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Racial and Socioeconomic Disparities in Pediatric Liver Transplant Outcomes: A Single-Center Experience

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Master of Public Health

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By

Rekha Thammana

Bachelor of Science

Cornell University

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Faculty Thesis Advisor: Rachel Patzer, PhD, MPH

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By Rekha Thammana

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Among 208 patients included in the cohort study, 51.0% were white, 34.6% black and 14.4% other races. A total of 27 patients (13.0%) experienced graft failure and 34 (16.4%) died during the median 8.3 years of study follow-up. In adjusted analyses, the rate of graft failure [HR 2.80, 95% CI (1.07, 7.34)] and mortality [HR 4.11, 95% CI (1.63, 10.37)] was significantly higher among minorities compared to whites.

After adjusting for SES and other clinical factors, minority race was associated with twice the rate of graft failure and four times the rate of mortality compared to white patients in a pediatric liver population. Further study of race and SES is warranted in this population.

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Chapter I: Background and Literature Review

Pediatric Liver Transplantation

Liver transplantation is indicated for a variety of reasons in pediatric populations, including congenital causes of liver disease such as biliary atresia, metabolic diseases in infants and young children, and acquired liver disease in older children (1, 2). End-stage liver disease (ESLD) necessitating transplant can be chronic or acute in onset (1, 2).

Children with chronic liver disease requiring transplant may have progressive primary cholestatic disease (e.g. patients with biliary atresia leading to cirrhosis after initial Kasai portoenterostomy) or hepatic-based metabolic disease with high risk of multi-system involvement (e.g. urea cycle defects, hemochromatosis, tyrosinemia.)(1). For those with chronic ESLD, the United Network of Organ Sharing (UNOS) maintains a waiting list of patients requiring liver transplantation.

Acute liver failure (ALF) is most commonly due to viral hepatitis or drug toxicities, although it is idiopathic in many pediatric cases (1, 2). Congenital causes of liver disease like hemochromatosis can also present with perinatal acute hepatic failure (1, 2). The natural history of ALF is not well understood, and transplant is currently the best treatment option for most patients (1, 3). Malignancy is another indication for transplantation, most well-described in children with hepatoblastoma and hepatocellular carcinoma (1).

The Organ Procurement and Transplantation Network (OPTN) instituted a numerical system for distributing liver grafts to recipients with the highest medical urgency. The Pediatric End-stage Liver Disease (PELD) score, developed in 2002, uses variables of bilirubin, INR, serum albumin, age greater than 1 year, and growth failure (4). PELD results from Studies of Pediatric Liver Transplantation (SPLIT), which is a registry that combines 44 centers in North America to examine transplant outcomes and their clinical risk factors (4-10). OPTN places most patients who present with ALF at the top of waiting lists as status 1A, while PELD scores are reserved for chronic liver

failure patients (3). OPTN uses PELD to identify patients who will benefit from transplantation and avoid transplant in futile cases, and the post-PELD era has shown an overall survival benefit after PELD introduction (11). Centers sometimes request exception letters for patients (~30% of all transplants nationally) who are thought to have a greater need for transplant than reflected in PELD scores (11-13).

Contraindications to liver transplantation include sepsis or high risk of sepsis, multi-organ failure, and malignancy outside liver (14). Several factors are associated with patient and graft survival in the pediatric liver transplantation population, including both pre- and post-transplant factors (15). Of 1790 children who underwent transplant in the U.S between 2007 and 2009, 52% of transplanted patients were white, 18% were black, 22% were Hispanic, 6.5% were Asian, and 2.2% were other races (16). Race has not been shown to correlate with post-transplant outcomes of graft survival and mortality thus far in pediatric populations. Patients age 1 to 5 years receive the most transplants, and children less than 1 year old have the highest mortality and graft failure rates (9, 16). Studies have not shown an overall effect of recipient age on long-term survival for those older than 1 year (3). Gender has not been found to correlate with patient outcomes (9). ESLD due to ALF is an independent predictor of mortality(9).

Donor and intra-operative characteristics are also predictors of pediatric patient and graft survival. Use of pediatric donors (<18 years old) in pediatric recipients correlates with improved outcomes due to improved size matching, while donor age less than 6 months old is associated with higher mortality (6, 9). Due to the limited supply of deceased donor liver grafts, living donor, split[1], and reduced sized[2] graft transplantation have emerged as alternatives to whole deceased donor grafts. Alternative grafts are associated with an increased complication rate, graft loss, and patient mortality (6, 8, 9). ABO incompatibility is associated with poor outcomes, while donor-recipient sex mismatch and intra-operative characteristics of cold and warm ischemic time have not been strongly associated

[1] Split liver grafts involve splitting one deceased donor graft into a left lateral segment used in pediatric patient and a medial and right segment used in an adult patient.
[2] Reduced sized grafts most often use a left lateral segment of a deceased donor.

with outcomes (8, 9). Post-transplant complications due to operative factors such as hepatic artery thrombosis, portal vein thrombosis, and biliary complications are associated with increased mortality and graft loss(9). More than one acute rejection episode after transplant is associated with decreased graft survival and less strongly associated with decreased patient survival (9).

Race and Socioeconomic Status in Pediatric Health Outcomes

A renewed global attention is being placed on social inequality (17). A large body of research defines the role of social class, economic and social resources, race/ethnicity, and a variety of other social environmental factors that play a role in determining health (18-27). The U.S. government includes social determinants of health in Healthy People 2020, which defines 10–year national objectives to improve the health of the nation (28).

In children, minority race and low socioeconomic status (SES) are correlated with negative health outcomes (19, 29). Racial discrimination and social inequality in a child's perinatal life and childhood can affect long-term health and cause premature mortality (30). Black race is a predictor of poor health outcomes in all life stages, possibly due to an increased effect of social stressors due to discrimination creating an allostatic load[3], measured by inflammatory biomarkers like cortisol (19, 29). The negative effects of black and minority race may be potentiated or even caused by low SES (31).

Link and Phelan argue that low SES and poor social support represent fundamental causes of disease (32). These factors signify an individual's and family's access to resources and knowledge needed to improve health (32). Moreover, experiences of social inequality in childhood can lead to chronic stress, relating to the development of many chronic diseases (e.g. hypertension, diabetes, cardiovascular disease) and inability to access and maintain treatment regimens (29, 30, 33). In children and adolescents, familial factors like parental education, family structure, social support and social capital are implicated in individual SES beyond social class and income/wealth (18, 20). The

[3] Allostatic load represents an individual's response to environmental challenges.

social gradient and degree of inequality in a community or region also has a large contribution to health in childhood (29).

Neighborhood Demographic Characteristics in Health Outcomes

Neighborhood demographic characteristics are powerful predictors of health status, sometimes used in conjunction with individual level demographic variables (24, 25, 34-38). When comparing the effects of neighborhood exposures of social inequality versus individual exposures, neighborhood exposures mirror individual SES measures and serve to enhance understanding of the effects of social variables on health (37, 38).

Neighborhood-level variables include percentages of individuals or households in a given geographic area with certain characteristics believed to relate to health and illness. As with individual descriptors of SES, these variables include wealth, income, household size, occupational class, employment status, education, crowding, and population density (25). Neighborhood indicators of low SES correlate with perinatal outcomes of low birthweight and preterm birth, which further correlate with adult conditions of diabetes and high blood pressure (29, 37, 38). Neighborhood SES also correlates with childhood and adolescent behaviors such as cigarette smoking, injuries, and mental health problems (39-41).

Background Summary

Race and SES are important variables in pediatric health outcomes at individual and neighborhood levels. These characteristics mediate a child's access to medical care and a family's ability to manage chronic disease. It is important to measure race and SES in the context of other demographic variables to optimize medical therapy and interventions for pediatric liver transplant recipients.

Chapter II: Manuscript

Racial and Socioeconomic Disparities in Pediatric Liver Transplant Outcomes: A Single-Center Experience

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Abstract

Racial and socioeconomic (SES) disparities have been found to affect liver transplantation outcomes in adult populations, but little research exists in pediatric liver transplant populations. The purpose of this study is to examine the effect of race on patient outcomes of graft survival and mortality following liver transplantation.

A retrospective cohort of pediatric patients (ages 0-22) who received a first liver transplant at Children's Hospital of Atlanta (CHOA) between 1998 and 2008 were followed through 2011 to capture graft failure and mortality events. Information on individual race, clinical, demographic, and SES variables were determined from CHOA records, referrals to the Georgia Transplant Foundation, and United Network for Organ Sharing (UNOS). Neighborhood characteristics were derived from US Census 2000 data by patient addresses. The association between race and the probability of graft failure and mortality was examined using Cox-Proportional Hazard models. Black and other non-white races were combined in analyses.

Among 208 patients included in the cohort study, 51.0% were white, 34.6% black and 14.4% other races. A total of 27 patients (13.0%) experienced graft failure and 34 (16.4%) died during the median 8.3 years of study follow-up. In adjusted analyses, the rate of graft failure [HR 2.80, 95% CI (1.07, 7.34)] and mortality [HR 4.11, 95% CI (1.63, 10.37)] was significantly higher among minorities compared to whites.

After adjusting for SES and other clinical factors, minority race was associated with twice the rate of graft failure and four times the rate of mortality compared to white patients in a pediatric liver population. Further study of race and SES is warranted in this population.

Introduction

Liver transplantation is the definitive treatment for end-stage liver disease (ESLD) in pediatric populations. Patient survival has improved in recent decades, with overall 1-year survival rates currently approaching 90% as compared to below 70 % prior to 1980 (42, 43). Research examining risk factors for patient and graft survival following transplantation have focused on recipient variables (patient demographics, ESLD etiology, comorbidities, previous transplant, health status and laboratory values at time of transplant), donor variables (e.g. graft type, donor age, ABO compatibility, donor-recipient matching), intraoperative variables (e.g. surgical technique, cold and warm ischemic time), and post-transplant treatment (immunosuppression) and complications (e.g. acute and chronic rejection, biliary leakage, hepatic artery thrombosis, infection) (1, 3, 6-9, 14, 15, 33). While many studies include race in demographic risk-stratification if available, the effects of health disparities such as race and socioeconomic status (SES) have not been studied in-depth in this population.

Health disparities are increasingly appreciated as important factors in the health status of pediatric population (28, 44). Moreover, the effects of health disparities in childhood have profound effects on health in adulthood (19, 23). As mortality due to severe childhood illness such as ESLD continues to decline, improved understanding of predictors of long-term health is necessary to limit morbidity and maintain quality of life.

SES is often difficult to describe in epidemiological studies due to a lack of standardized reporting of the many social variables related to health. Social support, family composition, parental education, as well as family income and wealth can all contribute to measures of SES in children and adolescents (18, 20-23, 25). In any population, social inequality and social gradients are useful in describing the effects of SES (27, 32). Along with individual SES factors, neighborhood measures of SES and inequality help describe the effects of sociodemographic variables on a child's health status (18, 25, 35). A combination of community-level factors may be useful in describing environmental

effects on SES, as Messer et al. used to describe perinatal outcomes in a diverse multi-state U.S. population (37, 38).

Several studies among the adult liver transplant population have examined the role of race and SES in transplant outcomes with variable results (45-51). Black race has been found to be an independent predictor of mortality in adult liver transplant recipients, even after the introduction of MELD scores intended to improve equity of organ allocation (47-49). SES has not been found to be an independent predictor of transplant outcomes, but national studies that examine the effects of SES in liver transplant outcomes are limited by the inadequate measurement of SES factors(45, 46, 50). For example, one study among the adult liver transplant population found that neighborhood-level income was not an independent predictor of poor outcomes, but the main exposure was measured on the zip-code rather than individual level, a less sensitive and robust measure of poverty (24, 46) .

The influence of race and SES on pediatric liver transplant outcomes is still not well understood. Very few studies in the pediatric ESLD population have examined the impact of sociodemographic factors on transplant outcomes. A study of national pediatric and adult data showed no significant difference in pediatric patient and graft survival (at 1, 3, 5, and 10 years) between racial/ethnic groups when examining national Scientific Registry of Transplant Recipients (SRTR) data from 1994 to 2006, although regional differences were not explored (52). Studies show African-American race as an independent predictor of acute and chronic graft rejection, which are risk factors for graft loss (8, 53). SES factors are associated with non-adherence to immunosuppressive medications in pediatric transplant recipients, placing them at greater risk of graft rejection and graft failure (33). In other solid organ transplantation, research has suggested an effect of race and/or SES on patient access and outcomes in pediatric populations (54). The Southeastern U.S. has been found to have higher levels of racial and socioeconomic inequalities, and health disparities have been described in adult access to transplantation (55, 56).

Research among adult liver transplant recipients suggests there may be racial and socioeconomic disparities in transplant outcomes, but little is known about the impact of race and SES among pediatric liver transplant recipients. The purpose of this study is to examine the association of race with outcomes following liver transplantation, including patient and graft survival. We hypothesize that minority race and low SES are associated with poor pediatric liver transplant outcomes at a large children's transplant center in the Southeastern U.S.

Methods

Data Sources

All pediatric patients (age 0-22 yrs) who received a transplant at Children's Hospital of Atlanta (CHOA) from January 1998 to December 2008 were included in this cohort study. Clinical, demographic, and outcome data were abstracted from patient charts using CHOA electronic medical systems (Epic and OTTR) and were used to determine exposure and outcome variables. Among Georgia residents, patients in need of financial aid were referred to Georgia Transplant Foundation (GTF); specific reasons included cost of medications, financial emergency, lodging, and difficulty accessing insurance. GTF provided individual SES and social support variables for those referred. The United Network for Organ Sharing (UNOS) provided data for donor characteristics, intraoperative characteristics, and post-transplant outcomes of graft failure and mortality.

Study Population

The study population consisted of 208 patients with first transplants at CHOA. All patients were included regardless of geographic region (17% of patients lived outside Georgia during the study period).

Outcome Variables

Outcome data on dates of patient mortality and graft failure were examined through November 2011, allowing a minimum of three years of follow-up. Dates of graft failure and mortality

were derived from UNOS data as well as CHOA medical charts. There was 100% agreement between mortality dates from both data sources. Two dates of graft failure reported in CHOA medical charts were not reported in UNOS, and these were included in analyses.

Primary Explanatory Variable

The primary explanatory variable for all analyses was race, as reported in CHOA medical charts or GTF records. If discrepant race/ethnicity was found from these sources, confirmation was sought from CHOA medical charts. Race was categorized as white, black, and other (non-white Hispanic, Asian, Native Hawaiian/Other Pacific Islander, Multi-racial, Unknown) for analysis. Race and ethnicity (e.g. non-white Hispanic) were reported as one variable in all data sources.

Patient-level Covariates

Clinical and demographic variables were obtained from CHOA medical charts, including age at transplant (further characterized <1, 1-5, 6-10, 11-17, and 18-22 years), sex (male, female), and etiology of ESLD (categorized as acute hepatic necrosis, biliary atresia, cholestatic liver disease/cirrhosis, metabolic disease, benign and malignant neoplasms, non-cholestatic liver disease/cirrhosis, and other diseases). Transplant characteristics from UNOS data included graft type (deceased donor whole, deceased donor reduced, split, or living donor), donor age (<1 or >17, 1-17 years), donor sex, and intra-operative cold ischemia time (hours).

Insurance type was determined from CHOA medical charts and GTF records. Insurance was categorized as public insurance (Medicaid, Peachcare for Kids[4]), private insurance, or other (COBRA, charity care, other) (57). Those categorized as private included participants with some public coverage (8.9% of cohort)[5] (57). All other secondary individual SES factors were from GTF at the time of initial evaluation; these include net monthly income (used to calculate net yearly income),

[4] Peachcare for Kids is part of the State Children's Health Insurance Program to cover families who meet 235% of federal poverty limits.
[5] Combined private/public insurance includes those who use the Katie Beckett Medicaid waiver, available regardless of family income, for disabled children who live at home.

highest parental employment (unemployed/disabled/retired, part-time, or full-time employment), highest parental education (some high school, completed high school or general equivalency diploma, some college or technical degree, traditional college or graduate school), usage of public assistance(supplemental security income (SSI), temporary assistance for needy families (TANF), other governmental welfare), and family structure (single or widowed, divorced or separated, married).

Neighborhood Level Covariates

Patient addresses from CHOA medical charts were geocoded and linked with census tracts for all patients residing in the U.S; census tracts are small geographic areas including approximately 4000 individuals. Thirteen (6.2%) of participants had only zip-code level data, in which case the closest geographical census tract was used. Neighborhood characteristics from the 2000 U.S. Census were used to create a composite neighborhood deprivation index (Neighborhood Change Database, GeoLytics, Inc., East Brunswick, NJ, 2003).

Neighborhood deprivation index (NDI) methodology is detailed elsewhere (37). It includes 8 variables within several domains related to health outcomes: income, poverty, employment, occupational status, family structure, and housing. Once all census data was pooled for 19 heterogeneous cities in the U.S., Messer et al. used a principal components analysis to create the index. The mean was standardized at 0 with standard deviations at 1 and -1. A higher (more positive) number represents more neighborhood-level deprivation while a lower (negative) number represents less deprivation. Six of the eight components of the index were also analyzed independently (% household (HH) poverty rate, % HH seeking public assistance, % female-headed HH, % HH with male unemployment, %HH with annual income <$30,000) for the entire population as well as for the subset of individuals referred to GTF.

Data Analysis

All demographic, clinical, and socio-demographic status variables were compared by race, graft status, and mortality. Differences were assessed by chi-squared or analysis of variance tests (Fisher or Wilcoxon signed-rank tests were used if data were non-parametric).

Separate Cox-proportional Hazards models were created to examine the effect of minority race on 1) time to graft failure and 2) time to mortality. The proportional hazards (PH) assumption was evaluated for all baseline variables determined to be influential *a priori (58)*. Individual level SES variables collected from GTF on a subset of patients were not considered for further analysis of graft failure and mortality due to high degree of missingness (~50%). Collinearity was assessed for all variables in both models. For purposes of modeling, variables were regrouped *a priori* into high risk and low risk groups. Minority races were combined (black + other races) to compare against white race. New variables were categorized as such: age at transplant (<1 vs. ≥1 year old), disease etiology (biliary atresia and acute hepatic necrosis vs. other etiologies), graft type (technical variants vs. cadaveric whole), donor age (1-17 y.o. vs. other ages), insurance type (public vs. private); the neighborhood deprivation index was used as a continuous variable.

Bivariate analyses between race and included variables were performed for outcomes of graft failure and mortality. Variables determined *a priori* and were sequentially added to the model with race to adjust for clinical and demographic factors, and then SES variables were added to create the fully adjusted model. Interaction was assessed between SES variables (insurance type and NDI) and race using likelihood ratio tests. Likelihood ratio tests were also used to assess model significance as well as for addition and removal of individual variables. Hazard ratios (HR) and 95% confidence intervals (CI) for the effect of minority race were reported for each model. Because of the small sample size, we further explored interaction between racial and SES variables using stratified analyses. We examined homogeneity of HR stratified by race and insurance status, then adding NDI to each stratum. We then calculated the interaction contrast across strata to test for positive and negative interaction.

For all analyses, a two-tailed significance level of $p<0.05$ was used. All statistical analyses were performed with SAS 9.3 (Cary, NC), and geocoding was performed using ArcGIS 10 (Redlands, CA). Study protocol was approved by Emory University IRB.

Results

Our cohort consisted of patients categorized as white (50.1%), black (34.9%), non-white Hispanic (7.1%), Asian (4.7%), Native Hawaiian or Pacific Islander (0.9%), and multi-racial or of unknown race (1.4%). For analysis, participants were grouped into white (50.1%), black (34.9%) and other race/ethnicities (14.2%) and then further characterized to white (50.1%) and minority races (49.9%) due to small sample size. Compared to national racial demographics, our cohort shows higher percentages of black patients (Figure 1). Median follow-up time was 8.3 years and varied between white, black and other races (8.4, 8.8, 5.7 years; $p=0.1327$). Median age at transplant for all participants was 3.5 years [interquartile range (IQR) 1.0, 13.2] with a majority of patients receiving transplants at ages <5 years old (60.0%). Black and other minority participants had higher frequencies of transplant at age <1 year compared to white patients (Table 1). Biliary atresia accounted for the most common reason for transplantation amongst all participants, with higher relative frequencies in minority patients (Table 1). White patients received a higher percentage of whole grafts from deceased donors relative to black and other minority patients (59.3% vs. 55.4% & 46.7%; $p<0.001$). Black patients received a lower percentage of grafts from donors ages at low risk for complication (1-17 y.o.) compared to white and other minority participants (33.8% vs. 51.4% & 63.3%; $p=0.0099$). Sex, donor-sex mismatch and cold ischemic intraoperative time did not vary significantly across all three racial categories (all $p>0.05$).

Health insurance type was missing for six patients (2.8%), four of whom had passed away post-transplant (of whom n=2 were black and n= 2 were white). While health insurance coverage was almost evenly split between public/other and private overall (51% vs. 49%), black and other minority races accounted for significantly higher percentages of public insurance utilization (35.2%

vs. 63.9 & 75.9%, p<0.0001). Neighborhood indicators of income, poverty, public assistance usage, female-headed households, and male unemployment were all significantly different across racial groups, with the highest percentages of low SES indicators found for black participants (p<0.001, Table 2a). Overall neighborhood deprivation based on the indicators above was highest for black patients as well (p<0.0001). In addition, Georgia Transplant Foundation (GTF) provided assistance to 55% of the cohort, with highest percentages for all individual indicators of low SES or social support present in black patients (Table 2b). When neighborhood indicators were analyzed for the subset of GTF (for whom individual level SES measures were available), neighborhood level indicators greatly underestimated individual-level SES and social support in all but unemployment figures (Figure 2).

A total of 30 patients (14.2%) experienced death-censored graft failure. When comparing baseline clinical, demographic, and SES indicators across graft status post-transplant, only graft type, donor age, and neighborhood deprivation index level were found to be significantly different by graft status after first transplant (Table 3). Thirty-five (16.5%) were deceased at the end of the study period. Among all indicators analyzed for mortality, only age at transplant was found to differ significantly (Table 4).

In multivariable Cox models for graft failure and mortality, interaction was not found to be significant when assessed between our two included SES variables (insurance type and NDI) and race and SES variables. In stratified analyses, positive interaction between race and private vs. public insurance status as well as neighborhood deprivation was found for both graft failure (white| private: HR=0.47, public: HR=0.43; minority| private: HR=2.11, public: HR=2.32) and mortality (white| private: HR=0.32, public: HR=0.18; minority| private: HR= 3.15, public: HR=5.61).

The crude model for race alone showed a non-significant increased rate of graft failure among minority participants across the follow-up period [HR 1.60, 95% CI (0.71, 3.58)]. When adjusted for clinical and demographic factors, this increased to 2.2 times the rate of white participants

[HR 2.23, 95% CI (0.93, 5.38)]. After SES variables were included, the rate of graft failure in minority participants increased to 2.8 that of white participants [2.80, 95% CI (1.07, 7.34)] (Table 5).

An increased rate of mortality was found when examining the effect of minority race as compared to white patients [3.32 95% CI (1.55, 7.15)]. After adjusting for clinical and demographic factors, the rate of mortality for minorities remained similar to crude estimates [HR 3.33, 95% CI (1.48, 7.50)]. When SES variables were also included, the rate of mortality increased to 4.1 times the rate of white participants [HR 4.11, 95% CI (1.63, 10.37)] (Table 5).

Discussion

Our study is the first to directly examine the effect of race on pediatric liver transplant outcomes while adjusting for additional baseline demographic, clinical, and SES characteristics. The degree of racial and socioeconomic inequality found in the Southeastern U.S. is reflected in the stark findings of this study. The effect of minority race led to four times the rate of mortality as compared to white patients even when adjusting for appropriate clinical and SES factors, while graft failure increased twofold after full adjustment. In fact, both models showed an increased effect size after SES adjustment, implying that SES does not fully explain the effects of race. The adjusted effect size of minority race on mortality is comparable to serious complications like post-operative sepsis or portal vein thrombosis in a larger multi-center cohort (9). The effect of minority race on graft failure is comparable to ICU admission and intubation prior to transplant (9).

While national studies have not shown an association between race and transplant outcomes, there are racial differences between our cohort and national pediatric liver transplant populations in proportions of black and other races (Figure 1). These differences may follow regional patterns and require further study. Our population includes a higher percentage of black patients and lower percentages of other minority races as compared to a national population. Overall insurance status is similar to recent national statistics, which include an approximately even ratio of private to public insurance coverage for pediatric patients (16). These insurance statistics are not stratified by race for

further comparison. While national cohorts and reported national statistics include reported race, there are no standardized measures of SES beyond insurance categories.

Race is often included in baseline characteristics but either not further examined in its relationship to transplant outcomes or examined without inclusion of other social determinants of health. One major strength of our study is the first use of individual SES (insurance status) in combination with neighborhood deprivation in pediatric transplant literature. The index used to describe levels of deprivation in our population is based on census tract data, which is more sensitive and robust than data based on zip code level information (35).

Our study also uniquely involves a subset of patients with detailed demographic information, which has not been described well previously in transplant outcomes research. The CHOA transplant population included many families with low socioeconomic status and low social support indicators (Table 2). For all who were referred for assistance to Georgia Transplant Foundation, 56% received public assistance at the time of initial evaluation and 26% had partial high school listed as highest parental education. The prevalence of low SES indicators is even more pronounced when stratified by race (Table 2). All individual indicators of low SES were present at higher percentages in our black patients. Neighborhood indicators show a similar distribution. Furthermore, we can compare neighborhood and individual indicators for patients who were referred to GTF. While they should not be used as a proxy for individual level indicators, neighborhood census data used in analysis severely underestimates the true level of deprivation for many individuals in our study, especially when examined by race (Figure 2).

Interaction between race and insurance status and NDI was not found to be statistically significant in modeling both graft failure and mortality. Yet, in stratified analyses, we found that the effect of minority race on both graft failure and mortality varied by health insurance status which is suggestive of interaction. A paradoxical effect of private vs. public insurance was found for white participants in risk of graft failure and mortality: public insurance led to a higher HR than private

insurance, which is the opposite of its expected effect. The lack of statistical significance and paradoxical findings in interaction analyses are most likely due to the small size of our cohort.

Several limitations exist in this study relating to the small sample size, limitations of data sources, and length of patient follow-up time. Racial categories were combined for analysis, which limits conclusions that can be drawn for other race/ethnicities. Further, this study was a single-center study in the Southeastern U.S.; results may not be generalizable to other pediatric liver transplant recipients outside of this region. While we used numerous individual and neighborhood SES factors, our assessment of SES for each patient may be incomplete. Multiple data sources provided different estimates of factors like insurance type which required further comparison in the transplant record, and insurance type also varies based on timing of data sources due to normal changes in coverage. Also, insurance status provides incomplete information on economic status in the case of children because of additional programs and eligibilities for families to improve coverage.

Direct individual SES and social support characteristics were limited to those referred to GTF for financial need, but these more detailed SES measures were not available to the ~50% of our cohort who did not seek assistance from GTF. However, since CHOA offers information about GTF services to all patients, we assume that those who did not seek GTF assistance were of a higher SES than those who did seek assistance. Using U.S. Census 2000 data for neighborhood characteristics is another limitation, as many families in the Southeast experienced large economic fluctuations in the decade between 2000 and 2010. Yet, the negative economic trend in the Southeastern U.S. implies that neighborhood covariates underestimate SES for our cohort of patients. Thus, our estimates of the impact of minority race on poor outcomes post-transplant could potentially underestimate the racial disparities that exist in mortality and graft failure following pediatric liver transplantation.

Additionally, there may be additional unmeasured factors that could account for some of the observed racial differences in outcomes. For example, we were unable to measure several clinical

factors in our study. PELD scores, which are only available for patients with chronic liver failure, were not determined in out cohort due to high degree of missingness and exceptions in our population. Clinical changes in operative characteristics and treatment post-transplant also occurred over the study period and were only partially accounted for in multivariable analyses. Thus, residual or unmeasured confounding could partially explain some of the observed racial differences in patient and graft survival that we observed.

Future Directions

The results of this study imply a need to risk-stratify for racial and socioeconomic variables when examining pediatric liver transplant outcomes. The large associations between minority race and negative outcomes post-transplant implore further research in this area. As survival after ESLD and pediatric liver transplantation continues to improve, a thorough understanding of neighborhood factors is needed to ensure equality of outcomes across racial and socioeconomic groups. In order to reduce morbidity and improve quality of life for pediatric liver transplant recipients, both individual and neighborhood SES and social support factors must be examined in conjunction with other clinical and demographic characteristics. An area of future research is examining the effect of SES on a national pediatric liver transplant population as well as exploring regional differences.

Tables

Table 1. Clinical and demographic characteristics of study population at time of transplantation (1998-2008).

Clinical Variables	Study Population N= 208	White N(%) N= 106 (51.0)	Black N(%) N=72 (34.6)	Other N (%) N= 30 (14.4)	p value
Age at transplant, median (IQR)	3.5 (1.0, 13.0)	4.2 (1.3,13.5)	3.3 (0.9, 13.5)	1.2 (0.7, 5.4)	**0.014**
Age categories, N (%), years					**0.0234**
<1	55 (26.4)	19 (17.9)	23 (31.9)	13 (43.3)	
1 to 5	71 (34.1)	41 (38.7)	20 (27.8)	10 (33.3)	
6 to 10	25 (12.0)	15 (14.2)	7 (9.7)	3 (10.0)	
11 to 17	36 (17.3)	21(19.6)	12 (16.2)	4 (13.3)	
18 to 22	21 (10.1)	10(9.4)	11 (15.3)	0 (0)	
Female Sex, N(%)	117 (56.3)	55 (51.9)	46 (63.9)	16 (53.3)	0.2683
Disease etiology					**0.0008**
Acute hepatic necrosis	32 (15.4)	11 (10.4)	12 (16.7)	9 (30.0)	
Biliary atresia	83 (39.9)	30 (28.3)	40 (55.6)	13 (43.3)	
Cholestatic liver disease/cirrhosis	10 (4.8)	5 (4.7)	3 (4.2)	2 (6.7)	
Metabolic disease	24 (11.5)	18 (17.0)	4 (5.6)	2 (6.7)	
Neoplasms (benign and malignant)	9 (4.3)	7 (6.6)	1 (1.4)	1 (3.3)	
Non-cholestatic liver disease/cirrhosis	35 (16.8)	23 (21.7)	11 (15.3)	1 (3.3)	
Other	15 (7.2)	12 (11.3)	1 (1.4)	2 (6.7)	
Transplant Characteristics (first transplant only)					
Transplant graft type, N (%)					**<0.0001**
Deceased Donor, Whole	117 (56.3)	64 (60.4)	39 (54.2)	14 (46.7)	
Deceased Donor, Reduced	63 (30.3)	23 (21.7)	25 (34.7)	15 (50.0)	
Split	8 (3.9)	0 (0.0)	7 (9.7)	1 (3.3)	
Living Donor	20 (9.6)	19 (17.9)	1 (1.4)	0 (0.0)	
Donor-recipient sex mismatch*	107 (51.7)	52 (49.5)	37 (51.4)	18 (60.0)	0.5976
Donor age, N (%)*					**0.0099**
1-17 y.o.	97 (46.9)	53 (50.5)	25 (34.7)	19 (63.3)	
0-1 y.o., >17 y.o.	110 (53.1)	52 (49.5)	47 (66.3)	11 (36.7)	
Cold Ischemic Time, mean± SD †	8.5 ±3.8	8.6 ± 4.6	8.5 ± 2.4	7.9 ±2.8	0.7460

*0.4% of patients missing; †30.1% of patients missing; p-values in bold are statistically significant ($p<0.05$)

Table 2a. Socioeconomic and social status variables by race for study population, from transplantation through follow-up period (1998-2011).

Socioeconomic and Social Status	Study Population N= 208	White N(%) N= 106 (51.0)	Black N(%) N=72 (34.6)	Other N (%) N= 30 (14.4)	p value
Health Insurance Coverage+					**<0.0001**
Public (or Other)	104 (51.5)	37 (35.9)	45 (64.3)	22 (75.9)	
Private	98 (48.5)	66 (64.1)	25 (35.7)	7 (24.1)	
Neighborhood level indicators ++					
% Poverty, median (IQR)	9.0 (3.9, 17.3)	5.8 (3.3, 13.3)	14.4 (8.0, 23.0)	6.3 (2.6, 13.1)	**<.0001**
% Low parental education (did not complete High School), median (IQR)	18.4 (10.6, 30.8)	16.6 (9.4, 28.0)	25.5 (11.7, 35.5)	13.6 (6.7, 20.7)	**0.0023**
% Seeking public assistance (SSI, TANF, Welfare), median (IQR)	5.5 (2.2, 10.5)	4.7 (2.2, 8.6)	9.6 (4.5, 16.3)	3.1 (1.7, 6.1)	**<.0001**
% Yearly income <$30,000, median (IQR)	24.4 (12.2, 38.5)	18.9 (11.0, 32.1)	32.0(21.7, 48.7)	14.2 (7.6, 28.7)	**<.0001**
% Female-headed Household, median (IQR)	20.8 (11.8, 33.9)	16.8 (10.0, 26.4)	31.7 (21.4, 47.3)	15.8 (10.0, 29.4)	**<.0001**
% Male Unemployment, median (IQR)	4.0 (2.4, .4)	3.0 (2.1, 5.2)	6.2 (3.5, 8.9)	3.4 (2.4, 5.0)	**<.0001**
Neighborhood Deprivation Index (NDI)*, mean ± SD	-0.34 ± 0.93	-0.59 ± 0.72	0.18 ± 1.01	-0.73 ± 0.84	**<.0001**

*NDI represents the level of socioeconomic deprivation in a census tract based on an analysis of 19 heterogeneous U.S. cities using 2000 U.S. census data (37). If NDI=0, deprivation for a given area is at the mean of this broad sample of U.S. cities. +1 or -1 represents a standard deviation of deprivation above or below the mean respectively. [Deprivation is based on %household (HH) poverty rate, % HH seeking public assistance, % female-headed HH, % HH with unemployed persons, %HH with annual income <$30,000, % males employed in managerial and professional occupations, % residents with crowded housing.]

+2.8% missing

++represents information regarding all households in a participant's census tract; 0.9% missing due to addresses outside U.S.

Table 2b. Socioeconomic and social status variables by race for study population from Georgia Transplant Foundation, from transplantation through follow-up period (1998-2011).

Socioeconomic and Social Status	Study Population N= 208	White N(%) N= 106 (51.0)	Black N(%) N=72 (34.6)	Other N (%) N= 30 (14.4)	p value
Sought GTF assistance, N (%)	114 (54.8)	50 (47.2)	49 (68.1)	15 (50.0)	**0.0195**
Among n= 114 who sought assistance					
Net Yearly Income <30,000, N (%)[1]	79 (70.5)	27 (55.1)	41 (85.4)	11 (73.3)	**0.0045**
Highest Parental Education, N (%) [2]					**0.0012**
Partial High School	20 (26.0)	6 (15.8)	14 (46.7)	0	
High School Graduate	40 (52.0)	21 (55.3)	13 (43.3)	6 (66.7)	
Partial College	7 (9.1)	2 (5.3)	3 (10)	2 (22.2)	
Standard College or Master's Degree	10 (11.7)	9 (23.7)	0	1 (11.1)	
Parental Employment status, N (%)[3]					**0.0018**
Full-time or Student	44 (44.4)	25 (56.8)	10 (23.8)	9 (69.2)	
Part-time	14 (14.1)	5 (11.4)	6 (14.3)	3 (23.1)	
Unemployed, Disabled, or Retired	41 (41.4)	14 (31.8)	26 (61.9)	1 (7.7)	
Income source, N (%)[4]					0.0504
Public assistance (SSI, TANF, Welfare)	58 (56.9)	22 (47.8)	31 (70.5)	5 (41.7)	
Family structure, N (%)[5]					**<0.0001**
Married	45 (42.1)	25 (53.2)	10 (21.7)	10 (71.4)	
Divorced or Separated	12 (11.2)	11 (23.4)	0	1 (7.1)	
Single or Widowed	50 (46.7)	11 (23.4)	36 (78.3)	3 (21.4)	

[1] 1.8% missing
[2] 32.5% missing
[3] 13.2% missing
[4] 10.5% missing
[5] 6.1% missing
p-values in **bold** are statistically significant ($p<0.05$)

Table 3. Clinic, demographic, and socioeconomic variables by graft status.

Clinical and demographic variables	Study Population N= 208	Graft Failure=Yes N= 27 (13.0%)	Graft Failure= No N= 181 (87.0%)	p-value
Age at transplant, median (IQR)	3.5 (1.0, 13.0)	1.2 (0.8, 12.8)	3.9 (1.0,13.4)	0.0744
Age categories, years, N (%)				**0.0444**
<1	55 (26.4)	12 (44.4)	43 (23.8)	
1 to 5	71 (34.1)	8 (29.6)	63 (34.8)	
6 to 10	25 (12.0)	0 (0.0)	25 (13.8)	
11 to 17	36 (17.3)	3 (11.1)	33 (18.2)	
18 to 22	21 (10.10)	4 (14.8)	17 (9.4)	
Female Sex, N(%)	117 (56.3)	13 (48.2)	104 (57.5)	0.4090
Disease etiology				0.8635
Acute hepatic necrosis	32 (15.4)	4 (14.8)	28 (15.5)	
Biliary atresia	83 (39.9)	11 (40.7)	72 (39.8)	
Cholestatic liver disease/cirrhosis	10 (4.8)	2 (7.4)	8 (4.4)	
Metabolic disease	24 (11.5)	4 (14.8)	20 (11.1)	
Neoplasms (benign and malignant)	9 (4.3)	2 (7.4)	7 (3.9)	
Non-cholestatic liver disease/cirrhosis	35 (16.8)	3 (11.1)	32 (17.7)	
Other	15 (7.2)	1 (3.7)	14 (7.7)	
Transplant Characteristics (first transplant only)				
Transplant graft type, N (%)				**<.0001**
Deceased Donor, Whole	117 (56.3)	10 (37.0)	107 (59.1)	
Deceased Donor, Reduced	63 (30.3)	9 (33.3)	54 (29.8)	
Split	8 (3.9)	2 (7.4)	6 (3.3)	
Living Donor	20 (9.6)	6 (22.2)	14 (7.7)	
Donor-recipient sex mismatch*	107 (51.7)	13 (48.2)	94 (52.2)	0.8368
Donor age, N (%)*				**<.0001**
1-17 y.o.	97 (46.9)	4 (14.8)	106 (58.9)	
0-1 y.o., >17 y.o.	110 (53.1)	23 (85.2)	74 (41.1)	
Cold Ischemic Time, mean± SD†	8.5 ±3.8	8.4 ± 2.9	8.5 ± 3.9	0.8794
Socioeconomic Status				
Health Insurance Coverage+				0.8366
Public (or Other)	104 (51.5)	13 (48.2)	91 (52.0)	
Private	98 (48.5)	14 (51.9)	84 (48.0)	
Neighborhood level indicator				
Neighborhood Deprivation Index ++, mean ± SD	-0.34 ± 0.93	-0.76± 0.78	-0.27 ± 0.93	**0.0099**

*0.4% of patients missing; †30.1% of patients missing

+2.8% missing, ++represents information regarding all households in a participant's census tract; 0.9% missing due to addresses outside U.S.; p-values in **bold** are statistically significant ($p<0.05$)

Table 4. Clinic, demographic, and socioeconomic variables by mortality.

Clinical and demographic variables	Study Population N= 208	Deceased N= 34 (16.4%)	Alive N= 174 (83.7%)	p-value
Age categories, yrs, N (%)				**0.0025**
<1	55 (26.4)	13 (38.2)	42 (24.1)	
1 to 5	71 (34.1)	8 (23.5)	63 (36.2)	
6 to 10	25 (12.0)	0 (0.0)	25 (14.4)	
11 to 17	36 (17.3)	5 (14.7)	31 (17.8)	
18 to 22	21 (10.10)	8 (23.5)	13 (7.5)	
Female Sex, N(%)	117 (56.3)	20 (58.8)	97 (55.8)	0.8506
Disease etiology				0.9065
Acute hepatic necrosis	32 (15.4)	7 (14.4)	25 (14.4)	
Biliary atresia	83 (39.9)	14 (41.2)	69 (39.7)	
Cholestatic liver disease/cirrhosis	10 (4.8)	1 (2.9)	9 (5.2)	
Metabolic disease	24 (11.5)	5 (14.7)	19 (10.9)	
Neoplasms (benign and malignant)	9 (4.3)	1 (2.9)	8 (4.6)	
Non-cholestatic liver disease/cirrhosis	35 (16.8)	5 (14.7)	30 (17.2)	
Other	15 (7.2)	1 (2.9)	14 (8.1)	
Transplant Characteristics (first transplant only)				
Transplant graft type, N (%)				0.7543
Deceased Donor, Whole	117 (56.3)	19 (55.9)	98 (56.3)	
Deceased Donor, Reduced	63 (30.3)	11 (32.4)	52 (29.9)	
Split	8 (3.9)	2 (5.9)	6 (3.5)	
Living Donor	20 (9.6)	2 (5.9)	18 (10.3)	
Donor-recipient sex mismatch*	107 (51.7)	16 (47.1)	91 (52.6)	0.5544
Donor age, N (%)*				0.6882
1-17 y.o.	97 (46.9)	17 (50.0)	80 (46.2)	
0-1 y.o., >17 y.o.	110 (53.1)	17 (50.0)	93 (53.8)	
Cold Ischemic Time, mean± SD†	8.5 ±3.8	8.5 ± 3.1	8.5 ±3.9	0.9492
Socioeconomic Status				
Health Insurance Coverage+				0.3301
Public (or Other)	104 (51.5)	18 (60.0)	86 (50.0)	
Private	98 (48.5)	12 (40.0)	86 (50.0)	
Neighborhood level indicators ++				
Neighborhood Deprivation Index, N (%)	-0.34 ± 0.93	-0.13 ± 1.04	-0.38 ± 0.91	0.1514

*0.4% of patients missing; †30.1% of patients missing

+2.8% missing;

++0.9% missing due to addresses outside U.S., represents information regarding all households in a participant's census tract

p-values in **bold** are statistically significant ($p<0.05$)

Table 5. Multivariable Cox-Proportional Hazard Models for Effect of Minority Race on Graft Failure and Mortality, Adjusted for Clinical and Demographic Characteristics

Variables	Minority race*: White HR (95% CI)	p value
Models for Graft Failure		
Crude models		
Race alone	1.60 (0.74, 3.45)	0.2290
Bivariate Analyses		
Race + Age at transplant	1.37 (0.62, 3.01)	0.0707
Race + ESLD Etiology	1.69 (0.75, 3.82)	0.4479
Race + Donor Age	1.84(0.85, 3.97)	**<.0001**
Race + Graft Type	1.52 (0.70, 3.28)	0.0678
Race + Insurance	1.79 (0.80, 4.02)	0.3368
Race + Neighborhood Deprivation Index (NDI)	2.18 (0.99, 4.76)	**0.0040**
Race adjusted for Clinical/Demographic Factors Race+ Age at transplant + Donor Age + Graft Type +ESLD Etiology	2.23 (0.89, 5.57)	**<.0001**
Fully Adjusted Model Race+ Age at transplant + Donor Age + Graft type + ESLD Etiology + Insurance + NDI	2.80 (1.07, 7.34)	**<.0001**
Models for Mortality		
Crude model		
Race alone	3.32 (1.55, 7.15)	**0.0009**
Bivariate Analyses		
Race + Age at transplant	3.10 (1.44, 6.70)	**0.0022**
Race + ESLD Etiology	3.40 (1.53, 7.60)	**0.0041**
Race + Donor Age	3.35 (1.60, 7.21)	**0.0040**
Race + Graft Type	3.32 (1.55, 7.15)	**0.0041**
Race + Insurance	4.03 (1.68, 9.68)	**0.0021**
Race + NDI	3.19 (1.45, 7.04)	**0.0036**
Race adjusted for Clinical/Demographic Factors Race + Age at transplant + Donor Age + Graft type + ESLD Etiology	3.33 (1.48, 7.50)	**0.0228**
Fully Adjusted Model Race + Age at transplant + Graft type + NDI+ Insurance + ESLD Etiology + Donor Age	4.11 (1.63, 10.37)	**0.0755**

*Minority race includes patients categorized as African-American and Other races

p-values in **bold** are statistically significant ($p<0.05$)

Figures

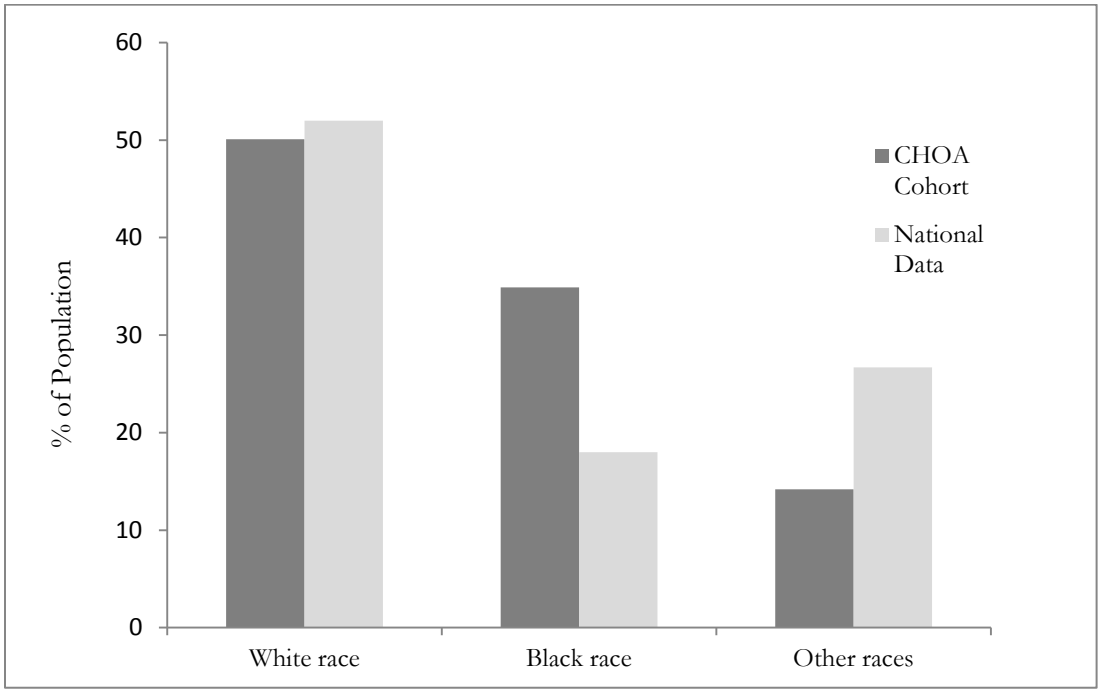

Figure 1. Comparison of racial distribution of patients in our Children's Hospital of Atlanta (CHOA) cohort versus national pediatric liver transplantation data (16).

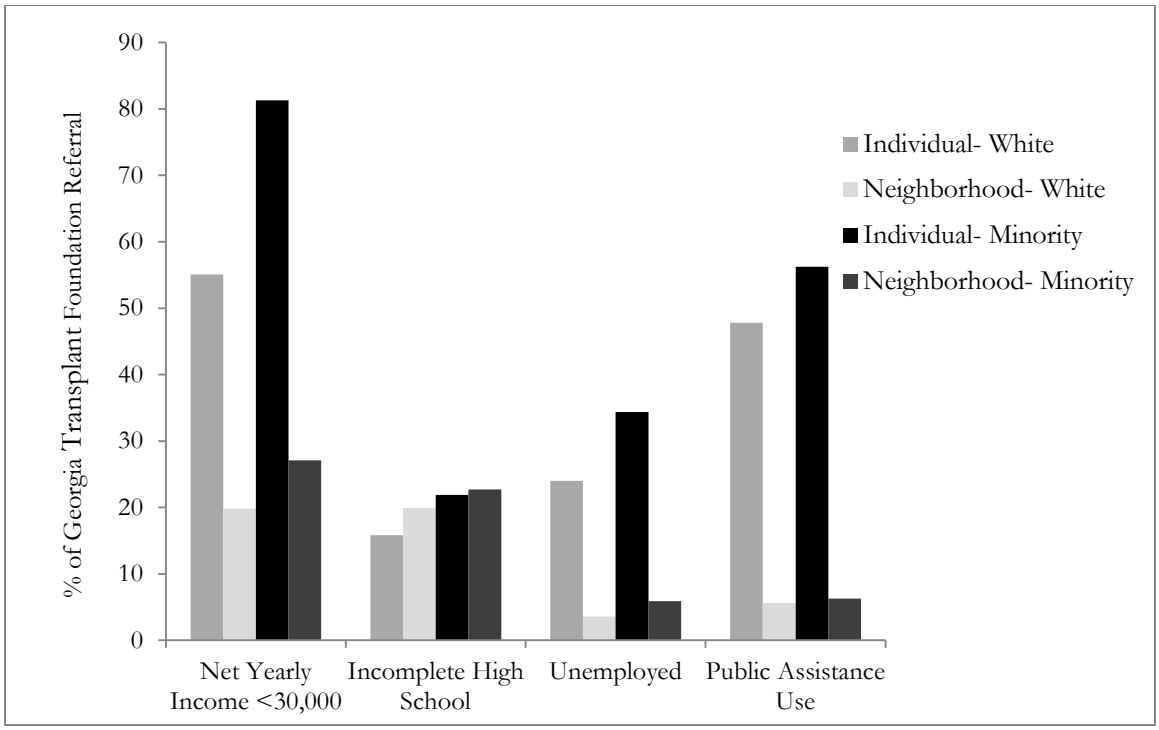

Figure 2. Comparison of individual and neighborhood sociodemographic factors in population referred to Georgia Transplant Foundation (GTF) for financial assistance (N=114).

Chapter III: Summary, Public Health Implications, Possible Future Directions

Summary

Race is a strong independent predictor of graft failure and mortality in a large pediatric transplant center in the Southeastern U.S. After adjustment for clinical and demographic factors, minority race is associated with greater than 4 times greater rate of mortality and 2 times rate of graft failure compared to whites [mortality: HR 4.11, 95% CI (1.63, 10.37); graft failure: HR 2.80, 95% CI (1.07, 7.34)] (Table 5). These findings reflect the racial and SES disparities found in the Southeastern U.S. (55).

Public Health Implications

Between 2007 and 2009, 1790 children received liver transplants in the U.S., with approximately 800 children added to liver transplant wait lists annually (16). While these children only account for a tiny fraction of the 74.2 million children living in the U.S., the public health impact of their illness is broad-reaching (59). Due to improvements in transplantation and treatment regimens, children post-transplant have the opportunity to live longer and more fulfilling lives as adults.

Along with other survivors of childhood illness, these patients represent a new challenge to health care delivery and chronic care management (5, 7, 10). Survivors of liver transplant receive long-term immunosuppressive therapies, increasing their risk of infection and other complications (10). They continue to utilize high levels of health care resources and experience a great deal of morbidity from their disease, although health-related quality of life (HRQOL) in liver transplant recipients is comparable to other survivors of childhood illness like (7).

Research in social determinants of health will help to understand predictors of poor health outcomes and to maintain quality of life for transplant recipients. More importantly, SES and race relate to post-transplant complications and non-adherence to therapy, leading to increased morbidity

and decreased HRQOL (6, 33, 53). Post-transplant complications are the most important predictors of graft and patient survival as seen in a large multivariable analysis, making race and SES factors even more crucial to fully understand (9).

Possible Future Directions

Many future directions exist in this field. A regional multi-center study looking a race and SES will help to understand if these disparities are present in similar centers. A national pediatric study examining regional variations will better elucidate whether of racial and SES disparities are present in this population. Further national studies with larger patient populations can also analyze race and SES by other clinical and demographic factors known to be relevant to transplant outcomes, like ESLD etiology, donor-recipient matching, and several others. Pre-transplantation factors like waiting list time and referral to transplant have not been studied in this population. Racial and SES variables may be important to these processes, as they relate to access to healthcare and healthcare utilization (19, 29).

In our population, further study is needed to understand the cause of racial disparities in graft and patient survival. Post-transplant outcomes are an important area of research, and differences in post-transplant therapy and hospitalization are important to explore. We will also examine post-transplant complications like portal vein thrombosis to see if there is any racial and/or SES components.

In the pediatric liver transplant recipient population, it is important to collect comprehensive individual SES data, as insurance status used in our study does not fully describe individual SES in pediatric populations. Pediatric populations have greater access to public insurance due to greater eligibility for insurance compared to adults[6] (57). One method to describe individual SES may be creating a survey specific to pediatric populations, as described in Goodman et al. (22). This method

[6] In the state of Georgia, children are eligible for Medicaid at 185% the federal poverty level (FPL) under 1 year old, 133% for ages 1 to 5, and 100% FPL for ages 6 to 19. Non-pregnant adults with children are eligible at 26% of FPL by contrast.

involves asking pediatric patients about their subjective social status using a ladder analogy to compare themselves to the U.S. population (22). Another method is qualitative interviews to assess families' perceived needs in the transplantation process. For those deemed to be at-risk, these studies will identify areas for future intervention and support for at-risk patients, hopefully reducing the disparities seen in our study.

Potential interventions to decrease disparities in our population include close clinical follow-up and improving a family's ability to access health care. In order to improve both of these factors, CHOA should strengthen relationships with referring providers and maximize follow-up near families' homes. While 83% of patients live outside of Georgia, many do not live in the Atlanta metro area where CHOA is located. Furthermore, we can examine the use of multi-disciplinary education sessions to stress the importance of follow-up and adherence as well as follow-up provided by nurse educators (60). After further study described above, we can target interventions to the most vulnerable time period (pre-transplant vs. during transplant vs. post-transplant). In pediatric asthma patients, interventions that examine psychosocial assessments of barriers to care are useful tools to reduce disparities (60). In other pediatric conditions, use of community organizations, home visits, and the use of lay outreach workers have all been successful components of interventions to decrease health disparities (60). Most importantly, integrating any intervention into existing healthcare and community frameworks ensures sustainability of these interventions (60).

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