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Research article

Comparison of interstitial lung disease diagnoses in urban and rural areas among participants in the pulmonary fibrosis foundation patient registry

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ABSTRACT

Little is known about differences in interstitial lung disease (ILD) diagnosis by geographic location. The aim of this study is to evaluate differences in cross-sectional ILD diagnosis between patients in urban and rural areas.

Methods: This is a retrospective analysis of participants (n = 1992) in the Pulmonary Fibrosis Foundation (PFF) Patient Registry. Diagnoses were grouped as follows: idiopathic pulmonary fibrosis (IPF); idiopathic interstitial pneumonia other than IPF (IIP, non-IPF); connective tissue disease-associated ILD (CTD-ILD); fibrotic hypersensitivity pneumonitis (fibrotic HP); exposure-related ILD; and other ILDs. Patient-reported zip codes were mapped to county Federal Information Processing Series (FIPS) codes using data from U.S. Department of Housing and Urban Development (HUD). Frequencies of ILD diagnoses were compared between urban and rural groups using two-sample Z-test with 0.05 significance level. County-level variables including occupation and fuel use were then compared by ILD diagnosis using analysis of variance (ANOVA) with 0.05 significance level.

Results: Median age at consent was 69 years, 63 % were male, and 89.5 % were white. By county classification, 12 % resided in a rural area. Rates of IPF, IIP (non-IPF), and CTD-ILD diagnosis were similar between urban and rural residents, however rates of fibrotic HP and exposure-related ILD were higher among rural residents. Residence in a county with coal fuel use or wood fuel use was higher among those with exposure-related ILD ($p < 0.0001$ and $p = 0.0001$, respectively).

Conclusion: ILD diagnoses differ in urban versus rural ILD patients, with fibrotic HP and exposure-related ILD being significantly more prevalent among residents in rural areas. Type of fuel use also was associated with fibrotic HP and exposure-related ILD.

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1. Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders characterized by pulmonary inflammation and scarring and impaired lung function [1]. Pulmonary fibrosis (PF) may be related to underlying connective tissue diseases, exposures, or may be idiopathic. Additionally, several risk factors for ILD have been identified. For example, air pollution is associated with fibrotic ILD [2], and farming occupations are associated with idiopathic pulmonary fibrosis (IPF) [3]. While there may be significant heterogeneity in exposure to certain risk factors by geographic location, little is known about patterns in ILD diagnosis based on geographic location. Specifically, there is a paucity of published data regarding ILD diagnoses in rural vs urban locations. Two prior studies showed an association between rural residence and hypersensitivity pneumonia in India [4], and a positive association was reported between rural residence and IPF in US veterans [5]. Identifying distinctive distribution in diagnoses across geographic areas may shed light on potential causative agents and identify a pattern that may optimize resource allocation. To our knowledge, no studies have investigated differences in rates of ILD diagnoses between urban and rural areas in the US.

The Pulmonary Fibrosis Foundation Patient Registry (PFF-PR) is a prospectively collected registry of well-characterized patients across ILD centers in the US. This study aims to utilize the PFF-PR to evaluate differences in cross-sectional ILD diagnosis between patients in urban and rural areas in the PFF-PR.

2. Methods

2.1. Pulmonary fibrosis foundation patient registry

The PFF-PR is a prospective cohort study of well-characterized patients with ILD across 42 clinical sites in the United States. Details about the Registry have been previously published [6]. Patients were eligible to participate in the registry if they were seen at a participating Pulmonary Fibrosis Foundation Care Center Network site, were at least 18 years old, and had a diagnosis of ILD based on the treating clinician's clinical opinion. For the purposes of analysis, we grouped ILD diagnoses as follows: idiopathic pulmonary fibrosis (IPF); idiopathic interstitial pneumonia other than IPF (IIP, non-IPF); connective tissue disease-associated ILD (CTD-ILD); fibrotic hypersensitivity pneumonitis (fibrotic HP); exposure-related ILD (exposure was not specified in the registry); and other ILDs.

Data collected at enrollment included age at diagnosis, current age, sex, race/ethnicity, marital status, insurance, zip code, smoking status, and pulmonary fibrosis diagnosis. Race, ethnicity, and marital status were participant-reported. Pulmonary fibrosis diagnosis was determined by expert opinion at the registry site.

Table 1
Characteristics of study population.

Characteristic	Overall (n = 1840)
Age at consent (median, IQR)	69, 11
Sex	
Male	1155 (62.8 %)
Female	685 (37.2 %)
Race	
Asian	45 (2.4 %)
Black or African-American	95 (5.2 %)
White	1647 (89.5 %)
Other	5 (0.3 %)
Unknown or Not Reported	48 (2.6 %)
Ethnicity	
Hispanic or Latino	115 (6.3 %)
Not Hispanic or Latino	1664 (90.4 %)
Unknown or Not Reported	61 (3.3 %)
Smoking History	
Ever Smoker	1073 (58.3 %)
Never Smoker	766 (41.6 %)
Unknown or Not Reported	1 (0.1 %)
ILD Diagnosis	
IPF	1128 (61.3 %)
IIP, non-IPF	192 (10.4 %)
CTD-ILD	302 (16.4 %)
Chronic HP	147 (8.0 %)
Exposure-related ILD	13 (0.7 %)
Other ILD	58 (3.2 %)
County Classification by NCHS	
Large Metro	1153 (62.7 %)
Medium Metro	322 (17.5 %)
Small Metro	145 (7.9 %)
Micropolitan	199 (10.8 %)
Noncore	21 (1.1 %)

2.2. Geographic and exposure data

Patient-reported zip codes were mapped to county Federal Information Processing Series (FIPS) codes using data from U.S. Department of Housing and Urban Development (HUD) [7]. For zip codes that crossed county lines, the county containing the greatest proportion of residential addresses from that zip code was used.

Using the county FIPS code, each participant was classified as living in an urban or rural location by classification from the USDA Economic Research Service using data from the Bureau of Economic Analysis and U.S. Census Bureau. We assessed urbanization using the National Center for Health Statistics (NCHS)'s Urban-Rural Classification of Counties [8]. For the purposes of analysis, urban encompassed large metropolitan, medium metropolitan, and small metropolitan areas; rural encompassed micropolitan and noncore regions [9]. We used the US Census Bureau's 2015 American Community Survey (ACS) to link each participant's county FIPs code with county coal or fuel use.

2.3. Statistical analysis

Frequencies of ILD diagnoses were compared between urban and rural groups using two-sample Z-test for proportions with 0.05 significance level. County fuel use and occupation were reported as frequency and percent with p-values derived from Chi-square test. Numbers for county fuel use were mean (standard deviation) percent of households and were compared by ILD diagnosis using analysis of variance (ANOVA) with 0.05 significance level.

3. Results

There were 1992 registry participants at the time of analysis. Of these, 1840 had sufficient baseline data for analysis. Table 1 shows the characteristics of the registry participants in our study population. Median age at consent was 69 years, 63 % were male, and 89.5 % of participants were white. The most common pulmonary fibrosis diagnosis was IPF (61.3 %), followed by CTD-ILD (16.4 %) and IIP (non-IPF) (10.4 %). 220 registry participants (12 %) resided in rural areas, and the majority of participants (62.7 %) lived in a large metropolitan area by NCHS classification.

ILD diagnoses were compared between urban and rural areas (Table 2). Rates of IPF, IIP (non-IPF), and CTD-ILD diagnosis were similar between urban and rural residents, however rates of fibrotic HP ($p = 0.0491$) and exposure-related ILD ($p = 0.0461$) were significantly higher among rural residents. However, the number of exposure-related ILDs was very small for the entire cohort.

We examined whether ILD diagnoses are associated with county fuel use and county occupation (Table 3). County occupation refers to each county's economic dependence and includes farming, mining or manufacturing (USDA County Typology Codes https://www.ers.usda.gov/data-products/county-typology-codes). There was no significant difference in county occupation among the ILD diagnoses. However, coal fuel use was significantly higher among those with exposure-related ILD ($p < 0.0001$), whereas wood fuel use was significantly higher among those with fibrotic HP ($p = 0.0001$).

4. Discussion

To our knowledge, this is the first study to examine the association between rural residence and specific ILD diagnoses. In our analysis, there were less PFF-PR participants (12 %) that reside in rural areas by census classification compared to 17 % who live in a rural area based on zip code [10] or 15 % as defined by the US Census Bureau per the CDC (CDC.gov/ruralhealth). However, fibrotic HP and exposure-related ILD were significantly more prevalent among residents in rural areas. The total number of exposure-related ILDs was very small, making it difficult to know if this finding is clinically significant. Our findings are consistent with a study from India showing an association between rural residence and HP [4]. Contrary to a recent study of the U.S. Veteran population [5], we did not find an association between rural residence and IPF diagnosis.

We failed to find an association between ILD diagnosis and residence in a county with agricultural occupations. However, rates of residence in an agricultural region were low among participants in the PFF-PR overall. Prior studies have had mixed results, with some showing an association between IPF and agricultural exposures such as farming and livestock [3]. However, a case-control study from Australia did not report an association between farming and IPF [11]. Although exposure to silica is implicated in the pathogenesis of scleroderma [12], our study did not identify an association between county mining or manufacturing occupations and rate of CTD-ILD within the PFF-PR cohort. This may be due to the heterogeneity of the CTD-ILD diagnoses included in the registry or the heterogeneity

Table 2
ILD diagnoses among PFF registry participants in urban and rural locations.

ILD Diagnosis	Urban (n = 1620)	Rural (n = 220)	p-value
IPF	996 (61.5 %)	132 (60.0 %)	0.6721
IIP, non-IPF	170 (10.5 %)	22 (10.0 %)	0.8221
CTD-ILD	275 (17.0 %)	27 (12.3 %)	0.0772
Fibrotic HP	122 (7.5 %)	25 (11.4 %)	0.0491
Exposure-related ILD	9 (0.6 %)	4 (1.8 %)	0.0461
Other ILD	48 (3.0 %)	10 (4.6 %)	0.2075

Table 3
County-level occupations and fuel use.

ILD Diagnosis	IPF (n = 1128)	IIP, non-IPF (n-192)	CT-ILD (n = 302)	Fibrotic HP (n = 147)	Exposure-related ILD (n = 13)	Other ILD (n = 58)	p-value
County occupation							
Agriculture	8 (0.7 %)	2 (1.0 %	2 (0.7 %)	3 (2.0 %)	0	0	0.5963
Mining	25 (2.2 %)	4 (2.1 %)	7 (2.3 %)	3 (2.0 %	2 (15.4 %)	4 (6.9 %)	0.1578
Manufacturing	88 (7.8 %)	14 (7.3 %)	23 (7.6 %)	9 (6.1 %)	0	3 (5.2 %)	0.8379
Census tract fuel use, mean (SD)							
Coal	0.15 (0.79)	0.18 (0.50)	0.10 (0.34)	0.08 (0.34)	**1.40 (3.43)**	0.24 (0.61)	<0.0001
Wood	1.63 (2.77)	1.72 (3.35)	1.80 (3.19)	**3.01 (5.29)**	2.46 (2.54)	2.02 (2.93)	0.0001

within these occupations.

We also found that rates of census tract coal and wood fuel use were higher among exposure-related ILD and chronic HP, respectively. Census tract coal use has been associated with COPD [9], however studies of biomass exposure and ILD are more limited. Woodsmoke is a significant source of particulate matter $\leq$2.5μ (PM2.5), which can penetrate the deep lung and permanently alter respiratory defense mechanisms [13]. A recent epidemiologic study revealed an association between PM2.5 exposure and mortality among those with fibrotic ILD [14].

The strength of this study is a well characterized cohort of patients with interstitial lung disease across the United States. ILD diagnosis was assigned based on expert clinician review at a PFF care center, increasing the likelihood of accurate diagnosis compared to a claims-based data source. Another strength of the study is the geographic diversity of the registry. We were able to incorporate standard geographic classifications using data from HUD.

One limitation of our study is that we were only able to assess participants who received care at a PFF care center site, which are predominantly medical centers with specialized expertise in ILD and are generally in urban areas. Not surprisingly, the percentage of rural patients in the registry is less than the percentage of the general population who live in rural US areas. This may limit the generalizability of our findings or obscure some differences. This is a cross-sectional analysis, with urban or rural residence defined based on participant zip code at the time of enrollment in the registry. Participants may have lived in more than one region in their lifetime, which we did not incorporate in our analysis. We also were not able to assess individual level exposures at work or at home as these data were not available in the registry. However, our analysis of census tract fuel use and county occupation follows previously published work in chronic obstructive pulmonary disease COPD [9]. As our analysis was exploratory, we did not adjust our p-values for Type I error or multiple testing, so we cannot rule out that some statistically significant findings may be due to random chance. In addition, the sample size was quite low for exposure-related ILD, a category of particular interest. Future studies may wish to gather more information from patients in this disease category, to strengthen the findings found here.

Our study provides support for future research into differences in ILD care and outcomes in urban versus rural patients. Future studies could assess how rurality affects access to care for patients with interstitial lung disease as well as more specific environmental and occupational exposures that are associated with rural residence.

CRediT authorship contribution statement

Anne E.F. Dimmock: Writing – review & editing, Writing – original draft, Conceptualization. **Yuka Furuya:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Emily White:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Elizabeth Freiheit:** Writing – review & editing, Data curation, Conceptualization. **Rebecca Bascom:** Writing – review & editing, Conceptualization. **Hyun Joo Kim:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

Ethics approval

Institutional Review Board approval was obtained at each PFF-PR site as well as at the Data Coordinating Center at the University of Michigan. Review and/or approval by an ethics committee was not needed for this study because PFF-PR participants consented to participate in the registry and for use of their data for studies. All participants were informed that consent to participate in the study and publish their data would be assumed on completion and submission of the registry activities. No individual personal information was published in this study.

Data availability statement

The data comes from the Pulmonary Fibrosis Foundation Patient Registry, which the PFF owns. The data is not publicly available.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hyun Joo Kim reports a relationship with Tvardi Therapeutics that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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