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Authors
Wadhwani, Sharad I
Beck, Andrew F
Bucuvalas, John
et al.

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Neighborhood socioeconomic deprivation is associated with worse patient and graft survival following pediatric liver transplantation

Sharad I. Wadhwani[1], **Andrew F. Beck**[2,3], **John Bucuvalas**[4,5], **Laura Gottlieb**[1], **Uma Kotagal**[2,3], **Jennifer C. Lai**[1]

[1.]University of California San Francisco, San Francisco, CA

[2.]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[3.]University of Cincinnati College of Medicine, Cincinnati, OH

[4.]Icahn School of Medicine at Mount Sinai, New York, NY

[5.]Mount Sinai Kravis Children's Hospital, New York, NY

Abstract

Long-term outcomes remain suboptimal following pediatric liver transplantation; only one-third of children have normal biochemical liver function without immunosuppressant comorbidities 10 years post-transplant. We examined the association between an index of neighborhood socioeconomic deprivation with graft and patient survival using the Scientific Registry of Transplant Recipients. We included children <19 years who underwent liver transplantation between 1/1/2008–12/31/2013 (n=2868). Primary exposure was a neighborhood socioeconomic deprivation index—linked via patient home ZIP code—with a range of 0–1 (values nearing 1 indicate neighborhoods with greater socioeconomic deprivation). Primary outcome measures were graft failure and death, censored at 10 years post-transplant. We modeled survival using Cox proportional hazards. In univariable analysis, each 0.1 increase in the deprivation index was associated with a 14.3% (95%CI: 3.8%−25.8%) increased hazard of graft failure and a 12.5% (95%CI: 2.5%−23.6%) increased hazard of death. In multivariable analysis adjusted for race, each 0.1 increase in the deprivation index was associated with a 11.5% (95%CI: 1.6%−23.9%) increased hazard of graft failure and a 9.6% (95%CI: −0.04%−20.7%) increased hazard of death. Children from high deprivation neighborhoods have diminished graft and patient survival following liver transplantation. Greater attention to neighborhood context may result in improved outcomes for children following liver transplantation.

Correspondence Andrew F. Beck, Andrew.Beck1@cchmc.org.

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DATA AVAILABILITY STATEMENT
Research data are not shared.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

INTRODUCTION

Although one-year survival following pediatric liver transplantation hovers at 90%,[1] at ten years, only 1/3 of children have the ideal outcome—defined as allograft health as estimated by normal serum ALT and GGT levels in the absence of comorbidities related to immunosuppression.[2,3] Even this estimate is optimistic since 50% of pediatric liver recipients have evidence of structural allograft injury even in the face of normal liver tests.[4] While immune and non-immune mediated allograft injury and complications from immunosuppression play a central role, ineffective self-management increases risk for nonadherence and graft injury.[2,4–7] Social determinants of health (SDH), including neighborhood context, influence self-management capabilities in children with chronic conditions and are key contributors to health outcomes but have not been routinely collected by transplant registries[8] or implicated directly in liver transplant outcomes.[5,9–11] While transplant registries collect insurance status, this metric does not accurately reflect one's SES—especially in the Affordable Care Act era where increasing percentages of children are covered by Medicaid.[12] Moreover, public insurance coverage is particularly high among children with complex chronic diseases, such as those requiring transplantation, further complicating its use as an SES proxy.[13,14]

Neighborhood-level socioeconomic data (linked via home ZIP code) provide information that can contextualize a child's living environment, including the extent of neighborhood socioeconomic resources. These data might provide a more comprehensive understanding of the socioeconomic milieu in which a patient experiences and manages his or her chronic disease.[9] Such geographic, place-based data are associated with adverse health outcomes across diseases,[2,3] and this knowledge has been used to improve other medical outcomes for children of low socioeconomic status (SES).[10,18–20] Using a validated index of neighborhood socioeconomic deprivation in a cohort of pediatric liver transplant recipients, we previously demonstrated that children from the most deprived neighborhoods have twice the rates of nonadherence.[21] This index, available for every US census tract and ZIP code, incorporates 6 measures of neighborhood SES from the US Census Bureau/American Community Survey. Yet gaps in knowledge remain as to how graft and patient survival outcomes more broadly differ by neighborhood characteristics. In this study, we examined the association between this same neighborhood deprivation index and long-term graft and patient survival in pediatric liver transplant recipients. We hypothesized that higher levels of neighborhood socioeconomic deprivation would be associated with a higher risk of graft loss and mortality.

METHODS

Data Source

We used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidate, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

This study was reviewed by and deemed exempt by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Study Population

We identified pediatric patients (<19 years) who received a liver transplant between January 1, 2008 and December 31, 2013 in the US (N=2868). Patients (N=330) were excluded if their home ZIP code could not be matched to the deprivation index. Patients who did not have an available home ZIP code to match to the deprivation index for our analyses differed from those who were otherwise included in this study by race (they were more likely to be white and less likely to be black or other race), insurance (they were more likely to have "other" insurance and less likely to have public health insurance), and they were more likely to have metabolic disease as the indication for liver transplantation (Supplemental Table 1).

Primary Exposure

Our primary exposure was a validated index of neighborhood socioeconomic deprivation.[1,2] The index has a range of [0,1] with values closer to 1 indicating more deprived neighborhoods. The neighborhood deprivation index was derived using data from the US Census Bureau's 2015 American Community Survey. The deprivation index is available at the census tract level as well as at the ZIP code level.[24] Intended to be a composite measure of neighborhood socioeconomic deprivation, the deprivation index is calculated from: fraction of the population below the federal poverty line, median household income, fraction of adults with a high school education, fraction of households receiving public assistance, fraction of the population with no health insurance, and fraction of housing units that are vacant.[23,25] For the present analyses, the deprivation index was determined at the ZIP code level. While census tract level analyses are considered to be more robust,[26] transplant databases currently only include patient ZIP code. The ZIP code-level neighborhood deprivation index was matched to a patient by the home ZIP code at the time of transplant as reported to SRTR. The deprivation index was analyzed as a dichotomous measure (below and above the median) and as a continuous measure.

Primary Outcomes

Our primary outcomes were post-transplant graft failure and patient death. We evaluated these measures as time-to-event occurrence.

Statistical Analyses

Descriptive statistics were calculated for patient demographic, allocation, and transplant characteristics. We classified patients as 'low' and 'high' deprivation by dichotomizing the cohort at the median deprivation index to visualize the relationship between the deprivation index and graft/patient survival. Patient characteristics were compared across those from low and high deprivation neighborhoods using the appropriate statistical test. The relationships between low/high deprivation and time to patient/graft survival were represented with Kaplan-Meier curves. We followed participants from the time of transplant until 10 years post-transplant, censoring for graft failure and death. We chose 10 years to ensure adequate follow up time and to ensure that we analyzed a cohort within the present era of pediatric liver transplantation. We used Cox proportional hazard models to then evaluate independent hazards of post-transplant graft failure and patient death. In these models, we used the deprivation index as a continuous variable to quantify the relationship between deprivation and graft failure/death. When used as a continuous variable, we adjusted hazard ratios to reflect a 0.1 increase in the deprivation index since the index only rages from 0–1. We used a causal inference approach and created a directed acyclic graph (Figure 1) to identify the set of key co-variables necessary to quantify the direct effect of neighborhood deprivation on graft failure and death. We classified participant race as "white", "black", or "other" because the remaining races made up a small minority of the cohort. We conceptualized race as a social construct (i.e., related to structural discrimination, segregation);[27] therefore, we opted to retain race in our multivariable models to determine the effect of neighborhood socioeconomic deprivation on outcomes after adjusting for race (Figure 1). Since insurance status can be considered a downstream result of lower SES (Figure 1), controlling for insurance status would compromise our ability to detect associations between neighborhood deprivation and our outcome measures. Furthermore, we posited that insurance type is not a surrogate for SES but rather an indicator of access to healthcare services that may not be a reliable indicator in children with chronic disease.[12–14] Therefore, we analyzed whether insurance status modified the effects of neighborhood deprivation on the outcomes, as previously demonstrated in asthma.[28] Since complications within the first year of transplant are more likely to be related to surgical/medical management of the transplant itself, we performed sensitivity analyses that censored graft failure and death at 1 year after transplant. Hazard of graft failure and death were again assessed with Cox proportional hazard models.

Significance levels were defined as $p<0.05$ and hypothesis testing was 2-sided. All analyses were conducted in R (version 3.6.1, The R Project for Statistical Computing).

RESULTS

Study population

A total of 2530 children who underwent liver transplantation in the US during our study period were included in our analyses. Baseline characteristics of the entire cohort are shown in Table 1. Overall, the median age of our cohort was 2.3 years (IQR: 0.8–9.2), and 51% of patients were female. A majority (78%) were non-Hispanic and 73% of the cohort was white race. The most common indication for transplant was biliary atresia (32%). The median neighborhood deprivation index score for our cohort was 0.37 (IQR: 0.30–0.46). Participants from high deprivation neighborhoods were younger at the time of transplant, more likely to be of Hispanic ethnicity, more likely to be black race, more likely to have public insurance, more likely to have a higher calculated Model for End Stage Liver Disease (MELD)/ Pediatric End Stage Liver Disease (PELD), more likely to have a younger donor, have longer cold ischemia time, and less likely to receive a living donor allograft. There was no association between the neighborhood deprivation index and causes of liver disease, allocation MELD/PELD, or Status 1a/1b status.

Graft survival

The overall 1-, 5- and 10-year graft survival estimates in our cohort were 92.7%, 89.3%, and 86.0%, respectively. Patients from high deprivation neighborhoods compared to those from low deprivation neighborhoods had similar estimated 1-year graft survival rates (90.8% vs 91.2%, p=0.07), but had lower estimated 5-year (87.5% vs. 91.1%, p=0.006) and 10-year (83.9% vs. 88.25, p=0.005) graft survival rates. Figure 2 depicts a Kaplan-Meier curve of 10-year graft survival with patients stratified as high deprivation and low deprivation. In univariable analysis, each 0.1 increase in the neighborhood deprivation index was associated with a 14.3% (95%CI: 3.8%−25.8%) increased hazard of graft failure. Black children had a 41.2% increased hazard of graft failure (95%CI: 7.1%−86.1%) compared to white children. In multivariable analysis adjusted for race, each 0.1 increase in the neighborhood deprivation index was associated with a 12.2% (95%CI: 1.6%−23.9%) increased hazard of graft failure (Table 2).

In a subgroup analysis of patients with public insurance (Figure 3), 10-year graft survival was similar for patients from high and low deprivation neighborhoods (84.0% vs. 86.1%, respectively; p=0.44). Each 0.1 increase in the neighborhood deprivation index was associated with a 9.1% (95%CI: −4.3%−24.5%) increased hazard of graft failure in patients with public insurance. For patients with private insurance, 10-year graft survival was lower for patients from high deprivation neighborhoods compared to those from low deprivation neighborhoods (83.0% vs. 89.3%, respectively; p=0.01). Each 0.1 increase in the neighborhood deprivation index was associated with a 16.5% (95%CI: −2.5%−39.3%) increased hazard of graft failure in patients with private insurance.

Patient survival

The overall 1-, 5- and 10-year patient survival estimates in our cohort were 92.8%, 88.2%, and 85.5%, respectively. Patients from high deprivation neighborhoods compared to those from low deprivation neighborhoods did not have differences in patient survival at 1 year (92.3% vs. 93.3%, p=0.4), 5 years (86.9% vs. 89.4%, p=0.08), or 10 year (84.3% vs. 86.7%, p=0.09). In univariable analysis, each 0.1 increase in the neighborhood deprivation index was associated with a 12.5% (95%CI: 2.5%−23.6%) increased hazard of death. Black children had a 58.2% increased hazard of death (95%CI: 21.8%−205.6%) compared to white children. In multivariable analysis adjusted for race, each 0.1 increase in the neighborhood deprivation index was associated with a 9.6% (95%CI: −0.4%−20.7%) increased hazard of death (Table 2).

In a subgroup analysis of patients with public insurance (Figure 3), 10-year patient survival was similar for patients from high and low deprivation neighborhoods (83.2% vs. 82.8, respectively; p=0.58). Each 0.1 increase in the deprivation index was associated with a 2.1% (95%CI: −13.6%−10.9%) decreased hazard of death in patients with public insurance. For patients with private insurance, 10-year patient survival for patients from high and low deprivation neighborhoods was 86.5% and 89.2%, respectively (p=0.10). Still, each 0.1 increase in the neighborhood deprivation index was associated with a 29% (95%CI: 7.7% −54.5%) increased hazard of death.

Sensitivity Analysis

Given that graft failure and mortality in the first year may be driven primarily by surgical and technical complications (as opposed to socioeconomic concerns), we performed a sensitivity analysis to determine if neighborhood deprivation was associated with outcomes censored at 1-year post-transplant. There was no association between neighborhood deprivation and graft failure (HR 1.07, 95%CI: 0.95–1.21) or death (HR 1.07, 95%CI: 0.94–1.21).

DISCUSSION

This study is the first to examine associations between neighborhood socioeconomic deprivation and graft loss and death in children who have undergone liver transplantation. Our findings show that post-transplant, children from more deprived neighborhoods are at increased hazard of graft failure and death after the first year of transplant. In this cohort 2530 children, there were an additional 44 graft losses and 27 deaths in children from neighborhoods above the median deprivation. Indeed, there was a 12% and almost 10% increased hazard of graft failure and death, respectively, with each 0.1 increase in the deprivation index in our adjusted models. Notably, this difference was not observed within the first year following transplant, which is the period most likely to be dependent on post-operative medical and surgical management. Outcomes between 1–10 years are more likely dependent on health maintenance and self-management.[5,29] Despite the modest observed differences in graft and patient survival across low and high deprivation neighborhoods, there is only a 9% difference in 1-year survival outcomes across the SRTR 5-tier rating system for transplant institutions.[30] Therefore, the observed differences may still have important implications for transplant center performance. Furthermore, since re-transplantation costs exceed $200,000, strong financial incentives exist to improve outcomes.

Advances in surgical and immunosuppressant management have enabled greater numbers of children to survive—and thrive—beyond the first year post transplant.[1] Yet little research to date has examined how success differs for children with fewer resources.[22] As children increasingly live past the first year of transplant, our research suggests that greater attention to social and economic factors could contribute to more equitable outcomes. Though such contextual factors are already known to influence chronic disease management,[5,29,32,33] this is the first research to extend these findings to a national sample of pediatric liver transplant recipients.[31]

Our data also suggest that insurance type modifies the effect of neighborhood deprivation on graft and patient survival. Overall, public insurance is associated with worse outcomes than private insurance, but outcomes in publicly-insured children are more equitable across neighborhood deprivation. In contrast, socioeconomic disparities emerge between sub-groups in the post-transplant outcomes of privately-insured children. There is some evidence that in the Affordable Care Act era, children with Qualified Health Plans (subsidized, private health insurance) have increased out-of-pocket expenditures and more difficulty accessing specialty services.[12] Children and families from low socioeconomic backgrounds enrolled in these health plans rather than public health insurance plans may be particularly vulnerable to the effects of these coverage limitations. Furthermore, public insurance may have incentive structures in place that positively support families in the management of chronic diseases.[34] Policymakers should examine more closely the out-of-pocket financial burden that pediatric liver transplant recipients and their families face with a Qualified Health Plan[12] to determine if this burden is prohibitively expensive.

Black race was associated with increased hazard of graft failure and death in univariable analysis. The association between black race and adverse outcome decreased when neighborhood socioeconomic deprivation was included in the models—suggesting that the effect of race on adverse outcome may partially be mediated through neighborhood socioeconomic deprivation. We conceptualize race and neighborhood deprivation are measures of distinct but related social constructs. Mainly we posit that race serves as a measure of inequitable race relations.[27] As such, we hypothesize that differences on the basis of race might be a reflection of interpersonal or institutional discrimination, bias, mistrust in the healthcare system, or increased exposure to adversity over time, as examples.[35] In contrast, neighborhood deprivation serves as a measure of inequitable class relations.[27] As such, we hypothesize that any differences on the basis of neighborhood deprivation may be due to financial strain (e.g. unable to make ends meet), transportation challenges, diminished access to primary care, or difficulty in accessing a pharmacy, as examples. In the present study, we demonstrate that neighborhood socioeconomic deprivation and black race are important predictors of adverse outcomes. Future studies are needed to identify why black children are at increased risk of graft failure and death after liver transplantation to realize equitable outcomes.

We acknowledge the following limitations to our study. First, our geographic resolution is at the ZIP code level. ZIP codes, while convenient, are not ideal geospatial units.[29] ZIP codes are drawn by the US Postal Service to ensure that mail is delivered efficiently. As such, they can be re-drawn by the US Postal Service to increase efficiency of mail delivery. However, the advantage that ZIP codes offer is that they are readily available within the SRTR database and they allow us to group patients within relatively small geographical units. Second, national registries can have poor data quality and completeness; however, the SRTR database is the most robust data source for transplant recipients. Third, while others have used neighborhood-level SES measures as a surrogate of individual SES,[31,36] this use may be subject to an ecological fallacy.[8] We posit that neighborhood deprivation might serve as a surrogate measure of individual SES risk—e.g. low literacy, housing instability, or food insecurity—which are factors that are known to affect chronic disease outcomes as well as provide neighborhood contextual information—e.g. diminished neighborhood cohesion.[37] However, determining the impact of neighborhood context on outcomes in excess of individual SES risk is outside the scope of the present work because SRTR does not capture robust household-level SES data.

Future work should characterize how both individual, or household, and neighborhood socioeconomic deprivation impact pediatric liver transplantation outcomes and should include efforts to characterize which children have access to the transplant waitlist and those that do not. This information would not only shed light on disparities and but also could be used to develop, and ideally evaluate, interventions aimed at mitigating these risks. This is likely to require new investments, since existing data registries only collect data at waitlist entry and do not include relevant individual- or household-level information. One alternative to changing registries is to establish a large, diverse prospective cohort that could be followed over time in order to better understand the prevalence and impact of unmet needs on pre- and post-transplant outcomes. In parallel, qualitative research would help to surface barriers to optimal care from the perspective of key stakeholders—including patients, families, and healthcare providers—that will similarly inform intervention targets.

As the data on pediatric liver transplantation disparities accrue, learnings from social care programs in general pediatrics might be used to guide future interventions. In other diseases, data on patients' social risks have been applied to improve patient health outcomes. For example, in pediatric primary care, social data have been used to target patients for in-hospital medication delivery prior to discharge[19] and patients who need legal or other social resources.[9,18] The health and cost implications of similar programs in the context of pediatric liver disease should be the focus of future evaluations. However, re-transplantation is a major healthcare expenditure and preventing even one episode of graft failure may realize cost savings. While it remains to be seen whether such programs will be cost-effective,[39] there is a strong moral imperative[40]—reiterated in Health People 2020[41]—to ensuring equitable child health outcomes.

Our findings suggest that the neighborhood socioeconomic deprivation index can be a useful tool for identifying patients at risk of adverse long-term outcomes. This index can serve as an easy to calculate, readily available surrogate for the constellation of socioeconomic factors that contribute to outcomes but are more difficult to quantify objectively on a large scale. Although the National Academy of Medicine[42,43] has called for the routine collection of neighborhood-level contextual data, their use remains limited in pediatric liver transplant – and perhaps in pediatrics generally.[17,44–46] To attain equitable long-term transplant success, however, will require mobilizing interventions—including those heralded in other disease (e.g. medication delivery,[19] patient integrators,[47] and medical-legal partnerships[18]) —to improve outcome equity.[48] A necessary first step is to better understand the challenges these children encounter to obtaining the ideal outcome. The resulting suite of interventions for children undergoing liver transplantation must include programs to help families overcome the socioeconomic barriers that shape long-term health and equity outcomes. Our data lay the foundation for the development of such programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CCM	chronic care model
DD	deceased donor
HR	hazard ratio
HRSA	Health Resources and Services Administration
MELD	Model for End-stage Liver Disease
OPTN	Organ Procurement and Transplantation Network
PELD	Pediatric End-state Liver Disease
SES	socioeconomic status
SRTR	Scientific Registry of Transplant Recipients
Yr	years

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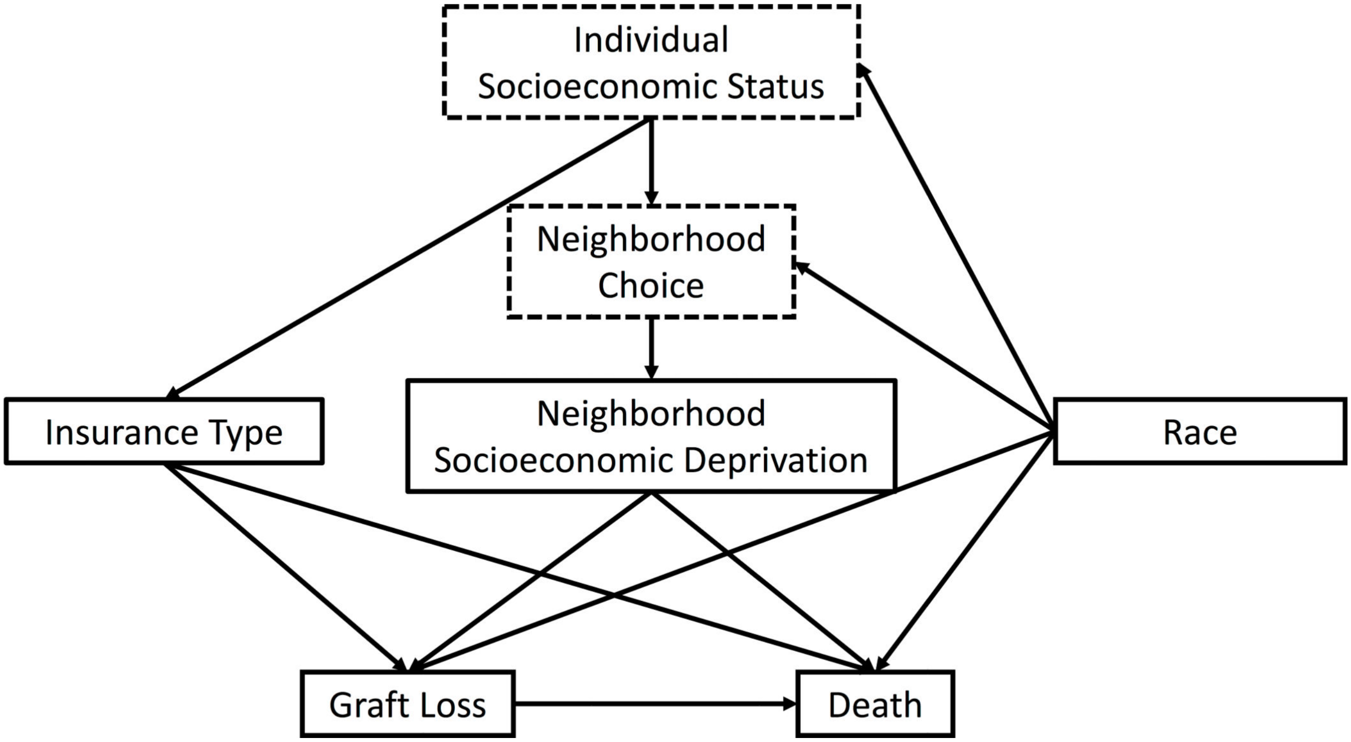

Figure 1. Direct acyclic graph of hypothesized causal pathway

The solid boxes indicate measurable variables while the dotted boxes indicate unmeasurable variables within the Scientific Registry for Transplant Recipient data system. This diagram is the theoretical model of the hypothesized causal pathway for the impact of neighborhood deprivation on outcomes for children following liver transplantation.

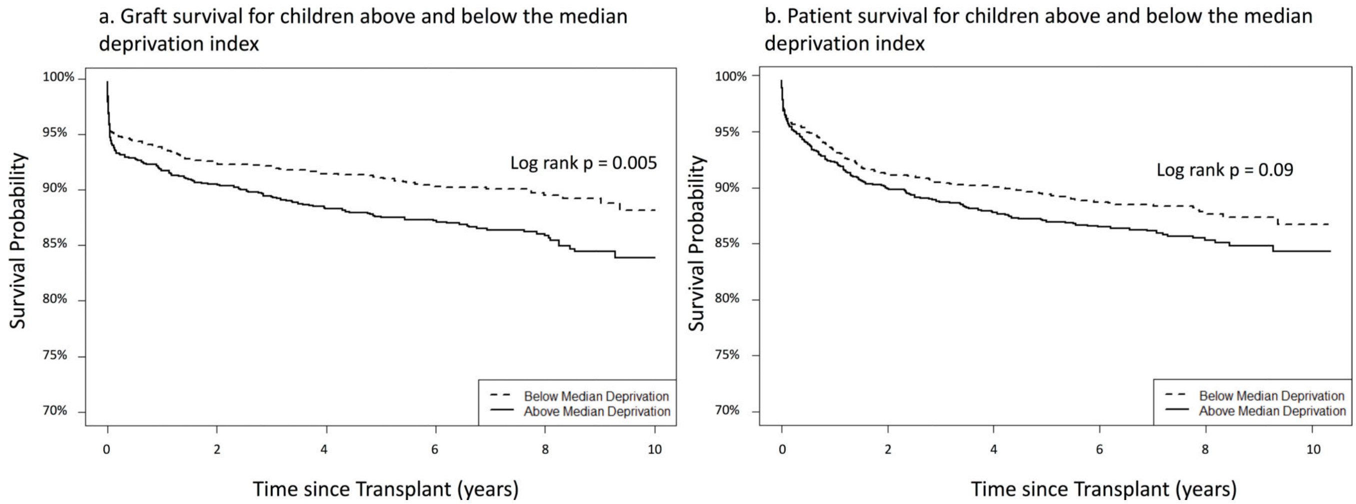

Figure 2. 10-year graft and patient survival curves by high and low neighborhood deprivation.
These figures depict graft survival (2a) and patient survival (2b) for patients from high and low deprivation neighborhoods. High and low deprivation were classified as above and below the median deprivation index of the cohort, respectively.

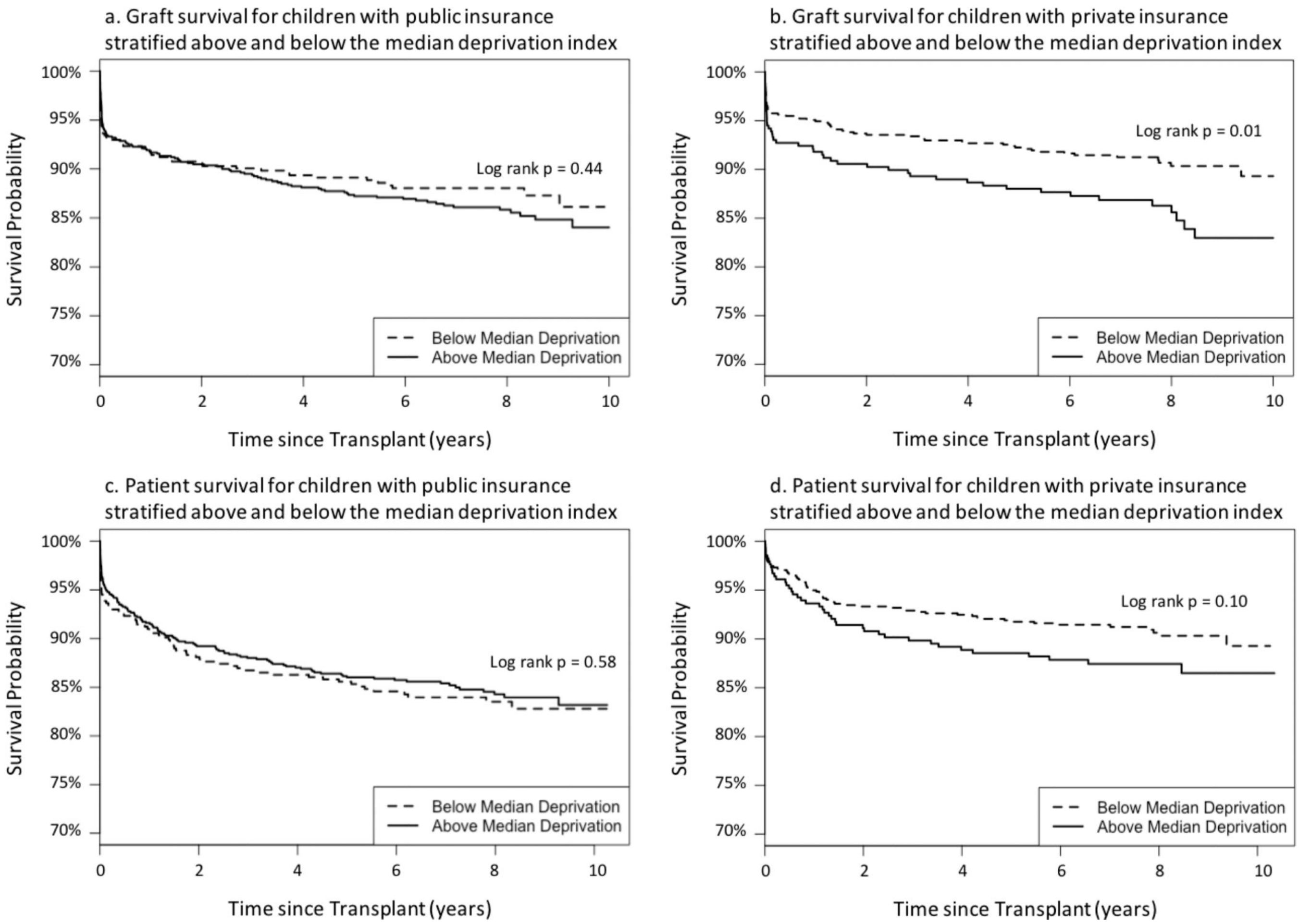

Figure 3. Subgroup analyses for patients with public and private insurance by high and low neighborhood deprivation.

Figure 3a and 3b display graft survival for patients with public insurance and private insurance, respectively. Figure 3c and 3d display patient survival for patients with public insurance and private insurance, respectively. High and low deprivation were classified as above and below the median deprivation index of the cohort, respectively.

Table 1.

Baseline characteristics by deprivation index, graft loss and patient mortality

	Overall	Neighborhood Deprivation Index N (%) or Median (IQR)		
	N = 2530	Low N=1265	High N=1265	p-value
Age at Transplant, years	2.3 (0.8, 9.2)	2.7 (0.9, 10.3)	2.0 (0.8, 7.8)	0.002
Gender				
Female	1284 (50.8%)	640 (50.6%)	644 (50.9%)	0.91
Ethnicity				
Hispanic	564 (22.3%)	174 (13.8)	390 (30.8%)	<0.001
Race				
White	1858 (73.4%)	996 (78.7%)	862 (68.1%)	<0.001
Black	445 (17.6%)	136 (10.8%)	309 (24.4%)	
Other	227 (9.0%)	133 (10.5%)	94 (7.4%)	
Primary Insurance				
Private	1106 (43.7%)	759 (60.0%)	347 (27.4%)	<0.001
Public	1375 (54.3%)	478 (37.8%)	897 (70.9%)	
Other	49 (1.9%)	28 (2.2%)	21 (1.7%)	
Recipient Diagnosis				
Biliary Atresia	798 (31.5%)	398 (31.5%)	400 (31.6%)	0.06
Other cholestatic	493 (19.5%)	233 (18.4%)	260 (20.6%)	
Acute Liver Failure	272 (10.8%)	123 (9.7%)	149 (11.8%)	
Metabolic	227 (9.0%)	123 (9.7%)	104 (8.2%)	
Tumor	214 (8.5%)	119 (9.4%)	95 (7.5%)	
Autoimmune Hepatitis	112 (4.4%)	66 (5.2%)	46 (3.6%)	
Other	414 (16.4%)	203 (16.0%)	211 (16.7%)	
Laboratory MELD/PELD at Transplant	15 (5, 25)	14 (4, 24)	16 (5, 26)	0.08
Allocation MELD/PELD at Transplant	25 (16, 32)	25 (16, 32)	25 (16, 32)	0.45
Status 1a/1b				
Yes	739 (29.2%)	362 (28.6%)	377 (29.8%)	0.55
Donor Age at Transplant, years	10 (2, 20)	11 (2, 22)	8 (1, 19)	<0.001
Transplant type				
Living Donor Transplant	272 (10.8%)	161 (12.7%)	111 (8.8%)	0.002
Cold Ischemia Time, hours	6.6 (5.0, 8.3)	6.5 (4.8, 8.0)	6.8 (5.0, 8.5)	0.03

Empty cells in p-value columns are because p-value represents comparison across all categories of a variable.

High and low deprivation were classified as above and below the median deprivation index of the cohort, respectively. IQR = interquartile range; MELD: The Model for End-stage Liver Disease; PELD: Pediatric End-stage Liver Disease

Table 2.

Multivariable Cox proportional hazard models on graft loss and patient mortality/death

	Graft Loss		Patient Death/Mortality	
	HR	CI	HR	CI
Deprivation Index	1.12	1.02 – 1.24	1.10	1.00 – 1.21[a]
Race				
White	REF		REF	
Black	1.31	0.99 – 1.74	1.49	1.14 – 1.95
Other	1.15	0.77 – 1.72	1.36	0.94 – 1.97

HR: Hazard ratio; CI: 95% confidence interval

[a.] p = 0.06