Original Article

A follow-up study of post infectious obliterative bronchiolitis in adults and comparative analysis with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: The objective is (1) To evaluate the change in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), dyspnea grading, body mass index, and oxygen saturation (SpO_2) in adults with postinfectious obliterative bronchiolitis (PIOB) over a period of time (2) To evaluate the same parameters in chronic obstructive pulmonary disease (COPD) patients and compare with PIOB. **Materials and Methods:** It was a retrospective observational study involving appropriately managed patients of PIOB and COPD with minimum 3 years of follow-up. Out of a total of 106 patients who followed up from January 2019 to December 2019 and had a follow-up data of more than 3 years, 61 (31 COPD and 30 PIOB) patients were included in the final analysis after applying the inclusion and exclusion criteria. **Results:** The baseline FEV_1 and FVC was significantly worse in PIOB group compared to COPD group. In PIOB group, there was nonsignificant increment in both the parameters (FVC by 18.79 ml and FEV_1 by 12.2 ml per year). There was a significant decline in FVC and FEV_1 in the COPD group by 106.8 ml and 63.25 ml per year, respectively. There was a significant difference between PIOB and COPD for the yearly change in FVC and FEV_1 (*P* value being 0.000083 and 0.000033, respectively). In PIOB group, there was increment in modified Medical Research Council (mMRC) score and nonsignificant change in SpO_2 whereas the SpO_2 and mMRC score had a yearly decline in the COPD group. **Conclusion:** The PIOB is characterized by a nonsignificant increase in lung function whereas COPD shows a significant progressive decline.

KEY WORDS: Chronic obstructive pulmonary disease, lung function test, Bronchiolitis, Exudative, Bronchiolitides, Constrictive, Bronchiolitis, Proliferative

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INTRODUCTION

Chronic obstructive airway disease (COAD) contributes significantly to the respiratory mortality and morbidity. It includes bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), bronchiectasis and obliterative bronchiolitis (OB).[1] Of these, BA is easily identifiable, reversible, and treatable. COPD leads to significant morbidity and mortality because of progressive decline in lung function. In developing countries, where tuberculosis and other infectious diseases are common, OB constitutes nearly 23% of COAD.[1]

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OB is due to the involvement of the small airways. It is characterized by concentric fibrosis in the submucosal layer of the bronchioles.[2,3] The OB commonly seen in developing countries due to infection is also called postinfectious obliterative bronchiolitis (PIOB).[4] In developing countries, the most common cause of OB is PIOB whereas in developed countries the most common cause of OB is transplant.[5,6] This disease of silent zone of lung is often very subtle and silent without any clinical signs till nearly 80% small airways are involved. They often present with respiratory failure if not detected in time. PIOB is diagnosed when all other known causes of chronic airflow obstruction have been ruled out based on the clinico-radiological assessment and there is a history of infection. The expiratory high-resolution computed tomography (HRCT) scan of the lung in the correct clinical context is considered diagnostic of OB.[7] The histopathological findings in OB are confusing due to overlap, and are rarely diagnostic.[8] PIOB is irreversible obstructive airway disease similar to COPD. However, the course and prognosis of COPD is known whereas that of PIOB is not known. There are many studies which have evaluated the decline in lung functions in COPD.[9,10] No such follow-up study is available for PIOB. A study was undertaken to evaluate the course and prognosis of PIOB in adults. A comparison was sought between PIOB and COPD as the course and prognosis of COPD is known.

MATERIALS AND METHODS

An observational comparative study was conducted in a tertiary care hospital of North India after the Institutional Ethics Committee approval. It was an analysis of the retrospective data available in the records of the patients. A valid informed consent was taken from the patients before collecting their data. The aim of the study was (1) to evaluate the fall/improvement in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), dyspnea grading, body mass index (BMI), and oxygen saturation (SpO_2) in patients with PIOB on regular treatment, (2) to evaluate the decline in FEV_1, FVC, dyspnea grading, BMI, and SpO_2 in COPD patients on regular treatment, (3) to compare the improvement/deterioration in FEV_1, FVC, dyspnea grading, BMI, SpO2 between COPD and PIOB.

The patients of PIOB and COPD diagnosed as per guidelines (described below) were included if they satisfied the inclusion criteria. The inclusion criteria were: (1) Regular follow-up in our department for at least 3 years. (2) Complete data of spirometry, BMI, SpO2 and record of dyspnea were available in their outpatient department (OPD) file. (3) Patients who were on optimal medical management and were taking inhalers with proper technique. (4) Ex-smokers who had quit smoking at least a year ago to avoid the decline related to continued smoking. (5) The spirometries were performed during stable state. The exclusion criteria were: (1) Overlap of two or more diseases, for example, asthma COPD overlap, occupational overlap. (2) The available spirometry reports were improperly performed. (3) The data available was <3 years. (4) Current smokers. (5) OB secondary to diseases other than infection.

We would like to emphasize here that our organization, i.e., employee state insurance corporation is bound to give prescribed inhalers free to our patients. They have to come to us periodically to get the prescription. This ensures proper compliance of the patients. Hence follow-up of these patients available in their papers was reliable in terms of compliance. We could extract the data mentioned on their papers because of this follow-up system.

Diagnosis

When the patients followed up in our OPD for continuation of medication in our OPD, they were scrutinized for the inclusion in the study based on inclusion and exclusion criteria. It was confirmed from the patient history and available records if they had COAD and could be classified into COPD as per the global initiative for chronic obstructive lung disease (GOLD) guidelines[11] or OB as per Turton's criteria.[1] The diagnosis of PIOB was based on definite history of respiratory infection in the past. HRCT (thorax) with expiratory scan was essential for including the patients in the study.[7]

Data collection

The detailed demographic profile of all the patients was recorded. Clinical history including grade of dyspnea, presence of cough, presence of expectoration, chest pain, or hemoptysis along with the duration was also noted. Dyspnea was graded using the modified Medical Research Council (mMRC) scale in both the groups. Smoking history, presence of comorbidities, past history of pulmonary tuberculosis or pneumonia was also recorded. History of vaccination, exacerbation, medications, and compliance to medications was evaluated in detail. As per the department protocol, spirometry with diffusion test is performed for all the subjects on Medisoft/Morgan Scientific Spiro Air in and is interpreted as per the American Thoracic Society guidelines.[12] FVC, FEV_1, FEV_1/FVC ratio were recorded from the available data. Chest radiograph and HRCT findings were also recorded.

The data were collected and recorded into MS-Excel and SPSS software version 17 (IBM, SPSS version 17, Chicago) software. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD) The statistical tests applied were as follows: Quantitative variables were compared using Independent *t*-test/Mann–Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-square test/Fisher's exact test. A $P < 0.05$ was considered statistically significant.

The sample size was calculated based on the formula:[13]

Patients per group = $2SD^2 (Z_{\alpha/2} + Z_{\beta})^2/d^2$.

Considering the power of study at 90%, SD = 300 ml, and clinically important effect size (d) =180 ml (60 ml drop per year), the sample size required is 29 patients per each group.

The follow-up data of both COPD and PIOB was matched in terms of age to ensure the age-related decline bias. The unmatched COPD patients were excluded from the analysis. The lung function parameters, SpO2 were noted for both the groups at the baseline and at the end of follow-up. The mean was calculated and the change over the period of follow-up was calculated. The yearly decline in lung function was computed using mean change in parameter over the total period of follow-up. Then, the yearly change was compared in the two groups.

RESULTS

A total of 106 patients who had regular 3 years' follow-up, complete data and proper spirometry were examined for inclusion. Of these, 36 patients were excluded because they had an overlap of two or more chronic obstructive disease or the cause of OB was other than postinfectious. Further, nine more patients of COPD were excluded to make population of PIOB and COPD age matched. A total of 61 patients (31 COPD and 30 PIOB) were included in the final analysis [Figure 1]. The characteristics of the patients are summarized in Table 1.

Of the patients with PIOB (n = 30), 20 (66.66%) were women and 10 (33.33%) were men. The mean age was 53.46 ± 6.8 years, and the mean BMI was 22.4 ± 4.83 kg/m^2. The cause of PIOB was found to be postchildhood pneumonia in 15 (50%) patients, posttuberculosis in 14 (46.67%), and postmeasles in 1 (3.33%) patient [Figure 2]. None of the PIOB patients were included in the study had tobacco exposure or exposure to biomass fuel. Twenty (66.66%) of PIOB patients had undergone pulmonary rehabilitation program and 29 (96.7%) had taken pneumococcal vaccination. All the patients of PIOB were treated with oral and inhaled bronchodilators (long-acting beta 2 agonists and long-acting muscarinic antagonists) along with inhaled corticosteroids as per the department protocol. None of them received oral corticosteroids. Of the COPD patients (n = 31), 4 (12.9%) were women and 27 (87%) were men. The mean age was 55.6 ± 5.84 years, and the mean BMI was 19.97 ± 3.19 kg/m^2. All the patients were smokers, 27 (87%) had undergone pulmonary rehabilitation program and 30 (96.7%) had taken pneumococcal vaccination. The COPD patients were been managed as per the GOLD guidelines.

The duration of follow-up in both the groups was for minimum of 3 years. The baseline FEV_1, FVC, SpO2, mMRC dyspnea grading, and BMI of both PIOB and COPD are given in Table 2. In PIOB group, the mean baseline FVC was 1.58 L, FEV_1 was 0.91 L and SpO2 was 95.9%. In COPD group, the mean baseline FVC was 2.2 L, FEV_1 was 1.13 L and the SpO_2 was 96.3%. The baseline lung function in terms of both FEV_1 and FVC was significantly better in COPD group compared to PIOB group though the SpO2 was similar. In the PIOB group, five patients (16.67%) had baseline SpO2 of less

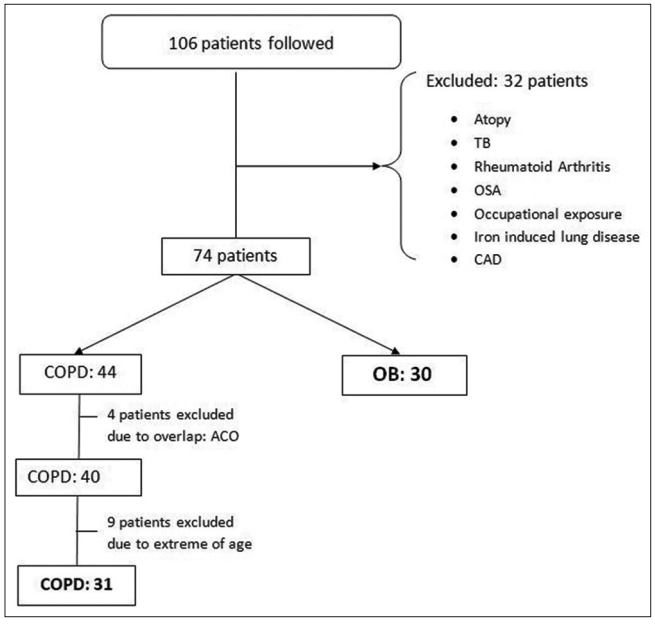

Figure 1: The flow chart showing the inclusion of patients in the final study after applying inclusion and exclusion criteria

Table 1: Characteristics of patients in postinfectious obliterative bronchiolitis and chronic obstructive pulmonary disease group

Characteristics	Mean±SD	
	COPD	PIOB
Age (year)	55.6±5.84	53.46±6.8
Female, *n* (%)	4 (12.9)	20 (66.66)
Male, *n* (%)	27 (87)	10 (33.33)
BMI (kg/m^2)	19.97± 3.19	22.4± 4.83
Smoking history, *n* (%)	31 (100)	0
Pulmonary rehabilitation, *n* (%)	27 (87)	20 (66.66)
Pneumococcal vaccination, *n* (%)	30 (96.7)	29 (96.6)

COPD: Chronic obstructive pulmonary disease, PIOB: Postinfectious obliterative bronchiolitis, SD: Standard deviation, BMI: Body mass index

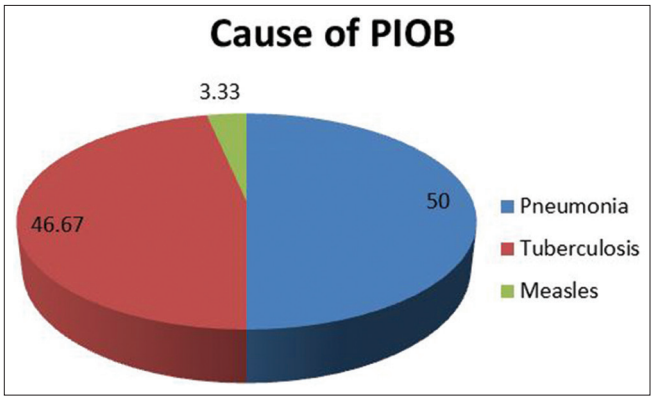

Figure 2: Pie-chart depicting the various causes of postinfectious obliterative bronchiolitis

than 92%. The arterial blood gas analysis in them had confirmed the presence of respiratory failure at the time of initial diagnosis. There was significant difference in baseline dyspnea between PIOB group and COPD group akin to the spirometry. In PIOB group, the most common baseline dyspnea grading was mMRC grade 3 seen in 17 (56.66%) patients followed by grade 2 in 10 (33.33%) patients. The baseline dyspnea grading commonly seen in COPD group was mMRC grade 2 (18 patients, i.e., 58.06%) followed by grade 3 in 8 (25.8%) and grade 1 in 5 (16.12%) patients. The mean BMI for the PIOB group was 22.4 kg/m^2 and for the COPD group was 19.97 kg/m^2. Thus PIOB patients presented with poorer lung function and worse dyspnea but better BMI.

The average follow-up period in COPD group was 3.8 years and that in PIOB group was 4.2 years. The lung function characteristics, dyspnea score, and BMI at the end of follow-up are summarized in Table 2. In PIOB group at the end of follow-up mean the FVC, FEV_1, and SpO2 were 1.63 L, 0.95 L, and 95.67%, respectively. In COPD group, at the end of follow-up, the mean FVC, FEV_1, and SpO2 were 1.86 L, 0.92 L, and 94.06%, respectively [Table 2]. The FVC, FEV_1, and SpO2 improved over the period of follow-up in the PIOB group by 50 ml, 40 ml and 0.3% respectively though the change was nonsignificant. But in the COPD group, there was a significant decline in the mean FVC, FEV_1 and SpO2 by 350 ml, 210 ml and 2.29%, respectively. Figure 3 shows the comparative change in lung functions from baseline to the end of follow-up in the COPD group and PIOB group.

At the end of follow-up the most common dyspnea grade in COPD group was grade 3 in 13 (41.9%) followed by grade 2 in 11 (35.48%), grade 4 in 6 (19.31%), and grade 1 in 1 (3.22%) patients. In OB group, at the end of follow-up the most common dyspnea grade was grade 2 in 16 (53.33%) followed by grade 1 in 9 (30%) then grade 3 in 4 (13.33%) and grade 4 in 1 (3.33%) patients. There was a significant improvement in PIOB group compared to COPD in terms of dyspnea grading [Table 2]. At the end of follow-up, the mean BMI in PIOB group was 22.98 and in COPD group was 19.73 [Table 2]. There was no significant change in BMI in both the groups at the end of follow-up, but there was marginal improvement in BMI in PIOB group and marginal decline in BMI in COPD group.

The annual decline in lung function was computed from the overall change averaged over the total period of follow-up. In the PIOB group, there was yearly increment in FVC by 18.79 ml and FEV_1 by 12.2 ml. In the COPD group, the yearly decline in FVC and FEV_1 was 106.8 ml and 63.25 ml, respectively [Table 3]. The difference between PIOB and COPD group was statistically significant, the *P* value being 0.000083 and 0.000033 for FVC and FEV_1 respectively. The yearly decline in SpO2 in COPD group was found to be 0.62 and in PIOB group was 0.10 and it was found to be statistically significant, *P* value being 0.018. The yearly change in dyspnea could not be calculated as it is a qualitative parameter. Hence, it was seen in our study that there was yearly decline in the lung function, SpO2, and worsening of mMRC score for the COPD group whereas in PIOB group, there was relative nonsignificant change in lung functions and SpO2.

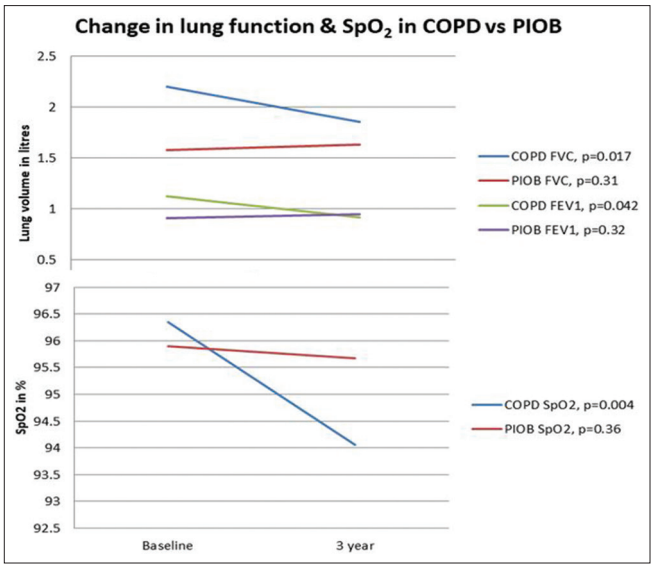

Figure 3: Line-chart showing the change in lung function and oxygen saturation from baseline to the end of follow up

Table 2: The forced vital capacity, forced expiratory volume in 1 s, oxygen saturation, modified Medical Research Council dyspnea grading and body mass index of both chronic obstructive pulmonary disease and postinfectious obliterative bronchiolitis at baseline and at the end of follow-up

Parameters	Mean±SD		*P*
	COPD	PIOB	
At baseline			
FVC	2.20±0.72	1.58±0.43	0.000058
FEV_1	1.13±0.53	0.91±0.32	0.032361
SpO_2	96.35±2.26	95.9%±2.94	0.28234
BMI	19.97±3.19	22.44±4.83	0.0106
mMRC grade	Grade 2	Grade 3	0.01892
At the end of follow-up			
FVC	1.86 ± 0.53	1.63 ± 0.41	0.032165
FEV_1	0.92 ± 0.4	0.95 ± 0.31	0.35490
SpO_2	94.06 ± 3.99	95.67 ± 3.48	0.0501
mMRC	Grade 3	Grade 2	0.02047
BMI	19.73± 2.85	22.98± 4.61	0.00077

FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s, BMI: Body mass index, SpO_2: Oxygen saturation, mMRC: Modified Medical Research Council, COPD: Chronic obstructive pulmonary disease, PIOB: Postinfectious obliterative bronchiolitis, SD: Standard deviation

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the spirometric follow-up in adult PIOB patients. Although a few studies have been reported in children, there is no such study in adults.[14-17] This is the very first study which has documented an annual change in lung function in PIOB patients. Furthermore, for the first time,

Table 3: Total (at the end of follow up) and yearly decline/improvement in lung function characteristics and body mass index

Parameters	Mean±SD		*P*
	COPD	PIOB	
Total (at the end of follow up) decline/improvement FVC (L)	−0.35±0.38	0.05±0.26	<0.00001
Total (at the end of follow up) decline/improvement FEV_1 (L)	−0.21±0.22	0.04±0.2	0.000013
Total (at the end of follow up) decline/improvement SpO_2	−2.29±3.34	−0.30±2.15	0.003872
Total (at the end of follow up) decline/improvement BMI (kg/m^2)	−0.24	0.54	0.07603
Yearly decline/improvement in FVC (ml)	−106.8	18.79	0.000033
Yearly decline/improvement in FEV_1 (ml)	−63.25	12.2	0.000083
Yearly decline/improvement in SpO_2	−0.62	−0.10	0.018592

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, PIOB: Postinfectious obliterative bronchiolitis, SD: Standard deviation, SpO_2: Oxygen saturation

a comparison has been sought between PIOB and COPD patients. We have also been able to document that the prognosis of PIOB is far superior to COPD though both are irreversible COAD. Despite the cessation of inciting agent the COPD continue to worsen as against PIOB who improve marginally. In this study, the patients were followed up for a minimum period of 3 years. The patients of both the group were provided with optimum treatment. We found that OB group at baseline had a higher mean BMI but lower FEV_1, FVC, SpO2 and better dyspnea score than the COPD group. At the end of follow-up in OB group, there was a nonsignificant increment in lung function, BMI, and dyspnea score and a nonsignificant change in SpO_2 and there was a significant decline in lung function, SpO2 and dyspnea score in the COPD group,

In PIOB group, there was a yearly increment in both the parameters, i.e. FVC by 18.79 mL and FEV_1 by 12.2 mL. Studies have been done in children regarding decline/improvement in lung function in PIOB patients. In a study by Sisman *et al*., with 30 children of PIOB, the lung function did not fall for about 7 years on follow-up.[14] In a study by Prudon *et al*., in 19 children the improvement, deterioration, and stability were variable.[16] There are no studies in adults with PIOB. In the COPD group, the yearly decline in FEV_1 was 63.25 mL. In a study by Kim *et al*., the annual rate of decline in the postbronchodilator FEV1 was 28.3 mL in COPD patients.[18] Similar to our study Tantucci and Modina found that the mean rate of FEV_1 decline in GOLD stages II and III was 47 to 79 mL/year and 56–59 mL/year, respectively.[10] There was significant difference between COPD and PIOB for the yearly change in FVC and FEV_1 (*P* value being 0.000083 and 0.000033 respectively). Thus, in PIOB, the lung function does not progressively decline. Our study is first to describe stability in lung function after the diagnosis and treatment of PIOB in adults.

The cause PIOB in our study was mainly secondary to pneumonia and tuberculosis. In a recent study from India by Suhas *et al*., 71% of the patients had OB secondary to tuberculosis.[1] They had also found that 23% of obstructive airway diseases are OB of which 88% were due to PIOB, suggesting that PIOB is a common cause of obstructive airway disease.[1] Another study by Gothi *et al*. had found that 13% of COAD had OB. Among the OB cases, 92% were due to PIOB secondary to tuberculosis or severe lower respiratory tract infection in childhood.[5] In our study, the most common cause of OB was not tuberculosis possibly because those who had a smoking history and tuberculosis fell in overlap group and were not included in the study.

PIOB is usually diagnosed long after the initial insult.[19] Suhas *et al*. observed that 22% of the patients were in respiratory failure at the time of diagnosis.[1] We too found that 16.67% of patients were in respiratory failure at the time of diagnosis. Our patients were without a diagnosis for a mean duration of 26.9 ± 15.48 years before they came to us and were diagnosed PIOB. The primary reason for delayed diagnosis is clinical manifestations are not apparent until approximately 80% of airways are involved.[1] Another reason for a delayed diagnosis is that OB persists for years after its onset in childhood and worsens due to exacerbations caused by viral infections, suppuration, atelectasis, and pneumonias.[5] Thus, the awareness regarding the disease needs to be increased in countries where the prevalence of tuberculosis and childhood infection is high so that the patients are diagnosed in time and progressive decline in lung function is averted. The developed countries where the awareness regarding the entity is well known the patients are picked up in childhood itself with PIOB. There too the lag phase between initial insult and diagnosis of about 2 years does exist.[14,15]

The treatment of COPD is standardized. However, that of PIOB is not standardized because definitive treatment for PIOB is unknown.[6] There is a role of inhaled bronchodilators and oral bronchodilators. The role of inhaled steroid is not assessed in any randomized trial though a few case reports have shown some benefit.[20] Bronchiolitis obliterans syndrome (BOS), i.e. OB following lung transplant is still a relatively well-studied entity. In BOS inhaled steroid, azithromycin and montelukast have been shown to have a role.[6,21,22] However, the role of azithromycin in PIOB has been ruled out in a small controlled study by Uyan *et al*.[23] Thus, our patients were given inhaled and oral bronchodilators and inhaled steroids. The future of small airway disease management lies in extrafine inhalers. These have recently

been launched in India and are known to work for uncontrolled obstructive airway disease with small airway involvement.[24] Randomized control trials are required using extrafine inhalers for patients of PIOB in future.

Our study has some limitations. The extremes of age were not included which if included might have further strengthened our study showing that even in elderly population OB group has preserved lung function. It was a retrospective study and the sample size was small. A prospective study with a larger sample size is required in this field.

CONCLUSION

The lung function remains relatively static in PIOB after diagnosis and appropriate treatment. This disease of silent zone of the lung should be identified early with spirometry in patients who have suffered respiratory infection to improve the morbidity related to this disease since very often they are diagnosed only when they come with respiratory failure.

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Conflicts of interest
There are no conflicts of interest.

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