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Original Research Article

The Impact of Geographic Demography on Autoimmune Severity: A Cross-Sectional Comparison of Rheumatoid Factor and Anti-Citrullinated Protein Antibody Profiles with Clinical Disease Indices in Rural and Urban Punjab

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Abstract: ***Aim of Study:*** To compare the serological profiles (Rheumatoid Factor and Anti-Citrullinated Protein Antibodies) and clinical disease severity indices between rural and urban patients with Rheumatoid Arthritis in the Punjab region of Pakistan, and to determine whether geographic demography independently predicts autoimmune severity. Study Duration: March 2024 to March 2025 Study Place: Aziz Fatima Medical College, Faisalabad, Pakistan ***Methodology:*** This cross-sectional comparative study enrolled 320 consecutive patients diagnosed with Rheumatoid Arthritis according to the 2010 ACR/EULAR classification criteria. Participants were stratified into rural (n=160) and urban (n=160) cohorts based on residential history of ≥10 years. Demographic data, clinical characteristics, and treatment history were recorded. Venous samples were collected for Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibody (ACPA) quantification using ELISA. Disease activity was assessed using the Disease Activity Score 28 (DAS28-ESR), while functional impairment was measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). Radiographic damage was evaluated using the Larsen Score. Statistical analysis employed independent t-tests, Mann-Whitney U tests, chi-square tests, and multivariate linear regression. ***Results:*** Rural patients demonstrated significantly higher serological positivity rates compared to urban patients (RF: 91.3% vs. 78.1%, p=0.002; ACPA: 88.8% vs. 74.4%, p=0.001). Mean RF titers (185.4±98.2 IU/mL vs. 112.7±76.5 IU/mL, p<0.001) and ACPA levels (168.3±87.6 U/mL vs. 94.2±69.8 U/mL, p<0.001) were markedly elevated in the rural cohort. Rural residents exhibited higher disease activity (DAS28: 5.8±1.2 vs. 4.6±1.1, p<0.001), greater functional disability (HAQ-DI: 1.8±0.6 vs. 1.2±0.5, p<0.001), and more advanced radiographic damage (Larsen Score: 34.7±15.3 vs. 21.4±12.8, p<0.001). Multivariate regression identified rural residence as an independent predictor of higher DAS28 scores (β=0.42, p<0.001) after adjusting for age, gender, disease duration, and treatment adherence. ***Conclusion:*** Rheumatoid Arthritis patients residing in rural Punjab exhibit more severe autoimmune profiles with higher serological titers and greater clinical disease activity compared to their urban counterparts. These disparities appear independent of traditional demographic factors and may reflect differential environmental exposures, healthcare access barriers, or occupational risk factors prevalent in rural settings.

Keywords: Rheumatoid Arthritis, Rural Health, Urban Health, Rheumatoid Factor, Anti-Citrullinated Protein Antibody, Disease Severity, DAS28, Punjab, Pakistan, Geographic Demography.

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INTRODUCTION

Rheumatoid Arthritis (RA) represents one of the most common systemic autoimmune disorders, affecting approximately 0.5-1.0% of the global population and constituting a major cause of disability, reduced quality of life, and premature mortality worldwide . The disease is characterized by chronic inflammation of the synovial joints, leading to progressive cartilage destruction, bone erosion, and systemic complications that extend far beyond the musculoskeletal system . In Pakistan, the burden of RA has escalated substantially over the past three decades, with recent Global Burden of Disease data demonstrating that between 1990 and 2021, the absolute number of prevalent RA cases increased from approximately 134,600 to 319,000, while disability-adjusted life years nearly doubled from 27,300 to 62,800 . These epidemiological trends underscore the growing public health challenge posed by RA in low- and middle-income countries, where healthcare resources remain constrained and specialized rheumatology services are often concentrated in major urban centers .

The pathogenesis of RA involves a complex interplay between genetic susceptibility and environmental triggers, with heritability estimates from twin studies ranging between 50-60%, indicating that non-genetic factors contribute substantially to disease risk and progression . The shared epitope within the HLA-DRB1 locus remains the strongest genetic risk factor, yet the incomplete concordance among monozygotic twins highlights the critical role of environmental exposures in triggering and perpetuating autoimmunity . Emerging evidence suggests that the environment may contribute to approximately 80% of disease susceptibility, with factors such as cigarette smoking, air pollution, occupational inhalants, infectious agents, and dietary patterns all implicated in RA pathogenesis . Understanding how these environmental determinants vary across geographic regions and populations is therefore essential for comprehending the full spectrum of disease expression and for developing targeted prevention and management strategies.

Geographic demography has recently gained recognition as a potentially important determinant of autoimmune disease severity, yet research examining urban-rural disparities in RA outcomes remains surprisingly limited, particularly in South Asian populations. The available evidence, primarily from high-income countries, suggests that rural residence may be associated with worse disease outcomes, though the mechanisms underlying this association remain poorly elucidated. A systematic review of global rural and remote patients with RA found that individuals living in rural areas consistently experience greater delays in diagnosis, reduced access to rheumatology specialty care, lower utilization of disease-modifying antirheumatic drugs, and poorer functional outcomes compared to urban dwellers . These disparities appear particularly pronounced in regions with centralized healthcare systems where rheumatology services are concentrated in major cities, forcing rural patients to travel long distances for specialist consultations and follow-up care .

In the Pakistani context, the urban-rural divide in healthcare infrastructure is particularly stark. Punjab province, the most populous region of the country, exemplifies this disparity, with advanced tertiary care facilities concentrated in major cities such as Lahore, Faisalabad, and Rawalpindi, while rural districts remain underserved by specialist services . A comprehensive systematic review of RA in Pakistani patients revealed that most affected individuals are female, approximately 55% are uneducated, and many have low disease knowledge and poor adherence to disease-modifying antirheumatic drugs . The direct monthly treatment cost, ranging from USD 16.47 to 100.68, represents a substantial financial burden given the socioeconomic profile of typical patients, potentially forcing difficult choices between medication adherence and other essential household expenditures . These economic realities may be particularly acute in rural areas, where agricultural livelihoods predominate and cash incomes are often limited and seasonal.

Beyond healthcare access barriers, rural and urban environments differ fundamentally in ways that may directly influence autoimmune disease pathogenesis and progression. Rural residents in Punjab are predominantly engaged in agricultural occupations, exposing them to a distinct set of potential triggers including pesticides, fertilizers, silica-containing

dusts, and animal-derived antigens. A recent comprehensive meta-analysis examining occupational inhalant exposures and RA risk identified fertilizers (relative risk 1.49), pesticides (relative risk 1.32), animal dust (relative risk 1.20), and silica (relative risk 1.36) as significant contributors to RA development . These exposures are substantially more prevalent in rural agricultural settings than in urban environments, raising the possibility that occupational factors may not only increase RA risk but also modulate disease severity through ongoing antigenic stimulation and immune activation. The same meta-analysis identified engine exhaust (relative risk 1.45) and asbestos (relative risk 1.39) as additional risk factors, exposures more commonly encountered in urban industrial settings, suggesting that both environments harbor distinct profiles of potential triggers .

Air quality represents another dimension of environmental exposure that differs markedly between rural and urban areas and may influence RA activity. Urban centers in Punjab, including Faisalabad, experience substantial air pollution from vehicular traffic, industrial emissions, and the burning of solid fuels. Recent research from Kuwait demonstrated that specific air quality components, particularly nitrogen dioxide and ozone, significantly influence RA disease activity as measured by the DAS28 score, with nitrogen dioxide exhibiting a two-month lag effect (effect score 0.43) and ozone a three-month lag effect (effect score 0.31) . These pollutants are thought to promote systemic inflammation and immune dysregulation through oxidative stress mechanisms, potentially exacerbating underlying autoimmune processes . While urban residents may face greater exposure to traffic-related pollutants, rural populations may encounter higher levels of agricultural burning emissions and indoor air pollution from biomass fuel use for cooking and heating, creating complex exposure profiles that require further investigation.

The serological profile of RA, particularly the presence and titer of Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA), provides important insights into disease pathogenesis and prognosis. ACPA-positive RA is associated with more aggressive disease course, greater radiographic progression, and poorer long-term outcomes compared to seronegative disease . Interestingly, serological positivity rates vary substantially across populations and geographic regions, suggesting that environmental factors may influence not only disease risk but also the specific autoimmune phenotype that develops. A study examining first-degree relatives of RA patients found that anti-CCP positivity was present in 8.5% of at-risk individuals, compared to only 3.6% in controls, while RF positivity was observed in 33.3% of relatives versus 7.3% of controls . These findings demonstrate that autoantibodies can predate clinical disease onset by years and that their presence identifies individuals at heightened risk, yet the factors determining who progresses from autoantibody positivity to clinical disease remain incompletely understood.

Despite growing recognition of geographic disparities in RA outcomes, few studies have systematically compared serological profiles and clinical disease severity between rural and urban populations using standardized measures and well-characterized cohorts. In Pakistan specifically, while epidemiological data on RA prevalence and burden have recently emerged, comprehensive studies examining urban-rural differences in disease characteristics remain scarce . A recent study from a Pakistani cohort highlighted that approximately one-third of patients present with non-polyarticular onset patterns, and diagnostic delays averaging 17.8 months are common, factors that may disproportionately affect rural populations with limited access to specialist care . Understanding whether rural residence independently predicts more severe disease, after accounting for delays in diagnosis and treatment, has important implications for healthcare resource allocation and the development of targeted interventions.

The Punjab province of Pakistan provides an ideal setting for investigating urban-rural disparities in RA severity. As Pakistan's most populous province, Punjab encompasses a diverse range of geographic and demographic environments, from densely populated urban centers like Faisalabad and Lahore to remote rural districts where agriculture remains the primary livelihood. The population is relatively homogeneous ethnically and linguistically, reducing potential confounding by genetic heterogeneity, yet exhibits substantial variation in environmental exposures, occupational patterns, healthcare access, and socioeconomic conditions. Aziz Fatima Medical College in Faisalabad serves a catchment area that includes both urban Faisalabad residents and rural populations from surrounding districts, providing access to a diverse patient population suitable for comparative studies.

The present study was therefore designed to address this knowledge gap by systematically comparing RF and ACPA profiles, along with comprehensive clinical disease indices, between rural and urban RA patients presenting to a tertiary care rheumatology center in Faisalabad, Punjab. We hypothesized that rural patients would exhibit more severe serological and clinical disease profiles compared to urban patients, and that these differences would persist after adjusting for potential confounders including age,

gender, disease duration, and treatment adherence. The specific objectives were to: (1) compare the prevalence and titers of RF and ACPA between rural and urban RA patients; (2) assess differences in disease activity (DAS28), functional disability (HAQ-DI), and radiographic damage (Larsen Score) across geographic strata; (3) examine the correlation between serological markers and clinical indices in each population; and (4) determine whether rural residence independently predicts disease severity using multivariate regression analysis.

By elucidating the relationship between geographic demography and autoimmune severity, this study aims to inform evidence-based healthcare planning and resource allocation in Pakistan and similar low- and middle-income settings. If rural residence is indeed associated with more severe disease, this would argue for the need to decentralize rheumatology services, develop outreach programs, and implement targeted interventions addressing the unique environmental and occupational exposures confronting rural populations. Furthermore, understanding the mechanisms underlying geographic disparities may generate hypotheses about environmental triggers that could be modified to reduce disease burden across all populations.

Methodology

Study Design and Setting

This cross-sectional comparative study was conducted at the Aziz Fatima Medical College, Faisalabad, Pakistan, over a 12-month period from March 2024 to March 2025. Aziz Fatima Medical College is a tertiary care teaching institution serving a catchment population of approximately 5-6 million individuals from both urban Faisalabad city and surrounding rural districts of Punjab province. The rheumatology department operates a weekly outpatient clinic managing approximately 150-200 patients with various rheumatic diseases, providing an adequate patient pool for comparative studies of urban and rural populations.

Sample Size Calculation

Sample size was calculated using OpenEpi software version 3.01, based on the primary outcome of difference in mean DAS28 scores between rural and urban populations. Assuming a clinically significant difference of 0.6 in DAS28 (equivalent to moderate versus high disease activity categories), with standard deviation of 1.2 derived from previous literature, a two-sided significance level of 0.05, and power of 90%, the required sample size was 138 per group. To account for potential dropouts, incomplete data, and sub-group analyses, we inflated this estimate by 15% to target 160 participants per group, yielding a total sample of 320 patients.

Participant Selection

Consecutive patients attending the rheumatology outpatient clinic during the study period were screened for eligibility. Inclusion criteria were: (1) diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria; (2) age ≥18 years; (3) disease duration ≥6 months to ensure stable disease phenotype; (4) residential history in either rural or urban area of Punjab for ≥10 consecutive years prior to enrollment; and (5) willingness to provide informed consent and comply with study procedures. Exclusion criteria included: (1) overlap with other systemic autoimmune diseases (systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease); (2) active infection requiring antibiotic therapy within 4 weeks; (3) pregnancy or lactation; (4) malignancy within 5 years; (5) inability to complete questionnaires due to cognitive impairment or language barriers; and (6) recent change in disease-modifying antirheumatic drug therapy within 3 months, which might affect disease activity measures.

Residential status was classified according to standardized definitions from the Pakistan Bureau of Statistics. Urban areas were defined as municipalities with population ≥50,000, population density ≥400 persons per square kilometer, and at least 75% of the male working population engaged in non-agricultural occupations. Rural areas were defined as all other areas, typically characterized by agricultural livelihoods, lower population density, and limited access to infrastructure and services. Participants were stratified into rural (n=160) and urban (n=160) cohorts based on their residential history.

Data Collection Procedures

Demographic and clinical data were collected through structured interviews and medical record review by trained research assistants blinded to the study hypotheses. Variables collected included age, gender, disease duration, educational attainment (categorized as no formal education, primary, secondary, or tertiary), occupation (agricultural, industrial, service, domestic, retired/unemployed), monthly household income (categorized in Pakistani rupees), tobacco use (never, former, current, with pack-years calculated for smokers), and family history of RA in first-degree relatives. Treatment history was comprehensively documented, including current and previous use of conventional synthetic disease-modifying antirheumatic drugs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents, and corticosteroids (current dose in prednisolone equivalents). Treatment adherence was assessed using the Compliance Questionnaire for Rheumatology (CQR), with scores <80% classified as poor adherence.

Laboratory Assessments

Venous blood samples (10 mL) were collected from each participant under aseptic conditions. Serum was separated by centrifugation at 3000 rpm for 10 minutes within 2 hours of collection and stored at -80°C until analysis. Rheumatoid Factor (RF) IgM was quantified using commercially available enzyme-linked immunosorbent assay kits (Organtec Diagnostika, Mainz, Germany) according to manufacturer instructions. The assay sensitivity was 3 IU/mL, with positivity defined as ≥20 IU/mL according to manufacturer recommendations. Anti-Citrullinated Protein Antibodies (ACPA) were measured using second-generation anti-cyclic citrullinated peptide (anti-CCP2) ELISA kits (Euroimmun, Lübeck, Germany), with positivity defined as ≥10 U/mL as per manufacturer guidelines. All assays were performed in duplicate, with intra-assay and inter-assay coefficients of variation <8% and <12%, respectively. Laboratory personnel were blinded to participants' residential status.

Clinical Disease Activity Assessment

Disease activity was assessed using the Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS28-ESR). The DAS28 incorporates: (1) tender joint count (28 joints assessed); (2) swollen joint count (28 joints assessed); (3) erythrocyte sedimentation rate (mm/hour); and (4) patient global assessment of disease activity on a 100-mm visual analog scale. Calculations were performed using the standard formula: $DAS28 = 0.56 \times \sqrt{(tender28)} + 0.28 \times \sqrt{(swollen28)} + 0.70 \times \ln(ESR) + 0.014 \times VAS$. Disease activity was categorized as remission (DAS28 <2.6), low (2.6-3.2), moderate (3.3-5.1), or high (>5.1). All joint counts were performed by a single trained rheumatologist (intra-rater reliability ICC >0.90) who was blinded to participants' residential status.

Functional Disability Assessment

Functional status was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI), a validated 20-item instrument assessing difficulty in performing activities of daily living across eight domains: dressing, arising, eating, walking, hygiene, reach, grip, and usual activities. Each item is scored from 0 (without any difficulty) to 3 (unable to do), with the domain score being the highest score within that domain. The total HAQ-DI score is calculated as the average of the eight domain scores, ranging from 0 (no disability) to 3 (completely disabled). The Urdu version of HAQ-DI, previously validated in Pakistani populations, was administered by trained interviewers.

Radiographic Assessment

Radiographic damage was assessed using the Larsen Score, a validated method for quantifying joint damage in RA. Plain radiographs of both hands and feet (posteroanterior views) were obtained using standardized techniques. Images were scored by a musculoskeletal radiologist with 15 years of experience who was blinded to clinical data and residential status. The Larsen Score evaluates 32 joints (16 per hand/wrist and 8 per foot) on a scale of 0 (normal) to 5 (mutilating damage), with total scores ranging from 0 to 160. Intra-reader reliability was assessed by re-scoring 20 randomly selected radiographs after a 4-week interval, yielding an intra-class correlation coefficient of 0.94.

Quality Control Measures

Several quality control measures were implemented to minimize bias and ensure data integrity. Research assistants underwent standardized training in questionnaire administration and data entry. Double data entry with validation checks was performed using EpiData software version 3.1. Laboratory assays included internal quality controls and were calibrated against international standards. Regular monitoring visits were conducted by the principal investigator to verify adherence to study protocols and identify any issues requiring corrective action.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Normally distributed variables were expressed as mean ± standard deviation and compared between groups using independent samples t-tests. Non-normally distributed variables were expressed as median with interquartile range and compared using Mann-Whitney U tests. Categorical variables were presented as frequencies and percentages, with comparisons performed using chi-square tests or Fisher's exact tests as appropriate.

Correlations between serological markers (RF and ACPA titers) and clinical indices (DAS28, HAQ-DI, Larsen Score) were examined using Pearson's correlation coefficient for normally distributed data or Spearman's rank correlation for non-normally distributed data. Correlation coefficients were compared between rural and urban groups using Fisher's z-transformation.

To determine whether rural residence independently predicted disease severity, multivariate linear regression analysis was performed with DAS28 as the dependent variable. Independent variables were selected based on clinical relevance and univariate associations ($p<0.10$) and included age, gender, disease duration, educational attainment, tobacco use, treatment adherence, and residential status.

Model assumptions were checked using residual plots, variance inflation factors (to assess multicollinearity), and influence diagnostics. A two-sided p-value <0.05 was considered statistically significant for all analyses.

Handling of Missing Data

Complete data were available for 308 participants (96.3%), with minimal missing values for laboratory parameters (n=4), clinical assessments (n=3), and radiographic scores (n=5). Given the low proportion of missing data (<5%), complete case analysis was performed for primary outcomes, with sensitivity analyses using multiple imputation by chained equations (10 imputations) to confirm robustness of findings.

RESULTS

Participant Characteristics

A total of 352 patients were screened for eligibility, of whom 32 were excluded: 14 due to overlap with other autoimmune diseases, 8 due to active infection, 6 due to recent change in disease-modifying therapy, and 4 due to inability to provide informed consent. The final study population comprised 320 patients, with 160 in the rural cohort and 160 in the urban cohort. Table 1 presents the baseline demographic and clinical characteristics stratified by residential status.

The study population was predominantly female (82.5%), reflecting the well-established gender disparity in RA prevalence. Rural and urban cohorts were comparable in age (rural: 44.7±12.3 years; urban: 46.2±13.1 years; p=0.29) and gender distribution (rural female: 82.5%; urban female: 82.5%; p=1.00). However, significant differences emerged in socioeconomic and educational parameters. Rural patients had lower educational attainment, with 48.1% having no formal education compared to 26.9% of urban patients (p<0.001). Monthly household income was significantly lower in the rural cohort (median: 18,000 PKR [IQR: 12,000-25,000] vs. 32,000 PKR [IQR: 22,000-45,000]; p<0.001). Occupational patterns differed markedly, with agricultural occupations predominating in rural areas (58.1% vs. 6.3%; p<0.001) while service sector (37.5% vs. 10.6%) and industrial (18.8% vs. 6.9%) occupations were more common in urban areas.

Tobacco use was more prevalent among rural residents, with 18.8% current smokers compared to 12.5% in urban areas (p=0.04). Family history of RA was similar between groups (rural: 15.0%; urban: 13.1%; p=0.63). Notably, treatment adherence measured by the Compliance Questionnaire for Rheumatology was significantly lower in the rural cohort (71.4±15.2% vs. 82.7±12.8%; p<0.001), suggesting that medication adherence barriers may contribute to differential outcomes. Disease duration was marginally longer in rural patients (median 5.0 vs. 4.0 years), approaching but not reaching statistical significance (p=0.08).

Serological Profiles

Table 2 presents the serological characteristics of the study population. Marked differences were observed between rural and urban patients across all serological parameters. RF positivity was significantly higher in the rural cohort (91.3% vs. 78.1%; p=0.002), with a corresponding odds ratio of 2.94 (95% CI: 1.46-5.92) for RF positivity associated with rural residence. Similarly, ACPA positivity was more prevalent among rural patients (88.8% vs. 74.4%; p=0.001), yielding an odds ratio of 2.70 (95% CI: 1.47-4.97). Double seropositivity (RF+/ACPA+) was observed in 82.5% of rural patients compared to 63.8% of urban patients (p<0.001).

Beyond positivity rates, quantitative titers revealed even more pronounced disparities. Mean RF titer in the rural cohort was 185.4±98.2 IU/mL compared to 112.7±76.5 IU/mL in the urban cohort (p<0.001), representing a 64.5% higher mean value. Restricting analysis to RF-positive patients only, the difference persisted (198.6±94.7 vs. 135.8±72.3 IU/mL; p<0.001). Similarly, mean ACPA titers were 78.6% higher in rural patients (168.3±87.6 vs. 94.2±69.8 U/mL; p<0.001), with comparable differences among ACPA-positive individuals (182.5±82.4 vs. 118.6±64.2 U/mL; p<0.001). Double seronegativity was significantly more common in the urban cohort (11.3% vs. 2.5%; p=0.003), suggesting that urban patients may present with a milder serological phenotype.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants by Residential Status

Characteristic	Rural Cohort (n=160)	Urban Cohort (n=160)	p-value
Age (years), mean ± SD	44.7 ± 12.3	46.2 ± 13.1	0.29
Female gender, n (%)	132 (82.5)	132 (82.5)	1.00
Disease duration (years), median (IQR)	5.0 (2.0-9.0)	4.0 (2.0-8.0)	0.08
Educational attainment, n (%)			<0.001
- No formal education	77 (48.1)	43 (26.9)	
- Primary	42 (26.3)	38 (23.8)	
- Secondary	28 (17.5)	45 (28.1)	
- Tertiary	13 (8.1)	34 (21.3)	
Monthly income (PKR), median (IQR)	18,000 (12,000-25,000)	32,000 (22,000-45,000)	<0.001
Occupation, n (%)			<0.001
- Agricultural	93 (58.1)	10 (6.3)	
- Industrial	11 (6.9)	30 (18.8)	
- Service	17 (10.6)	60 (37.5)	
- Domestic	31 (19.4)	42 (26.3)	
- Retired/unemployed	8 (5.0)	18 (11.3)	
Tobacco use, n (%)			0.04
- Never	102 (63.8)	118 (73.8)	
- Former	28 (17.5)	22 (13.8)	
- Current	30 (18.8)	20 (12.5)	
Family history of RA, n (%)	24 (15.0)	21 (13.1)	0.63
Treatment adherence (CQR score), %	71.4 ± 15.2	82.7 ± 12.8	<0.001

Table 2: Serological Profiles of Rheumatoid Arthritis Patients by Residential Status

Parameter	Rural Cohort (n=160)	Urban Cohort (n=160)	p-value
RF positive, n (%)	146 (91.3)	125 (78.1)	0.002
RF titer (IU/mL), mean ± SD	185.4 ± 98.2	112.7 ± 76.5	<0.001
RF titer among positive, mean ± SD	198.6 ± 94.7	135.8 ± 72.3	<0.001
ACPA positive, n (%)	142 (88.8)	119 (74.4)	0.001
ACPA titer (U/mL), mean ± SD	168.3 ± 87.6	94.2 ± 69.8	<0.001
ACPA titer among positive, mean ± SD	182.5 ± 82.4	118.6 ± 64.2	<0.001
Double positive (RF+/ACPA+), n (%)	132 (82.5)	102 (63.8)	<0.001
Double negative (RF-/ACPA-), n (%)	4 (2.5)	18 (11.3)	0.003

Figure 1: Distribution of Rheumatoid Factor Titers in Rural and Urban RA Patients

Titer Range (IU/mL)	Rural Cohort (n=160)	Urban Cohort (n=160)
<20 (negative)	14 (8.8%)	35 (21.9%)
20-99	28 (17.5%)	52 (32.5%)
100-199	45 (28.1%)	41 (25.6%)
200-299	42 (26.3%)	22 (13.8%)
≥300	31 (19.4%)	10 (6.3%)

Figure 2: Distribution of Anti-Citrullinated Protein Antibody Titers in Rural and Urban RA Patients

Titer Range (U/mL)	Rural Cohort (n=160)	Urban Cohort (n=160)
<10 (negative)	18 (11.3%)	41 (25.6%)
10-49	22 (13.8%)	38 (23.8%)
50-99	30 (18.8%)	35 (21.9%)
100-199	42 (26.3%)	28 (17.5%)
200-299	32 (20.0%)	12 (7.5%)

Titer Range (U/mL)	Rural Cohort (n=160)	Urban Cohort (n=160)
≥300	16 (10.0%)	6 (3.8%)

Figures 1 and 2 illustrate the distribution of RF and ACPA titers across the two populations, revealing a consistent shift toward higher titer categories among rural patients. For RF, 45.7% of rural patients had titers ≥200 IU/mL compared to only 20.1% of urban patients. For ACPA, 56.3% of rural patients had titers ≥100 U/mL versus 28.8% of urban patients, demonstrating a substantially heavier autoantibody burden in the rural population.

Clinical Disease Activity and Functional Status

Table 3 summarizes clinical disease activity, functional disability, and radiographic damage across the two cohorts. Rural patients exhibited significantly higher disease activity across all measures. Mean DAS28 score was 5.8±1.2 in the rural cohort compared to 4.6±1.1 in the urban cohort (p<0.001), representing a difference of 1.2 points, which exceeds the minimum clinically important difference of 0.6. When categorized by disease activity level, high disease activity (DAS28 >5.1) was observed in 63.1% of rural patients versus 31.9% of urban patients (p<0.001), while remission (DAS28 <2.6) was rare in both groups but significantly less common in the rural cohort (1.3% vs. 6.3%; p=0.02).

Table 3: Clinical Disease Activity, Functional Disability, and Radiographic Damage by Residential Status

Parameter	Rural Cohort (n=160)	Urban Cohort (n=160)	p-value
DAS28 score, mean ± SD	5.8 ± 1.2	4.6 ± 1.1	<0.001
DAS28 category, n (%)			<0.001
- Remission (<2.6)	2 (1.3)	10 (6.3)	
- Low (2.6-3.2)	8 (5.0)	22 (13.8)	
- Moderate (3.3-5.1)	49 (30.6)	77 (48.1)	
- High (>5.1)	101 (63.1)	51 (31.9)	
Tender joint count (28 joints), mean ± SD	11.4 ± 5.8	7.2 ± 4.6	<0.001
Swollen joint count (28 joints), mean ± SD	8.7 ± 4.9	5.1 ± 3.8	<0.001
ESR (mm/hour), mean ± SD	48.6 ± 18.4	34.2 ± 15.7	<0.001
Patient global VAS (0-100 mm), mean ± SD	64.8 ± 18.2	48.3 ± 16.5	<0.001
HAQ-DI score, mean ± SD	1.8 ± 0.6	1.2 ± 0.5	<0.001
Larsen Score (hand and foot), mean ± SD	34.7 ± 15.3	21.4 ± 12.8	<0.001

Components of the DAS28 were uniformly worse in the rural population. Tender joint counts (11.4±5.8 vs. 7.2±4.6; p<0.001), swollen joint counts (8.7±4.9 vs. 5.1±3.8; p<0.001), ESR (48.6±18.4 vs. 34.2±15.7 mm/hour; p<0.001), and patient global assessment (64.8±18.2 vs. 48.3±16.5 mm; p<0.001) were all significantly elevated in rural patients. These differences were clinically meaningful, with rural patients averaging approximately 4 additional tender joints and 3.5 additional swollen joints compared to urban patients.

Functional disability, measured by HAQ-DI, was substantially greater in the rural cohort (1.8±0.6 vs. 1.2±0.5;

p<0.001). A HAQ-DI score of 1.8 corresponds to moderate-to-severe disability, indicating difficulty performing most activities of daily living, while 1.2 represents mild-to-moderate disability. Radiographic damage, assessed by Larsen Score, was 62% higher in rural patients (34.7±15.3 vs. 21.4±12.8; p<0.001), indicating more advanced structural joint damage despite comparable disease duration. This finding suggests that rural patients may experience more aggressive disease progression or present at later stages with established damage.

Correlations Between Serological Markers and Clinical Indices

Table 4 presents the correlation coefficients between serological markers and clinical disease indices, stratified by residential status. In both cohorts, RF and ACPA titers showed moderate positive correlations with DAS28, HAQ-DI, and Larsen Score, consistent with the established relationship between autoantibody positivity and disease severity. However, the strength of these correlations differed between groups.

Table 4: Correlation Between Serological Markers and Clinical Indices by Residential Status

Correlation	Rural Cohort (r)	Urban Cohort (r)	p-value for difference
RF titer vs. DAS28	0.52*	0.38*	0.04
RF titer vs. HAQ-DI	0.48*	0.32*	0.03
RF titer vs. Larsen Score	0.56*	0.41*	0.02
ACPA titer vs. DAS28	0.58*	0.44*	0.03
ACPA titer vs. HAQ-DI	0.51*	0.35*	0.02
ACPA titer vs. Larsen Score	0.61*	0.46*	0.01

*All correlations significant at p<0.01

In the rural cohort, RF titer correlated more strongly with DAS28 (r=0.52 vs. 0.38; p=0.04), HAQ-DI (r=0.48 vs. 0.32; p=0.03), and Larsen Score (r=0.56 vs. 0.41; p=0.02) compared to the urban cohort. Similarly, ACPA titer demonstrated stronger correlations with all three clinical indices in rural patients, with the difference most pronounced for Larsen Score (r=0.61 vs. 0.46; p=0.01). These findings suggest that autoantibody titers may be more predictive of clinical severity in rural populations, potentially reflecting differential pathogenic mechanisms or the absence of confounding protective factors present in urban environments.

Multivariate Analysis

Multivariate linear regression was performed to determine whether rural residence independently predicted DAS28 scores after adjusting for potential confounders. The final model included age, gender, disease duration, educational attainment, tobacco use, treatment adherence, and residential status. Rural residence emerged as a significant independent predictor of higher DAS28 scores (β=0.42, 95% CI: 0.28-0.56; p<0.001), indicating that rural patients had DAS28 scores approximately 0.4 points higher than urban patients after accounting for other factors. Additional independent predictors included longer disease duration (β=0.18 per 5 years; p=0.01), current tobacco use (β=0.32; p=0.008), and lower treatment adherence (β=-0.24 per 10% increase; p=0.02). The model explained 38% of the variance in DAS28 scores (adjusted R^2=0.38), suggesting that while residential status contributes significantly to disease severity, substantial unexplained variation remains.

DISCUSSION

This cross-sectional comparative study provides compelling evidence that rural residence is associated with significantly more severe Rheumatoid Arthritis compared to urban residence in the Punjab province of Pakistan. Rural patients exhibited higher serological positivity rates, markedly elevated autoantibody titers, greater clinical disease activity, more functional disability, and advanced radiographic damage compared to their urban counterparts. These disparities persisted after multivariate adjustment for potential confounders, suggesting that geographic demography independently influences autoimmune disease expression and severity. To our knowledge, this represents the first comprehensive comparison of serological profiles and clinical indices between rural and urban RA populations in South Asia, addressing an important gap in the literature on geographic determinants of autoimmune disease outcomes.

The finding that rural patients demonstrate

substantially higher RF and ACPA titers is particularly noteworthy. RF positivity of 91.3% in the rural cohort exceeds the typical range of 70-80% reported in most RA populations , while the mean titer of 185.4 IU/mL represents a heavy autoantibody burden. Similarly, ACPA positivity of 88.8% and mean titer of 168.3 U/mL in rural patients are among the highest reported in the literature. These serological differences are not merely statistical artifacts but carry important clinical implications, as higher autoantibody titers are consistently associated with more aggressive disease course, greater radiographic progression, and poorer long-term outcomes . The higher prevalence of double seropositivity (82.5% in rural vs. 63.8% in urban patients) further reinforces the conclusion that rural patients exhibit a more severe autoimmune phenotype.

Several mechanisms may explain the observed serological and clinical disparities. First, differential environmental exposures between rural and urban settings likely play a crucial role. Rural residents in Punjab are predominantly engaged in agriculture, with consequent exposure to pesticides, fertilizers, silica-containing dusts, and animal-derived antigens. The recent meta-analysis by Liu and colleagues demonstrating that occupational inhalants including fertilizers (RR 1.49), pesticides (RR 1.32), animal dust (RR 1.20), and silica (RR 1.36) significantly increase RA risk provides a plausible biological basis for our findings . Beyond increasing disease risk, these exposures may continue to drive immune activation and autoantibody production after disease onset, resulting in higher titers and more severe clinical manifestations. The ongoing nature of occupational exposures in rural settings, where individuals typically continue agricultural work throughout their lives, may perpetuate the cycle of inflammation and autoimmunity in ways that intermittent urban exposures do not.

Air quality differences represent another potential explanatory mechanism. Urban areas in Punjab, including Faisalabad, experience substantial air pollution from vehicular traffic and industrial emissions, yet rural populations may face different but equally hazardous exposures. Biomass fuel use for cooking and heating remains common in rural Punjabi households, producing indoor air pollution with high concentrations of particulate matter and volatile organic compounds. Agricultural burning practices further contribute to seasonal air quality deterioration in rural areas. Recent research by Alsaber and colleagues demonstrating that nitrogen dioxide and ozone significantly influence RA disease activity, with lag effects of 2-3 months, suggests that air pollution may modulate disease activity through systemic inflammatory pathways . The differential exposure profiles between rural and urban environments, combined with potential interactions with occupational factors, could contribute to the observed severity gradient.

Healthcare access barriers almost certainly contribute to the disparities observed. Rural patients in our cohort had significantly lower educational attainment, reduced household income, and poorer treatment adherence compared to urban patients. The concentration of rheumatology services in major urban centers means that rural patients must travel substantial distances for specialist consultations, incurring direct transportation costs and indirect costs from time away from work. These barriers likely result in delayed diagnosis, inconsistent follow-up, and suboptimal medication adherence. The median diagnostic delay of 17.8 months reported in a recent Pakistani cohort may be even more pronounced in rural populations with limited access to primary care providers capable of recognizing early RA symptoms. The lower treatment adherence we observed in rural patients (71.4% vs. 82.7%) is particularly concerning, as poor adherence to disease-modifying antirheumatic drugs is associated with inadequate disease control, accelerated radiographic progression, and worse functional outcomes.

The stronger correlations between autoantibody titers and clinical indices observed in rural patients warrant careful consideration. One interpretation is that autoantibodies in rural patients may be more pathogenic, potentially due to differential glycosylation patterns, epitope spreading, or other qualitative differences not captured by quantitative ELISA. Alternatively, urban patients may possess protective factors that attenuate the relationship between autoantibodies and clinical disease expression. These protective factors could include dietary differences, with urban populations having greater access to anti-inflammatory foods, or lower exposure to adjuvant-like environmental triggers that potentiate autoantibody pathogenicity. The finding that double seronegativity was more common in urban patients (11.3% vs. 2.5%) suggests that urban environments may support the development of milder, serologically atypical forms of RA that would not meet traditional classification criteria in some cases.

The socioeconomic gradient observed in our study, with rural patients having lower education and income despite comparable age and gender distribution, reflects broader patterns of inequality in Pakistan and may contribute to disease severity through multiple pathways. Lower educational attainment is associated with reduced health literacy, which may impair understanding of disease chronicity, medication importance, and the need for regular monitoring . Financial constraints may force

patients to prioritize competing household expenditures over medication purchases, particularly given that direct monthly treatment costs of USD 16-100 represent a substantial burden relative to median rural incomes of approximately 18,000 PKR (USD 65) monthly . These economic realities may explain the lower treatment adherence observed in rural patients and likely contribute to the severity disparities documented.

The occupational differences between cohorts deserve particular attention. Agricultural work, predominant in the rural cohort, involves not only chemical exposures but also physical demands that may exacerbate joint symptoms and accelerate functional decline. Repetitive manual labor, heavy lifting, and prolonged standing or kneeling place mechanical stress on already inflamed joints, potentially worsening pain and accelerating damage. The inability to modify work activities or access workplace accommodations may force rural patients to continue physically demanding labor despite active disease, perpetuating a cycle of inflammation and disability. In contrast, urban occupational patterns, while presenting their own hazards, may offer greater opportunities for activity modification and less physically demanding work options.

Our findings align with and extend previous research on urban-rural disparities in rheumatic diseases. A recent study from Lahore, Pakistan, using the COPCORD model, found higher prevalence rates for osteoarthritis, soft tissue rheumatism, and rheumatoid arthritis in rural participants compared to urban counterparts, with pain reporting significantly higher in the rural sample . While that study focused on prevalence rather than severity, the consistency of findings across different Pakistani populations strengthens confidence in the generalizability of urban-rural disparities. Similarly, research from India's Lucknow district reported higher prevalence of rheumatic musculoskeletal symptoms in rural areas , suggesting that the pattern may extend across South Asia.

International comparisons provide additional context. Studies from Poland examining RA epidemiology found complex urban-rural patterns, with some reports suggesting higher morbidity in rural areas and others finding no significant differences . A Canadian study of patients with osteoarthritis revealed that rural residents had poorer realized spatial access to general practitioners, orthopedic surgeons, and physiotherapists , consistent with the healthcare access barriers we hypothesize contribute to our findings. The systematic review by Pianarosa and colleagues of global rural and remote patients with RA concluded that these populations consistently experience disparities in care access and outcomes , reinforcing the international relevance of our observations.

The serological findings in our study contribute novel information to the literature on geographic determinants of autoantibody profiles. While previous research has examined autoantibody prevalence across populations, few studies have quantitatively compared titers between rural and urban residents within the same geographic region and ethnic group. A study from Henan, China, found that rural populations had higher RA prevalence than urban populations (0.93% vs. 0.48%) but did not report comparative titer data . Our demonstration that not only prevalence but also quantitative autoantibody burden differs by residential status suggests that environmental factors influence both the likelihood of seropositivity and the magnitude of the autoimmune response.

The findings of this study have several important implications for clinical practice and health policy in Pakistan and similar settings. First, they highlight the need for targeted outreach to rural RA populations, who appear to bear a disproportionate burden of severe disease. Rheumatology services should be decentralized through satellite clinics, telemedicine programs, and regular outreach visits to district hospitals, reducing travel burdens and improving access to specialist care. The development of tele-rheumatology programs, which have shown promise in other settings for managing rural patients with inflammatory arthritis , could help bridge the access gap while awaiting expansion of physical infrastructure.

Second, interventions to improve treatment adherence among rural patients are urgently needed. The lower adherence we observed likely reflects multiple barriers including financial constraints, limited health literacy, and cultural factors. Patient education programs delivered in local languages by community health workers, combined with financial support mechanisms for medication costs, could address these barriers. Given that methotrexate remains the most commonly used and affordable disease-modifying antirheumatic drug in Pakistan , ensuring consistent adherence to this medication should be a priority.

Third, the environmental and occupational exposures identified in our study suggest opportunities for primary and secondary prevention. Raising awareness among agricultural workers about the potential risks of pesticide and fertilizer exposure, promoting use of protective equipment, and exploring modifications to agricultural practices could reduce exposure to potential triggers. For patients with established disease, vocational rehabilitation programs and workplace accommodations may help reduce disease

progression and maintain functional capacity. The association between tobacco use and higher disease activity reinforces the importance of smoking cessation programs, which should be integrated into rheumatology care.

Fourth, the socioeconomic gradient we observed underscores the need for broader social and economic interventions to address the root causes of health disparities. Educational attainment, income support, and poverty reduction are not merely social goals but have direct implications for health outcomes in chronic diseases like RA. Integrating rheumatology care with broader development programs could help address the multiple determinants of disease severity in vulnerable populations.

This study possesses several strengths that enhance confidence in its findings. The sample size was adequately powered to detect clinically meaningful differences between groups. The use of standardized, validated instruments for disease activity, functional status, and radiographic damage ensures comparability with international literature. Laboratory assays were performed in duplicate with rigorous quality control, and laboratory personnel were blinded to residential status, minimizing information bias. The comprehensive assessment of potential confounders allowed multivariate adjustment to isolate the independent effect of rural residence. The inclusion of both serological and clinical outcomes provides a multidimensional view of disease severity.

Several limitations must be acknowledged when interpreting our results. The cross-sectional design precludes determination of causality or temporal relationships between rural residence and disease severity. While we adjusted for measured confounders, residual confounding by unmeasured factors such as genetic polymorphisms, dietary patterns, or specific environmental exposures cannot be excluded. The single-center design, while ensuring consistent assessment methods, may limit generalizability to other regions of Pakistan with different agricultural practices, climate conditions, or healthcare infrastructure. Selection bias is possible if rural patients seeking care at a tertiary urban center differ systematically from the broader rural RA population, though the direction of such bias is difficult to predict.

The classification of residential status based on 10-year history, while standard in geographic health research, may not capture the full complexity of population mobility. Some individuals classified as rural may have previously lived in urban areas, and vice versa, potentially diluting observed differences. However, such misclassification would bias results toward the null, suggesting that our findings may underestimate true disparities. The lack of detailed environmental exposure assessment limits our ability to identify specific factors driving the observed differences. Future studies incorporating personal air monitoring, occupational exposure histories, and biomarker measurements of specific pollutants or pesticides would help elucidate mechanisms.

The absence of genetic data prevents examination of gene-environment interactions that might modify susceptibility to environmental triggers. The shared epitope and other genetic risk factors for RA vary across populations, and if rural and urban populations differ in genetic susceptibility profiles, this could confound our findings. However, the relative ethnic homogeneity of Punjab province reduces but does not eliminate this concern. Finally, the focus on a single tertiary center means that patients with very mild disease who never seek specialist care may be underrepresented, potentially overestimating severity in both groups but not necessarily biasing comparisons between them.

The findings of this study generate multiple hypotheses warranting further investigation. Longitudinal cohort studies following rural and urban RA patients prospectively from diagnosis would clarify whether disparities arise from differences at disease onset, differential progression rates, or cumulative effects of environmental exposures over time. Such studies could identify critical windows for intervention and determine whether modifying environmental or occupational exposures can alter disease trajectories.

Detailed exposure assessment studies are needed to identify specific environmental factors driving the observed disparities. Personal monitoring of air pollutants, analysis of pesticide residues in biological samples, and comprehensive occupational histories could pinpoint modifiable risk factors. Studies examining gene-environment interactions would help identify genetically susceptible subgroups who might benefit most from targeted interventions. The stronger correlations between autoantibodies and clinical indices in rural patients warrant investigation into whether qualitative differences in autoantibodies (glycosylation patterns, epitope specificity) contribute to enhanced pathogenicity.

Intervention studies evaluating the effectiveness of telemedicine programs, community health worker interventions, or financial support mechanisms for rural RA patients would provide evidence to guide health policy. Economic evaluations assessing the cost-effectiveness of decentralized rheumatology services could inform resource allocation decisions in resource-constrained settings. Finally, comparative

studies across different regions of Pakistan and South Asia would help determine the generalizability of our findings and identify region-specific factors requiring tailored interventions.

Conclusion

This study demonstrates that Rheumatoid Arthritis patients residing in rural Punjab, Pakistan, exhibit significantly more severe disease across multiple domains compared to their urban counterparts. Rural patients have higher rates of seropositivity, markedly elevated autoantibody titers, greater clinical disease activity, more functional disability, and advanced radiographic damage. These disparities persist after adjusting for demographic factors, disease duration, and treatment adherence, suggesting that rural residence independently predicts autoimmune severity. The findings highlight the urgent need for targeted interventions to address the disproportionate burden of severe RA in rural populations, including decentralized rheumatology services, telemedicine programs, adherence support, and occupational health interventions. Future research should focus on identifying specific environmental and occupational factors driving these disparities and evaluating interventions to mitigate them. Addressing geographic inequities in RA outcomes is essential for achieving health equity and reducing the overall burden of autoimmune disease in Pakistan and similar settings worldwide.

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