RESEARCH ARTICLE

Risk factors of idiopathic pulmonary fibrosis in Pakistani population: A matched case-control study

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Abstract

Objective: To evaluate the factors associated with idiopathic pulmonary fibrosis risk.

Method: The case-control study was conducted from January 5, 2017, to September 4, 2018, at the private-sector Aga Khan University Hospital and the public-sector Jinnah Postgraduate Medical Centre, two large tertiary care centres in Karachi, and comprised adult patients of either gender with diagnosed idiopathic pulmonary fibrosis, as defined by the Indian Chest Registry. Subjects without idiopathic pulmonary fibrosis but registered with the department of pulmonology of the two hospitals were enrolled as controls. Data was collected using a structured questionnaire, and anthropometric measurements were noted for each subject. Gastroesophageal reflux disease was assessed using GerdQ. This was followed by serological evaluations and spirometry. Data was analysed using SPSS 21.

Results: Of the 459 subjects, 154(33.6%) were cases and 305(66.4%) were controls. Among the cases, 81(52.6%) were females and 73(47.4%) were males with mean age 66.1±10.9 years. Among the controls, 162(53.1%) were females and 143(46.9%) were males with mean age 64.6±11.1 years (p>0.05.) The most common ethnicity was Urdu-speaking; 89(58%) among the cases and 150(49%) among the controls (p<0.05). Ethnicity, number of persons in the household per room, and type of house were significantly associated with the risk of developing idiopathic pulmonary fibrosis (p<0.05).

Conclusion: Ethnicity, type of house and the number of persons in a household per room were found to be the significant risk factors for idiopathic pulmonary fibrosis IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a chronic, progressive, fibrosing interstitial pneumonia of unknown aetiology. IPF is a rare disease with a median survival of only 3-5 years following diagnosis and has no definitive treatment except for a lung transplant.[1] The risk factors leading to the onset of the disease are not completely known.

Nonetheless, research has reported an association of IPF with exposure to tobacco smoke,[2] metal/wood/stone dust, and dusty environment, such as farms, livestock, hairdressing, exposure to birds/animals, vegetable dust, earthen floors and family history.[3-5] A review also reported strong relationship between diabetes mellitus (DM), gastro-oesophageal reflux disease (GERD), hepatitis C virus (HCV) infection, viral infection and IPF.[6] Weak association with dietary fat and meat intake has also been reported.[7]

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In the last two decades, a number of studies have explored the association of mutations in various genes with IPF.[8]

Moreover, racial, ethnic and geographical differences in the incidence and mortality of IPF have been observed.[9] A study reported that IPF occurs at an early age among South Asian population[10] but not many studies are available in this regard. It is therefore important to investigate the incidence, patterns and risk factors of interstitial lung diseases in the South Asian population. The endemic presence of tuberculosis (TB) in South Asia makes the IPF diagnosis difficult as it mimics the symptoms.[11]

Information regarding IPF risk factors in Pakistan is scarce. Data from Karachi indicates that IPF is the most common interstitial lung disease (ILD) in the metropolitan population.[11] Another study from Karachi has reported the factors that increased the odds of IPF-related mortality[12] The current study was planned to investigate the risk factors of IPF in adult, urban population.

Patients and Methods

The case-control study was conducted from January 5, 2017, to September 4, 2018, at the private-sector Aga Khan University Hospital (AKUH) and the public-sector Jinnah Postgraduate Medical Centre (JPMC) in Karachi, which is

the largest city and economic hub of Pakistan with a multi-ethnic population of more than 25 million, with representation of population from across the country. The two hospitals receive patients from all over Pakistan but most of the patients seeking care happen to be based in Karachi. Both hospitals provide tertiary care with well-established pulmonology units delivering outpatient, inpatient and 24-hour emergency services. They also offer services in all major medical specialties and subspecialties. The AKUH is a 704-bed tertiary care hospital, with a 70-bed dedicated pulmonology unit. On an average 1,500 patients visit outpatient clinics per month with approximately 8-10 patients having IPF. The Department of Chest Medicine at the JPMC comprises 110 beds. Approximately 3,300 patients are seen in the pulmonology outpatient department (OPD) per month, with 5-8 patients having IPF.

After approval from the ethics review committee of AKUH and permission from the JPMC administration, the sample size was calculated at 5% level of significance and power 80%, assuming an exposure of various risk factors among controls as 15% and exposure among cases as 25% and odds ratio (OR) of 1.9.[13,14]

All adults of either gender who lived within the defined boundaries of Karachi and were either visiting the outpatient pulmonology clinics or admitted at either of the two study hospitals were approached. The individuals were assessed for IPF after obtaining informed consent from each of them. Eligible cases who could not be included because they were too ill or declined to take part were documented. Patients not sufficiently well to be interviewed were not included, but their age, gender and the reason for refusal or exclusion, if any, were noted. In order to avoid any inconvenience to the study participants, they were approached when they were relatively stable and only with permission from the attending clinicians.

Cases were defined using the diagnostic criteria outlined by the Indian Chest Registry[1] as it is a practical way of diagnosing IPF in a low-income setting. Those included were patients who were diagnosed with IPF by trained pulmonologists working in respective units, and met the 4-point criteria: adult patients with history and physical examination suggestive of IPF; restrictive pattern on pulmonary function testing, with normal ratio between forced expiratory volume in the first one second (FEV1) and the forced vital capacity (FVC) of the lungs, reduced FVC, low total lung capacity (TLC), and decreased diffusing capacity of the lungs for carbon monoxide (DLCO); usual interstitial pneumonia (UIP) or probable UIP pattern on high-resolution computed tomography (HRCT) of the chest, defined as basal, subpleural, peripheral, reticular infiltrates associated with or without traction bronchiectasis and honeycombing; and exclusion of other known causes of UIP pattern on HRCT, like asbestosis, connective tissue disease-associated ILD and drug-induced lung toxicity, by clinical evaluation. Exclusion was done by serological evaluation for rheumatoid factor, anti-cyclic citrullinated peptide and anti-nuclear antibody titer and pattern even in the absence of signs and symptoms of connective tissue disease (CTD).

For each case that was recruited, a prescribed algorithm was used to select two controls of the same gender within a 5-year age band within inpatient or outpatient setting of the pulmonary ward of the same hospital for any reason other than IPF. The controls were chosen that came on the same day as the case, and if none was available, the recruitment was done within 72 hours of the case recruitment. If more than the required number of eligible controls were available on a given day, the one whose age matched that of the case most closely was chosen. Informed consent was obtained from the controls as well, and those. who declined to participate were replaced.

At the AKUH, after recruiting the case from a pulmonary clinic, the controls were recruited consecutively from the same clinic. JPMC has a separate IPF clinic, and after the selection of the cases, the controls were consecutively enrolled from other pulmonary clinics. For the cases recruited from the pulmonary wards (in-patients), the respective controls were also recruited from the wards.

Data was collected by trained interviewers through one-on-one interviews that were conducted in a separate room allocated for the purpose. A structured questionnaire was used, which was developed after literature review.[13,15-17] Information was collected about socio-demographic characteristics, potential occupational, environmental and behavioural exposures, recent and past medical history, recent medications, family history of IPF, passive smoking, use of chewable tobacco, lifetime use of different fuels for cooking and heating, and type of house. GERD was assessed using the 6-item GERD Questionnaire (GerdQ).[18] The questionnaire was translated into the local language Urdu. Furthermore, the patient's medical record was accessed in order to extract information on the diagnosis. Subsequently, measurements of height, weight, waist and hip were made using a height meter, digital scales and a tape measure. Blood was then obtained from each case for serological evaluation for rheumatoid factor, anti-cyclic citrullinated peptide and anti-nuclear antibody titer and pattern. All cases were later subjected to spirometry for severity assessment of IPF.

Data was coded and entered into Epi Data version 3.0. Data was analysed using SPSS 21. Normality of continuous

variables was assessed using Kolmogorov-Smirnov test and Shapiro-Wilk test. Socio-demographic and other risk factors were compared between the cases and the controls using chi-square test for categorical variables, and independent sample t-test for continuous variables. Fisher Exact test was used when the expected count was <5 in more than 20% of the cells. Mann-Whitney U test was used for skewed continuous variables. Univariate and multivariate conditional logistic regression was used to assess the association of IPF with socio-demographic, environmental and behavioural risk factors and comorbidities. All factors with $p<0.1$ in univariate analysis were included in the multivariate model. Crude and adjusted matched ORs along with associated 95% confidence intervals (CI) were calculated. P<0.05 was considered significant.

Results

Of the 459 subjects, 154(33.6%) were cases and 305(66.4%) were controls. Among the cases, 81(52.6%) were females and 73(47.4%) were males with mean age 66.1±10.9 years. Among the controls, 162(53.1%) were females and 143(46.9%) were males with mean age 64.6±11.1 years ($p>0.05$.) The most common ethnicity was Urdu-speaking; 89(58%) among the cases and 150(49%) among the controls ($p<0.05$). There were no significant differences

Table-1: Socio-demographic characteristics of cases and controls.

Characteristic	Cases [% (n)] n=154	Control [% (n)] n=305	*p*-value
Mean Age (years)	66.1±10.9	64.6±11.1	0.155
Gender			
Female	52.6 (81)	53.1 (162)	0.916
Male	47.4 (73)	46.9 (143)	
Ethnicity			
Sindhi	1.9 (3)	12.1 (37)	0.004
Punjabi	14.3 (22)	10.2 (31)	
Pakhtoon	6.5 (10)	7.9 (24)	
Urdu-speaking	57.8 (89)	49.2 (150)	
Other	18.8 (29)	18.7 (57)	
Missing	0.6 (1)	2.0 (6)	
Income per month(PKR)			
≤25000	44.8 (69)	48.2 (147)	0.214
> 25000	51.3 (79)	44.6 (136)	
Missing	3.9 (6)	7.2 (22)	
Education			
Illiterate	43.5 (67)	37.4 (114)	0.642
Up to Secondary	33.8 (52)	36.4 (111)	
Higher than Secondary	20.8 (32)	23.9 (73)	
Missing	1.9 (3)	2.3 (7)	
House ownership			
Rented	21.4 (33)	22.0 (67)	0.746
Owned	76.0 (117)	74.1 (226)	
Missing	2.6 (4)	3.9 (12)	
Socio-economic status (based on household items)			
Low (1-2 items)	61.0 (94)	62.6 (191)	0.741
High (3-4 item)	39.0 (60)	37.4 (114)	

Table-2: Environmental and behavioural risk factors and comorbidities in cases and controls.

Characteristic	Cases [% (n)] n=154	Control [% (n)] n=305	p-value
Environmental Risk Factor			
Residence (Last five years)			
Urban	98.1 (151)	94.8 (289)	0.249
Rural	1.9 (3)	4.6 (14)	
Missing	0.0 (0)	0.7 (2)	
Type of house (spent major part of life)			
Katcha	9.1 (14)	14.4 (44)	0.024
Apartment	22.7 (35)	12.8 (39)	
Bungalow	13.0 (20)	16.1 (49)	
Pakka	55.2 (85)	55.4 (169)	
Missing	0.0 (0)	1.3 (4)	
House flooring			
Hard floor	68.8 (106)	62.6 (191)	0.481
Earthen	22.7 (35)	26.9 (82)	
Carpeted	6.5 (10)	9.2 (28)	
Missing	1.9 (3)	1.3 (4)	
Number of persons per room			
Mean±SD	1.83±1.41	1.42±1.39	
Median (IQR)	5.0 (3.0 – 7.0)	4.0 (3.0 – 7.0)	<0.001*
Worked in dusty environment			
No	68.8 (106)	70.8 (216)	0.907
Yes	16.2 (25)	15.1 (46)	
Missing	14.9 (23)	14.1 (43)	
Birds in home			
No	78.6 (121)	81.3 (248)	0.523
Yes	16.9 (26)	16.1 (49)	
Missing	4.5 (7)	2.6 (8)	
Behavioural Risk Factors			
Ever smoked cigarettes			
No	79.2 (122)	70.2 (214)	0.044
Yes	20.8 (32)	29.5 (90)	
Missing	0.0 (0)	0.3 (1)	
Ever used chewable tobacco			
No	89.0 (137)	87.9 (268)	0.826
Yes	11.0 (17)	10.2 (31)	
Missing	0.0 (0)	2.0 (6)	
Second hand tobacco smoke			
No	92.9 (143)	83.9 (256)	0.014
Yes	7.1 (11)	13.4 (41)	
Missing	0.0 (0)	2.6 (8)	
Comorbidities			
Hypertension			
No	58.4 (90)	50.2 (153)	0.093
Yes	41.6 (64)	49.8 (152)	
Diabetes mellitus			
No	63.0 (97)	73.4 (224)	0.021
Yes	37.0 (57)	26.6 (81)	
Tuberculosis			
No	93.5 (144)	91.1 (278)	0.381
Yes	6.5 (10)	8.9 (27)	
Ischaemic heart disease (IHD)			
No	85.1 (131)	87.5 (267)	0.461
Yes	14.9 (23)	12.5 (38)	

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Table-2: *Continued from previous page.*

Characteristic	Cases [% (n)] n=154	Control [% (n)] n=305	*p*-value
Gastroesophageal reflux disease (GERD)			
No	72.7 (112)	74.1 (226)	0.753
Yes	27.3 (42)	25.9 (79)	
Metabolic risk factor			
None (Both BMI and WHR are normal)	12.3 (19)	10.2 (31)	0.288
At least one of BMI or WHR is abnormal	43.5(67)	41.3 (126)	
Both BMI and WHR is abnormal	42.9 (66)	43.9 (134)	
Missing	1.3 (2)	4.6 (14)	

*Mann-Whitney U test *p*-value; SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, WHR: Waist-hip ratio.

Table-3: Multivariate conditional logistic regression for factors associated with interstitial pulmonary fibrosis (IPF).

Variable	Adjusted mOR (95% Confidence Interval)	*p*-value
Ethnicity		
Sindhi	Reference	
Punjabi	5.67 (1.67 – 19.29)	0.005
Pakhtoon	4.30 (1.18 – 15.74)	0.027
Urdu	5.51 (1.71 – 17.81)	0.004
Others	4.93 (1.47 – 16.50)	0.010
Type of house (spent major part of life)		
Katcha	Reference	
Apartment	1.60 (0.83 – 3.08)	0.158
Bungalow	0.94 (0.46 – 1.95)	0.875
Pakka	1.17 (0.65 – 2.11)	0.603
Number of persons per room*	1.18 (1.06 – 1.31)	0.002
Secondhand tobacco smoke		
No	Reference	
Yes	0.64 (0.34 – 1.19)	0.156
Diabetes mellitus		
No	Reference	
Yes	1.27 (0.90 – 1.78)	0.169

*Continuous variable; mOR: Matched odds ratio.

between the groups with respect to income, education, house ownership and assets (Table 1).

Type of house, number of persons per room in the house, smoking history, exposure to second-hand tobacco, and DM comorbidity were significantly different between the two groups ($p<0.05$). There was no significant difference with respect to hypertension (HTN), tuberculosis (TB), ischaemic heart disease (IHD), GERD, body mass index (BMI), and Waist-hip ratio (WHR) (Table 2).

Ethnicity, number of persons in the household per room, and type of house were significantly associated with the risk of developing IPF in the multivariate model. Compared to Sindhi ethnicity, Punjabi (adjusted matched OR [mOR] 5.67 [95% CI: 1.67-19.29]), Pakhtoon (adjusted mOR 4.30 [95% CI: 1.18-15.74]), Urdu-speaking (adjusted mOR 5.51 [95% CI: 1.71-17.81]) and other ethnicities (adjusted mOR 4.93 [95% CI: 1.47-16.50]) had higher odds of IPF. Similarly, with increase of 1 person in household per room, there was 18% increase in the odds of IPF (adjusted mOR 1.18 [95% CI: 1.06-1.31]) (Table 3).

Discussion

The current study is the first to systematically assess IPF risk factors in Pakistani or South Asian population. Ethnicity, type of house and number of persons in households per room were significant risk factors of IPF. No significant association of IPF was found with smoking, occupation, socio-economic status, DM, HTN and GERD which was reported previously.[3-5,19,20]

Compared to Sindhi ethnicity, people of other ethnicities had higher odds of IPF. Studies have shown that there are regional and ethnic differences in the incidence and mortality of IPF.[21,22] These differences may be due to differences in environmental and occupational exposures which could be associated with a particular ethnicity. It has been postulated that there are occult environmental exposures which may be missed in epidemiological studies due to small sample in a specific strata.[23] This calls for in-depth assessment of environmental risk factors of IPF in population substrata. Smoking has also been reported as a risk factor of IPF.[2] In contrast to the literature, the current study did not find a significant association of smoking with IPF, which is similar to previous studies from Pakistan.[12]This risk factor needs further exploration. Smoking affects the lung functions through various mechanisms. It affects oxidant/anti-oxidant balance, cellular apoptosis, inducing lung fibrosis and altered activities of macrophages.[24] Another risk factor which has been consistently reported in the literature is occupational exposure to various dusts, such as metal and wood[3,4] Similarly, some occupational groups have been identified as being at risk, like farmers, hairdressers, stone cutters, bird fanciers, and livestock workers[3,15,25] The current study did not find a significant association of occupation with IPF. The current sample was more generalised and did not cover specific occupational groups. As such, the sample was not large and diverse enough to analyse occupational risk factors. 'Housewives' represented a major section of the study population, and other common occupational groups were office-based workers, who are either not exposed to any occupational hazard or are less exposed to potential IPF risk factors.

The current study did not find a significant association of IPF with type of house and type of floor, which is in contrast to a study done in Mexico.[16] Similarly, there was no significant association between socio-economic status and IPF in the current study, which is in agreement with an earlier finding.[26] In the current study, the number of

persons per room was a significant predictor of IPF and increase of 1 person per room was associated with 18% increase in the odds of IPF. A study in Mexico, however, did not find any association between household density and IPF.[17] Increasing number of household members lead to increase in the activities which may generate dust, smoke or other exposures as well increase the risk of respiratory infections that are known IF predictors.[3,4,7]

DM and GERD have been associated with higher risk of IPF in a number of studies.[19,20] The current study, however, did not find a significant association with either of these conditions. These discrepancies in the results could be due to different methods used for the ascertainment of these chronic conditions which were based on self-reports and may underestimate the associations.

The current study used standardised procedures and criteria for the diagnosis of IPF and included various personal, behavioural and environmental variables to adjust for their confounding effects. The researchers took a purist view for the design of case-control study where controls were selected from the same specialty to compare them with similar population. The controls mainly included patients who were diagnosed with respiratory conditions. This provided an opportunity to segregate factors that were, maybe, erroneously associated with IPF earlier. While considering that respiratory conditions would have similar risk factors, several sensitivity analyses were conducted, excluding several subgroups of respiratory conditions which may have similar risk factors, to validate the findings. Additional sensitivity analyses were conducted and different regression models were developed based on age and study sites to assess the robustness of the final model.

However, the study has certain limitations. Firstly, it was not able to recruit the required number of cases and controls because of time and budgetary constraints. This has affected the power of the study. Post-hoc power calculation showed that the power of the study with the current sample size was 73%. Secondly, the study was conducted in two hospitals of a single city which may limit the generalisability of the findings. However, the factor may have a minimal effect as Karachi is a multi-ethnic city with people from all across the country. This is also evident from the sample which had all the major ethnic groups of the country. Thirdly, the study population was mainly urban, and, therefore, results may not be generalisable to the rural population who may have different environmental and occupational exposures. Furthermore, the study did not adequately explore occupational groups and risk factors of IPF. Also, it was unable to capture the established genetic risk factors, namely, mucin 5B (MUC5B), telomeres and telomerase length abnormalities. The study decided to forgo genetic testing due to financial constraints and a lack of specialized laboratories available to carry out genetic testing. Lastly, the assessments of various risks factors were self-reported which may have allowed reporting bias and may have resulted in underestimation of associations.

Large-scale multicentre studies are recommended that may focus on occupational groups to generate local evidence on the risk factors which may be different from other populations.

Conclusion

Ethnicity, number of persons in the household per room, and type of house were significantly associated with the risk of developing IPF.

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