

# Frequency of Allergic Bronchopulmonary Aspergillosis in Patients with Bronchial Asthma and its Relationship with Severity of Disease

ZIA-UL-HAQ<sup>1</sup>, MUHAMMAD ANUS BASHIR<sup>2</sup>, MUHAMMAD ASAD ULLAHA<sup>3</sup>, SADIA MAHMOOD<sup>4</sup>, ANAM KHAN<sup>5</sup>, ALI RAZA<sup>6</sup>

<sup>1</sup>Senior Registrar Sir Ganga Ram Hospital Lahore,

<sup>2</sup>Consultant Physician THQ Ferozewala,

<sup>3</sup>Consultant Surgeon THQ Ferozewala,

<sup>4</sup>Postgraduate Resident Sir Ganga Ram Hospital, Lahore,

<sup>5</sup>Postgraduate Resident Sir Ganga Ram Hospital, Lahore,

<sup>6</sup>Assistant Professor of Pathology Sahara Medical College, Narowal

Correspondence to Dr. Zia-ul-Haq, E-mail: idrzia@yahoo.com

## ABSTRACT

**Aim:** To determine the frequency of allergic bronchopulmonary aspergillosis in patients with bronchial asthma and its relationship with severity of disease.

**Design of study:** It was a descriptive cross-sectional study.

**Study duration and settings:** This study was carried at the Pulmonology Department of Sir Ganga Ram Hospital Lahore from December 2018 to January 2020.

**Methods:** This study involved 100 patients of both genders, aged between 18-60 years presenting with bronchial asthma. Spirometry was performed to determine the severity of asthma while ABPA was diagnosed on total and *A. fumigatus* specific IgE levels, peripheral blood eosinophil count and high-resolution computed tomography (HRCT) of the thorax. A signed written consent was taken from every patient.

**Result:** There was a male predominance (1.5:1) among patients with bronchial asthma with a mean age of 35.4±10.3 years and mean duration of disease of 11.9±4.6 years. 25% patients were smoker. Allergic bronchopulmonary aspergillosis was diagnosed in 20% asthmatic patients. Its frequency increased significantly with increasing severity of asthma; intermittent vs. mild vs. moderate vs. severe (4.8% vs. 13.3% vs. 21.4% vs. 36.7%; p-value=0.028) asthma while no relationship was observed with patient's age, gender as well as disease duration and tobacco smoking.

**Conclusion:** In the present study, a considerable proportion of patients with bronchial asthma had allergic bronchopulmonary aspergillosis and its frequency increased significantly with increasing severity of asthma which might suggest a cause and effect relationship and warrants routine screening of patients with bronchial asthma for ABPA so that timely identification and management of ABPA may improve clinical outcome in bronchial asthma.

**Keywords:** Bronchial Asthma, Allergic Bronchopulmonary Aspergillosis, Severity of Asthma

## INTRODUCTION

Asthma is considered to be a chronic inflammatory disease that may result from the interaction of environment and genetic factors<sup>1</sup>. Frequent clinical features of asthma are represented by airway obstruction, bronchial hyper responsiveness and greater airway wall thickening, with episodes of various symptoms, including chest tightness, wheeze, cough, and shortness of breath. Epithelial destruction of the airways, especially ciliated cells, is also recognized in most asthmatic patients<sup>2,3</sup>. In the US, this disease is ranked eighth among diseases needing a physician's visit. Its prevalence and mortality has sharply increased over the past decades<sup>4</sup>. There are approximately 300 million people worldwide suffering from asthma with 180,000 deaths annually. This numbers increases by 50% every decade<sup>3</sup>. Based on the estimation of the Institute for Health Metrics and Evaluation (IHME), a gradual increasing in morbidity and mortality of asthma with a prevalence of 4% is specifically found in adults<sup>3,4</sup>. The prevalence of asthma in children is much higher compared to adults especially in the age range of 0-17 years. The prevalence of uncontrolled asthma was estimated to be 35% of

54% in those with respiratory complaints<sup>5</sup>. Infants are also at risk of developing asthma, which maybe a result of exposure to various factors when they are in utero<sup>1,5</sup>. Control of asthma is usually an obligatory requirement for patient management. Such a control should include management of rhinitis, smoking and low adherence to inhaled corticosteroid. Therefore, controlling asthma leads to a better life with less time spent in emergency and hospital rooms<sup>1,3</sup>.

Sensitization to the fungal allergen is the most effective factor to trigger or worsen asthma<sup>6</sup>. Antigens of *Aspergillus* species are a common type of allergen responsible for developing or stimulating such allergic diseases. Exposure of the respiratory epithelial tissues to the *Aspergillus* antigen may initiate from two sources; the entering spores or from colonization of fungi in the pulmonary system in the form of aspergillosis disease<sup>6,7</sup>. There are different types of pulmonary Aspergillosis with variable invasive ability into the pulmonary system. Allergic Bronchopulmonary Aspergillosis (ABPA) is the most frequent type of aspergillosis recognized to associate with asthma, especially that caused by *A. fumigatus*<sup>8</sup>. A strong correlation between asthma and aspergillosis makes it difficult to understand which one has more effect on the other. Much clinical evidence supports the fact that Aspergillosis plays a major role in asthma. Others

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demonstrated that asthma is the main predisposing factor for the development of aspergillosis<sup>9,10</sup>. The reported frequency of ABPA among asthmatic patients varies from as low as 0.7%<sup>11</sup> to as high as 90%<sup>12</sup> in the published literature. A possible explanation for this conflict among studies can be the population and geographical variation as well as selection bias where none of the studies has correlated positivity for ABPA with the severity of asthma. Owing to this controversy in the existing literature and lack of local such published material need for the present study was felt.

## MATERIAL AND METHODS

It was a descriptive cross-sectional study carried at the Pulmonology Department of Sir Ganga Ram Hospital, Lahore from December 2018 to January 2020. Sample size of 100 cases was calculated with 95% confidence level and 5% margin of error while taking expected frequency of ABPA to be 7.0%<sup>13</sup> among patients presenting with bronchial asthma. Patients of both genders, aged between 18-60 years having bronchial asthma were included in the study. FEV1 was measured at baseline followed by repeat spirometry 15 minutes after two puffs of levosalbutamol (100µg). Diagnosis of asthma was established on increase in FEV1s by >12% in comparison to the baseline value. FEV1 was used for determination of the severity of asthma using GINA guideline<sup>1</sup>. Patients with malignant disease of the airway, previous thoracic surgery, steroids intake, immunosuppressants and chemotherapy were excluded.

The Aspergillus skin test was performed using commercially prepared A. fumigatus antigen (Aspergillin; Hollister-Stier Laboratories; Spokane, WA, USA). Type I and III hypersensitivity reactions were recorded. Those demonstrating positive type I response were further investigated with total and A. fumigatus specific IgE levels, peripheral blood eosinophil count and high-resolution computed tomography (HRCT) of the thorax. The diagnosis of ABPA was made if the patients met the following diagnostic criteria: (1) Bronchial asthma; (2) Type I cutaneous reactivity to A. fumigatus antigen; (3) raised total serum IgE levels ( $\geq 1000$  IU/ml); (4) fleeting or fixed radiological opacities; (5) raised serum IgE specific against A. fumigatus ( $\geq 0.35$  kU/L); (f) peripheral blood eosinophilia ( $\geq 1000$  cells/ml); and (6) HRCT of thorax showing proximal bronchiectasis.

All the data was entered and analyzed through SPSS version 20. Numerical variables like age and disease duration have been described as mean $\pm$ sd. Categorical variables like gender, severity of asthma, smoking and ABPA have been described as frequency and percentage. The frequency of ABPA has been stratified for age, gender, disease duration and severity of asthma followed by chi-square test to compare the frequency of ABPA across each stratum taking p-values $\leq 0.05$  as statistically significant.

## RESULTS

The mean age of the patients was 35.4 $\pm$ 10.3 years (ranged from 18-60 years). 33(33%) patients were aged between 18-27 years, 26(26%) patients were aged between 28-37 years while 41(41%) patients were aged 38 years and above. There were 60(60%) male and 40 (40%) female

patients in the study group with a male to female ratio of 1.5:1. History of smoking was positive in 25(25%) patients. The disease duration ranged from 4 years to 26 years with a mean of 11.9 $\pm$ 4.6 years. The severity of asthma was categorized as intermittent (21%), mild 30 (30%), moderate (19%) and severe (30%) as shown in Table 1. Allergic bronchopulmonary aspergillosis was diagnosed in 20(20%) patients with bronchial asthma as shown in Table 2. The frequency of ABPA increased significantly with increasing severity of asthma as shown in Table 3.

Table 1: General Characteristics of Asthmatic Patients

Characters	Asthmatic patients
Age (years)	35.4 $\pm$ 10.3
18-27 years	33(33%)
28-37 years	26(26%)
$\geq 38$ years	41(41%)
<b>Gender</b>	
Male	60(60%)
Female	40 (40%)
Duration of Disease (years)	11.9 $\pm$ 4.6
4-14 ears	56(76.7%)
15-26 years	17(23.3%)
<b>Smoking</b>	
Yes	25(25%)
No	75(75%)
<b>Severity of Asthma</b>	
Intermittent	21(21%)
Mild	30(30%)
Moderate	19(19%)
Severe	30(30%)

Table 2: Frequency of ABPA in Asthmatic Patients

ABPA	Frequency	%age
Yes	20	20.0
No	80	80.0
Total	100	100.0

Table 3: Comparison of Frequency of ABPA across various Subgroups of Asthmatic Patients

Subgroup	n	ABPA	P value
<b>Age (years)</b>			
18-27 years	33	6 (18.2%)	0.916
28-37 years	26	5 (19.2%)	
$\geq 38$ years	41	9 (22.0%)	
<b>Gender</b>			
Male	60	12 (20.0%)	1.000
Female	40	8 (20.0%)	
<b>Duration of Disease (years)</b>			
4-14 years	56	13 (19.1%)	0.748
15-26 years	17	7 (21.9%)	
<b>Smoking</b>			
Yes	25	6 (24.0%)	0.564
No	75	14 (18.7%)	
<b>Severity of Asthma</b>			
Intermittent	21	1 (4.8%)	0.028*
Mild	30	4(13.3%)	
Moderate	19	4(21.4%)	
Severe	30	11 (36.7%)	

Chi-square test was performed, \* the observed difference was significant

## DISCUSSION

Hundreds of Aspergillus spores are inhaled into the respiratory tract every day without any effects on human

health. However in susceptible individuals, the epithelial cells of the respiratory tract become sensitized after any contact with *Aspergillus* antigen leading to the development of Allergic Bronchopulmonary Aspergillosis (ABPA) or Severe Asthma with Fungal Sensitization (SAFS)<sup>8,9</sup>. Inflammation in the airway of patients with asthma increases after the inhalation of *Aspergillus* antigens<sup>9</sup>. Thus, individuals with allergic asthma are always under the risk of developing pulmonary aspergillosis. Aspergillosis can lead to asthma after long-term exposure to *Aspergillus* antigens<sup>9</sup> while asthma can also encourage infection with aspergillosis in many cases<sup>7,8</sup>. Thus, asthma and aspergillosis have shared responsibility to form each other in a reversible relationship<sup>7-9</sup>.

In the present study, the mean age of the asthmatic patients was 35.4±10.3 years. 33(33%) patients were aged between 18-27 years, 26(26%) patients were aged between 28-37 years while 41(41%) patients were aged 38 years and above. A similar mean age of 35.0±8.2 years has been reported by Ahmad et al<sup>14</sup> (2011) among adult patients presenting with bronchial asthma at Allergy Centre National Institute of Health, Islamabad. Baig et al<sup>15</sup> (2019) reported similar mean age of 36.7±15.3 years among such patients presenting at tertiary care hospitals of Hyderabad. In an Indian study, Salvi et al<sup>16</sup> (2015) reported similar mean age of 37±17.5 years among asthmatic patients in India. A comparable mean age of 38.3±12.8 years has been reported by another Indian study by Nath et al<sup>17</sup> (2017). A similar distribution of 18-27 years (32.6%), 28-37 years (24.5%) and ≥38 years (42.9%) age groups has been reported by Razzaq et al<sup>18</sup> (2018) among such patients in Karachi while Singh et al.<sup>19</sup> (2015) reported the frequency of 18-27 years, 28-37 years and ≥38 years age groups to be 33.5%, 26.4% and 40.1% in Indian such patients.

We observed that there were 60 (60%) male and 40(40%) female patients in the study group with a male to female ratio of 1.5:1. A similar male predominance among asthmatic patients has been observed by Ahmed et al<sup>20</sup> (2018) who reported it to be 1.5:1 at Liaquat National Hospital, Karachi. Khan et al<sup>21</sup> (2015) reported similar male predominance with male to female ratio of 1.8:1 at University of Sindh, Jamshoro while Ahmad et al<sup>14</sup> (2011) reported it to be 2:1 at Allergy Centre National Institute of Health, Islamabad. Salvi et al<sup>16</sup> in 2015 (1.5:1) and Prasad et al<sup>22</sup> in 2007 (1.6:1) also reported similar male predominance among asthmatic patients in India.

In the present study, 25.0% of asthmatic patients were smoker. Dar et al<sup>23</sup> (2017) observed similar frequency of tobacco smoking in asthmatic patients at Fatima Jinnah Women University, Rawalpindi and reported it to be 23%. Khan et al<sup>24</sup> (2016) reported the frequency of smoking to be 26.0% among asthmatic patients presenting at Nishtar Hospital, Multan. A comparable frequency of 25.8% has also been reported in Indian asthmatic patients by Singh et al<sup>19</sup> in 2015. Kim et al<sup>25</sup> in 2018 (25.6%) in China and Tomisa et al<sup>26</sup> in 2019 (27.8%) in Hungary also reported similar frequency of smoking among asthmatic patients.

We observed that the mean duration of asthma was 11.9±4.6 years upon presentation. A similar mean duration

of asthma upon presentation was observed by Moghtaderi et al<sup>27</sup> (2019) who reported it to be 11.0±10 years in Iran while Prasad et al<sup>22</sup> (2007) reported it to be 11.2±8.6 years among Indian such patients.

We observed that the asthma was intermittent in 21%, mild in 30.0%, moderate in 19.0% and severe in 30.0% cases. A similar distribution of intermittent (21.7%), mild (29.2%), moderate (18.3%) and severe (30.8%) asthma has been reported by Singh et al.<sup>19</sup> in Indian asthmatic patients. A comparable frequency of intermittent, mild, moderate and severe asthma has been reported by Shaikh et al<sup>28</sup> (2016) in another Indian study who observed it to be 22.2%, 30.5%, 17% and 30.3% respectively.

In the present study, allergic bronchopulmonary aspergillosis was diagnosed in 20% of asthmatic patients and its frequency increased significantly with increasing severity of asthma. A similar frequency of ABPA among Indian asthmatic patients has been observed by Agarwal et al<sup>29</sup> (2007) who reported it to be 20.5%. In another Indian study, Nath et al<sup>17</sup> (2017) reported the frequency of ABPA to be 21.7% in line with the present study. This observed frequency of ABPA is much higher than reported in other populations where Moghtaderi et al<sup>27</sup> (3.4%) in Iran, Al-Mobeireek et al<sup>30</sup> (2.3%) in KSA, Ma et al<sup>31</sup> (2.5%) in China and Mahdi et al<sup>32</sup> (12.6%) in Iraq reported much lower frequency of ABPA among asthmatic patients. This variation in studies can be attributable to population, geographic and environmental differences.

The present study is first of its kind in local population and establishes that a considerable proportion of patients with bronchial asthma have allergic bronchopulmonary aspergillosis. As mentioned above both ABPA can cause asthma and asthma may cause ABPA. In the present study, the frequency of ABPA increased significantly with increasing severity of disease which might suggest a cause and effect relationship and warrants routine screening of patients with bronchial asthma for ABPA so that timely identification and management of ABPA may improve the clinical outcome of bronchial asthma.

The strengths of the present study were its large sample size of 100 cases. We stratified the data to address effect modifiers and minimize bias. A very strong limitation to the present study was that we didn't consider the treatment response of asthma in patients with versus without ABPA nor we considered the effect of ABPA management on treatment response of asthma which could have further highlighted the relationship between ABPA and bronchial asthma. Such a study is highly recommended in future research.

## CONCLUSION

In the present study, a considerable proportion of patients with bronchial asthma had allergic bronchopulmonary aspergillosis and its frequency increased significantly with increasing severity of asthma which might suggest a cause and effect relationship and warrants routine screening of patients with bronchial asthma for ABPA so that timely identification and management of ABPA may improve the clinical outcome of patients with bronchial asthma.

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