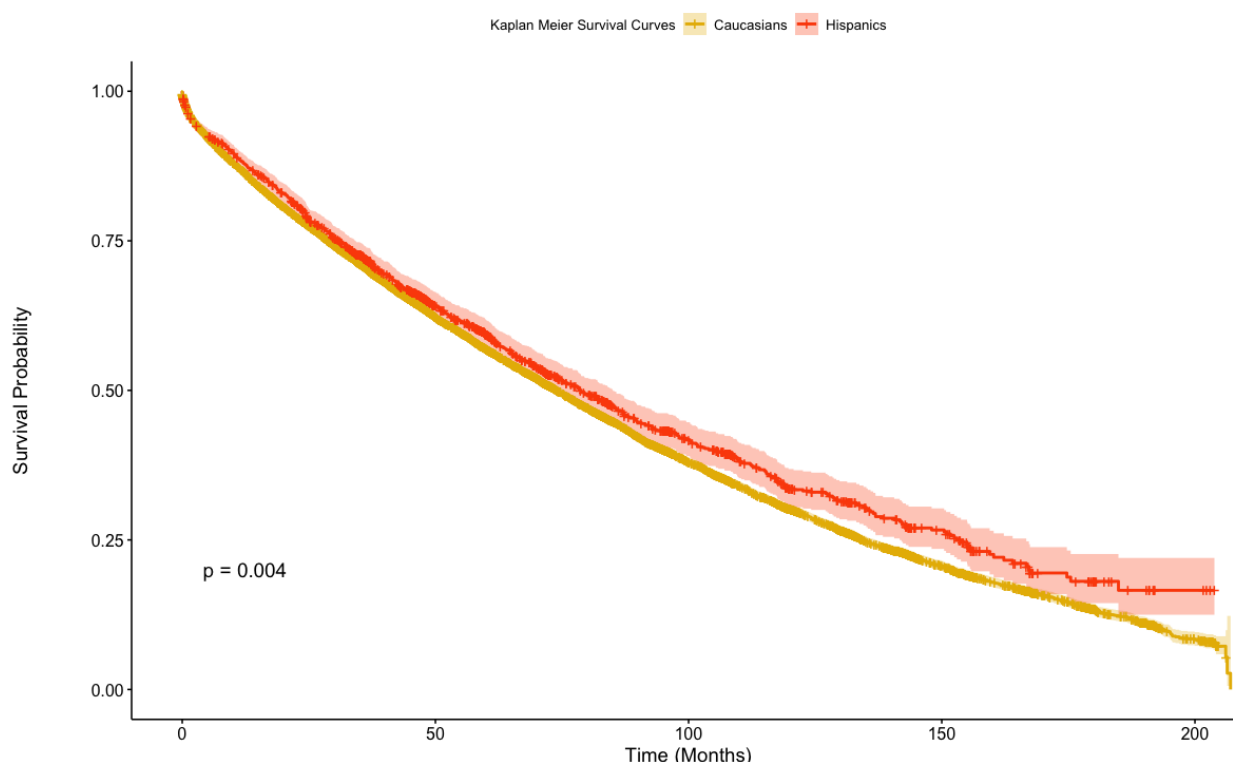| Time Post-LTx	Hispanics Patient Survival Rate (n = 1,832) [95% CI]	Whites Patient Survival Rate (n = 21,699) [95% CI]	P Value
30 days	96.77[95.86, 97.49]	97.08[96.85, 97.29]	<0.0001
1 year	88.59[87.03, 89.67]	87.22[86.77, 87.66]	<0.0001
3 years	72.79[70.66, 74.79]	71.44[70.83, 72.04]	<0.0001

Figure 1 Kaplan Meier survival curves for Caucasians (yellow) and Hispanics (red).

The Cox proportional hazard model showed that being of Hispanic ethnicity was protective (HR: 0.931, p = 0.030) in regard to post-LTx survival after controlling for age, gender, pre-LTx diagnosis, and type of LTx (single vs. double), Table 4. Of note, a higher age (HR: 1.009, p < 0.0001), being of male gender (HR: 1.059, p < 0.0001), receiving a single lung transplant (HR: 1.357, p < 0.0001), and have a pre-LTx diagnosis in either Group B (HR: 1.189, p = 0.0001) or Group D (HR: 1.075, p < 0.0001) all correlated with worse survival outcomes following lung transplantation.

Table 4 Cox proportional hazards model assessing independent effects of each variable on post-LTx survival outcomes.

Variable (Reference Group)	Hazard Ratio [95% CI]	Standard Error	P Value
Hispanic (White)	0.931	0.033	0.0304
Recipient Age (per 1 year)	1.009	0.001	<0.0001
Gender (Female)	1.059	0.016	0.0004

Group B (Group A)	1.189	0.045	0.0001
Group C (Group A)	0.983	0.035	0.6322
Group D (Group A)	1.075	0.018	<0.0001
Single LTx (Double LTx)	1.357	0.017	<0.0001

After assessing the post-LTx observed outcomes of acute rejection episodes and numbers of deaths, the only statistically significant differences between Hispanics and Caucasians were in acute rejection episodes and the total number of deaths, Table 5. Caucasians had higher rates of acute rejection episodes reported at the 1 year (p < 0.0001) and 2 year (p = 0.0273) follow-up visits and a higher number of total deaths at 6 months (p = 0.0067). Hispanics had a higher rate of acute rejection episodes noted at the 6 month follow-up (p < 0.0001).

Table 5 Acute rejection episodes and recipient deaths within 3 years post-LTx based on OPTN data as of March 10, 2023. Includes data from follow-ups for death, graft failure, or lost to follow-up in the follow-up periods when they occurred.

Timepoint		Hispanics	Caucasians	P-Value
Hospital Discharge	Validated Forms	1934	22767	
	Acute Rejection Episodes	151(7.81%)	1939(8.52%)	0.2815
	Total Deaths Reported	98(5.07%)	1056(4.64%)	0.3897
	Deaths Due to Infection	12(0.62%)	177(0.78%)	0.4389
	Deaths Due to Rejection	1(0.05%)	7(0.03%)	0.6345
6 Month Follow-Up	Validated Forms	1689	18991	
	Acute Rejection Episodes	4(2.37%)	132(0.70%)	<0.0001
	Total Deaths Reported	55(3.26%)	893(4.70%)	0.0067
	Deaths Due to Infection	10(0.59%)	172(0.91%)	0.1782
	Deaths Due to Rejection	0(0%)	0(0%)	N/A
1 Year Follow-Up	Validated Forms	1752	20488	
	Acute Rejection Episodes	351(20.03%)	5329(26.01%)	<0.0001
	Total Deaths Reported	77(4.39%)	1088(5.31%)	0.0971
	Deaths Due to Infection	22(1.26%)	168(0.82%)	0.0548
	Deaths Due to Rejection	0(0%)	2(0.01%)	0.6755
2 Year Follow-Up	Validated Forms	1652	19311	
	Acute Rejection Episodes	217(13.14%)	2928(15.16%)	0.0273
	Total Deaths Reported	147(8.90%)	1840(9.53%)	0.4015
	Deaths Due to Infection	16(0.97%)	172(0.89%)	0.7406
	Deaths Due to Rejection	0(0%)	2(0.01%)	0.6844
3 Year Follow-Up	Validated Forms	1515	17423	
	Acute Rejection Episodes	150(9.90%)	1805(10.36%)	0.5725
	Total Deaths Reported	157(10.36%)	1725(9.90%)	0.5659
	Deaths Due to Infection	22(1.45%)	188(1.08%)	0.1873
	Deaths Due to Rejection	0(0%)	0(0%)	N/A

4. Discussion

In our retrospective review of OPTN data, we sought to better understand the survival outcomes of Hispanic transplant recipients and identify possible contributing factors. We observed that Hispanic transplant candidates were younger, had worse pulmonary physiologic parameters, worse comorbid state, and worse functional status at the time of transplantation in comparison to Caucasians. Given this information alone, it would be expected that they would also have inferior post-LTx outcomes. Interestingly, however, Hispanics demonstrated significantly better long term post-LTx survival outcomes. Of note, Hispanics had a larger proportion of females, were transplanted at a younger age, and were more likely to receive a double lung transplant. All of these variables were considered protective factors according to our Cox proportional hazards model which may explain the improved long-term survival outcomes. Lastly, the only significant difference in the observed death rates over the first three years post-LTx showed that Caucasians have a higher death rate at 6 months.

Survival after lung transplantation is multifactorial and although there are identified factors that can contribute to a poor outcome, the role of race/ethnicity has not been clearly delineated. Prior studies have suggested possible race-based disparities may be playing a role. Despite comprising approximately 19% of the population of the United States [20], Hispanics are underrepresented among lung transplant recipients. According to the OPTN, Hispanics being transplanted in worse health is likely driven by decreased access to healthcare prior to referral for lung transplantation [21]. According to Mooney et al., waitlist access is lower in Black, Hispanic, and Asian candidates [12]. However, the 2020 OPTN/Scientific Registry of Transplant Recipients (SRTR) data report showed that the proportion of non-White lung transplant candidates has increased, with Black, Asian, Hispanic, and "other" races comprising 28.2% of the waiting list [21]. Despite the recent increase in access to the waitlist for Hispanics, a retrospective analysis of OPTN data published in 2021 showed Caucasian candidates were more likely to get allocated for a lung transplant than patients of any other ethnic group with similar LAS [22]. Hispanics also had a higher unadjusted waitlist mortality, but this was not significant after full risk adjustment [12].

Of interest, Iguidbashian et al. utilized standardized mortality ratios (SMR) to compare the mortality of the larger population to patients 10 years post-lung transplantation [23]. A SMR is the ratio of the number of deaths observed in a population over a given period to the number that would be expected over the same period if the study population had the same age-specific rates as the standard population. In this study, the largest discrepancy between observed and expected mortality were in Hispanics. Iguidbashain attributes this large SMR to the "well-known discrepancy in long-term survival for Hispanic and Black recipients" and the non-hospitalized Hispanic control group having a longer-life expectancy in general [23].

One of our additional unique findings was that a higher percentage of the Hispanic LTx recpients carried a diagnosis of restrictive lung disease (Group D) or pulmonary vascular disease (Group B) as the primary indication for transplantation. Additionally, the Cox proportional hazards model showed that Group B and D diagnoses were associated with significantly worse survival outcomes than that of Groups A or C. In alignment with our data, the 2020 OPTN/SRTR data report also noted that those with a Group C category (Cystic Fibrosis) had the best five-year survival followed by Group A (COPD), Group B (pulmonary vascular diseases), and then finally Group D (restrictive lung diseases) diagnoses [21]. Given this data, the Hispanic LTx recipients are being transplanted for diseases that have been associated with having the worst five-year survival rates, which does not align with their observed survival outcomes.

This contradiction has been termed the "Hispanic paradox" and has been described in both the general Hispanic population [24, 25] and in liver transplant recipients [26, 27]. Several non-biologic factors have been proposed to explain this finding, including "cultural effects" of strong family and social support, "healthy migrant effects," and "salmon-bias effects" that may off-set the initial "disadvantage" due to more severe disease state [25, 28]. None of these, however, have been substantially validated [29, 30] and it is unclear to what degree these factors are present within the lung transplant population. Nonetheless, post-transplant patients have close-follow-up and frequently utilize resources to improve health literacy, reduce medication errors, and break down cultural barriers.

We recognized the limitations of this study. First, statistical analyses should be interpreted with caution due to the very large sample size differences between Hispanics and Caucasians. Second, our study does not analyze all possible etiologies of the difference in survival outcomes, including socioeconomic factors, education status, etc.

In summary, we report that Hispanics are transplanted in worse health than that of Caucasians, yet exhibit higher long-term survival rates. Possible explanations according to our results include the higher percentage of females, transplantation occurring at a younger age, and a higher proportion of double lung transplants occurring in Hispanic patients. Further studies should be performed to assess underlying factors that may explain these findings, including but not limited to, cultural factors, education status, socioeconomic factors, and the variations of preceding lung pathology.

Abbreviations

6-MWD	Six-minute walk distance
BMI	Body mass index
BOS	Bronchiolitis obliterans syndrome
CF	Cystic fibrosis
CO	Cardiac output
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
LAS	Lung Allocation Score
LTx	Lung transplant
mPAP	Mean pulmonary arterial pressure
OPO	Organ procurement organizations
OPTN	Organ Procurement and Transplantation Network
PADP	Pulmonary artery diastolic pressure
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary capillary wedge pressure
SMR	Standardized mortality ratios
SRTR	Scientific Registry of Transplant Recipients
UNOS	United Network for Organ Sharing
WHO	World Health Organization

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Author Contributions

Michelle N. Bremer: Manuscript writing/editing, obtained data, data analysis, interpretation of data, study design. **Garrick J. Gama:** Manuscript editing, interpretation of data. **Omkar Rao:** Manuscript writing. **Eugene Golts:** Study concept. **Deepa Kurup:** Manuscript editing. **Aarya Kafi:** Manuscript editing, interpretation of data, study design. **Christine M. Lin:** Manuscript editing. **Gordon Yung:** Manuscript editing. **Kamyar Afshar:** Manuscript writing/editing, obtained data, study concept.

Competing Interests

The authors have declared that no competing interests exist.

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