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Original Research Article

Urban vs Rural Exposure Patterns in Hypersensitivity Pneumonitis and their Clinical Outcomes

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Abstract:

Aim: This paper examines urban versus rural exposure patterns in HP, with an emphasis on how domestic, occupational, and environmental antigens influence presentation, disease behavior, and clinical outcomes in fibrotic and non-fibrotic disease. The specific objective is to synthesize the available literature on exposure epidemiology and prognosis outcomes, and to frame a clinically useful comparison of urban and rural HP for physicians and researchers working in interstitial lung disease.

Materials and Methods: This narrative review was developed from published registry data, review articles, and prognostic literature addressing HP epidemiology, exposure sources, and outcomes. Particular weight was given to the prospective ILD-India registry because it directly reported urban-rural residence patterns, antigen patterns, and exposure odds within a large multicenter cohort of newly diagnosed interstitial lung disease patients in India. Additional prognostic evidence was taken from a comprehensive review of chronic HP that summarized survival determinants, the role of antigen identification and avoidance, lung function decline, radiologic fibrosis, and factors associated with mortality. Supporting background on reversibility of early disease and the poorer outlook of fibrotic HP was integrated from standard clinical references.

Results: The available evidence does not support a simplistic view that HP is either a rural or urban disease, because both settings harbor relevant antigens but with different profiles. In the Indian registry, 70% of HP patients resided in urban areas, yet rural residence independently increased the odds of HP compared with other ILDs, with an adjusted odds ratio of 1.64. Urban HP clustered more around indoor environmental exposures such as birds, air-conditioners, air-coolers, visible molds, and poorly maintained ventilation or cooling systems, whereas rural HP more often reflected farming, moldy organic dust, avian contact, and work-related organic aerosols. Across both settings, birds showed the strongest adjusted association with HP, followed by air-conditioners, molds, rural residence, and air-coolers in the Indian data.

Conclusion: Urban and rural residence should be interpreted as proxies for exposure contexts because the clinical course is driven primarily by antigen burden, chronicity of exposure, and the extent of established lung fibrosis. Rural living may increase the odds of disease through agricultural and organic dust exposures, but urban populations can carry a large absolute burden because of household birds, molds, cooling devices, and ambient pollution-linked vulnerability. Outcomes are best when the disease is recognized early and the antigen is identified and avoided; prognosis worsens with fibrotic transformation, lower baseline pulmonary function, older age, smoking, pulmonary hypertension, and recurrent or ongoing antigen exposure.

Keywords: Hypersensitivity Pneumonitis; Urban Exposure; Rural Exposure; Environmental Antigens; Clinical Outcomes.

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Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease caused by sensitization to inhaled environmental antigens[6], but the distribution of exposure sources and outcomes differs between urban and rural settings because the relevant antigen mix, housing conditions, occupational profiles, and environmental co-exposures are not the same across these populations[5,7]. Historically the disease was strongly linked to agricultural work, bird breeding, and occupational organic dust inhalation[6], which encouraged the impression that HP was predominantly a rural disease. Contemporary data show a more complicated pattern in which urban populations also contribute substantially to disease burden because domestic birds, molds,

humidification and cooling devices, and occult indoor exposures are common in cities[4,7].

This urban-rural contrast is clinically relevant because location shapes the type, frequency, and persistence of the antigen source, and therefore influences whether the disease presents as a recognizable exposure-related syndrome or as chronic fibrotic interstitial lung disease that can mimic idiopathic pulmonary fibrosis[6,11]. In the ILD-India registry, HP constituted 47.3% of new-onset ILD diagnoses, indicating a very large burden in the studied population[1], and exposure profiling revealed strong associations with birds, air-conditioners, molds, rural residence, and air-coolers[4]. Importantly, although rural residence raised the adjusted odds of HP, most HP patients in that cohort actually lived in urban areas, emphasizing that relative risk and absolute case burden are not identical[1,4].

The need to distinguish urban from rural exposure patterns is also important for prevention and prognosis. Urban patients may experience prolonged low-grade domestic exposure from birds kept in apartments, hidden dampness, evaporative cooling systems, or contaminated air-handling devices[4,7], while rural patients may encounter intense occupational and household contact with moldy hay, poultry, farming aerosols, and other bioaerosols[5,6]. These differing settings may alter the ease of antigen recognition, feasibility of avoidance, and speed of referral. When exposure remains unidentified or elimination is incomplete, chronic inflammation may progress to fibrosis, which is the strongest consistent adverse determinant of survival in chronic HP[6,11].

Another reason this topic warrants focused analysis is that diagnostic failure often stems from an incomplete exposure history. The ILD-India experience showed that some patients who might otherwise have been labeled idiopathic pulmonary fibrosis were reclassified as HP when detailed exposure data were obtained. This reflects a broader challenge described in prognostic reviews: chronic HP is heterogeneous, frequently difficult to distinguish from other fibrotic ILDs, and often lacks a single definitive diagnostic test[6,11]. Urban-rural framing can therefore sharpen clinical questioning rather than replace multidisciplinary diagnosis[1].

The present paper reviews the epidemiologic evidence on urban and rural exposure patterns in HP, compares major antigen profiles in the two settings, summarizes their clinical correlates, and examines how exposure context interacts with prognosis. It also provides observation tables to organize the available data in a clinically interpretable format, followed by a statistical section translating key reported effect sizes into practice-oriented interpretation. The overarching premise is that geography matters chiefly because it structures exposure opportunity, whereas outcomes depend on exposure persistence, fibrosis burden, physiological impairment, and success of antigen avoidance[6,11].

Materials & Methods

This paper is a structured narrative review prepared from peer-reviewed published sources that addressed HP epidemiology, exposure determinants, and prognosis. The central source base included the prospective multicenter ILD-India registry analysis of HP and a narrative review of prognostic factors in chronic HP.

Study Design: The work was designed as a narrative synthesis rather than a de novo meta-analysis because the currently available studies differ substantially in design, population, exposure definitions, and outcome reporting. The ILD-India registry supplied original multicenter prospective observational data from 27 centers and 1084 adults with new-onset ILD, of whom 513 were diagnosed with HP. The prognostic review synthesized retrospective and longitudinal cohorts from multiple countries, permitting a broader understanding of survival determinants in chronic and fibrotic HP.

Eligibility of Evidence: Included evidence had to contain at least one of the following: explicit description of antigen exposure patterns relevant to HP, comparison of residence or setting variables such as urban versus rural residence, or reported clinical outcomes such as lung function decline, survival, exacerbation, fibrosis progression, or transplant-free survival. Sources that were purely descriptive without clinical relevance, or that lacked interpretable information on exposure context or prognosis, were not emphasized in the narrative synthesis.

Data Domains Extracted: The following domains were extracted and organized for synthesis: demographic profile, residence pattern, identifiable antigens, domestic versus occupational sources, radiological phenotype, lung function data, symptom burden, fibrosis status, and prognostic variables. Particular attention was paid to adjusted odds ratios for exposure factors and to longitudinal indicators of adverse outcome, such as fibrosis, reduced FVC, decline in FVC over follow-up, unidentified inciting antigen, and survival estimates in fibrotic disease[1,2].

Analytic approach Outcome interpretation prioritized factors consistently associated with poor prognosis across studies, especially older age, baseline physiological impairment, established fibrosis, and inability to identify or avoid the inciting antigen[1,2].

Observation Tables

Table 1: Residence and Exposure Profile in ILD-India Registry HP Cohort

Variable	Observation
Total new-onset ILD patients	1084
HP cases	513, representing 47.3% of new-onset ILD
Urban residence among HP	70% of HP patients lived in urban areas
Identifiable exposure	78.9% had an identifiable exposure; 21.1% had none identified
Common exposure: air-coolers	48.1%
Common exposure: air-conditioners	26.3%
Common exposure: birds	21.4%
Common exposure: molds	20.7%
Occupational exposure	5.8%
Predominant phenotype	About 96% were chronic/fibrotic HP

Table 2: Urban Versus Rural Exposure Tendencies in HP

Domain	Urban tendency	Rural tendency
Major setting	Indoor residential and built environments, often with hidden or mixed domestic exposures	Agricultural, livestock, avian, and organic dust environments with occupational overlap
Frequent antigens	Birds, molds, air-conditioners, air-coolers, ventilation or cooling reservoirs	Farming aerosols, poultry or bird contact, moldy organic material, work-related bioaerosols
Exposure recognition	Often delayed because exposures may be occult or normalized within homes and appliances	May be easier to suspect when farming or bird-related history is obvious, but chronic exposure may still be normalized
Pollution interaction	Urban air pollution may amplify vulnerability or coexist with occult indoor antigens	Less emphasized in current prognostic literature than organic dust burden and occupational contact
Absolute burden	Can be high because most patients in some cohorts live in urban areas	Relative odds may be elevated despite fewer absolute cases in certain cohorts

Table 3: Exposure Associations Reported in ILD-India Registry

Environmental factor	Adjusted OR (95% CI)	Interpretation
Birds	3.52 (2.29-5.40)	Strongest reported association with HP in the analyzed cohort
Air-conditioner	2.23 (1.59-3.14)	Important urban indoor exposure marker
Molds	1.79 (1.23-2.60)	Relevant in both urban and rural damp environments
Rural residence vs urban	1.64 (1.12-2.42)	Rural living increased odds relative to urban residence in comparison with other ILDs
Air-cooler	1.45 (1.11-1.90)	Common practical exposure, especially where evaporative cooling is used
Occupational exposure	1.39 (0.76-2.56)	Directionally positive but not statistically significant in this model

Table 4: Determinants of Clinical Outcome in Chronic HP

Prognostic factor	Outcome relationship
Early antigen avoidance	Symptoms and inflammatory changes may improve, especially in nonfibrotic disease
Fibrosis on HRCT or biopsy	Consistently associated with worse survival and more progressive disease
Older age	Repeatedly associated with increased mortality
Lower baseline lung function	Worse FVC or DLCO predicts poorer survival
Unidentified inciting antigen	Often associated with poorer survival or more difficult management
Smoking	Frequently associated with worse overall survival in several cohorts
Pulmonary hypertension/comorbid burden	Associated with substantially worse outcomes
Honeycombing/UIP-like fibrosis	Can confer survival approaching that of IPF in severe fibrotic phenotypes

Results

Rural residence increased the adjusted odds of HP in the ILD-India registry, which supports the long-recognized contribution of agricultural and organic dust exposures. At the same time, 70% of HP patients in that registry were urban residents, demonstrating that city living does not protect against HP and may generate a large absolute burden through domestic and built-environment exposures. Bird exposure emerged as the strongest independent association in the Indian data, followed by air-conditioners, molds, rural residence, and air-coolers. This pattern is highly informative because it bridges classic rural antigens with modern urban indoor exposures. In practice, the urban patient with birds on a balcony, visible dampness, or a poorly serviced cooling system may be at no less clinical risk than a rural patient with farm-related organic dust exposure if the exposure is chronic and unrecognized.

Outcome differences were more consistently linked to disease phenotype than to place of residence alone. Nonfibrotic disease can be reversible when recognized early and followed by strict antigen avoidance, whereas fibrotic HP is less reversible and may progress even after the exposure has ceased. Older age, lower baseline FVC or DLCO, established fibrosis, and honeycomb or UIP-like radiologic change repeatedly predicted worse survival across reviewed cohorts.

Overall, the results support three practical inferences. First, rural residence is a significant risk context, but urban HP is common and clinically important. Second, domestic built-environment exposures deserve the same diagnostic attention as occupational rural exposures. Third, prognosis is driven chiefly by fibrosis burden, physiological impairment, and success of exposure elimination rather than by a simple urban versus rural label.

Statistical Analysis: The most directly quantifiable urban-rural comparison in the reviewed evidence comes from the ILD-India registry multivariate model. In that analysis, rural residence compared with urban residence had an adjusted odds ratio of 1.64 with a 95% confidence interval of 1.12 to 2.42, indicating a statistically significant increase in the odds of HP relative to other ILDs after adjustment for age, sex, smoking, occupational exposure, and multiple antigen variables. The confidence interval excludes 1.0, supporting statistical significance as reported in the original study.

Among specific exposures, birds had the highest adjusted odds ratio at 3.52, suggesting the strongest independent association with HP in that cohort. Air-conditioner exposure had an adjusted odds ratio of 2.23, molds had an adjusted odd ratio of 1.79, and air-coolers 1.45, all statistically significant, whereas occupational exposure had an adjusted odds ratio of 1.39 with a confidence interval crossing 1.0 and therefore was not statistically significant in that model. These findings indicate that indoor environmental exposures, often associated with urban or peri-urban living, can rival or exceed traditionally presumed rural occupational signals in multivariable analysis.

Discussion

Hypersensitivity pneumonitis (HP) has emerged as a leading cause of new-onset interstitial lung disease (ILD) in prospective registries, particularly in regions with high environmental exposures. The ILD-India registry highlights HP's prominence, while global comparisons reveal geographic variations influenced by antigen prevalence and pollution. The ILD-India registry enrolled 1,084 patients with new-onset ILD across 27 centers from 2012-2015, identifying HP as the most common diagnosis at 47.3%, surpassing connective tissue disease-ILD (13.9%) and idiopathic pulmonary fibrosis (13.7%). This contrasts with U.S. claims data from 2004-2013, where HP prevalence rose with age to 11.2 per 100,000 in those over 65, with chronic HP comprising 56-68% of cases. In China, a population-based study reported distinct HP characteristics, though specific prevalence was lower, emphasizing regional diagnostic differences[1-3]

Multidisciplinary discussion (MDD) improved diagnostic concordance in the Indian registry, with Cohen's κ of 0.618 between national and U.S. experts, underscoring ILD's diagnostic challenges. Veterans Affairs data from 2008-2015 showed high ILD incidence, positioning it as a major health concern in that cohort. Recent Indian prescription monitoring at a tertiary center confirmed ILD's burden, tracking outcomes and adverse reactions.[4] Prospective data from the ILD-India registry specifically on HP (n=513) confirmed exposures in 48.1%, mainly air coolers, with 47.3% of new ILDs classified as HP at high diagnostic confidence. Birds, cooling devices, and visible molds were top antigens, reflecting tropical environmental factors. This high HP rate in India likely stems from widespread use of contaminated cooling systems and agricultural practices[5,1]

U.S. epidemiology indicates fibrotic HP in 1,852 cases over a decade, with cumulative incidence of 0.63–1.08 per 100,000 for chronic forms. Chinese data describe clinical traits and outcomes, noting population-specific progression. A rural Appalachian U.S. study found similar exposures to urban cohorts but higher smoking and non-avoidance rates, linking to poor outcomes. A 2025 urban-rural comparison in the Pulmonary Fibrosis Foundation registry highlighted diagnostic disparities, with rural areas showing different ILD

patterns. Geographic variability persists, as Australian data linked pollution to outcomes.[2,3,6]

HP arises from inhaled antigens in sensitized individuals, with 62 unique exposures identified in a scoping review associating specific ones with phenotypes. Occupational factors contribute 12-28% of cases, per population attributable fractions. Nature Reviews primer emphasizes complete avoidance as key treatment.[7,8,9] In India, air coolers dominate, while global reports note molds, birds, and farmer's lung. Rural Appalachia mirrored U.S. norms with molds and birds.[6,5] Occupation versus environment debate favors environmental dominance in some analyses, though both trigger HP. Pollution exacerbates ILD, as narrative reviews link air quality to disease. Ultrafine particulate matter worsens fibrotic ILD outcomes[10,7]. HP phenotypes range from acute to fibrotic, with progression despite avoidance in some. Scoping review tied exposures to phenotypes. Fibrosing ILD real-world course shows variable trajectories.[8,9]

Air pollution narrative ties ILD to ambient pollutants, advocating quality improvements. Ultrafine particles associate with worse fibrotic outcomes. 2025 study confirms geographic pollution effects on ILD.[10] Rural Appalachian HP had higher fibrosis, smoking, and mortality. Urban-rural registry comparison notes diagnosis differences. Veterans network revealed high ILD prevalence.[4,6] Avoidance remains cornerstone, with immunosuppressants for chronic HP. Indian prescription study monitored patterns and reactions. Rural cohorts show poorer outcomes from non-avoidance.[8,6] MDD enhances accuracy, as Indian registry κ scores indicate. High-confidence HP diagnoses rely on history, CT, and BAL.[1,8] Registries like ILD-India inform etiology via prompted exposures. Pollution control could mitigate progression.[1]

Clinical outcomes are shaped less by residence itself than by the interaction of exposure persistence, antigen identification, diagnostic delay, and the presence of fibrotic remodeling. Early nonfibrotic disease may improve substantially with strict antigen avoidance, but once fibrosis is established the disease often becomes only partially reversible and can progress despite apparent removal of exposure. This explains why lower baseline pulmonary function, radiologic or histologic fibrosis, honeycombing, and UIP-like patterns repeatedly predict poorer survival across chronic HP studies.

Conclusion

For researchers, the urban-rural comparison highlights the need for better exposure phenotyping rather than simple residential classification. Future studies should separately record household, occupational, seasonal, structural, and pollution-related exposures; distinguish urban, peri-urban, and rural environments more precisely; and link these variables to radiology, bronchoalveolar lavage findings, pulmonary function decline, and survival. Prospective longitudinal cohorts are particularly needed because much of the current prognostic evidence remains retrospective and heterogeneous.

For clinicians, the main implication is practical and immediate. Every patient with possible HP should undergo a comprehensive environmental history that crosses the false boundary between home and workplace and between assumptions of urban and rural risk. If this principle is applied consistently, earlier diagnosis, better exposure control, and improved outcomes may be achievable for patients who would otherwise progress to chronic fibrotic disease.

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