Title
Social and Environmental Impacts on Lung Transplant Outcomes

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Publication Date
2022

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Social and Environmental Impacts on Lung Transplant Outcomes

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Health Policy and Management

by

Olawale Odunayo Amubieya

2022

ABSTRACT OF THE DISSERTATION

Social and Environmental Impacts on Lung Transplant Outcomes

by

Olawale Odunayo Amubieya

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2022

Professor Ninez A. Ponce, Co-Chair

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Lung transplantation is a life-saving therapy for a carefully selected subset of patients with end-stage lung diseases. Life expectancy post-transplant is modest with a median survival of 5.5-6.5 years. The identification of potentially modifiable risk factors for poor outcomes after lung transplant is of great importance. In this dissertation, we explore the impacts of neighborhood-level social and environmental factors on lung transplant outcomes using mixed effects semiparametric and parametric survival models to estimate the hazard of death or graft failure. We find that neighborhood disinvestment, operationalized as the ZIP code level Social Vulnerability Index (SVI) is associated with a 6% increase in the hazard of death or graft failure

after transplant, though this finding does not reach statistical significance. We utilize previously reported estimates of annual $PM_{2.5}$ levels in North America to create ZIP code estimates of average yearly exposure. We find that annual $PM_{2.5}$ exposure above the EPA standard of 12 $\mu g/m^3$ is associated with an 8% increase in the hazard of death or graft failure. Furthermore, this relationship appears to hold true at lower thresholds of exposure. Understanding the effects of social and environmental factors on lung transplant outcomes will allow transplant practitioners to better identify patients at high risk of poor outcomes. It may also direct future policy decisions to mitigating these risks.

The dissertation of Olawale Odunayo Amubieya is approved.

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Dedication

To my loving wife Funmi, for supporting me through this exciting journey and whose own brilliance and accomplishments are an example that I strive to emulate. To my amazing children Kemi and Feyi, for inspiring me and giving me an example of the joy and enthusiasm that I can approach each day with. To my parents David and Sinabu, for showing me the tremendous power that comes about when love and hard work are applied in tandem. To my siblings Opeyemi, Aderonke, Funmilayo, and Olabanji, whose life-long encouragement have been instrumental to my every success. And to my in-laws and extended family whose love and support are with me everyday.

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Acknowledgements

Dr. Amubieya received tuition and salary support from the UCLA Department of Medicine Specialty Training & Advanced Research (STAR) Program. He also received research and salary support from the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) training grant HL072752.

Research was made possible by data from the United Network for Organ Sharing (UNOS). This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

I would like to acknowledge the guidance and dedication of this dissertation committee. I thank Dr. Nicholas Jackson for his statistical consulting. I also thank Drs. John Belperio, Sam Weigt, Michael Shino, and the entire UCLA Lung Transplant Program for being wonderful mentors in the field of lung transplantation research. I truly could not have done this without all of your support.

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Chapter 1: Background

Lung Transplantation

Lung transplantation is an effective treatment for a carefully selected subset of individuals with a range of end-stage lung diseases. It is designed to be a life-prolonging intervention for patients with irreversible terminal lung conditions, but life expectancy post-transplant remains modest with a median survival of 5.5 – 6.5 years.[1,2] According to the 2021 consensus document for the selection of lung transplant candidates, lung transplant should be considered for patients with chronic end-stage lung disease who have a high (>50%) risk of death from lung disease within 2 years if lung transplant is not performed and have a high (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided there is adequate graft function. [3] The indications for lung transplantation are varied and include an array of diseases affecting the lung parenchyma, vasculature, and airways causing end-stage respiratory failure. Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis (CF), and idiopathic pulmonary arterial hypertension (IPAH) are among the four most common indications. The process of taking a patient from end stage lung disease to lung transplantation is complex and involves the identification of potentially suitable candidates, referral to a lung transplant center, multidisciplinary evaluation of candidacy, decision making on the timing of listing for transplantation, and finally transplantation itself. The determination of candidacy requires a thorough evaluation to select appropriateness of transplantation and optimize the individual's status to provide them the best chance for a successful outcome.[4] The decision regarding timing of listing for transplant takes into

consideration disease severity and trajectory, estimated wait time for donor organs, estimated survival time without transplant, and the candidate's readiness for transplant.[5]

History

The technical feasibility of human lung transplantation was proven in 1963 when Dr. James Hardy performed the first left single lung homotransplantation in man.[6] Due to the experimental nature of the procedure, the transplant team chose a recipient who was ill and had a high likelihood of mortality independent of the surgery. In this case, they chose a 58-year-old male prisoner with locally invasive squamous cell lung carcinoma, poor nutritional status, and renal insufficiency. The surgery was a technical success and proved the viability of the procedure, but the patient died 18 days post-operatively with progressive renal failure. After this initial proof of concept, many unsuccessful attempts were made at human lung transplantation. The next successful transplant was not reported until 1981 when Drs. Bruce Reitz and Norman Shumway described the first successful combined heart and bilateral lung transplants.[7] Reitz and Shumway published on their heart-lung transplantation of three patients: a 45-year-old woman with primary pulmonary hypertension, a 30-year-old man with atrial and ventricular septal defects causing Eisenmenger's syndrome, and a 29-year-old woman with transposition of the great vessels and associated defects. The donor hearts and lungs were transplanted *en-bloc* with anastomoses made at the aorta, trachea, and left atrial cuff at the confluence of the superior vena cava, inferior vena cava, and right atrium. The first two patients were doing well at the time of reporting, 10 and 8 months postoperatively respectively, but the third patient died four days postoperatively due to hepatic, renal, and pulmonary complications after prolonged cardiopulmonary bypass during the surgery. The first successful single lung

transplant was performed in 1983.[8] This distinction warrants note as the procedures of single and bilateral lung transplants differ technically from the *en-bloc* heart-lung with anastomoses made at the mainstem bronchus of the lung, the pulmonary artery, and the left atrial cuff at the insertion of the pulmonary veins for the lungs.[9,10]

Since these early advancements and with improvements in immunosuppressive medications in the 1990s, the field of lung transplantation has grown considerably with more than 4500 lung transplants performed per year worldwide and more than 2500 in the US.[11] As of 2018 there are more than 15,000 people living with a lung transplant in the United States.[12]

Economics

The costs of lung transplantation are difficult to assess in the US given its complex interplay of multiple payors and institutions providing care. One study estimates the mean total cost of the index lung transplant hospitalization paid my Medicare is more than $135,000.[13] A 1995 study by a research group at the University of Washington estimated the lifetime cost of a lung transplant at ~$425,000 with $170,000 in charges for the transplant as well as monthly charges of $12,000 in the first year post-transplant and $4500 thereafter.[14] Around the same time, a group from the University of Pittsburg estimated the average cost of lung transplantation at $154,000 summing the physician cost and adjusted charges for the inpatient operative admission.[15] The US Organ Procurement Transplant Network Annual Report estimates the per-person per-year reimbursement for lung recipients with primary Medicare coverage transplanted between 2008 and 2013 to be $239,000.[16] This cost was slightly lower when restricting to those patients who survived the first transplant year ($196,000) and considerably higher for those who required retransplant ($642,000) or died in the first year

($761,000). The total Medicare reimbursement during the first year post-transplant for lung recipients was $674 million. The total cost paid by Medicare for recipients alive with lung transplant and intact graft function was estimated at $301 million in 2013 and $309 million in 2014. Despite the relatively small population of patients, lung transplantation represents a substantial amount of healthcare spending in the US.

Benefits

In addition to the survival benefit incurred by the treatment of an otherwise irreversible progressive lung disease, lung transplantation is also associated with improved quality of life. Lung transplant recipients reported higher happiness and more satisfaction in their life and health on the Medical Outcome Study Health Survey compared to patients pre-transplant.[17] Recipients also reported better scores on the St. George Respiratory Questionnaire (SGRQ) than pre-transplant patients.[18] The same study demonstrated lung transplant recipients had scores on the Hospital Anxiety and Depression Scale and the Mental Component Scale of the 36-Item Short Form Survey (SF-36) that were similar to those published for the general population. A more recent longitudinal study following lung transplant recipients pre- and post-surgery demonstrated an improvement in the SF-36 Physical Component Score of 10.9 points from baseline but no change in the Mental Component Score which was below population norms both before and after transplant.[19]

Another benefit of lung transplantation is the possibility of returning to the workforce. Patients with advanced lung disease who undergo lung transplantation are typically too ill to participate in the workforce pre-transplant. A survey from the Toronto General Hospital lung transplant group estimated that 37% of post-transplant respondents obtained paid

employment.[20] Another study in the US and Canada estimated 22% of respondents regained employment after transplant and an additional 38% were unemployed but medically able to work.[21]

Mortality After Lung Transplant

Life-expectancy post lung transplant is modest with a median survival of 5.5-6.5 years.[1] The causes for mortality after lung transplant differ depending on the time-frame post-surgery. Mortality is highest in the first year post-transplant and appears to improve conditional upon survival to that point. When restricting to the most recent cohort of lung transplant candidates, median survival is 6.5 years, but for patients who survive the first post-transplant year median conditional survival is 8.7 years.[11] Early mortality (<30 days post-transplant) is most commonly due to early graft failure, infection, and other surgical complications. Infection remains the largest contributor to mortality for the rest of the first year post transplant.[1] After 1 year, the main cause of mortality for lung transplant patients is chronic lung allograft dysfunction (CLAD). CLAD is a form of chronic graft dysfunction after lung transplantation which can be characterized by obstructive phenotype with obliteration of the airways, a restrictive phenotype characterized by pleural and parenchymal fibrosis, a mixed phenotype, and undefined.[22,23] CLAD has a 5- and 10- year prevalence of 50 and 77%, respectively.[24] Given the resource-intensive nature of the procedure and the finite supply of donor organs, a great deal of effort has gone into developing strategies to optimize the post-transplant course. This begins with the determination of risk factors for poor outcomes after the surgery.

Currently known risk factors for poor outcomes can be divided into recipient-, donor-, and transplant-level characteristics. Transplant recipients with an underlying diagnosis of

idiopathic pulmonary arterial hypertension (IPAH) and patients being re-transplanted after a failed graft are at highest risk of dying within the first year. Other recipient factors associated with higher risk of death within the first year include comorbid conditions and markers of overall illness including the need for dialysis and hospitalization, need for IV inotropes, and need of mechanical ventilatory support at the time of transplant. Diabetes in the donor and transplant cytomegalovirus (CMV) donor/recipient seroprevalence status mismatch are also associated with increased risk of 1-year mortality.[25] The risk factors for 5-year mortality are largely the same except IPAH as an indication for transplant is no longer significantly associated with mortality.[1]

Selection

Lung transplant selection attempts to address these issues, identifying those patients with the highest likelihood of success post-transplant. Given the world-wide scarcity of donor organs and the need to ration these limited societal resources, selection for transplantation is a medical and ethical decision. The ethical principles of *utility*, *justice*, and *respect for persons* underpin the recommendations for the selection of lung transplant candidates. *Utility* requires that survival be maximized when choosing candidates – this may include both survival at the patient level and at the societal level. Of particular importance is the concept that a failed transplant not only affects the recipient but also any potential alternate recipient who did not have the opportunity to be transplanted due to scarcity. The principle of *justice* requires that all patients with the potential for survival benefit be given equal consideration and opportunity for transplant, and thus an individual's status or "value" in society should hold no place in the decision-making process. Lastly, *respect for persons* emphasizes a patient's right to make his or

her own decision to consent or not consent for a lung transplant. With these principles in mind, recommendations on patient selection are made and largely based on observational and registry data. Per the International Guidelines for the Selection of Lung Transplant Candidates, risk factors that negatively impact post-transplant survival and should be taken into consideration for selection include older age, significant comorbid disease, documented non-adherence to therapies and follow-up, untreated psychiatric disease, and poor social support [3-5,26]. While selection is incredibly important to ensure scarce resources are used optimally, it is in its nature exclusionary. It is critically important to identify potentially modifiable biological, socioeconomic, and environmental risk factors for poor outcomes.

New Contributions

While much attention has been paid to the biological risk factors for poor lung transplant outcomes, there has been a relative paucity of research into socioeconomic and environmental risk factors. Individual-level risk factors that have been identified include insurance status, work status, and BMI. Insurance status is associated with long-term mortality in lung transplant patients both among cystic fibrosis patients and the larger transplant population. In one study, insurance status did not have an impact on short term survival, but Medicare and Medicaid patients both had lower survival at 3-years and later as compared to private insurance.[27] Among CF lung transplant patients, lower educational attainment, and nonprivate insurance status were associated with lower survival rates at 2, 5, and 10 years.[28] Recipient working status was associated with lower 5- and 10-year mortality in lung transplant, a difference which persisted after controlling for socioeconomic status (SES).[29] This may be reflective of a higher functional status and overall health among patients who are able to return

to work after lung transplant. Race has been evaluated as a potential factor in survival rates. Comparing the historical era of lung transplant before 1996 to a more modern era of 2005-2009, the percentage of recipients who identify as non-white increased from 8.8% to 15%. The 5-year survival for non-whites was lower than white recipients in the historical era. This was particularly true for black recipients with a 5-year survival of 39% compared to 47% for white recipients. This survival gap appears to close over time as differences did not persist in the modern era with 5-year survival of 52.5% for whites and 51.6% for non-whites.[30]

Even less work is available studying the impacts of neighborhood-level and environmental factors that may affect lung transplant outcomes. Niazi *et al.* found that County Health Ranking and its length of life, quality of life, clinical care, social and economic factor, and physical environment sub-scales were each independently associated with graft failure and patient survival, but none of these differences persisted after controlling for patient and transplant center factors.[31] Interestingly, there appears to be a difference in survival of CF patients between the US and Canada both on the waitlist and post-transplant.[32] During the study time-period 15.8% of US candidates died on the waitlist compared to 6.5% in Canada. The 1-, 3-, and 5-year post-transplant survival rates were 88.3%, 71.8%, and 60.3% respectively in the US compared with 90.5%, 79.9%, and 69.7% in Canada. When stratifying US patients by insurance status, those with Medicare or Medicaid insurance had worse survival and those with other forms of insurance had similar survival to the Canadian cohort.

Research Questions

The purpose of this dissertation is to better elucidate the effect of neighborhood-level socioeconomic and environmental factors on health outcomes after lung transplant. Chapter 4

addresses the research question: does neighborhood social disinvestment as defined by the Social Vulnerability Index (SVI) have an impact on lung transplant outcomes? Chapter 5 asks if particulate matter air pollution exposure has an impact on lung transplant outcomes.

Social and Environmental Factors

Composite Measures of Neighborhood Social Disinvestment

Several composite measures of neighborhood social disinvestment exist and are increasingly being used in health services research. These tools score and combine neighborhood attributes in the realm of economic prosperity and social marginalization to create a measure of social and economic disadvantage. Individual measures tend to differ in which indicators are incorporated from what sources and aggregated at what geographic subdivision. The Social Vulnerability Index (SVI) is a tool developed by the Center for Disease Control and Prevention's (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) to identify and map communities that are most likely to need support during a hazardous event.[33] The 2010 SVI construct uses Census 2010 and American Community Survey (ACS) 2006-2010 data to rank US counties and census tracts across four domains: Socioeconomic Status, Household Composition & Disability, Minority Status & Language, and Housing Type & Transportation. The individual components of the SVI and its theme scores are illustrated in Figure 1 and discussed in more detail below. These components are compiled into a percentile score with higher values representing greater neighborhood disinvestment and higher need for support in the case of a disaster.

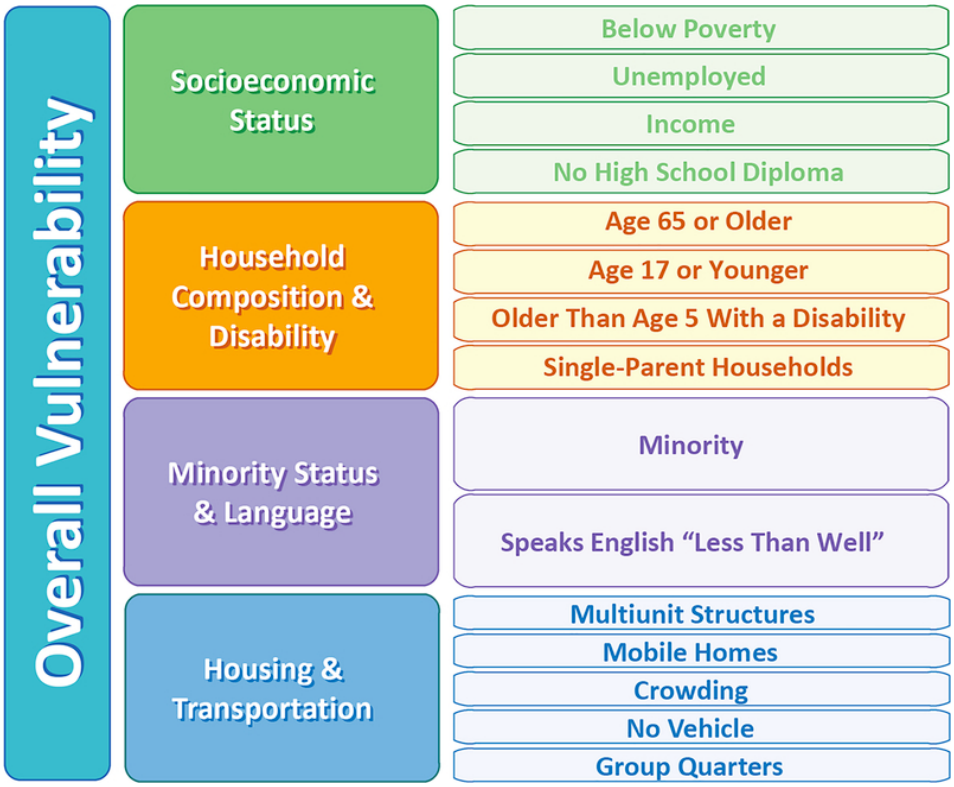

Figure 1: Social Vulnerability Index Composition: American Communities Survey variables and composite themes included in the Social Vulnerability Index [33]

The Area Deprivation Index (ADI) is an alternative measure initially compiled by the US Health Resources and Services Administration (HRSA) but more recently maintained and distributed by the Neighborhood Atlas at the University of Wisconsin Center for Health Disparities Research.[34,35] The ADI combines 21 variables from the ACS to create a percentile ranking of neighborhood disinvestment at the census block group level. The Social Deprivation Index (SDI) is produced by the Robert Graham Center for health policy combining 7 ACS variables to produce a percentile ranking at the census tract and ZIP code.[36] The Community Need Index (CNI) is a joint venture of Dignity Health and IBM Watson Health combining 9 ACS variables to produce a scale of 1.0 – 5.0 at the ZIP code level.[37] Lastly, the Distressed Community Index (DCI) was created by the Economic Innovation Group, a bipartisan public

policy organization, combining 7 variables from the ACS and business partner data to produce a ZIP code percentile ranking.[38,39] The components of each index are described below in Table 1.

These indices have been applied to determine associations with various health outcomes across multiple disciplines, including lung health[40-45] Higher neighborhood ADI has been associated with a 29% increase in the lung cancer incidence among a cohort of 40,000 smokers.[46] Higher ADI was associated with lower lung function as measured by the forced expiratory volume in 1 second (FEV1) on pulmonary function testing,[47] and higher SVI has been associated with higher rates of healthcare encounters for asthmatics.[48] A recent study assessing neighborhood-level disadvantage in patients with fibrotic interstitial lung diseases demonstrated elevated ADI is associated with higher rates of death or lung transplantation.[49] Interestingly, this study also followed a Canadian cohort using the Canadian Index of Multiple Deprivation and did not see this effect of neighborhood disadvantage on outcomes in the Canadian group. Additionally, idiopathic pulmonary fibrosis (IPF) patients in the highest ADI group had lower rates of transplantation as compared to lower ADI, a relationship that again was not present among the Canadian cohort.

The choice of which index to use in a given circumstance depends on multiple factors. For our study, we feel the SVI is advantageous. It is one of only two discussed here that include minority composition of the neighborhood in its construction. Given the structural factors that influence neighborhood disinvestment including structural racism, redlining, and historical restrictive covenants, we feel it is important to include racial admixture in our measure.[50-52] Additionally, the SVI is the only of these five tools that incorporates subtheme scores for

additional analysis and inquiry into the potential mechanism behind any association that is discovered.

Table 1: Components of the five indices of neighborhood disinvestment

	Social Vulnerability Index	**Area Deprivation Index**	**Social Deprivation Index**	**Community Need Index**	**Distressed Communities Index**
Organization	CDC	National Atlas	Robert Graham Center	Dignity Health / IBM Watson	Economic Innovation Group
Geography	Census tract	Census block group	Census tract or ZIP code	ZIP code	ZIP code
Measure	Percentile ranking	Percentile ranking	Percentile ranking	Scale (1.0 – 5.0)	Percentile ranking
Composition	15 variables	21 variables	7 variables	9 variables	7 variables
Variables	• Below poverty • Unemployed • Income • No high school diploma • Age 65 or older • Aged 17 or younger • Civilian with disability • Single parent household • Minority • Speak English less than well • Multiunit structure • Mobile homes • Crowding	• Educational distribution • Median family income • Income disparity • Occupational composition • Unemployment rate • Family poverty rate • Pop below 150% poverty • Single parent household rate • Home ownership rate • Median home value • Median gross rent • Median monthly mortgage	• Below poverty • <12 yrs education • Percent nonemployed • Percent in renter occupied units • Percent single parent households with dependents • Percent without car • Percent high needs population	• Household below poverty line • Families with children below poverty line • Female headed family with children below poverty line • Percent minority • Speak English poorly • Population without high school diploma • Unemployed • Without health insurance	• No high school diploma • Poverty rate • Adults not working • Housing vacancy rate • Median household income • Change in employment • Change in establishments

	• No vehicle • Group quarters	• House crowding • Households without telephone access • Without plumbing • Without motor vehicles • English language proficiency • Divorce rate • urban population • Immigrant population		• Renting their home	
Stratification	Yes – across 4 themes	No	No	No	no
Data sources	American Community Survey – Census	American Community Survey	American Community Survey	American Community Survey	American Community Survey and business partner data

Particulate Matter Air Pollution

Air pollution is one of the biggest environmental factors affecting lung health. Air pollutants can be gaseous such as carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides, and ozone (O_3) or solid/liquid particles suspended in the air. Particulate air pollution is categorized according to the size of the particles. PM_{10} are inhalable particles with diameters that are 10 μm or smaller such as dust, pollen, and molds. $PM_{2.5}$ are fine inhalable particles with diameters that are generally 2.5 μm and smaller and can include particles from combustion reactions, organic compounds, metals, and other materials.[53] Intake of particulate matter air pollution has a wide range of adverse health effects. PM air pollution uptake can take place by ingestion of contaminated materials or direct inhalation of particles via the respiratory tract. Adverse effects can be dependent on where those inhaled particles land. PM_{10} tends to land in the upper airways whereas $PM_{2.5}$ are small enough to descend to the lower airways and can theoretically be absorbed in the respiratory capillary bed.[54]

Ambient particulate matter pollution is estimated to be the 9th leading cause of global disease burden with 3.2 million deaths attributable per year.[55] The individual health impacts of particulate matter air pollution are varied and include both short- and long-term effects, with the largest body of literature available on their impacts on cardiovascular and respiratory health. In the US, acute increases in exposure to $PM_{2.5}$ pollution were associated with a 1.21% increase in all-cause mortality, 1.78% increase in respiratory-related mortality, and a 1.03% increase in stroke related morality in the days following the exposure.[56] A 5 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with a 15% increase in cardiovascular event risk with even higher risk estimates observed among participants living in low socioeconomic status

neighborhoods.[57] A 2014 meta-analysis assessing time-series studies demonstrated an 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with a 1.04% increase in the risk of death and 1.51% increase in risk of respiratory death.[58] In a Vancouver-based study, increased long-term exposure to traffic-related air pollution was associated with a 3% increase in coronary heart disease (CHD) hospitalizations and a 6% increase in CHD mortality.[59] Elevated $PM_{2.5}$ exposure has also been associated with a 13% increase odds of stroke.[60] This study also estimates that 6.55% of all strokes in the study population were attributable to $PM_{2.5}$ exposure. In a cohort of US women, increased long-term exposure to $PM_{2.5}$ air pollution was associated with a 14% increased odds of incident asthma.[61] $PM_{2.5}$ exposure has also been associated with worse health outcomes during the current COVID-19 pandemic. Among patients in a New York City cohort, elevated annual $PM_{2.5}$ exposure levels at the residential address was associated with an 11% increase in risk of death and 13% increase in risk of ICU admission.[62]

The pathophysiology of ambient particulate air pollution exposure's negative impacts on health is thought to be via direct injury to the lungs as well as other systemic effects. $PM_{2.5}$ exposure increases inflammatory cell infiltration, hyperemia, and inflammatory cell counts in the bronchoalveolar lavage fluid (BALF) of rats, and also increases proinflammatory mediators including TNF-α, IL-6, IL-1β, and ICAM-1.[63] The instillation of $PM_{2.5}$ into the lungs of healthy mice led to increased alveolar collapse, lung tissue inflammation, and oxidative stress damage.[64] *In vitro* exposure of lung epithelial cells to $PM_{2.5}$ induces oxidative stress and increases ICAM-1 via an IL-6 and NF-kB dependent pathway.[65]

The specific effects of $PM_{2.5}$ on health in lung transplant recipients have been investigated in very few studies. One study looking at a cohort of 5707 lung transplant

recipients across 12 lung transplant centers in Europe demonstrated an increase in all-cause mortality in recipients who were exposed to higher levels of PM_{10} as well as an increased incidence of CLAD in that population.[66] A separate study looking at 520 lung transplant recipients in France demonstrated that higher 1-yr average exposure to particulate air pollution was associated with worse lung function as defined by decreased forced vital capacity (FVC) for both $PM_{2.5}$ and PM_{10}.[67] This effect was largely attenuated by the use of macrolide antibiotics like azithromycin which are used for treatment of and prophylaxis against bronchiolitis obliterans syndrome (BOS).[68-70] To our knowledge, there have been no large cohort-based studies looking at particulate matter air pollution and its impact on lung transplant outcomes in the United States. In this dissertation, we seek to better understand the impacts of neighborhood social need and ambient particulate matter air pollution exposure on mortality in lung transplant recipients.

Chapter 2: Conceptual Model

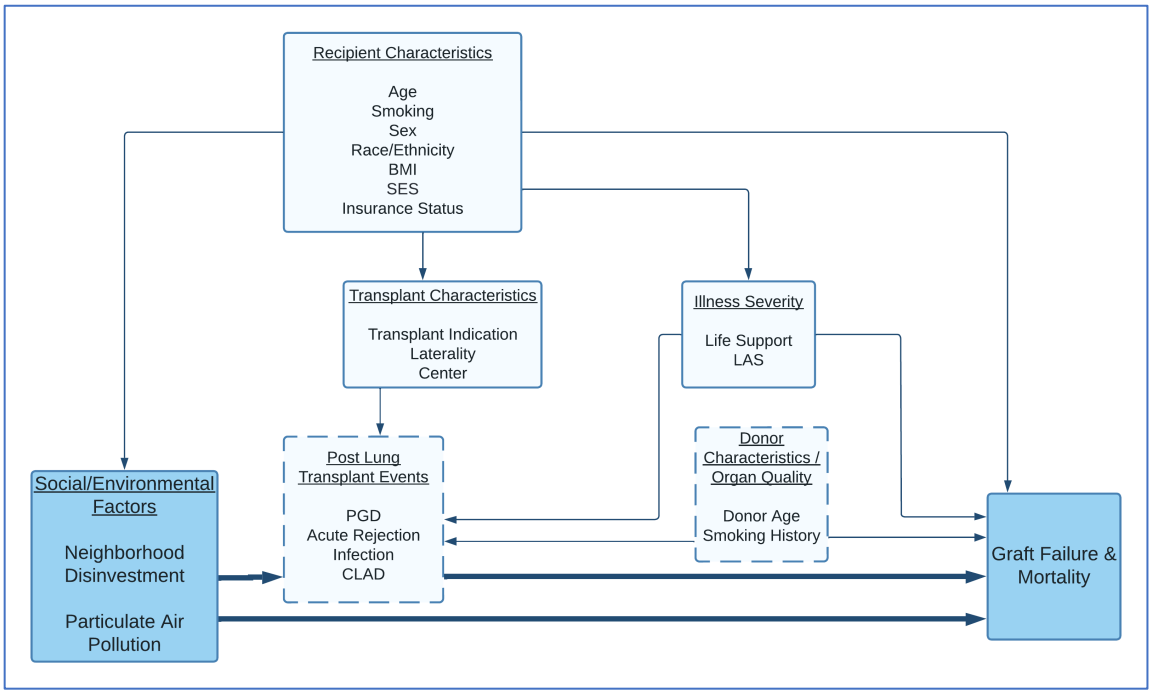

Figure 2: Conceptual model of factors impacting lung transplant outcomes. Dashed boxes denote factors that are unmeasured in the dataset.

The conceptual model above summarizes the potential relationships of the social and environmental factors of neighborhood social disinvestment and particulate air pollution exposure on graft failure and mortality in lung transplantation. Solid boxes represent factors across multiple domains that may have an impact on the effect between these social and environmental factors and lung transplant graft failure and mortality. Boxes with dashed lines represent factors that affect the relationship but are unable to be measured in this study. Specifically, Post Lung Transplant Events are an intermediary on the path to graft failure and mortality. Primary graft dysfunction (PGD), acute rejection, infection, and CLAD are each negative outcomes that increase the later risk for graft failure, and thus are potential mediators on the path between social and environmental factors and graft failure and mortality. These intermediate outcomes are not captured in the study dataset and thus this effect mediation

cannot be estimated. As noted in the literature above, recipient factors that increase the risk of worse lung transplant outcomes include older age, race/ethnicity, positive smoking history, elevated BMI, and the presence of public insurance. The patient's severity of illness as estimated here as LAS or presence of life support also impacts both mortality and the presence of the intermediary post-transplant events.[71] Donor organ characteristics such as donor smoking history and donor age impact graft failure/mortality and intermediate post-transplant events but are unmeasured in the dataset. Characteristics of the transplant are also noted to affect this relationship. As noted previously, the transplant indication impacts the risk of PGD and subsequent survival. Recipients who undergo bilateral lung transplant tend to have longer survival than single, but this is heavily confounded by recipient age and transplant indication. Transplant center also has an effect on post-transplant events and graft failure as high-volume transplant centers tend to have better outcomes.[25,72-75] Additionally, the relative medical and operative risk of patient that a center accepts for listing will impact that center's post-transplant outcomes.

Chapter 3: Data Source and Overarching Methods

The United Network for Organ Sharing

The coordination of donor organ procurement and recipient transplantation is a complex endeavor. From the mid 1950s to the 1970s, individual transplant hospitals and local organ procurement organizations in the US managed aspects of organ recovery and transplantation. Donor organs were typically identified and used within the same hospital without the requirement of sharing across hospitals or geographies. In 1984, the US Congress passed the National Organ Transplant Act (NOTA) which formed the framework for a national organ recovery and allocation system to help ensure organ allocation is carried out in a fair and efficient way. It called for a national Organ Procurement and Transplantation Network (OPTN) to be created and run by a private, non-profit organization under federal contract through the Health Resources and Service Administration (HRSA).[76] In 1977, the South-Eastern Organ Procurement Foundation (SEOPF), an association of donation and transplant professionals, established a database that allowed each of its member institutions to list candidates and help them find matches for allografts that they could not use locally – the United Network for Organ Sharing (UNOS). In March 1984 UNOS incorporated as an independent organization, and in 1986 it received the initial federal contract to operate the OPTN and subsequently establish its Scientific Registry of Transplant Recipients (SRTR). This made it responsible for allocation policy, organ placement, data collection and analysis, and both public and professional education on organ transplantation. UNOS manages and incorporates organ procurement organizations (OPOs) across the country into a unified network. Each OPO serves a distinct geographic region,

its donation service area (DSA), which are further clustered into 11 regions. UNOS is used by every transplant center in the US to register and track transplant patients placed on the waitlist and transplanted.

Database Construction

We analyzed data from the UNOS transplant registry. The UNOS Standard Transplant Analysis Research (STAR) file is a dataset that contains de-identified patient-level information for transplant recipients and waiting list candidates and is publicly available to transplant centers. For this dissertation, a restricted version of the dataset which contains some patient identifiable information and geographic identifiers was obtained. Data is available on patient and donor level factors for every patient who has been placed on a solid organ transplant waitlist since its inception in 1987 and up to the time of database procurement August 2020. The dataset includes one record per thoracic transplant (heart, lung, or heart-lung) waitlist registration and/or transplant. Data is input on recipient characteristics at the time of waitlisting as well as transplantation and is updated at least yearly after transplant. Recipient residential ZIP code at the time of listing and transplantation are also recorded.

Summary of Study Population

Our studies assess patients who have undergone lung transplantation between May 2005 and August 2020. Heart and combined heart-lung transplants are excluded from the analyses. The analyses are restricted to after May 2005 as that marked a major programmatic change in the way donor lungs were allocated in the United States. The Lung Allocation Score (LAS) was instituted at that time. It accounts for factors including recipient underlying diagnosis, age, size, functional status, and various hemodynamic parameters in an attempt to balance the

risk of death while awaiting transplant and risk factors that impact post-transplant mortality.[77] This change in organ allocation scheme introduced significant changes in the demographics of patients being transplanted including a relative increase in the number of transplants for ILD and increase in the number of transplants performed in older patients.[78]

Measurements and Variable Definitions

The outcome variable is the time to death or lung allograft failure. For UNOS purposes, graft failure is defined as "when organ removal, death, or replacement on chronic allograft support system has occurred." As no feasible, chronic support system exists for severe respiratory failure, graft failure is only coded at the time of death or retransplant. As both death and graft failure can be considered equivalent terminal events for the allograft, they will be handled as a composite rather than as competing events.

Measures of neighborhood-level social and environmental factors will include SVI and baseline ambient $PM_{2.5}$ air pollution exposure. ZIP code SVI is a proportion ranging from 0-1. Analysis was completed with SVI handled as a categorical variable separating into groups of high SVI (SVI above 90th percentile) and lower SVI (below 90th percentile). SVI was alternatively binned into quartiles and handled as a continuous variable scaled up by 100x. SVI theme scores were also available for analysis. Baseline ambient $PM_{2.5}$ air pollution exposure is operationalized as the average $PM_{2.5}$ level for the year of transplant at the ZIP code of residence. $PM_{2.5}$ exposure is measured as a continuous variable and dichotomized into a categorical variable. The Environmental Protection Agency (EPA) publishes standards for acceptable yearly average $PM_{2.5}$ exposure as less than 12 $\mu g/m^3$.[79] Using this cut point, we will

split the population into those who live in areas that meet those standards and those who live in areas that exceed those standards.

Other patient, transplant, and center-level covariates are included as specified in the conceptual model. Age is included as a continuous variable. Gender is included as a binary male vs female. Race/Ethnicity are encoded by UNOS as white non-Hispanic/Latino, black non-Hispanic/Latino, Hispanic/Latino, and other. Underlying lung disease is grouped into four broad categories: Obstructive Lung Disease consists mostly of COPD/emphysema, Pulmonary Vascular Disease consist of the different forms of pulmonary hypertension, Cystic Fibrosis and other forms of bronchiectasis are grouped together, and Restrictive Lung Diseases encompasses the diffuse parenchymal lung diseases like Idiopathic Pulmonary Fibrosis. The presence of life support is a dichotomous variable denoting the use of extracorporeal membrane oxygenation (ECMO) or mechanical ventilation at the time of transplant. The lung allocation score is a numerical value used to indicate severity of illness pre-transplant with higher numbers representing a higher likelihood of dying on the waitlist. We have operationalized it as a categorical variable with groupings <35, 35-45, 45-55, and >55. This grouping schema is consistent with current practices in lung transplant research. Type of insurance is categorized as Private, Medicare (including both fee for service and choice plans), Medicaid, other public payor, and other/unknown. Estimated per capita income at the ZIP code of residence is linked from the American Community Survey. The medical center of transplantation is encoded as a categorical variable.

Table 2: List of measurements and variable construction used across analyses

Variable	Specification	Type	Description
Outcome Variable			
	Death or Graft Failure	Time to event	Composite of 1 year mortality and lung allograft failure. The presence of the event is encoded as 1, censored is encoded as 0. Time of last follow-up is encoded in days post-transplant and transformed to years for analysis. For lung transplant, graft failure only occurs at the time of death or retransplant.
Primary Regressor of Interest			
	ZIP Code SVI	Continuous	ZIP code level overall social vulnerability index x 100. Range is 0-100.
	ZIP Code SVI Quartile	Categorical	ZIP code level overall social vulnerability index binned into quartiles.
	High SVI	Categorical	ZIP Code level overall social vulnerability index $\geq$0.8 (90th percentile) is encoded as 1. SVI <0.8 is encoded as 0.
	High SVI SES Theme	Categorical	ZIP Code level social vulnerability index Socioeconomic Status theme $\geq$0.82 (90th percentile) is encoded as 1. SVI SES Theme <0.82 is encoded as 0.
	High SVI Household Composition & Disability Theme	Categorical	ZIP Code level social vulnerability index Household Composition and Disability Theme $\geq$0.79 (90th percentile) is encoded as 1. Theme Score <0.79 is encoded as 0.
	High SVI Minority Status	Categorical	ZIP Code level social vulnerability index Minority Status & Language theme $\geq$0.77 (90th percentile) is encoded as 1. Theme Score <0.77 is encoded as 0.

	& Language Theme		
	High SVI Housing Type & Transportation	Categorical	ZIP Code level social vulnerability index Housing Type & Transportation theme $\geq$0.82 (90th percentile) is encoded as 1. Theme Score <0.82 is encoded as 0.
	Median $PM_{2.5}$ Exposure	Continuous	Estimate of average ambient $PM_{2.5}$ air pollution level at the ZIP code of residence in the year of transplantation
	High $PM_{2.5}$ Exposure	Categorical	ZIP Code $PM_{2.5}$ Estimate greater than or equal to the EPA standard for yearly average of 12 $\mu g/m^3$ is encoded as 1. Below the standard is encoded 0.
Secondary Predictors			
Patient Variables	**Age**	Continuous	Age in years at the time of transplantation
	Sex	Categorical	Sex of patient encoded as male or female.
	Race/Ethnicity	Categorical	Within the UNOS Registry, *race* is a categorical variable which consists of white, black, Hispanic/Latino, and other.
	BMI	Continuous	Calculated BMI at the time of wait list registration
	Underlying Lung Disease	Categorical	The *lung diagnosis* is a categorical variable which includes Obstructive Lung Disease, Pulmonary Vascular Disease, Cystic Fibrosis/Bronchiectasis, and Restrictive Lung Diseases
	Life Support	Categorical	Life Support is a dichotomous variable with 0 = patient not on mechanical ventilator or Extracorporeal Membrane Oxygenation (ECMO) at the time of transplant and 1 = patient on either mechanical ventilator or ECMO at time of transplant.
	Lung Allocation Score / Disease Severity	Categorical	The *lung allocation score* is a scoring system designed to numerically score the probability of survival on the weight list, with higher numbers being sicker and more likely to die on the waitlist. We have separated it into a categorical variable including <35, 35-45, 45-55, and >55.
	Insurance	Categorical	Insurance type is a categorical variable including Private, Medicaid, Medicare (both FFS and Choice), Other public payor, and Other/Unknown.

	Per Capita Income	Continuous	Individual patient income is not recorded in the UNOS registry. As a proxy, we use per capita income is at the ZIP code of residence inflation adjusted to 2019 dollars. Estimates come from Census and ACS data.
	Laterality	Categorical	The variable *bilateral* is a dichotomous variable where 0 = single lung transplant and 1 = bilateral lung transplant.
Level Two Variable	**Center**	Categorical	Transplant hospital is a categorical variable delineating what hospital performed the transplant. Inclusion of center is meant to capture variability of practice patterns across institutions.

Human Subjects and Data Protection

The study protocols were reviewed by the institutional review board of the University of California, Los Angeles and exemptions granted (IRB# 22-000186 and IRB# 19-002039) as neither study was considered human subjects research. Data are supplied already de-identified by the United Network for Organ Sharing. Data were stored on a secure, encrypted laptop in accordance with UNOS requirements and backed up onto a secure, password-protected server. Data were transmitted for statistical analysis using the same server. Only the principal investigator, coinvestigator, and statistician have access to the raw data. Statistical analyses were conducted using STATA/MP version 16.1 (Statacorp College Station, TX).

Chapter 4: Association of Neighborhood Social Disinvestment with Worse Survival After Lung Transplant

Abstract

Background

Lung transplantation is an effective tool for the treatment of select patients with a range of end-stage lung diseases, but life expectancy post-transplant remains modest with median survival of 5.5-6.5 years and donor organs are a scarce resource. Few studies have evaluated the impact of neighborhood-level social and environmental factors on lung transplant outcomes. The Social Vulnerability Index (SVI) is a tool used to identify communities most likely to need support during a hazardous event and has been associated with poor health outcomes across of range of diseases.

Objectives

We hypothesize that greater neighborhood social need as defined by higher SVI will be associated with a higher hazard for mortality and graft failure in lung transplant patients.

Methods

We conducted a retrospective analysis of panel data provided by the United Network for Organ Sharing. National census tract level SVI was converted to ZIP code level using US Department of Housing and Urban Development Crosswalk procedures. Kaplan Meier Survival Curves were produced for time to death or graft failure. Gamma shared frailty cox proportional hazards model was used to produce unadjusted and adjusted hazard ratios to estimate the effect of neighborhood SVI and its component scores on graft failure or mortality.

Results

Data for 27,159 lung transplants conducted between May 2005 and August 2020 were included. Having a ZIP code level SVI in the highest decile was associated with an 8% increase in the hazard of death or graft failure (p=0.022) in unadjusted analysis and 6% increase (p=0.081) after adjusting for covariates. Highest decile Household Composition and Disability Theme score was associated with an 8% increased hazard (p=0.017) in adjusted analysis.

Conclusions

Greater neighborhood disinvestment was associated with a modest increase in the hazard of death or graft failure in lung transplant recipients. Further study is required to better understand this relationship and elucidate the mechanism behind it.

Introduction

Lung transplantation is a life-saving treatment for a carefully selected subset of patients with a broad range of end stage lung diseases. Life expectancy following lung transplant is modest with median survival of 5.5-6.5 years.[1,80,81] Given the resource-intensive nature of the procedure and the finite supply of donor organs, a great deal of effort has gone into the development of strategies to optimize the post-transplant course. This begins with the determinations of risk factors for poor outcomes post-transplant.

Currently known risk factors for poor outcomes can be divided into recipient-, donor- and transplant-level characteristics. Transplant recipients with an underlying diagnosis of idiopathic pulmonary arterial hypertension (IPAH) and patients being re-transplanted after a failed lung allograft are at the highest risk of dying within the first year.[25] Other recipient factors associated with higher risk of death within the first year include comorbid conditions and markers of overall illness including the need for dialysis and hospitalization, need for IV inotropes, and need of mechanical ventilatory support at the time of transplant.[1,82-84] Diabetes in the donor and transplant cytomegalovirus (CMV) donor/recipient seroprevalence status mismatch are also associated with increased risk of 1-year mortality.[85] The risk factors for 5-year mortality are largely the same except IPAH as an indication for transplant is no longer significantly associated with mortality[1]

There has been a relative paucity of research into neighborhood-level environmental and social factors that may contribute to the development of allograft failure and mortality. The Social Vulnerability Index (SVI) is a tool developed by the Center for Disease Control and Prevention's (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) to identify and

map communities that are most likely to need support during a hazardous event. [33] It measures neighborhood disinvestment and social need by using US Census and American Community Survey (ACS) data to rank US counties and census tracts using 15 variables across four domains: Socioeconomic Status, Household Composition & Disability, Minority Status & Language, and Housing Type & Transportation. Geographic areas are percentile ranked and given a score between 0 and 1 with higher number signifying higher disinvestment and elevated need for external support in case of a disaster.

Increasingly, the SVI has been used in public health research to identify communities at higher risk of poor outcomes from a wide variety of medical conditions. High SVI has been associated with worse surgical outcomes in cancer patients,[40] higher rates of death from cardiovascular disease,[41] and higher incidence of and worse survival in COVID-19.[42] The impact of the SVI on lung transplant outcomes has not previously been investigated.

Aims & Hypotheses

Aim 1.1: Model the effect of neighborhood social disinvestment on risk of death or graft failure after transplant.

Hypothesis 1.1: Greater neighborhood social disinvestment as defined by higher SVI is associated with higher graft failure and mortality in lung transplant patients.

Hypothesis 1.2a-d: Higher SVI SES, Household Composition & Disability, Minority Status & Language, and Housing Type & Transportation scores are each associated with higher graft failure and mortality in lung transplant patients.

Methods

Data Source

We analyze data from the United Network for Organ Sharing (UNOS) transplant registry. UNOS is the system used by every transplant center in the US to register and track waitlist candidates and transplant recipients. Data is available on patient and limited donor-level factors for every patient who has been placed on a solid organ transplant waitlist since its inception in 1987, including the ZIP code of residence at the time of transplant. We restrict our analyses to those recipients transplanted after May 2005 when the Lung Allocation Score (LAS) for waitlist prioritization was introduced. Heart and combined heart-lung transplants are excluded. 27,159 recipients are included in the analysis (Figure 3).

Variable Construction

The SVI incorporates data from the ACS and decennial U.S. Census across 15 domains and four theme areas. The Socioeconomic Status theme incorporates the proportion of the population below the poverty level, proportion of persons age 16+ who are unemployed, per capita income estimate, and proportion of persons age 25+ with no high school diploma. Each of these values is given a percentile ranking for all US census tracts and these percentile rankings are then summed into a raw score for the Socioeconomic Status theme. The SES sum score is then given a percentile ranking among US census tracts and the resultant value is the SVI SES Theme Score. The Household Composition theme similarly treats the proportion of persons aged 65 and older, proportion of persons aged 17 and younger, and proportion of single parent households with children under 18; percentile ranks them; sums them, and percentile ranks the sum into the SVI Household Composition & Disability Theme Score. Of

note, the Household Composition & Disability Theme Score for other years includes a disability variable, but this data was not included in the 2010 Census or 2006-2010 ACS, so it was not included in the 2010 SVI construct. The proportion of the population that is minority (all persons except white non-Hispanic) and proportion of persons age 5+ who speak English "less than well" are similarly combined into the SVI Minority Status & Language Theme Score. The proportion of housing structures with 10 or more units, proportion of mobile homes, proportion of households with more people than rooms, proportion of households with no vehicle available, and proportion of persons in group quarters are combined into the SVI Housing & Transportation Theme Score. Each of the four theme scores are then summed and percentile ranked to give the Overall SVI Score. In 2010, this process was completed for each census tract and each county both for the US and for each state individually. For the purposes of these studies, the census tract SVI for the entire country will be used.

ZIP code level SVI was constructed using the CDC/ATSDR 2010 SVI dataset for census tracts in the United States.[86] Census tract SVI was transformed into ZIP code SVI using the US Office of Housing and Urban Development (HUD) ZIP code to census tract crosswalk files which contains data on the proportion of each census tract that exists within a given ZIP code and vice versa.[87] Transformation of the SVI from census tract level to ZIP code level appropriately produces a variable that is a proportion with bounds of 0 and 1 but is no longer a percentile with a uniform distribution. The ZIP code SVI remains useful in this form as the relationship of higher numbers representing higher social need and lower numbers representing lower social need still holds. This process is repeated for each of the four theme components of the SVI.

The outcome of interest is time to death or lung allograft failure. Other covariates include recipient age, gender, race/ethnicity, underlying lung disease, need for life support prior to transplantation, LAS, type of insurance, and medical center of transplantation. The need for life support is defined as use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at the time of transplant. LAS scores are grouped into <35, 35-45, 45-55, and >55.

Statistical Analysis

This study is a retrospective cohort analysis of panel data from the UNOS registry. Descriptive statistics were calculated at the patient level comparing groups with ZIP Code SVI above or below the 90th percentile. The 90th percentile was chosen based on the fact that the CDC/ATSDR flags geographies above the 90th percentile for each of the SVI variables. Continuous variables were compared between groups using Welch's t-test, while categorical variables were compared using chi-square tests. Time-to-event analyses were conducted for the composite endpoint of death or graft failure. Analysis was censored at 10-years of follow-up time. Kaplan-Meier survival curves were produced for high and low SVI and log-rank test performed to determine equality of the survival functions for the comparison groups. Hazard ratios for high SVI were estimated using the cox proportional hazards (PH) model for both unadjusted estimates and after adjustment for covariates. A cox proportional hazards model including cluster-specific random effects at the level of the transplant center was performed using a gamma shared frailty model.[88] Violations of the proportional hazards assumption were assessed visually by plotting Schoenfeld residuals against time and plotting the log log survival time vs log time. We also formally test using the Grambsch and Therneau test but recognize

that with our large sample size this may be and overly sensitive assessment. Associations for the four SVI theme scores are also estimated using the main adjusted gamma shared frailty cox proportional hazards model.

Sensitivity Analysis

We test multiple cox proportional hazards models to assess how best to handle variation in outcomes at the level of transplant center. We test separate models clustering using the transplant center with robust standard errors and using gamma shared frailty for a random intercept model.[89] We additionally test multiple parametric survival models including Exponential Distribution, Weibull Distribution, and a Log-Log Accelerated Failure Time model. As a non-proportional hazards model, the loglogistic model will ensure our findings are robust to any potential violations of the proportional hazards assumption.

While we theorize that hazard of death or graft failure will be highest in the neighborhoods with the highest social need, we do not expect this effect to remain linear at lower SVI levels. Highest risk groups are likely to be exposed to more environmental hazards and social stressors than the general populace, but we do not necessarily expect that those with the lowest social need to be less exposed than the general populace. We explore this relationship by running a sensitivity analysis using SVI as a continuous variable, scaled up by 100x to represent a score ranging from 0 to 100. The study protocols were reviewed by the institutional review board of the University of California, Los Angeles and exemption granted (IRB# 22-000186) as it was not considered human subjects research.

Results

A total of 27,159 lung transplant recipients were included in the analysis. 2,245 (8%) had residences in ZIP codes whose overall SVI was in the highest decile (SVI $\geq$0.8). Patient characteristics are found in Table 3. High SVI patients were slightly younger than lower SVI (54.6 vs 56.2 years). There was also a higher proportion of women in the higher SVI group (46% vs 40%). There was a lower proportion of white recipients and higher proportion of Black and Hispanic/Latino transplant recipients in the High SVI group (44% White vs 85% white, 25% Black vs 8%, and 28% Hispanic/Latino vs 5% in the higher and lower SVI groups respectively). There were fewer recipients with private insurance (42% vs 50%) and more patients with Medicaid insurance (15% vs 6%) in the high SVI group as compared to lower. There was no difference in the use of life support prior to transplant between groups. There were slightly more patients who received bilateral transplants in the high SVI group (72% vs 70%).

Kaplan-Meier survival curves for the high and low SVI groups are shown in Figure 4. Log-rank test with p=0.022 rejects the null hypothesis that the two survival curves are the same with a prespecified α of 0.05. An unadjusted cox proportional hazards model was fit and demonstrated high SVI was associated with an 8% increase in the hazard of death or graft failure, p=0.022. Separate cox proportional hazards models with gamma shared frailty around the transplant center were fit adjusting for patient age, sex, and race/ethnicity (Model 1), and then adding BMI and Insurance (Model 2), and lastly underlying diagnosis, life support, and transplant laterality in the final model (Model 3) (See Table 4). Hazard ratios for death or graft failure for high SVI were 1.07 p=0.045, 1.06 p=0.099, and 1.06 p=0.081 for Models 1, 2, and 3 respectively. The data did not appear to violate the proportional hazards assumption by visual

inspection (see Figure 5 and Figure 6). The SVI variable does not violate the PH assumption based on a Grambsch and Therneau test with χ^2 0.02 and p=0.883 (Table 5). Using this test, multiple covariates violate the PH assumption and the global test demonstrated violation with χ^2=163.38 p<0.001.

To test different model specifications cox proportional hazards model with clustered-robust standard errors for transplant center was fit as well as parametric models using Exponential, Weibull, and Log-log AFT distributions with results displayed in Table 6. The High SVI group has a 9% p=0.009, 6% p=0.079, and 7% p=0.060 increased hazard of death or graft failure in the Cox PH with cluster robust standard errors, exponential distribution, and Weibull distribution models respectively. The Loglogistic AFT model demonstrates a coefficient (e^{β}) of 0.89 p=0.008 representing an 11% decrease in the estimated median survival time for the High SVI group, consistent with the other tested models.

Analysis of the individual SVI theme scores demonstrated a hazard ratio (HR) of 1.03 p=0.461, 1.08 p=0.017, 1.02 p=0.621, and 1.08 p=0.086 for the high SVI socioeconomic, household composition & disability, minority status & language, and housing type & transportation themes respectively (See Table 7). Refitting the main cox PH model with gamma shared frailty respecifying overall SVI in quartiles and as a continuous variable did not demonstrate a statistically significant association between SVI and death or graft failure (Table 8 and Table 9). The estimated hazard ratios of death or graft failure graphed against SVI are plotted in Figure 7.

Discussion

In this large registry analysis of lung transplant recipients, we examine the effect of neighbor disinvestment on lung transplant outcomes. In unadjusted analysis, residence in a ZIP code with an SVI in the highest decile was associated with an 8% increase in the hazard of death or graft failure. This difference in mortality and graft failure was statistically significant in unadjusted estimates using the log-rank test comparing Kaplan-Meier survival curves and Wald test for cox PH model with α 0.05. After adjusting for covariates, the estimated hazard ratio remained stable, but standard deviation increased and p-value rose above 0.05. Interestingly, the handling of the center effects appeared to have a significant impact on the standard deviation of the estimates. The increase in hazard of death or graft failure was statistically significant when center was handled as a clustering variable with robust standard errors but not when handled as a random effect using the gamma shared frailty models. These results suggest elevated neighborhood disinvestment as measured by the SVI may be associated with worse survival and graft failure in lung transplant recipients and a portion of this variance may be attributable to transplant center differences. Interestingly, this effect does not appear to be linear in nature as is evidenced by the lack of an association when SVI is grouped by quartiles or as a continuous variable. Our analysis suggests there may be a quadratic relationship between SVI and lung transplant with higher hazard in the lowest and highest SVI groups and lower hazard in the middle. When analyzing the individual theme scores of the SVI, only the Household Composition & Disability theme demonstrated a statistically significant increase in the hazard of death or graft failure for the highest risk group.

We are unsurprised at the relatively modest effect size of the association of SVI with poor outcomes as a significant amount of the risk of SVI on potential outcomes is selected out in the candidate selection process. Many of the same attributes that on the neighborhood-scale represent a high SVI, on the individual level may disqualify a person from transplant candidacy. Neighborhood level per capita income and poverty levels map onto individual level inability to pay for medication copays which would disqualify a candidate. Similarly, neighborhood level proportion without a vehicle maps onto an individual not having transportation to clinic visits, which would disqualify a candidate. The fact that we still have a suggestion of an effect even after selection illustrates it may be worthwhile to flag these individuals from high SVI environments for additional resources post-transplant.

It warrants noting that the SVI is a tool developed to identify groups that require additional resources in the case of adverse events. It measures and codifies the effects of neighborhood clustering based on income, poverty level, socioeconomic status, and race. As clinicians attempting to limit the risk of poor outcomes after the distribution of a scarce resource like the donor lung allograft, the first inclination may be to add SVI to the selection criteria attempting to remove patients most at risk. This would be unjust and antithetical to the intent of the measure. The SVI must not be used to exclude an already disadvantaged group from potentially life-saving therapy.

Limitations

This study uses panel data to test the association between neighborhood social disinvestment as measured by high SVI and graft failure and mortality after lung transplant. The use of registry data allows for complete capture of the population of lung transplant recipients

in the United States with very little missingness in our variables of interest. A major limitation of the study is the potential for misclassification error. Patient residence is only specified at the ZIP code level in the UNOS registry. Transformation of SVI from census tract level to ZIP code level has the potential to introduce misclassification bias as the measured disadvantage of a given census tract is distributed to its constituent ZIP codes purely based on population and cannot take into account variability within that census tract. Additionally, the ZIP code may not be a good proxy for neighborhood as they are relatively large and may encompass multiple and disparate communities. To date, the CDC/ATSDR has recalculated the SVI for years 2000, 2010, 2014, 2016, and 2018. Because it is not available for all years of the study, we have chosen to use the 2010 SVI for all analyses. This has the potential to introduce bias if a given geography had significant changes in demographics and social composition across years.

As noted previously, our main cox PH gamma shared frailty model violates the proportional hazards assumption using the Grambsch and Therneau test, which is likely overly sensitive given the large sample size. The data did not appear to violate the PH assumption on visual assessment. Additionally, sensitivity analysis using the loglogistic AFT model which does not hold to the PH principle continues to demonstrate an effect.

Conclusion

In this large registry analysis of lung transplant patients, neighborhood disinvestment seems to have a modest association with worse mortality and graft failure among lung transplant patients. Further research is needed to better understand the mechanism behind this association and determine whether or not it is modifiable. The SVI may prove to be a useful

tool to help identify patients at higher risk of poor outcomes who may benefit from increased resources or closer follow-up from the transplant team.

Tables and Figures

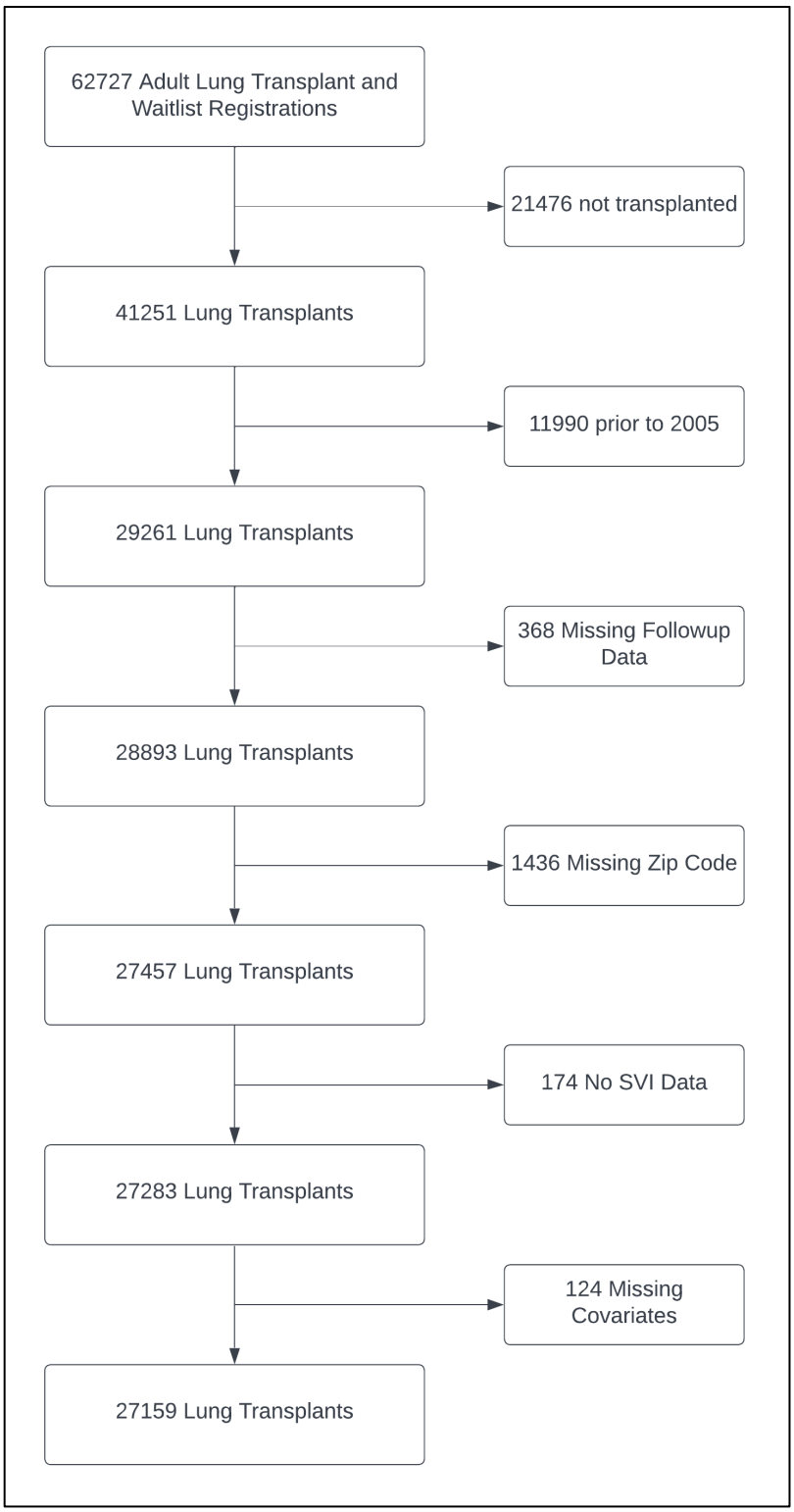

Figure 3: Patient flow chart

Table 3: Baseline patient characteristics, comparing lower SVI and high SVI groups

Characteristic	ZIP Code SVI		
	Low SVI < 0.8	**High SVI ≥0.8**	**[1]p**
Number, N (%)	24,914 (92%)	2,245 (8%)	
Age (years), mean (SD)	56.2 (13.1)	54.6 (12.8)	<.001
Female, %	40%	46%	<.001
Race Ethnicity, %			<.001
White	85%	44%	
Black	8%	25%	
Hispanic/Latino	5%	28%	
Other	2%	3%	
BMI (kg/m^2), mean (SD)	25.3 (4.6)	25.6 (4.5)	0.005
Diagnosis, %			<.001
Obstructive pulmonary disease	28%	27%	
Pulmonary vascular disease	4%	5%	
Cystic Fibrosis	11%	7%	
Restrictive Lung Disease	57%	61%	
LAS, %			<.001
<35	25%	20%	
>35 - 45	37%	37%	
>45 - 55	15%	17%	
>55	23%	26%	
Insurance, %			<.001
Private	50%	42%	
Medicaid	6%	15%	
Medicare	41%	38%	
Other Public	3%	3%	
Other	0%	1%	
Mechanical Ventilation or ECMO at time of match, %	8%	8%	0.523
Bilateral Transplant, %	70%	72%	0.026

Data are percent or mean (standard deviation)
[1]p value based on chi-square or Welch's t-test.

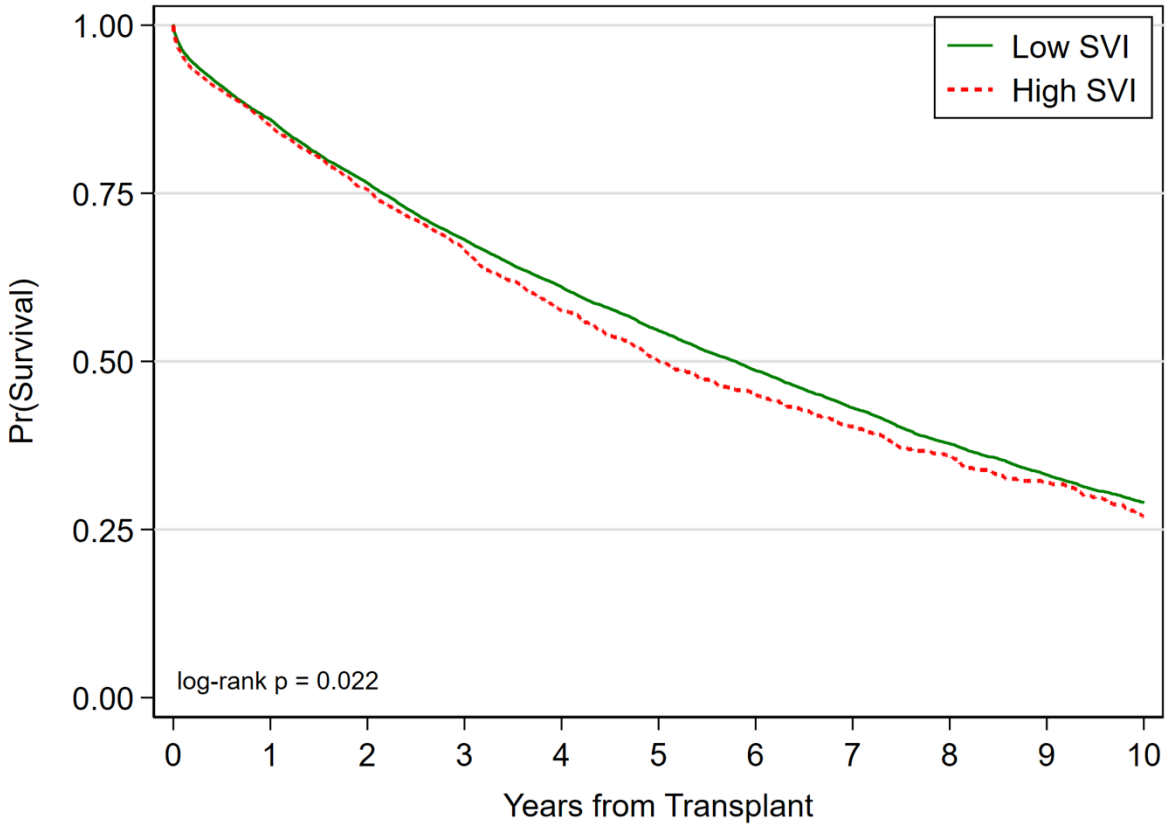

Figure 4: Kaplan-Meier survival within 10 years by SVI. SVI = Social Vulnerability Index

Table 4: Cox proportional hazards models for SVI, unadjusted and adjusted models

Predictors	[a]Unadjusted Hazard Ratio (95% CI)	p	[b]Model 1 Hazard Ratio (95% CI)	p	[b]Model 2 Hazard Ratio (95% CI)	p	[b]Model 3 Hazard Ratio (95% CI)	p
Model BIC	226932.6		226603.4		226518.7		226227.5	
High SVI (≥0.8)	1.08 (1.01, 1.15)	0.022	1.07 (1.00, 1.15)	0.045	1.06 (0.99, 1.13)	0.099	1.06 (0.99, 1.14)	0.081
Recipient Age, *per 10 years*			1.07 (1.05, 1.08)	<.001	1.06 (1.04, 1.08)	<.001	1.03 (1.01, 1.05)	0.006
Female Sex			0.94 (0.91, 0.98)	0.002	0.94 (0.91, 0.98)	0.001	0.95 (0.91, 0.99)	0.007
Race								
White			ref		ref		ref	
Black			0.95 (0.89, 1.01)	0.110	0.94 (0.87, 1.00)	0.048	0.95 (0.89, 1.02)	0.174
Hispanic/Latino			0.92 (0.85, 1.00)	0.039	0.90 (0.83, 0.98)	0.011	0.87 (0.80, 0.94)	<.001
Other			0.92 (0.80, 1.05)	0.212	0.92 (0.81, 1.05)	0.237	0.88 (0.77, 1.00)	0.054
BMI, *per 5 kg/m^2*					1.02 (1.00, 1.04)	0.125	0.99 (0.97, 1.02)	0.620
Insurance								
Private					ref		ref	
Medicaid					1.25 (1.16, 1.35)	<.001	1.25 (1.16, 1.34)	<.001
Medicare					1.11 (1.07, 1.15)	<.001	1.11 (1.07, 1.16)	<.001
Other Public					0.97 (0.86, 1.10)	0.668	0.96 (0.86, 1.09)	0.550
Other					0.92 (0.70, 1.22)	0.563	0.91 (0.69, 1.20)	0.503
Diagnosis								
Obstructive Lung Disease							ref	
Pulmonary Vascular Disease							1.28 (1.15, 1.42)	<.001
Cystic Fibrosis							1.04 (0.95, 1.13)	0.370
Restrictive Lung Disease							1.13 (1.08, 1.18)	<.001
[1]Life Support							1.44 (1.35, 1.54)	<.001
Bilateral Transplant							0.74 (0.71, 0.77)	<.001

[1]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance
Model 3 – adjusted for Model 2 covariates and diagnosis, [1]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model
[b]Gamma shared frailty Cox proportional hazards model.

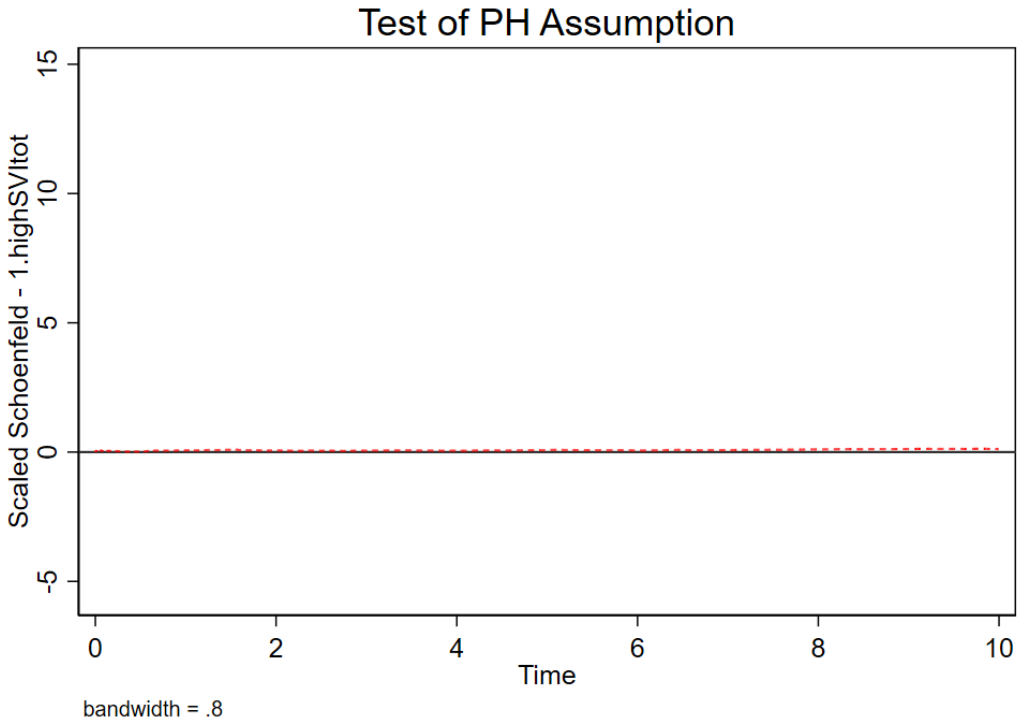

Figure 5: Test of the proportional hazards assumption for SVI. Plot of Schoenfeld residuals versus time

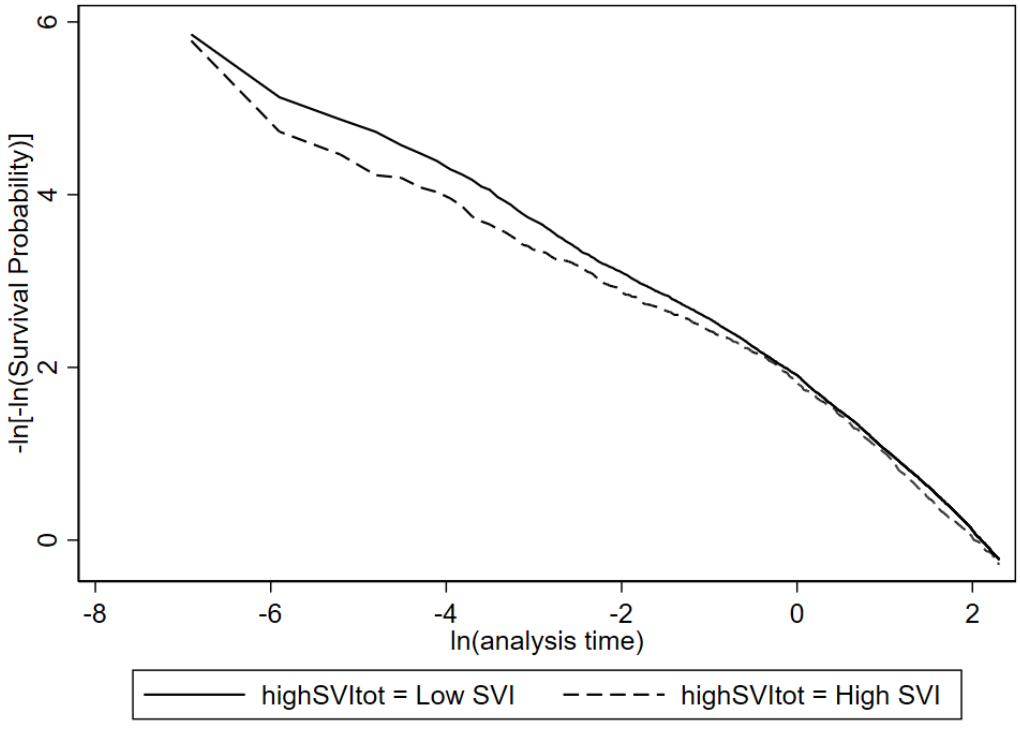

Figure 6: Test of the proportional hazards assumption for SVI. Plot of log(log(survival probability)) versus log(time)

Table 5: Test of proportional hazards assumption. Grambsch and Therneau test

Variable	rho	$\chi 2$	p
High SVI	-0.00132	0.02	0.883
Recipient Age, *per 10 years*	0.02704	9.97	0.001
Female Sex	0.01314	2.07	0.150
Race			
White	Ref	Ref	Ref
Black	-0.01722	3.67	0.055
Hispanic/Latino	0.00347	0.15	0.696
Other	-0.00187	0.04	0.836
BMI, *per 5 kg/m²*	0.01105	1.57	0.210
Insurance			
Private	Ref	Ref	Ref
Medicaid	0.01962	4.73	0.029
Medicare	0.00882	0.96	0.326
Other Public	0.00032	0.00	0.970
Other	0.00047	0.00	0.958
Diagnosis			
Obstructive Lung Disease			
Pulmonary Vascular Disease	-0.02755	9.31	0.002
Cystic Fibrosis	0.00208	0.05	0.821
Restrictive Lung Disease	-0.03611	16.07	<.001
Life Support	-0.04779	29.08	<.001
Bilateral Transplant	-0.04896	33.11	<.001
Global Test		163.38	<.001

Table 6: Alternate survival models for SVI

Predictors	[a]Cox PH w/ Clustered SE		[b]Mixed Effects Parametric Survival *Exponential Distribution*		[b]Mixed Effects Parametric Survival *Weibull Distribution*		[c]AFT Parametric Survival *Log-Logistic Distribution*	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	e^{β} (95% CI)	p
[1]Model BIC	226446.4		72861.3		72209.7		66178.0	
High SVI (≥0.8)	1.09 (1.02, 1.17)	0.009	1.06 (0.99, 1.14)	0.079	1.07 (1.00, 1.14)	0.060	0.89 (0.81, 0.97)	0.008
Recipient Age, *per 10 years*	1.03 (1.01, 1.06)	0.017	1.03 (1.01, 1.06)	0.002	1.02 (1.00, 1.04)	0.039	0.98 (0.95, 1.01)	0.232
Female Sex	0.95 (0.91, 0.99)	0.010	0.95 (0.91, 0.99)	0.007	0.95 (0.91, 0.99)	0.007	1.08 (1.03, 1.15)	0.004
Race								
White	ref		ref		ref		ref	
Black	0.99 (0.91, 1.07)	0.728	0.95 (0.89, 1.02)	0.181	0.96 (0.89, 1.02)	0.207	0.99 (0.91, 1.09)	0.913
Hispanic/Latino	0.91 (0.84, 0.98)	0.014	0.87 (0.80, 0.94)	<.001	0.87 (0.80, 0.94)	<.001	1.16 (1.05, 1.29)	0.003
Other	0.88 (0.76, 1.01)	0.063	0.88 (0.77, 1.00)	0.058	0.88 (0.77, 1.01)	0.060	1.18 (0.97, 1.44)	0.104
BMI, *per 5 kg/m^2*	1.00 (0.97, 1.03)	0.979	0.99 (0.97, 1.02)	0.633	0.99 (0.97, 1.02)	0.599	1.00 (0.97, 1.04)	0.853
Insurance								
Private	ref		ref		ref		ref	
Medicaid	1.26 (1.18, 1.35)	<.001	1.25 (1.16, 1.35)	<.001	1.22 (1.13, 1.31)	<.001	0.78 (0.72, 0.86)	<.001
Medicare	1.12 (1.07, 1.17)	<.001	1.12 (1.07, 1.16)	<.001	1.09 (1.05, 1.14)	<.001	0.89 (0.85, 0.94)	<.001
Other Public	0.93 (0.82, 1.06)	0.274	0.97 (0.86, 1.09)	0.595	0.96 (0.86, 1.09)	0.551	1.08 (0.93, 1.25)	0.330
Other	0.95 (0.70, 1.29)	0.746	0.91 (0.69, 1.21)	0.519	0.91 (0.69, 1.20)	0.484	1.06 (0.73, 1.55)	0.757
Diagnosis								
Obstructive Lung Disease	ref		ref		ref		ref	
Pulmonary Vascular Disease	1.26 (1.10, 1.44)	<.001	1.30 (1.17, 1.45)	<.001	1.25 (1.13, 1.39)	<.001	0.70 (0.60, 0.83)	<.001
Cystic Fibrosis	1.04 (0.94, 1.14)	0.465	1.05 (0.96, 1.14)	0.276	1.02 (0.93, 1.11)	0.699	1.00 (0.88, 1.13)	0.992
Restrictive Lung Disease	1.12 (1.05, 1.18)	<.001	1.14 (1.09, 1.19)	<.001	1.12 (1.07, 1.17)	<.001	0.86 (0.79, 0.93)	<.001
[2]Life Support	1.42 (1.26, 1.60)	<.001	1.46 (1.37, 1.56)	<.001	1.43 (1.34, 1.52)	<.001	0.58 (0.49, 0.68)	<.001

Bilateral Transplant	0.73 (0.67, 0.78)	<.001	0.74 (0.71, 0.77)	<.001	0.74 (0.71, 0.77)	<.001	1.46 (1.31, 1.62)	<.001

[1]Model BIC is not comparable between semi-parametric (e.g. Cox PH) and parametric models (e.g. mixed effects; log-logistic)
[2]Mechanical Ventilation or ECMO
[a]Clustered-Robust Standard Errors (Huber-White sandwich estimator) for Center
[b]Random intercept for Center
[c]Parametric log-logistic Accelerated Failure Time model with gamma shared frailty and Clustered-Robust Standard Errors (Huber-White sandwich estimator) for Center

Table 7: Cox proportional hazards gamma shared frailty models of SVI theme scores

Predictors	Socioeconomic Status		Household Composition & Disability		Minority Status & Language		Housing Type & Transportation	
	Hazard Ratio (95% CI)	**p**	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**	**p**
Model BIC	226229.9		226225.0		226230.2		226227.6	
[1]High SVI	1.03 (0.95, 1.11)	0.461	1.08 (1.01, 1.16)	0.017	1.02 (0.96, 1.08)	0.621	1.08 (0.99, 1.19)	0.086
Recipient Age, *per 10 years*	1.03 (1.01, 1.05)	0.006	1.03 (1.01, 1.05)	0.005	1.03 (1.01, 1.05)	0.006	1.03 (1.01, 1.05)	0.006
Female Sex	0.95 (0.91, 0.99)	0.008	0.95 (0.91, 0.99)	0.007	0.95 (0.91, 0.99)	0.007	0.95 (0.91, 0.99)	0.008
Race								
White	ref		ref		ref		ref	
Black	0.96 (0.90, 1.03)	0.242	0.95 (0.89, 1.01)	0.124	0.96 (0.90, 1.03)	0.264	0.96 (0.90, 1.03)	0.274
Hispanic/Latino	0.88 (0.81, 0.95)	0.001	0.87 (0.80, 0.94)	<.001	0.87 (0.80, 0.95)	0.001	0.88 (0.81, 0.95)	0.001
Other	0.88 (0.77, 1.00)	0.056	0.88 (0.77, 1.00)	0.055	0.88 (0.77, 1.00)	0.052	0.88 (0.77, 1.00)	0.051
BMI, *per 5 kg/m^2*	0.99 (0.97, 1.02)	0.624	0.99 (0.97, 1.02)	0.624	0.99 (0.97, 1.02)	0.629	0.99 (0.97, 1.02)	0.631
Insurance								
Private	ref		ref		ref		ref	
Medicaid	1.25 (1.16, 1.35)	<.001	1.25 (1.16, 1.34)	<.001	1.25 (1.16, 1.35)	<.001	1.25 (1.16, 1.35)	<.001
Medicare	1.11 (1.07, 1.16)	<.001	1.11 (1.06, 1.15)	<.001	1.11 (1.07, 1.16)	<.001	1.11 (1.07, 1.16)	<.001
Other Public	0.97 (0.86, 1.09)	0.564	0.96 (0.86, 1.09)	0.556	0.97 (0.86, 1.09)	0.560	0.97 (0.86, 1.09)	0.564
Other	0.91 (0.69, 1.20)	0.500	0.91 (0.69, 1.20)	0.505	0.91 (0.69, 1.20)	0.504	0.91 (0.69, 1.20)	0.498
Diagnosis								
Obstructive Lung Disease	ref		ref		ref		ref	
Pulmonary Vascular Disease	1.28 (1.15, 1.42)	<.001	1.28 (1.15, 1.42)	<.001	1.28 (1.15, 1.42)	<.001	1.28 (1.15, 1.42)	<.001
Cystic Fibrosis	1.04 (0.95, 1.13)	0.385	1.04 (0.96, 1.13)	0.358	1.04 (0.95, 1.13)	0.391	1.04 (0.95, 1.13)	0.384
Restrictive Lung Disease	1.13 (1.08, 1.18)	<.001	1.13 (1.08, 1.18)	<.001	1.13 (1.08, 1.18)	<.001	1.13 (1.08, 1.18)	<.001
[2]Life Support	1.45 (1.35, 1.54)	<.001	1.45 (1.35, 1.54)	<.001	1.45 (1.35, 1.54)	<.001	1.44 (1.35, 1.54)	<.001

Bilateral Transplant	0.74 (0.71, 0.77)	<.001	0.74 (0.71, 0.77)	<.001	0.74 (0.71, 0.77)	<.001	0.74 (0.71, 0.77)	<.001

[1]High SVI defined as: Socioeconomic Status Theme (≥ 0.82); Household Composition Theme (≥ 0.79); Minority Status Theme (≥ 0.77); Housing Type Theme (≥ 0.82);
[2]Mechanical Ventilation or ECMO
Shared frailty Cox proportional hazards model.

Table 8: Cox proportional hazards models for SVI quartiles analysis, unadjusted and adjusted models

Predictors	[a]Unadjusted Hazard Ratio (95% CI)	p	[b]Model 1 Hazard Ratio (95% CI)	p	[b]Model 2 Hazard Ratio (95% CI)	p	[b]Model 3 Hazard Ratio (95% CI)	p
Model BIC	226947.0		226535.7		226245.4		226227.5	
SVI – 1st Quartile (<0.30)	ref		ref		ref		ref	
SVI – 2nd Quartile (0.30-0.46)	0.93 (0.88, 0.98)	0.003	0.95 (0.90, 0.99)	0.030	0.94 (0.90, 0.99)	0.026	0.95 (0.90, 1.00)	0.045
SVI – 3rd Quartile (0.46-0.64)	0.95 (0.90, 0.99)	0.030	0.96 (0.91, 1.01)	0.126	0.95 (0.91, 1.00)	0.064	0.97 (0.92, 1.02)	0.181
SVI – 4th Quartile (≥0.64)	0.99 (0.94, 1.04)	0.598	0.99 (0.94, 1.05)	0.832	0.98 (0.93, 1.03)	0.450	1.00 (0.94, 1.05)	0.931
Recipient Age, *per 10 years*			1.07 (1.05, 1.08)	<.001	1.06 (1.04, 1.08)	<.001	1.03 (1.01, 1.05)	0.007
Female Sex			0.94 (0.91, 0.98)	0.002	0.94 (0.91, 0.98)	0.001	0.95 (0.91, 0.99)	0.007
Race								
White			ref		ref		ref	
Black			0.95 (0.89, 1.02)	0.170	0.94 (0.88, 1.01)	0.093	0.96 (0.90, 1.03)	0.230
Hispanic/Latino			0.93 (0.86, 1.01)	0.071	0.91 (0.84, 0.99)	0.023	0.87 (0.81, 0.95)	0.001
Other			0.92 (0.80, 1.05)	0.216	0.92 (0.81, 1.06)	0.243	0.88 (0.77, 1.00)	0.057
BMI, *per 5 kg/m^2*					1.02 (1.00, 1.04)	0.120	0.99 (0.97, 1.02)	0.624
Insurance								
Private					ref		ref	
Medicaid					1.26 (1.17, 1.35)	<.001	1.25 (1.16, 1.35)	<.001
Medicare					1.11 (1.07, 1.16)	<.001	1.11 (1.07, 1.16)	<.001
Other Public					0.98 (0.87, 1.10)	0.738	0.97 (0.86, 1.09)	0.591
Other					0.92 (0.70, 1.22)	0.578	0.91 (0.69, 1.20)	0.508
Diagnosis								
Obstructive Lung Disease							ref	
Pulmonary Vascular Disease							1.27 (1.14, 1.42)	<.001

Cystic Fibrosis	1.04 (0.95, 1.13)	0.395
Restrictive Lung Disease	1.13 (1.08, 1.18)	<.001
[1]Life Support	1.45 (1.35, 1.54)	<.001
Bilateral Transplant	0.74 (0.71, 0.77)	<.001

[1]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance
Model 3 – adjusted for Model 2 covariates and diagnosis, [1]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model
[b]Shared frailty Cox proportional hazards model.

Table 9: Cox proportional hazards models for SVI continuous analysis, unadjusted and adjusted models

Predictors	[a]Unadjusted Hazard Ratio (95% CI)	p	[b]Model 1 Hazard Ratio (95% CI)	p	[b]Model 2 Hazard Ratio (95% CI)	p	[b]Model 3 Hazard Ratio (95% CI)	p
Model BIC	226937.2		226607.0		226520.0		226230.3	
SVI, *per 0.10*	1.00 (0.99, 1.01)	0.483	1.00 (0.99, 1.01)	0.575	0.99 (0.99, 1.00)	0.241	1.00 (0.99, 1.01)	0.655
Recipient Age, *per 10 years*			1.07 (1.05, 1.08)	<.001	1.06 (1.04, 1.08)	<.001	1.03 (1.01, 1.05)	0.007
Female Sex			0.94 (0.91, 0.98)	0.002	0.94 (0.91, 0.98)	0.001	0.95 (0.91, 0.99)	0.008
Race								
White			ref		ref		ref	
Black			0.96 (0.90, 1.03)	0.284	0.95 (0.89, 1.02)	0.169	0.97 (0.90, 1.04)	0.355
Hispanic/Latino			0.94 (0.87, 1.02)	0.122	0.92 (0.85, 1.00)	0.046	0.88 (0.81, 0.96)	0.002
Other			0.92 (0.80, 1.05)	0.217	0.92 (0.81, 1.06)	0.244	0.88 (0.77, 1.00)	0.056
BMI, *per 5 kg/m^2*					1.02 (1.00, 1.04)	0.114	0.99 (0.97, 1.02)	0.639
Insurance								
Private					ref		ref	
Medicaid					1.26 (1.17, 1.36)	<.001	1.25 (1.16, 1.35)	<.001
Medicare					1.11 (1.07, 1.16)	<.001	1.11 (1.07, 1.16)	<.001
Other Public					0.98 (0.87, 1.10)	0.727	0.97 (0.86, 1.09)	0.581
Other					0.93 (0.70, 1.22)	0.582	0.91 (0.69, 1.20)	0.510
Diagnosis								
Obstructive Lung Disease							ref	
Pulmonary Vascular Disease							1.27 (1.15, 1.42)	<.001
Cystic Fibrosis							1.04 (0.95, 1.13)	0.412
Restrictive Lung Disease							1.13 (1.08, 1.18)	<.001
[1]Life Support							1.45 (1.35, 1.54)	<.001
Bilateral Transplant							0.74 (0.71, 0.77)	<.001

[1]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance
Model 3 – adjusted for Model 2 covariates and diagnosis, [1]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model
[b]Shared frailty Cox proportional hazards model.

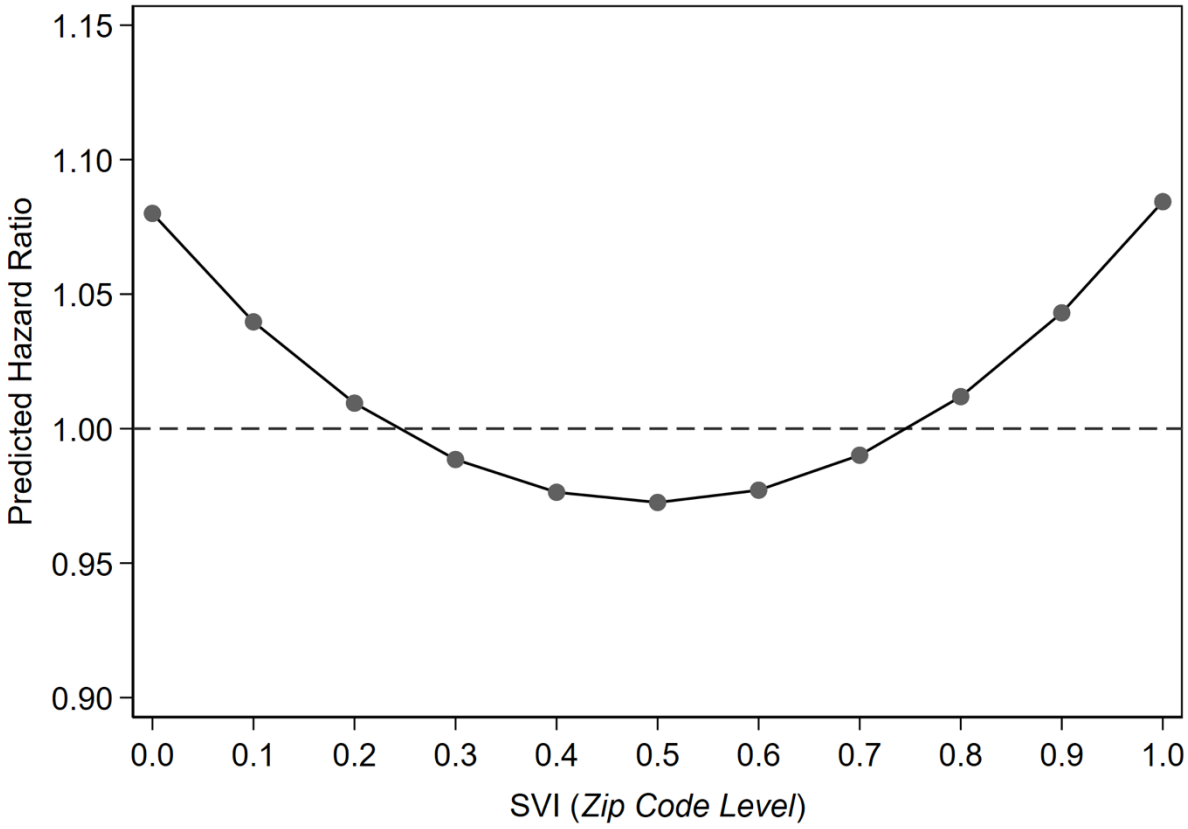

Figure 7: Cox proportional hazards model of continuous SVI. Plot of hazard ratio versus SVI using fully adjusted model with quadratic term

Chapter 5: Association of Ambient Air Pollution Exposure with Poor Outcomes in Lung Transplantation

Abstract

Background

Elevated ambient $PM_{2.5}$ air pollution exposure has been associated with poor health outcomes across several domains. Few studies have evaluated its impact in lung transplant recipients.

Objectives

We hypothesize that greater $PM_{2.5}$ exposure at the ZIP code of residence will be associated with a higher hazard for mortality and graft failure in lung transplant patients.

Methods

We conducted a retrospective analysis of panel data provided by the United Network for Organ Sharing. ZIP code level annual $PM_{2.5}$ exposure was constructed using previously published North American estimates. Kaplan Meier Survival Curves were produced for time to death or graft failure. Gamma shared frailty cox proportional hazards model was used to produce unadjusted and adjusted hazard ratios to estimate the effect of ZIP code $PM_{2.5}$ exposure at the time of transplant on graft failure or mortality.

Results

Data for 18,331 lung transplants conducted between May 2005 and December 2016 were included. Having an annual $PM_{2.5}$ exposure level above the EPA standard 12 $\mu g/m^3$ is associated with an 11% increase in the hazard of death or graft failure ($p<0.001$) in unadjusted analysis and 8% increase ($p=0.022$) after adjusting for covariates. Annual $PM_{2.5}$ exposure in the highest quartile (>10.1 $\mu g/m^3$) is associated with a 7% increase, $p=0.041$.

Conclusions

Elevated ambient $PM_{2.5}$ exposure was associated with an increased hazard of death or graft failure in lung transplant recipients. Further study is needed to better understand this relationship and may guide risk modification strategies at the individual and population levels.

Introduction

There is a relative dearth of research on the impacts of neighborhood-level and environmental factors that may affect lung transplant outcomes. Niazi *et al.* found that County Health Ranking and its length of life, quality of life, clinical care, social and economic factor, and physical environment sub-scales were each independently associated with graft failure and patient survival, but none of these differences persisted after controlling for patient and transplant center factors.[31]

Air pollution is among the largest environmental factors affecting lung health. Ambient particulate matter (PM) pollution is estimated to be the 9th leading cause of global disease burden with 3.2 million attributable deaths per year.[55] Elevated PM air pollution exposure has been associated with increased all-cause mortality, coronary heart disease hospitalizations and deaths, asthma incidence, and stroke risk.[56,59-61] $PM_{2.5}$ are fine inhalable particles with diameters that are 2.5 μm or smaller and can include particles from combustion reactions, organic compounds, metals, and other materials. A 2014 meta-analysis assessing time-series studies demonstrated an 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with a 1.04% increase in the risk of death and 1.51% increase in risk of respiratory death.[58]

The specific effects of air pollution on health in lung transplant recipients has been investigated in very few studies. The development of chronic lung allograft dysfunction (CLAD) and bronchiolitis obliterans syndrome (BOS) have each been associated with density of roadways near a patient's residence or proximity to roadways.[90,91] One study looking at a cohort of 5707 lung transplant recipients across 12 centers in Europe demonstrated an increase in all-cause mortality in recipients who were exposed to higher levels of PM_{10} (PM air pollution

with a diameter <10 μm) as well as an increased incidence of CLAD in that population.[66] A separate study assessing 520 recipients in France demonstrated that higher 1-year average exposure to particulate matter air pollution was associated with worse lung function as defined by a decreased forced vital capacity (FVC) for both $PM_{2.5}$ and PM_{10}.[67] To our knowledge, there have been no large cohort-based studies investigating particulate matter air pollution and its impact on lung transplant outcomes in the United States.

Aims and Hypotheses:

Aim 2.1: Model the effect of high $PM_{2.5}$ exposure on the risk of death or graft failure after lung transplant

Hypothesis 2.1: Higher baseline average concentration of $PM_{2.5}$ at the ZIP code of residence is associated with higher graft failure and mortality after lung transplant.

Methods

Data Source

We analyze data from the United Network for Organ Sharing (UNOS) transplant registry, used by every transplant center in the US to register and track waitlist candidates and transplant recipients. Data is available on patient and limited donor-level factors for every patient who has been placed on a solid organ transplant waitlist since its inception in 1987, including the ZIP code of residence at the time of transplant. We restrict our analysis to those recipients transplanted between May 2005 when the Lung Allocation Score (LAS) for waitlist prioritization was introduced and December 2016 constrained by the availability of air pollution data. Heart and combined heart-lung transplants are excluded. 18,331 recipients are included in the analysis (Figure 8).

Variable Construction

ZIP code level annual $PM_{2.5}$ exposure estimates are constructed for each transplant recipient. Meng *et al.* have previously published yearly estimates of long-term $PM_{2.5}$ concentration across North America.[92] Their model combines data from chemical transport modeling, satellite-based measures, and ground-based measures to produce estimates of $PM_{2.5}$ concentration at a resolution of 1km x 1km with data available from 1981 to 2016. Using ArcGIS Pro, we overlay each map of yearly estimated $PM_{2.5}$ with a shapefile of ZIP code tabulation areas (ZCTA) for the US. Using zonal statistics, we calculate the median $PM_{2.5}$ estimate within the geographic boundary of each ZCTA for each year of analysis (see Figure 9). Patient baseline $PM_{2.5}$ exposure is pulled from the ZIP code of residence and year of transplantation.

The outcome of interest is time to death or lung allograft failure. Other covariates include recipient age, gender, race/ethnicity, underlying lung disease, need for life support prior to transplantation, LAS, type of insurance, and medical center of transplantation. The need for life support is defines as the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at the time of transplant. LAS scores are grouped into <35, 35-45, 45-55, and >55.

Statistical Analysis

This study is a retrospective cohort analysis of panel data from the UNOS registry. Descriptive statistics were calculated at the patient level comparing the estimated average annual ZIP Code $PM_{2.5}$ exposure above or below the EPA standard of 12 $\mu g/m^3$. Continuous variables were compared between groups using Welch's t-test, while categorical variables were compared using chi-square tests. Time-to-event analyses were conducted for the composite

endpoint of death or graft failure. Analysis was censored at 10-years of follow-up time. Kaplan-Meier survival curves were produced for high and low $PM_{2.5}$ exposure and log-rank test performed to determine equality of the survival functions for the comparison groups. Hazard ratios for high $PM_{2.5}$ were estimated using the cox proportional hazards model for both unadjusted estimates and after adjustment for covariates. A cox proportional hazards model including cluster-specific random effects at the level of the transplant center was performed using gamma shared frailty model.[88] Violations of the proportional hazards assumption were assessed visually by plotting Schoenfeld residuals against time and plotting the log log survival time vs log time. We also formally test using the Grambsch and Therneau test but recognize that with our large sample size this may be and overly sensitive test.

Sensitivity Analysis

We test multiple cox proportional hazards models to assess how best to handle variation in outcomes at the level of transplant center. We test separate models clustering using the transplant center with robust standard errors and using gamma shared frailty to estimate random effects.[89] We additionally test multiple parametric survival models including Exponential Distribution, Weibull Distribution, and a Loglogistic Accelerated Failure Time (AFT) model. As a non-proportional hazards model, the log-log AFT model is meant to ensure our findings are robust to any potential violations of the proportional hazards assumption.

We expect that $PM_{2.5}$ exposure will correlate with measures of neighborhood-level socioeconomic status and test the model with and without the inclusion of ZIP code level per capita income as a covariate. As we are solely measuring $PM_{2.5}$ levels at the year of

transplantation, we perform sensitivity analyses with censoring at 1 and 3 years to ensure the effect is consistent between the medium- and long-term outcomes.

We theorize the effect of $PM_{2.5}$ on the hazard of death or graft failure to be linear. To explore this relationship, we run sensitivity analyses binning annual $PM_{2.5}$ exposure into quartiles and alternatively as a continuous variable in $\mu g/m^3$. The study protocols were reviewed by the institutional review board of the University of California, Los Angeles and exemption granted (IRB# 19-002039) as it was not considered human subjects research.

Results

A total of 18,331 lung transplant recipients were included in the analysis. 1,790 (10%) had residences in ZIP codes whose annual $PM_{2.5}$ exposure was above the EPA standard of 12 $\mu g/m^3$. Patient characteristics are found in Table 10. Ages were similar between groups with mean age 54.7 in the higher and 55.4 in the lower $PM_{2.5}$ group. There were 42% females in the high and 40% in the low $PM_{2.5}$ group. There was a statistically significant difference in the distribution of races and ethnicities between groups. There was a lower proportion of white recipients and higher proportion of Black and Hispanic/Latino transplant recipients in the higher $PM_{2.5}$ group (White: 73% vs 85%, Black: 14% vs 11%, and Hispanic/Latino: 11% vs 5% in the higher and lower $PM_{2.5}$ groups respectively). LAS score distribution was similar between groups. There were more recipients with private insurance (62% vs 51%) and fewer patients with Medicare insurance (27% vs 39%) in the high $PM_{2.5}$ group as compared to lower. The ZIP code per-capita income was slightly higher in the high $PM_{2.5}$ group with $34,485 as compared to $33,535 in the lower. There were slightly fewer patients on ECMO or mechanical ventilation in

the high $PM_{2.5}$ group (6% vs 8%) and fewer patients who received bilateral transplants in the high in the high $PM_{2.5}$ group (58% vs 68%).

Kaplan-Meier survival curves for the high and low $PM_{2.5}$ groups are shown in Figure 10. Log-rank test with $p<0.001$ demonstrates a statistically significant difference between the two survival functions. An unadjusted cox proportional hazards model was fit and demonstrated residence in a ZIP code with $PM_{2.5}$ exposure above EPA standards was associated with an 11% increase in the hazard of death or graft failure, $p<0.001$. Separate cox proportional hazard models with gamma shared frailty around the transplant center were fit adjusting for patient age, sex, and race/ethnicity (Model 1), then adding BMI and insurance (Model 2), and lastly underlying diagnosis, life support, and transplant laterality in the final model (Model 3) (See Table 11). Hazard ratios for death or graft failure for high $PM_{2.5}$ were 1.08 p=0.018, 1.09 p=0.007, and 1.08 p=0.022 for Models 1, 2, and 3 respectively. The data did not appear to violate the proportional hazards assumption by visual inspection plotting Schoenfeld residuals against time (see Figure 11) and plotting the log log survival time vs log time (see Figure 12). The $PM_{2.5}$ variable and global test demonstrate violations of the PH assumption using the Grambsch and Therneau test (see Table 12).

To test different model specifications cox proportional hazards model with clustered-robust standard errors for transplant center was fit as well as parametric models using Exponential, Weibull, and Log-log AFT distributions with results displayed in Table 13. The High $PM_{2.5}$ group has an 11% p=0.005, 9% p=0.009, and 12% $p<0.001$ increased hazard of death or graft failure in the cox PH with cluster robust standard errors, exponential distribution, and Weibull distribution models respectively. The Loglogistic AFT model demonstrates a coefficient

(e^{β}) of 0.80 p<0.001 representing a 20% decrease in the estimated median survival time for the High SVI group, consistent with the other tested models.

Results remain consistent when removing ZIP code per capita income from the model with HR 1.08 p=0.022 (Table 14). The strength of the association of elevated $PM_{2.5}$ with mortality and graft failure increases when censoring is decreased to 3-year (HR 1.17 p <0.001) and 1-year follow-up (HR 1.27 p<0.001) (Table 15).

Refitting the main cox PH model with gamma shared frailty respecifying annual $PM_{2.5}$ exposure in quartiles demonstrates a HR for death or graft failure of 0.99 p=0.671 comparing quartile 2 (7.2 – 8.6 $\mu g/m^3$) to quartile 1 ($\leq$ 7.2 $\mu g/m^3$), 1.06 p=0.080 comparing quartile 3 (8.6-10.1 $\mu g/m^3$) to quartile 1, and 1.07 p=0.041 comparing quartile 4 (>10.1 $\mu g/m^3$) to quartile 1 (see Table 16). Kaplan Meier survival curves for each quartile are displayed in Figure 13 with log-rank test p=0.001 demonstrating a statistically significant difference in the survival functions. When treating annual ZIP code $PM_{2.5}$ exposure as a continuous variable, each 1 $\mu g/m^3$ increase in exposure is associated with a 1% increase in the hazard of death or graft failure, p=0.004 (Table 17).

Discussion

In this large registry analysis of lung transplant recipients, we examine the effect of ZIP code annual estimated $PM_{2.5}$ exposure in the year of transplant on lung transplant outcomes. Annual $PM_{2.5}$ levels above the EPA standard were associated with an 8% increase in the hazard of death or graft failure. The strength of association of air pollution exposure in the year of transplant with worse mortality and graft failure is higher when censoring at shorter follow-up. We expect the true effect of air pollution exposure on lung transplant outcomes may vary over

time as air pollution exposure changes. We intended this analysis to determine whether the exposure in the year of transplantations was enough to predict poor long-term outcomes. Our findings remain consistent when changing to alternative parametric survival models, including the loglogistic AFT model which is not subject to the proportional hazards assumption. This effect appears to be dose dependent as quartile analysis demonstrates stronger association for quartiles 3 and 4 respectively. This begs the question if dropping $PM_{2.5}$ exposure below the current EPA standard of 12 $\mu g/m^3$ may have additional benefit on lung transplant survival.

Limitations

This study uses panel data to test the association between high particulate matter air pollution exposure and graft failure and mortality after lung transplant. The use of registry data allows for complete capture of the population of lung transplant recipients in the United States with very little missingness in our variables of interest. A major limitation of the study is the potential for misclassification error. Patient residence is only specified at the ZIP code level in the UNOS registry. This is a less than ideal measure of neighborhood. The registry also does not capture if a patient relocates their residence during follow-up, so estimation of longitudinal exposure is not possible. Despite this weakness, establishing an association between air pollution exposure at baseline is of great clinical utility as it allows practitioners to flag an at-risk population at the time of transplant. Another limitation is that the UNOS registry does not capture information on chronic treatment of patients, so we are also unable to adjust for chronic immunosuppression or macrolide therapy. Prior studies have theorized that macrolide administration may attenuate the effect of air pollution exposure on lung transplant outcomes.[66,67] The lack of macrolide use information would bias our results towards the null, so

the demonstration of an effect despite this omission is encouraging. We theorize that controlling for differences at the center level partially captures some of the variation in treatment. Lastly, the registry does not capture other intermediate negative outcomes after lung transplant like primary graft disfunction, acute rejection, or CLAD which also may be impacted by air pollution exposure.

Conclusion

We demonstrate that elevated $PM_{2.5}$ exposure at the ZIP code of residence at the time of transplant is associated with increased hazard of death or graft failure in the first large, multicenter registry analysis of its kind in the US. Further research is needed to better understand the mechanism behind this association and determine whether it is modifiable at the individual and population levels.

Tables and Figures

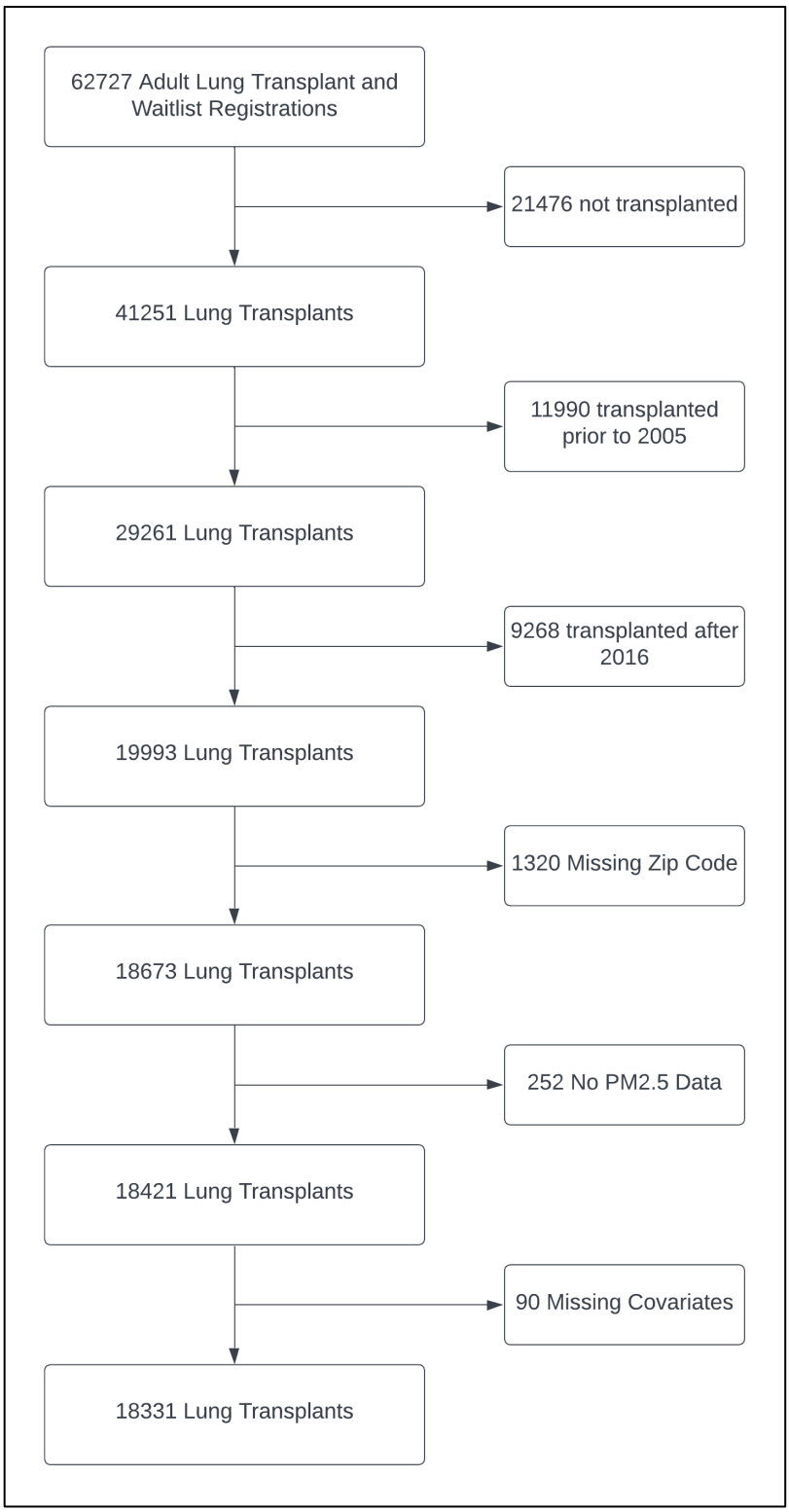

Figure 8: Patient flow chart

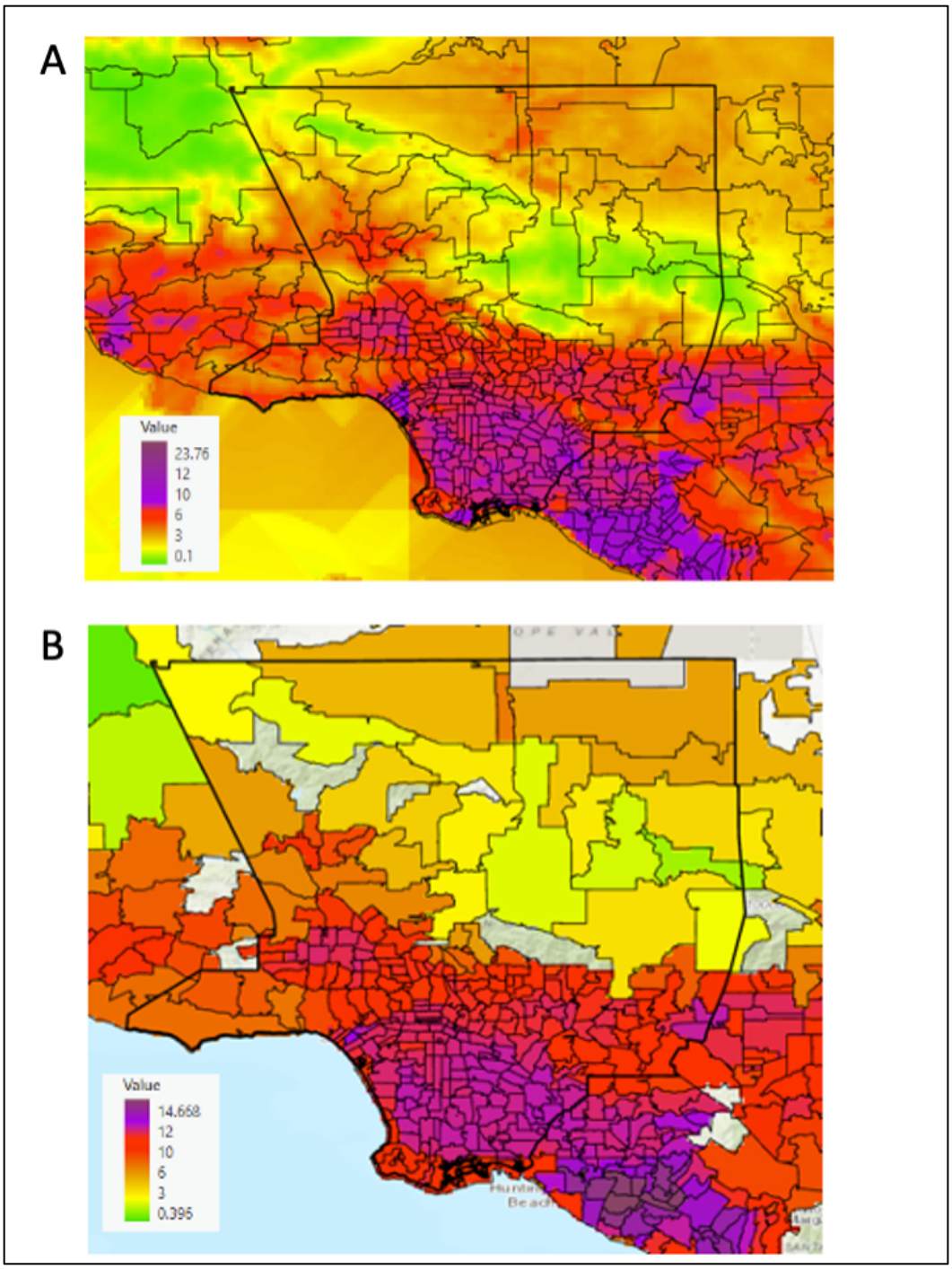

Figure 9: Average annual concentration of particulate matter with an aerodynamic diameter ≤2.5μm for Los Angeles County (Panel A) and after zonal statistics to produce estimates for each ZIP code tabulation area (Panel B)

Table 10: Baseline patient characteristics, comparing the groups above and below the EPA standard

Characteristic	ZIP Code $PM_{2.5}$		
	$PM_{2.5}$ Below EPA Standard < 12 µg/m³	**$PM_{2.5}$ Above EPA Standard ≥12 µg/m³**	**[2]p**
Number, N (%)	16,475 (90%)	1,790 (10%)	
Age (years), mean (SD)	55.4 (13.2)	54.7 (12.7)	0.054
Female, %	40%	42%	0.085
Race Ethnicity, %			<.001
White	85%	73%	
Black	8%	14%	
Hispanic/Latino	5%	11%	
Other	2%	2%	
BMI (kg/m²), mean (SD)	25.1 (4.6)	25.0 (4.6)	0.302
Diagnosis, %			0.016
Obstructive pulmonary disease	30%	31%	
Pulmonary vascular disease	3%	3%	
Cystic Fibrosis	12%	9%	
Restrictive Lung Disease	56%	57%	
LAS, %			0.147
<35	25%	27%	
>35 - 45	37%	37%	
>45 - 55	16%	15%	
>55	22%	20%	
Insurance, %			<.001
Private	51%	62%	
Medicaid	6%	8%	
Medicare	39%	27%	
Other Public	3%	2%	
Other	1%	1%	
[1]ZIP Code Per Capita Income ($), mean (SD)	33,535 (13,406)	34,485 (16,876)	0.021
Mechanical Ventilation or ECMO at time of match, %	8%	6%	0.002
Bilateral Transplant, %	68%	58%	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]p value based on chi-square or Welch's t-test.

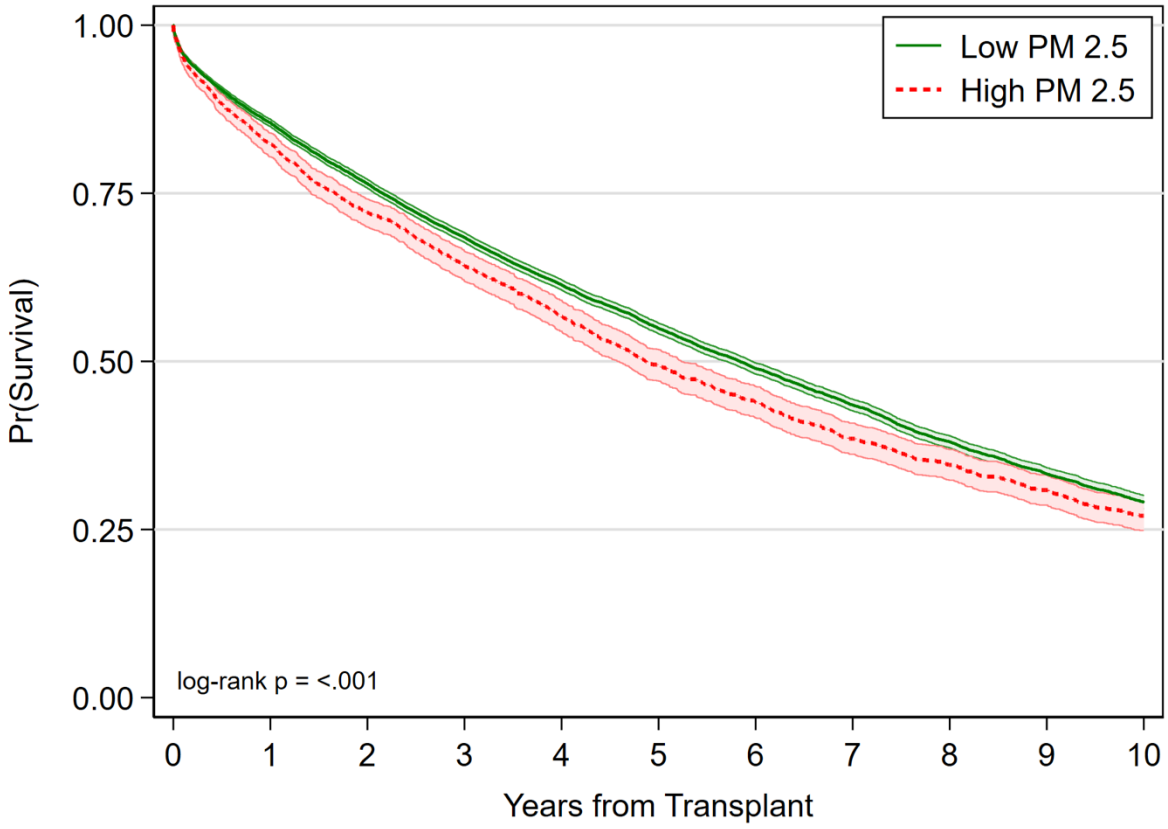

Figure 10: Kaplan-Meier survival within 10 years by $PM_{2.5}$ exposure level. Shaded area represents confidence intervals

Table 11: Cox proportional hazards models for $PM_{2.5}$, unadjusted and adjusted models

Predictors	[a]Unadjusted Hazard Ratio (95% CI)	p	[b]Model 1 Hazard Ratio (95% CI)	p	[b]Model 2 Hazard Ratio (95% CI)	p	[b]Model 3 Hazard Ratio (95% CI)	p
Model BIC	191851.2		191558.9		191565.3		191321.8	
$PM_{2.5}$ Above EPA Standard	1.11 (1.05, 1.18)	<.001	1.08 (1.01, 1.15)	0.018	1.09 (1.02, 1.16)	0.007	1.08 (1.01, 1.15)	0.022
Recipient Age, *per 10 years*			1.07 (1.05, 1.09)	<.001	1.06 (1.04, 1.08)	<.001	1.03 (1.01, 1.05)	0.010
Female Sex			0.94 (0.90, 0.98)	0.002	0.94 (0.90, 0.98)	0.001	0.94 (0.91, 0.98)	0.005
Race								
White			ref		ref		ref	
Black			0.93 (0.87, 1.00)	0.049	0.92 (0.85, 0.99)	0.021	0.94 (0.87, 1.01)	0.098
Hispanic/Latino			0.92 (0.84, 1.00)	0.053	0.90 (0.82, 0.98)	0.017	0.87 (0.80, 0.95)	0.002
Other			0.92 (0.79, 1.07)	0.269	0.92 (0.80, 1.07)	0.285	0.89 (0.76, 1.03)	0.108
BMI, *per 5 kg/m^2*					1.01 (0.99, 1.03)	0.378	0.99 (0.97, 1.01)	0.425
[1]Per Capita Income, *per $10,000*					1.00 (0.99, 1.02)	0.743	1.00 (0.98, 1.01)	0.624
Insurance								
Private					ref		ref	
Medicaid					1.27 (1.17, 1.37)	<.001	1.26 (1.16, 1.36)	<.001
Medicare					1.12 (1.07, 1.17)	<.001	1.11 (1.07, 1.16)	<.001
Other Public					0.96 (0.85, 1.09)	0.558	0.95 (0.83, 1.08)	0.409
Other					0.97 (0.73, 1.30)	0.839	0.95 (0.71, 1.27)	0.742
Diagnosis								
Obstructive Lung Disease							ref	
Pulmonary Vascular Disease							1.21 (1.07, 1.36)	0.002
Cystic Fibrosis							1.04 (0.95, 1.14)	0.350
Restrictive Lung Disease							1.11 (1.06, 1.16)	<.001
[2]Life Support							1.42 (1.32, 1.53)	<.001

Bilateral Transplant	0.72 (0.69, 0.76)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance, [1]2011 per capita Income reported using 2019 CPI adjustment
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model.
[b]Shared frailty Cox proportional hazards model.

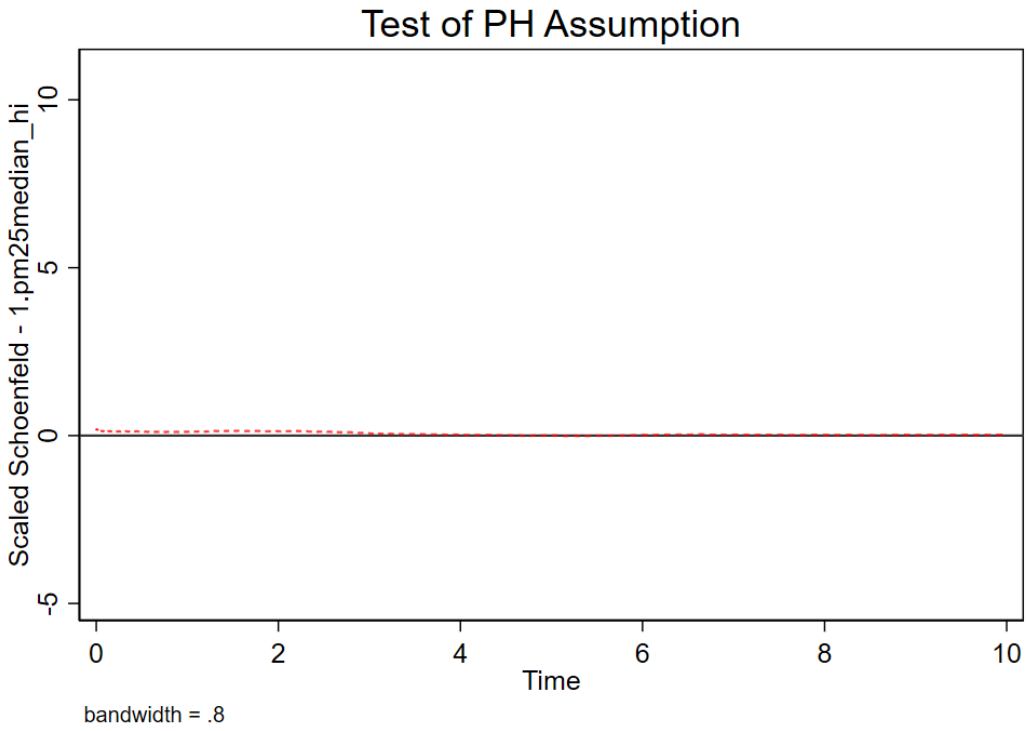

Figure 11: Test of the proportional hazards assumption for $PM_{2.5}$. Plot of Schoenfeld residuals versus time

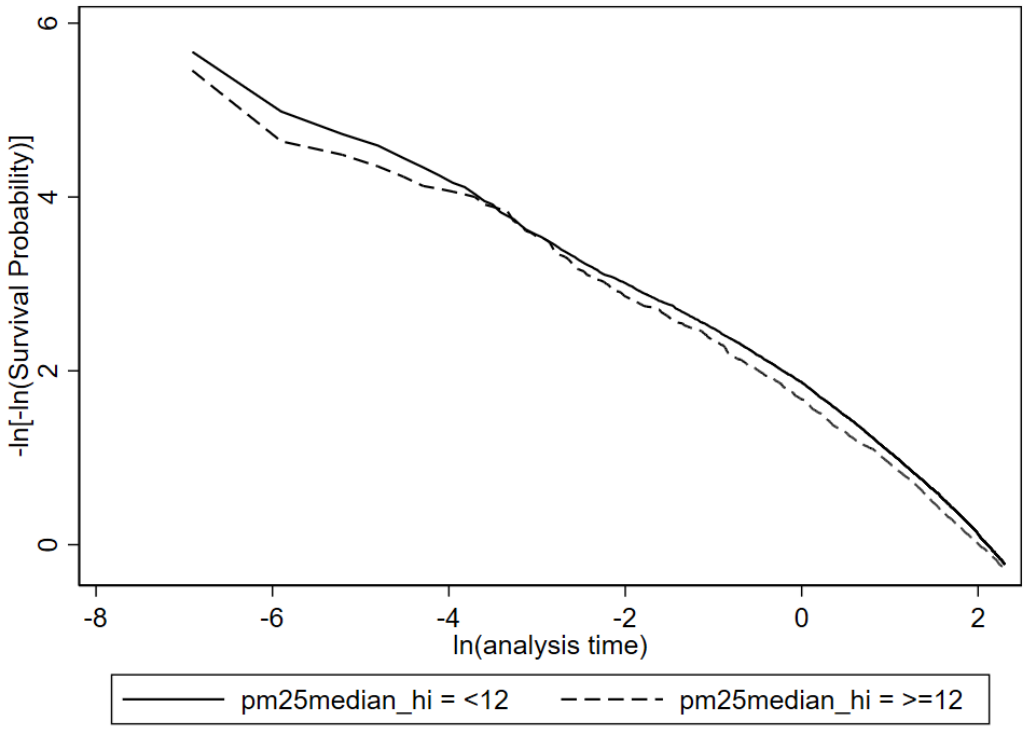

Figure 12: Test of the proportional hazards assumption for $PM_{2.5}$. Plot of log(log(survival probability)) versus log(time)

Table 12: Test of proportional hazards assumption. Grambsch and Therneau test

variable	rho	chi2	p
$PM_{2.5}$ Above EPA Standard	-0.03140	11.68	<.001
Recipient Age, *per 10 years*	0.03008	10.60	0.001
Female Sex	0.01880	3.67	0.055
Race			
White	Ref	Ref	ref
Black	-0.01379	2.06	0.151
Hispanic/Latino	0.00208	0.05	0.825
Other	-0.00097	0.01	0.920
BMI, *per 5 kg/m²*	0.01492	2.48	0.115
Per Capita Income, *per $10,000*	0.00724	0.61	0.436
Insurance			
Private	Ref	Ref	Ref
Medicaid	0.02148	4.91	0.026
Medicare	0.00715	0.55	0.460
Other Public	0.00347	0.15	0.703
Other	0.00313	0.11	0.745
Diagnosis			
Obstructive Lung Disease	Ref	Ref	Ref
Pulmonary Vascular Disease	-0.02493	6.59	0.010
Cystic Fibrosis	0.00363	0.13	0.716
Restrictive Lung Disease	-0.03484	12.97	<.001
Life Support	-0.04761	25.15	<.001
Bilateral Transplant	-0.04935	29.08	<.001
Global Test		158.65	<.001

Table 13: Alternate Survival Models for $PM_{2.5}$

Predictors	[a]Cox PH w/ Clustered SE Hazard Ratio (95% CI)	p	[b]Mixed Effects Parametric Survival *Exponential Distribution* Hazard Ratio (95% CI)	p	[b]Mixed Effects Parametric Survival *Weibull Distribution* Hazard Ratio (95% CI)	p	[c]AFT Parametric Survival *Log-Logistic Distribution* e^{β} (95% CI)	p
[1]Model BIC	191523.9		63388.9		62815.1		54349.1	
$PM_{2.5}$ Above EPA Standard	1.11 (1.03, 1.19)	0.005	1.09 (1.02, 1.16)	0.009	1.12 (1.05, 1.20)	<.001	0.80 (0.70, 0.90)	<.001
Recipient Age, *per 10 years*	1.04 (1.01, 1.07)	0.020	1.03 (1.01, 1.05)	0.011	1.02 (1.00, 1.05)	0.036	0.97 (0.94, 1.01)	0.161
Female Sex	0.94 (0.90, 0.99)	0.014	0.94 (0.90, 0.98)	0.004	0.94 (0.91, 0.98)	0.005	1.10 (1.03, 1.18)	0.004
Race								
White	ref		ref		ref		ref	
Black	0.97 (0.89, 1.06)	0.493	0.94 (0.87, 1.01)	0.099	0.94 (0.88, 1.01)	0.116	1.03 (0.93, 1.14)	0.618
Hispanic/Latino	0.93 (0.85, 1.02)	0.115	0.87 (0.79, 0.95)	0.001	0.87 (0.80, 0.95)	0.002	1.12 (0.99, 1.28)	0.072
Other	0.89 (0.76, 1.05)	0.170	0.88 (0.76, 1.02)	0.094	0.89 (0.77, 1.03)	0.124	1.14 (0.89, 1.46)	0.288
BMI, *per 5 kg/m^2*	0.99 (0.97, 1.02)	0.657	0.99 (0.97, 1.01)	0.387	0.99 (0.97, 1.01)	0.433	1.01 (0.97, 1.05)	0.548
[1]Per Capita Income, *per $10,000*	0.99 (0.97, 1.01)	0.515	1.00 (0.98, 1.01)	0.649	1.00 (0.98, 1.01)	0.654	1.01 (0.99, 1.04)	0.314
Insurance								
Private	ref		ref		ref		ref	
Medicaid	1.27 (1.18, 1.37)	<.001	1.25 (1.16, 1.36)	<.001	1.23 (1.13, 1.33)	<.001	0.77 (0.70, 0.84)	<.001
Medicare	1.12 (1.07, 1.18)	<.001	1.12 (1.07, 1.17)	<.001	1.10 (1.05, 1.15)	<.001	0.88 (0.82, 0.94)	<.001
Other Public	0.91 (0.78, 1.07)	0.248	0.95 (0.83, 1.08)	0.417	0.95 (0.84, 1.08)	0.445	1.10 (0.92, 1.31)	0.293
Other	0.99 (0.73, 1.36)	0.964	0.96 (0.71, 1.28)	0.762	0.94 (0.71, 1.26)	0.688	1.01 (0.68, 1.50)	0.960
Diagnosis								
Obstructive Lung Disease	ref		ref		ref		ref	

Pulmonary Vascular Disease	1.18 (1.02, 1.37)	0.026	1.22 (1.08, 1.37)	0.001	1.20 (1.06, 1.35)	0.003	0.75 (0.62, 0.91)	0.004
Cystic Fibrosis	1.04 (0.94, 1.15)	0.467	1.05 (0.95, 1.15)	0.337	1.03 (0.94, 1.12)	0.585	0.99 (0.86, 1.14)	0.892
Restrictive Lung Disease	1.10 (1.03, 1.17)	0.004	1.11 (1.06, 1.16)	<.001	1.09 (1.04, 1.15)	<.001	0.87 (0.79, 0.96)	0.003
[2]Life Support	1.40 (1.22, 1.59)	<.001	1.43 (1.34, 1.54)	<.001	1.41 (1.31, 1.51)	<.001	0.57 (0.46, 0.70)	<.001
Bilateral Transplant	0.72 (0.67, 0.78)	<.001	0.72 (0.69, 0.75)	<.001	0.73 (0.70, 0.76)	<.001	1.47 (1.33, 1.62)	<.001

[1]Model BIC is not comparable between semi-parametric (e.g. Cox PH) and parametric models (e.g. mixed effects; log-logistic)
[2]Mechanical Ventilation or ECMO
[a]Clustered-Robust Standard Errors (Huber-White sandwich estimator) for Center
[b]Random intercept for Center
[c]Parametric log-logistic Accelerated Failure Time model with gamma shared frailty and Clustered-Robust Standard Errors (Huber-White sandwich estimator) for Center

Table 14: Gamma shared frailty cox proportional hazards model excluding income

Excluding Income Adjustment Predictors	**[b]Model 3 – Original Hazard Ratio (95% CI)**	**p**
Model BIC	191312.2	
$PM_{2.5}$ Above EPA Standard	1.08 (1.01, 1.15)	0.022
Recipient Age, *per 10 years*	1.03 (1.01, 1.05)	0.011
Female Sex	0.94 (0.91, 0.98)	0.005
Race		
White	ref	
Black	0.94 (0.88, 1.01)	0.108
Hispanic/Latino	0.87 (0.80, 0.95)	0.002
Other	0.88 (0.76, 1.03)	0.104
BMI, *per 5 kg/m^2*	0.99 (0.97, 1.01)	0.442
Insurance		
Private	ref	
Medicaid	1.26 (1.16, 1.36)	<.001
Medicare	1.11 (1.07, 1.16)	<.001
Other Public	0.95 (0.83, 1.08)	0.420
Other	0.95 (0.71, 1.27)	0.745
Diagnosis		
Obstructive Lung Disease	ref	
Pulmonary Vascular Disease	1.21 (1.07, 1.36)	0.002
Cystic Fibrosis	1.04 (0.95, 1.14)	0.367
Restrictive Lung Disease	1.11 (1.06, 1.16)	<.001
[2]Life Support	1.42 (1.32, 1.53)	<.001
Bilateral Transplant	0.72 (0.69, 0.76)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance, [1]2011 per capita Income reported using 2019 CPI adjustment
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model.
[b]Shared frailty Cox proportional hazards model.

Table 15: Gamma shared frailty cox proportional hazards model with differential censoring

Differential Censoring	**[a]1-Year Censoring**		**[a]3-Year Censoring**	
Predictors	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**	**p**
Model BIC	52499.9		111808.3	
$PM_{2.5}$ Above EPA Standard	1.27 (1.12, 1.44)	<.001	1.17 (1.07, 1.28)	<.001
Recipient Age, *per 10 years*	1.08 (1.03, 1.13)	<.001	1.00 (0.97, 1.03)	0.980
Female Sex	0.86 (0.79, 0.93)	<.001	0.93 (0.88, 0.98)	0.005
Race				
White	ref		ref	
Black	0.96 (0.83, 1.11)	0.579	1.00 (0.91, 1.10)	0.937
Hispanic/Latino	0.89 (0.74, 1.05)	0.169	0.90 (0.80, 1.01)	0.067
Other	1.01 (0.77, 1.33)	0.936	0.87 (0.71, 1.06)	0.167
BMI, *per 5 kg/m^2*	0.98 (0.94, 1.03)	0.475	0.98 (0.95, 1.01)	0.153
[1]Per Capita Income, *per $10,000*	0.98 (0.96, 1.01)	0.313	1.00 (0.98, 1.02)	0.808
Insurance				
Private	ref		ref	
Medicaid	0.95 (0.80, 1.12)	0.534	1.15 (1.04, 1.28)	0.009
Medicare	1.02 (0.94, 1.11)	0.683	1.09 (1.03, 1.16)	0.002
Other Public	0.89 (0.69, 1.15)	0.386	0.91 (0.77, 1.09)	0.317
Other	0.75 (0.41, 1.36)	0.338	1.01 (0.70, 1.45)	0.970
Diagnosis				
Obstructive Lung Disease	ref		ref	
Pulmonary Vascular Disease	1.55 (1.24, 1.93)	<.001	1.34 (1.15, 1.57)	<.001
Cystic Fibrosis	0.99 (0.82, 1.20)	0.919	1.01 (0.90, 1.14)	0.865
Restrictive Lung Disease	1.29 (1.17, 1.42)	<.001	1.18 (1.11, 1.26)	<.001
[2]Life Support	2.10 (1.87, 2.37)	<.001	1.59 (1.46, 1.74)	<.001
Bilateral Transplant	0.88 (0.81, 0.97)	0.006	0.79 (0.74, 0.84)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance, [1]2011 per capita Income reported using 2019 CPI adjustment
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Shared frailty Cox proportional hazards model.

Table 16: Gamma shared frailty cox proportional hazards model for $PM_{2.5}$ quartiles analysis

Predictors	[a]Model 3 Hazard Ratio (95% CI)	p
Model BIC	191336.8	
$PM_{2.5}$ – 1st Quartile (≤ 7.2 μg/m^3)	ref	
$PM_{2.5}$ – 2nd Quartile (7.2-8.6 μg/m^3)	0.99 (0.93, 1.05)	0.671
$PM_{2.5}$ – 3rd Quartile (8.6-10.1 μg/m^3)	1.06 (0.99, 1.12)	0.080
$PM_{2.5}$ – 4th Quartile (> 10.1 μg/m^3)	1.07 (1.00, 1.14)	0.041
Recipient Age, *per 10 years*	1.03 (1.01, 1.05)	0.009
Female Sex	0.94 (0.91, 0.98)	0.006
Race		
White	ref	
Black	0.93 (0.87, 1.01)	0.072
Hispanic/Latino	0.87 (0.79, 0.95)	0.001
Other	0.89 (0.76, 1.03)	0.107
BMI, *per 5 kg/m^2*	0.99 (0.97, 1.01)	0.417
[1]Per Capita Income, *per $10,000*	1.00 (0.98, 1.01)	0.546
Insurance		
Private	ref	
Medicaid	1.26 (1.16, 1.36)	<.001
Medicare	1.12 (1.07, 1.17)	<.001
Other Public	0.95 (0.84, 1.08)	0.448
Other	0.95 (0.71, 1.27)	0.748
Diagnosis		
Obstructive Lung Disease	ref	
Pulmonary Vascular Disease	1.21 (1.07, 1.37)	0.001
Cystic Fibrosis	1.05 (0.96, 1.15)	0.315
Restrictive Lung Disease	1.11 (1.06, 1.16)	<.001
[2]Life Support	1.42 (1.32, 1.53)	<.001
Bilateral Transplant	0.72 (0.69, 0.76)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance, [1]2011 per capita Income reported using 2019 CPI adjustment
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Shared frailty Cox proportional hazards model.

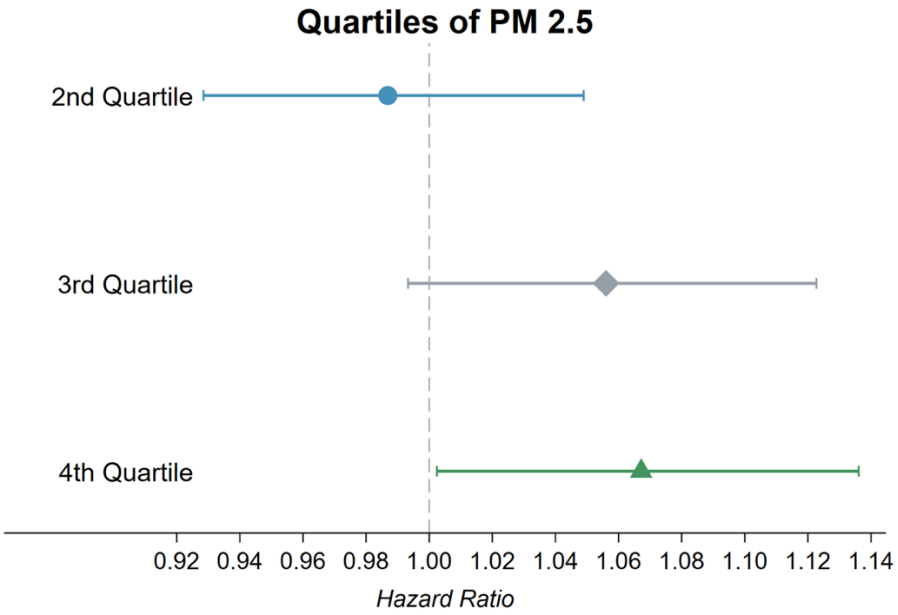

Figure 13: $PM_{2.5}$ quartile forest plots. Forest plots of effect estimate for gamma shared frailty cox proportional hazards complete model (covariates included are age, sex, race/ethnicity, BMI, insurance, ZIP code per capita income, diagnosis, life support = use of mechanical ventilation or ECMO, and laterality.

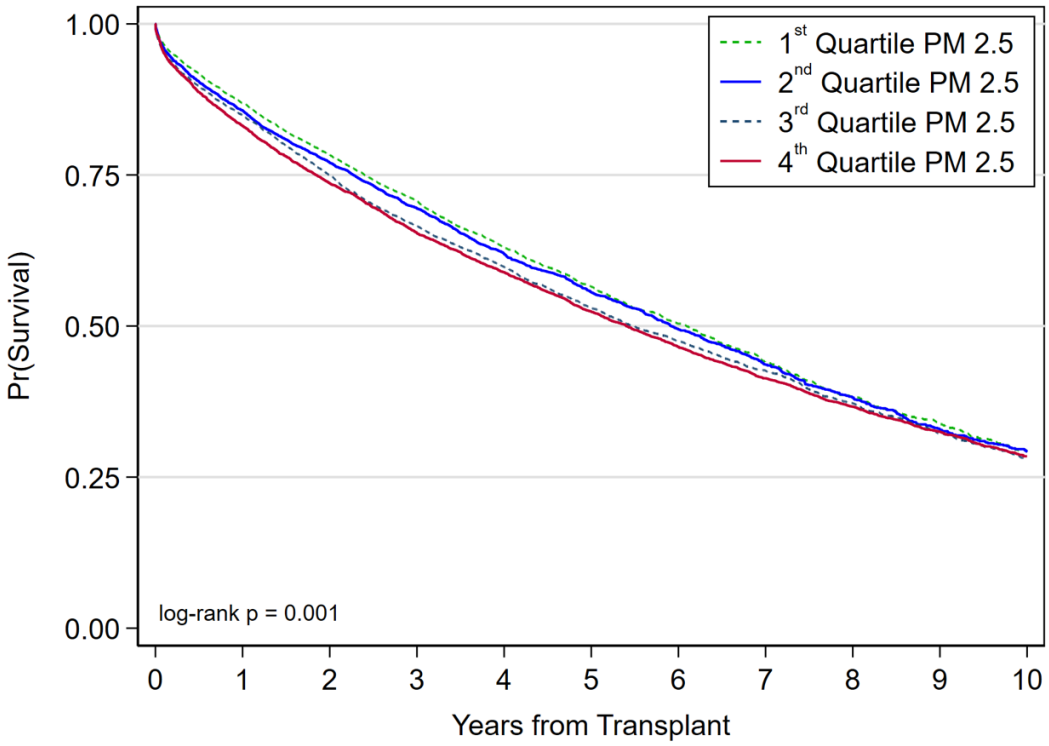

Figure 14: Kaplan-Meier survival within 10 years by $PM_{2.5}$ quartile.

Table 17: Cox proportional hazards models for $PM_{2.5}$ continuous analysis, unadjusted and adjusted models

Continuous $PM_{2.5}$	**[a]Unadjusted**		**[b]Model 3**	
Predictors	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**	**p**
Model BIC	191843.9		191318.9	
$PM_{2.5}$, *per 1 µg/m³*	1.02 (1.01, 1.03)	<.001	1.01 (1.00, 1.02)	0.004
Recipient Age, *per 10 years*			1.03 (1.01, 1.05)	0.008
Female Sex			0.94 (0.91, 0.98)	0.006
Race				
White			ref	
Black			0.93 (0.87, 1.01)	0.068
Hispanic/Latino			0.87 (0.79, 0.95)	0.001
Other			0.88 (0.76, 1.03)	0.105
BMI, *per 5 kg/m²*			0.99 (0.97, 1.01)	0.423
[1]Per Capita Income, *per $10,000*			1.00 (0.98, 1.01)	0.552
Insurance				
Private			ref	
Medicaid			1.26 (1.16, 1.36)	<.001
Medicare			1.12 (1.07, 1.17)	<.001
Other Public			0.95 (0.83, 1.08)	0.427
Other			0.95 (0.71, 1.27)	0.733
Diagnosis				
Obstructive Lung Disease			ref	
Pulmonary Vascular Disease			1.21 (1.07, 1.37)	0.001
Cystic Fibrosis			1.05 (0.96, 1.15)	0.325
Restrictive Lung Disease			1.11 (1.06, 1.16)	<.001
[2]Life Support			1.42 (1.32, 1.53)	<.001
Bilateral Transplant			0.72 (0.69, 0.76)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model.
[b]Shared frailty Cox proportional hazards model.

Chapter 6: Discussion and Future Work

In this set of analyses, we evaluate the association of neighborhood-level social and environmental factors with mortality and graft failure after lung transplantation. We sought to determine new factors on which to identify patients at higher risk of poor outcomes. Identification of these patients will aide further study of the mechanisms of their increased risk and potential modification of that risk.

Neighborhood Social Disinvestment and Lung Transplant Outcomes

In our first analysis, we assess the association of ZIP code level SVI with lung transplant outcomes. This study practically applies the SVI, which is developed at the county and census tract levels, to the ZIP code level using a crosswalk procedure developed by the US Department of Housing and Urban Development. This is a useful process that will allow the SVI to be applied to more topics and in more clinical cohorts that tend to use the ZIP code as a simple proxy for patient geographical location.

To our knowledge, only one study has applied a multidimensional SES index to outcomes after lung transplant. This small study of 73 patients found no difference in survival between the high and low Distressed Community Index (DCI) groups.[93] Given the low sample size, that study may have been underpowered to detect a difference in risk between their distressed and non-distressed groups. Additionally, the DCI only incorporates 7 ACS variables whereas the SVI incorporates 15 variables across more domains of socioeconomic status.[33,39] Our study also demonstrated the Household Composition & Disability Theme to be the component of the SVI that best correlated with adverse outcomes. The DCI does not

incorporate any of the variables that comprise the Household Composition & Disability Theme of the SVI.

After the discovery of SVI's association with higher incidence and poor outcomes in COVID-19, it was applied to health policy in an attempt to mitigate that risk. The SVI was used by the Massachusetts Department of Public health to identify COVID-19 testing disparities and direct resources to communities with limited testing capacity. The SVI was also used by the CDC's COVID-19 task force in vaccine allocation plans.[94] The UCLA hospital system has made use of the SVI in its allocation schematic for the distribution of the Evusheld (tixagebimab cigavimab) monoclonal antibodies for prophylaxis against COVID-19 infection.

We believe that with further study to validate and better understand the association between elevated SVI and lung transplant outcomes, it can be used by national organizations and individual transplant centers to identify groups at risk for bad outcomes and to allocate additional resources such as financial assistance for medications, mobile lab and radiography testing, home spirometry, or increased frequency of visits with the team via telehealth.

$PM_{2.5}$ Air Pollution Exposure and Lung Transplant Outcomes

Our second analysis assessed the association of baseline annual $PM_{2.5}$ exposure with mortality and graft failure in lung transplant. Elevated ambient $PM_{2.5}$ exposure is known to have adverse health effects across multiple domains. This chapter adds to a growing body of literature associating air pollution exposure with poor outcomes in lung transplantation, and is the first study to do this in a large US-based cohort.[66,67,90,91,95] We next sought to understand how PM2.5 exposure and neighborhood social disinvestment may interact with one another by including both measures with an interaction term into the same model. We fit a gamma shared

frailty cox proportional hazards model and determine that the association between elevated PM2.5 exposure and death or graft failure is attenuated in the high SVI group. Considering the lower SVI and lower PM2.5 group as the reference, low PM2.5 + high SVI has a HR of 1.07, high PM2.5 + low SVI has HR 1.10 and high PM2.5 + high SVI has HR 0.98 in the adjusted analysis (see Table 18 and Figure 15). The underlying mechanism behind this attenuated effect is unclear and warrants further investigation.

We believe lung transplant recipients represent a group that may be highly susceptible to the impacts of $PM_{2.5}$ on pulmonary health, but this requires further research to prove mechanistically.[96] Mitigation of the risk of $PM_{2.5}$ exposure on lung transplant outcomes may be approached at the population level or at the individual level. Recognizing the serious deleterious effects on health, the EPA has been working to decrease ambient air pollution exposure across the US. The National Ambient Air Quality Standards (NAAQS), setting standards for 24-hr average and annual average particulate matter air pollution exposure, were first established in 1971 as a result of the 1970 Clean Air Act.[97] In its first form, the NAAQS set the annual average standard for total suspended particles (TSP) at 75 $\mu g/m^3$. With further research and improvements in detection strategies that allowed the differentiation of PM by size of particles, the first annual average goals for $PM_{2.5}$ was set at 15 $\mu g/m^3$ in 1997.[98] The 24-hr average standard was decreased in 2006, and the annual standard was further decreased to 12 $\mu g/m^3$ after 2012.[79] With the release of each subsequent standard, states are required to submit infrastructure plans demonstrating they have the capabilities necessary to implement the NAAQS. Any area not able to designate attainment of those standards must outline state implementation plans demonstrating how they will comply. The EPA estimates that based on

the value associated with predicted reductions in excess mortality, incident health conditions, and improvement in social welfare effects, attaining the 2013 standards would be associated with a net benefit of between $1.1 and $26 billion by 2020.[79]

Our data demonstrates that lung transplant recipients in the fourth quartile (>10.1 $\mu g/m^3$) have increased mortality and graft failure and those in the third quartile of $PM_{2.5}$ exposure (8.6 – 10.1 $\mu g/m^3$) already demonstrate a trend towards worse outcomes. This may suggest that further health benefits may be achieved with even more stringent EPA standards and the public policies needed to attain them.

Limitations and Methodological Considerations

These analyses make use of the UNOS lung transplant registry which boasts complete capture of the population of lung transplant recipients within the US with very little missingness and excellent generalizability. The main limitation of both studies is the use of ZIP code for localization. The residential ZIP code is used in everyday life and correspondence and is therefore well known by the general populace, making it easy to incorporate into study intake forms. Unfortunately, ZIP codes in essence are administrative units comprised of lists of postal addresses and do not represent a precise geographic area. For geographic analyses, the ZIP code tabulation area (ZCTA) is constructed using census blocks to create a spatial representation of the ZIP code. ZIP codes and ZCTAs are larger than ideal for such neighborhood analyses which fosters the potential for greater socioeconomic heterogeneity within a unit. This would attenuate the measurement of socioeconomic differences between units, such as those we are measuring with the SVI.[99,100] In an ideal registry, patient residential addresses would be geocoded and recorded as longitude and latitude so that they can be

mapped to whatever geographical unit is needed for the intended analysis. Given the current construct of the UNOS registry, we are forced to accept the inherent weakness of the ZIP code localization as a trade-off for the benefit of the large population and high generalizability.

Ongoing Study

These analyses offer hypothesis generating results that warrant further study. The effect of neighborhood disinvestment on lung transplant outcomes may be further validated using alternate indices as the variable of interest. Particularly, the use of the DCI and CNI which are produced at the ZIP code level may offer additional insights without the issue of crosswalk from the census tract to ZIP code level. It would also be interesting to assess whether the SVI or other indices have an effect on mortality for patients on the waitlist. Such an association may warrant the inclusion of a measure of neighborhood disinvestment into the allocation score prioritizing high risk patients on the waitlist.

Further work is needed to better understand the mechanism behind $PM_{2.5}$ exposure's effect on lung allografts. We are actively working on mechanistic studies using our UCLA lung transplant cohort to assess for an association between elevated serum and bronchoalveolar lavage fluid inflammatory biomarkers and ambient air pollution exposure at the patient's residence.

As noted previously, mitigation of the effects of $PM_{2.5}$ exposure on lung transplant may happen at the population or individual level. Mitigation at the individual level has been investigated using high efficiency particulate air (HEPA) filters in patient residences. Studies assessing air purifier use among healthy patients have had mixed results, some demonstrating

decreases in serum biomarkers but no change in lung function,[101] and others demonstrating an improvement in FEV1 with filter use.[102] One randomized control trial comparing active and sham portable high efficiency air cleaner use in patients with moderate-to-severe COPD demonstrated reductions in the SGRQ symptom subscale, sputum scale, rates of moderate exacerbations, and rescue medication use.[103] We believe HEPA filtration in the homes of lung transplant recipients has the potential for even more robust results given the healthy starting point of the patients after lung transplantation but high susceptibility of the lungs to inflammation and potential for the development of CLAD.[66]

Conclusion

The identification of neighborhood-level social and environmental factors that are associated with poor outcomes after lung transplantation represents a significant advance to the body of literature in lung transplantation. Identifying high SVI and air pollution exposure as risk factors for worse mortality will be of great benefit by identifying groups of lung transplant candidates that will be of high risk after their surgery. This will allow clinicians and scientists to explore what additional resources may be needed to inform policies and programs to mitigate these increased risks. It must be noted that these neighborhood-level risk factors are inextricably tied to the various social pressures and structural systems which push vulnerable groups into unfavorable living circumstances. As such, we must not apply these factors to the selection process which would be unjustly further disadvantaging an already marginalized group. These tools are better used to identify high risk populations after transplantation so that additional resources may be allocated to them.

Tables and Figures

Table 18: Cox proportional hazards models for Interaction between PM2.5 and SVI

Predictors	[a]Unadjusted Hazard Ratio (95% CI)	p	[b]Model 3 Hazard Ratio (95% CI)	p
Model BIC	191864.4		191336.8	
PM 2.5 Above EPA Standard	1.14 (1.07, 1.21)	<.001	1.10 (1.03, 1.18)	0.005
High SVI (≥0.8)	1.09 (1.01, 1.18)	0.027	1.07 (0.98, 1.16)	0.136
PM 2.5 –by– High SVI	0.82 (0.69, 0.99)	0.034	0.83 (0.69, 1.00)	0.047
Recipient Age, *per 10 years*			1.03 (1.01, 1.05)	0.011
Female Sex			0.94 (0.91, 0.98)	0.005
Race				
White			ref	
Black			0.94 (0.87, 1.01)	0.083
Hispanic/Latino			0.87 (0.79, 0.95)	0.002
Other			0.88 (0.76, 1.03)	0.104
BMI, *per 5 kg/m^2*			0.99 (0.97, 1.01)	0.430
[1]Per Capita Income, *per $10,000*			1.00 (0.98, 1.01)	0.757
Insurance				
Private			ref	
Medicaid			1.25 (1.16, 1.36)	<.001
Medicare			1.11 (1.07, 1.16)	<.001
Other Public			0.95 (0.83, 1.08)	0.395
Other			0.95 (0.71, 1.27)	0.726
Diagnosis				
Obstructive Lung Disease			ref	
Pulmonary Vascular Disease			1.21 (1.07, 1.36)	0.002
Cystic Fibrosis			1.05 (0.95, 1.15)	0.336
Restrictive Lung Disease			1.11 (1.06, 1.16)	<.001
[2]Life Support			1.42 (1.32, 1.53)	<.001
Bilateral Transplant			0.72 (0.69, 0.76)	<.001

[1]2011 Income reported using 2019 CPI adjustment
[2]Mechanical Ventilation or ECMO
Model 1 – adjusted for age, sex, race
Model 2 – adjusted for Model 1 covariates and BMI, Insurance, [1]2011 per capita Income reported using 2019 CPI adjustment
Model 3 – adjusted for Model 2 covariates and diagnosis, [2]Mechanical Ventilation or ECMO at time of match, Bilateral Transplant
[a]Cox proportional hazards model.
[b]Shared frailty Cox proportional hazards model.

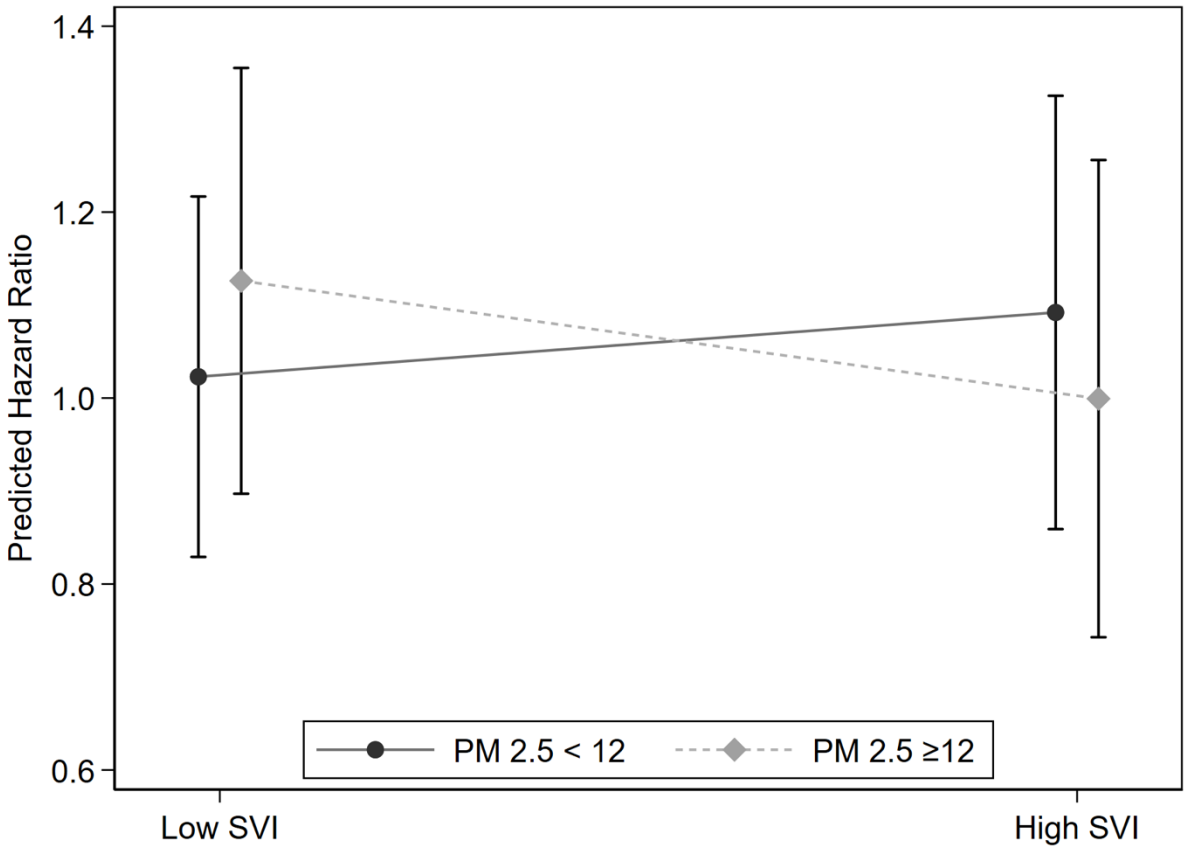

Figure 15: Predicted margins plot for interaction between PM2.5 and SVI

Appendices

Appendix A – Glossary of Abbreviations

Term	Definition
ACS	American Community Survey
ADI	Area Deprivation Index
AFT	Accelerated failure time
ATSDR	Agency for Toxic Substances and Disease Registry
BALF	Bronchoalveolar lavage fluid
BOS	Bronchiolitis obliterans syndrome
CDC	Centers for Disease Control and Prevention
CF	Cystic fibrosis
CHD	Coronary heart disease
CLAD	Chronic lung allograft dysfunction
CMV	Cytomegalovirus
CNI	Community Need Index
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
DCI	Distressed Community Index
DSA	Donation service area
ECMO	Extracorporeal membrane oxygenation
EPA	Environmental Protection Agency
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HEPA	High efficiency particulate air
HR	Hazard ratio
HRSA	Health Resources and Services Administration
HUD	US Office of Housing and Urban Development
ILD	Interstitial lung disease
IPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis
LAS	Lung allocation score
NAAQS	National Ambient Air Quality Standards
NOTA	National Organ Transplant Act
O_3	Ozone
OPO	Organ procurement organization
OPTN	Organ Procurement and Transplantation Network
PH	Proportional hazards
PM	Particulate matter
PM_{10}	PM air pollution with a diameter <10 μm
$PM_{2.5}$	PM air pollution with a diameter <2.5 μm
SDI	Social Deprivation Index
SEOPF	South-Eastern Organ Procurement Foundation

SES	Socioeconomic status
SF-36	36-item short form survey
SGRQ	Saint George Respiratory Questionnaire
SO_2	Sulfur dioxide
STAR	Standard transplant analysis research
SVI	Social Vulnerability Index
UNOS	United Network for Organ Sharing
ZCTA	ZIP code tabulation area

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