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RESEARCH ARTICLE
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HIGH IGE LEVELS IN ABPA: A RISK FACTOR FOR SEVERE ASTHMA EXACERBATION AMONG YOUNG POPULATION

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ABSTRACT

OBJECTIVE: To determine whether young adults with acute Allergic Bronchopulmonary Aspergillosis (ABPA) and very high serum total IgE levels and Aspergillus fumigatus-specific IgE exhibit a distinct clinical phenotype with preserved lung functions, yet are at significant risk of recurrent severe asthma exacerbations.

MATERIALS AND METHODS: This multicenter prospective cohort study was conducted across tertiary care hospitals in Pakistan, from June 2024 to July 2025. Seventy-two patients aged 18–35 years with acute ABPA (diagnosed per ISHAM criteria) and no bronchiectasis on HRCT were enrolled. Total IgE and Aspergillus fumigatus-specific IgE (AF-IgE) were measured using ImmunoCAP at a central laboratory. All participants received standardized oral prednisolone (0.5 mg/kg/day for 2 weeks, tapered over 6–8 weeks). Clinical assessments, spirometry (FEV_1), ACQ-5 scores, and serial IgE levels were recorded at baseline, Week 8, Week 12, and Week 24. Exacerbation frequency was documented prospectively. Data were analyzed using SPSS v28.0; paired t-tests, logistic regression, and Pearson correlation were applied; $p < 0.05$ was considered statistically significant.

RESULTS: Despite mean baseline ACQ-5 scores of 1.6 ± 0.4 (indicating mild control), 89% (n=64) experienced ≥2 severe exacerbations in the prior year. Mean total IgE was 3200 ± 1580 IU/mL; Mean total AF-IgE was 35 ± 22.1 kUA/L. Post-steroid, total IgE declined by 38% at 8 weeks ($p<0.001$) and 82% at 12 weeks. FEV_1 improved from 82% to 94% predicted ($p=0.002$). Notably, patients with IgE > 3000 IU/mL had 3.2 times higher exacerbation risk (OR 3.2, 95% CI 1.8–5.7, $p=0.001$) despite similar symptom scores.

CONCLUSION: High IgE levels in young ABPA patients can be misleading, as they often have relatively normal lung function and mild symptoms. However, these patients are at risk of severe asthma attacks, frequent exacerbations lead to hospitalization, that is not respondent with standard treatments like inhaled corticosteroids. IgE decline with oral corticosteroids correlates with clinical improvement, supporting IgE as both a biomarker and therapeutic indicator.

KEYWORDS: Allergic bronchopulmonary aspergillosis, Asthma, Aspergillus fumigatus-specific IgE, steroid, asthma exacerbation and Serum IgE

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex hypersensitivity disorder triggered by Aspergillus fumigatus in genetically predisposed individuals, predominantly those with Asthma, chronic obstructive pulmonary disease or cystic fibrosis [1]. First described by Hinson et al. in 1952 [2], ABPA remains a diagnostic and therapeutic challenge due to its variable clinical expression. Serum total IgE has long served as a cornerstone biomarker elevated beyond 500 IU/mL in most cases and is integral to diagnostic criteria established by the International Society for Human and Animal Mycology (ISHAM) [3].

Recent studies emphasize that total IgE levels above 4,000 IU/mL correlate with advanced disease, frequent relapses, and progression to central bronchiectasis [4,5]. Paradoxically, a subset of young patients presents with astronomical IgE levels (>3000 IU/mL) yet reports poor symptoms control like dyspnea and excessive wheeze despite of inhaled medication, raising questions about symptom-IgE discordance [6]. This phenomenon may reflect compensatory airway remodeling or delayed symptom perception in early disease.

The role of *A. fumigatus*-specific IgE (AF-IgE) has gained prominence as a more specific marker than total IgE. Levels ≥ 0.35 kUA/L kUA/L are now included in refined ABPA diagnostic algorithms [7]. However, few studies have examined the interplay between total IgE, AF-IgE, and exacerbation risk in young adults (18–35 years) a demographic often overlooked due to assumptions of milder disease [8]. Corticosteroids remain first-line therapy, with IgE decline considered a surrogate for treatment response [9]. Agarwal et al. demonstrated that a ≥25% drop in IgE at 8 weeks predicts sustained remission response [10]. Yet, data on the kinetics of IgE reduction in patients with baseline IgE >3000 IU/mL are scarce, particularly in acute-phase (non-chronic) ABPA.

Importantly, most literature focuses on chronic ABPA with bronchiectasis [11], whereas our cohort comprises patients with acute or subacute ABPA without structural lung damage, allowing isolation of immunological drivers of exacerbation independent of fixed airflow obstruction.

Our study addresses a critical gap: Do extremely high IgE levels in young ABPA patients signify silent disease progression with severe symptoms? And does rapid IgE decline post-steroid correlate with reduced exacerbation risk?

We hypothesize that young ABPA patients with total IgE >3,000 IU/mL and AF-IgE >35 kUA/L experience recurrent severe asthma exacerbations disproportionate to their symptom scores, and that corticosteroid-induced IgE suppression is both rapid and profound, indicating preserved immune responsiveness.

MATERIALS AND METHODS

This prospective observational cohort study was conducted at major tertiary care centers in Pakistan. The study spanned from June 2024 to July 2025, approved by the Institutional Review Boards (IRB) of participating centers. Written informed consent was obtained from all participants in their preferred language (Urdu or English), with assistance provided for low-literacy individuals. A total of 72 patients aged 18–35 years were enrolled based on strict inclusion and exclusion criteria. Inclusion Criteria included Age between 18 and 35 years, Pre-existing diagnosis of asthma (per GINA 2021 guidelines), Confirmed diagnosis of acute-phase ABPA using revised ISHAM criteria (2023) [3], defined as: Asthma with Total serum IgE ≥ 500 IU/mL, Positive immediate skin test to Aspergillus fumigatus OR elevated AF-IgE (≥ 0.35 kUA/L), Presence of precipitating antibodies (IgG) against A. fumigatus, Transient pulmonary infiltrates on chest radiograph or HRCT (e.g., fleeting opacities, “finger-in-glove” appearance). No evidence of chronic structural lung damage (i.e., central br4onchiectasis) on high-resolution computed tomography (HRCT) of the chest. At least two documented severe asthma exacerbations in the preceding 12 months requiring systemic corticosteroids or emergency care. Willingness to attend scheduled follow-up visits.

Exclusion Criteria excluded Radiological or clinical evidence of chronic pulmonary aspergillosis (CPA) or aspergilloma, Co-existing cystic fibrosis, tuberculosis, or active pulmonary infection (bacterial/fungal), History of immunosuppressive therapy (e.g., long-term steroids, biologics, chemotherapy), Pregnancy or lactation, Known diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) or other vasculitic syndromes, Inability to comply with follow-up schedule due to geographic or socioeconomic constraints, Patients were identified through outpatient allergy-pulmonology clinics and respiratory wards during routine evaluation for poorly controlled asthma. Of 98 screened individuals, 26 were excluded 14 due to bronchiectasis on HRCT, 6 had CPA, 4 were on omalizumab, and 2 declined participants. All diagnostic assessments followed standardized protocols adapted to local infrastructure: Skin Prick Testing (SPT), Performed at each center using commercially available Aspergillus fumigatus allergen extract (ALK-Abelló, Denmark). Histamine and saline served as positive and negative controls. A wheal diameter ≥3mm larger than saline control was considered positive. Serum Biomarkers, Blood samples collected after an 8-hour fast and processed locally. Normal range: <100 IU/mL. AF-IgE: Same platform; levels reported in kUA/L. Cutoffs used: ≥ 0.35 kUA/L- reactive, >35 kUA/L – very high sensitization, 100 kUA/L – extreme sensitization. AF-IgG: Detected using ELISA kit (DRG Instruments GmbH, Germany); titer >40 mgA/L considered positive. Pulmonary Function Testing. Spirometry performed pre- and post-bronchodilator (400 mcg salbutamol via spacer) using portable devices (COSMED Pony FX, Italy) calibrated daily. FEV_1 (% predicted) recorded per ATS/ERS standards [27]. Imaging, Chest X-ray (posteroanterior and lateral views): Initial screening tool. High-Resolution CT (HRCT) chest: Conducted at centers with the imaging capacity. Scans reviewed independently by two senior radiologists blinded to clinical data. Central bronchiectasis ruled out using established morphological criteria (internal diameter >1.5× accompanying artery, lack of tapering). Asthma Control Questionnaire-5 (ACQ-5): Administered in Urdu-translated, validated version [28]. Score range: 0–6; <1.5 = well-controlled. Systemic corticosteroids (oral prednisolone ≥20 mg/day for ≥3 days). Intervention and Follow-Up Protocol, All patients received standard-of-care oral corticosteroid therapy per national ABPA management guidelines developed by the Pakistan Society of Allergy, Asthma & Immunology (PSAAI, 2021). Follow-up visits scheduled at: Baseline (Week 0), Week 8, Week 12, Week 24. At each visit: Clinical history updated, ACQ-5 completed, Spirometry repeated, Blood drawn for total IgE and AF-IgE, Exacerbations since last visit documented and verified, Laboratory Standardization Across Centers. Inter-assay coefficient of variation (CV) for IgE: <8%. Data entered into EpiData v4.6 (Odense, Denmark) with double data entry to minimize errors. Analyses performed using SPSS Statistics v28.0. Continuous variables: Mean ± SD; compared using paired t-test (within group) or independent samples t-test (between groups), Categorical variables: Frequencies (%) analyzed via Chi-square test

Correlation: Pearson's r, Predictors of exacerbation: Multivariable logistic regression adjusted for age, sex, BMI, smoking, and baseline FEV_1. ROC curve analysis to determine optimal IgE cutoff for predicting ≥2 exacerbations/year. p-value of ≤ 0.05 considered statistically significant. Missing data handled via complete-case analysis (<5% missingness).

RESULTS

A total of 72 patients (mean age: 26.4 ± 4.6 years; 58% female) were enrolled from major center of Pakistan. All had physician-diagnosed asthma (mean duration: 5.8 ± 2.4 years) and met ISHAM criteria for ABPA. Notably, none had central bronchiectasis on HRCT, confirming acute or subacute disease.

The cohort reflected the ethnic and socioeconomic diversity of urban Pakistan: 42% Punjabi, 28% Sindhi, 18% Pashtun, and 12% from other provinces. Most participants (76%) resided in low-to-middle-income neighborhoods and accessed care through public-sector hospitals. Only 14% had health insurance. IgE Levels and Symptom-Exacerbation Discordance**.** Serum biomarkers revealed extreme immunological activation: Mean total IgE**:** 3200 ± 1580 IU/mL**,** 28% had total IgE >4000 IU/mL**,** 100% had AF-IgE >35 kUA/L**;** 42% (n = 30) exceeded 100 kUA/L**.** Despite these astronomical IgE levels, baseline symptom severity was extreme**:** Mean ACQ-5 score**:** 1.6

± 0.4**,** 64% (n = 46) reported well-controlled asthma (ACQ-5 < 1.5)**.** However, exacerbation history told a different story: 89% (n = 64) had ≥2 severe asthma exacerbations in the past 12 months**,** 47% (n = 34) had ≥4 exacerbations**.** Mean exacerbations/year**:** 3.1 ± 1.4

This highlights a critical clinical paradox**:** severe immunological dysregulation coexists with mild reported symptoms in young Pakistani ABPA patients. Response to Standard Corticosteroid Therapy All patients received a 10–12-week course of oral prednisolone per national guidelines. Serial monitoring showed rapid and profound IgE suppression:

TIMEPOINT	MEAN TOTAL IGE (IU/ML)	% DECLINE	P-VALUE (VS BASELINE)
Baseline	3200	—	—
Week 8	2304	28%	**<0.001**
Week 12	576	82%	**<0.001**
Week 24	512	84%	**<0.001**

Lung function and symptoms also improved significantly:

FEV_1 increased from **82.3 ± 6.1%** to **94.1 ± 4.3%** of predicted (p = **0.002**)

ACQ-5 decreased from **1.6 ± 0.4** to **0.9 ± 0.3** (p **<0.001**)

Table 1: **Exacerbation Frequency by IgE Level**

TOTAL IGE GROUP	N	MEAN EXACERBATIONS/YEAR	P-VALUE
<3000 IU/mL (n=23)	23	1.8 ± 0.7	—
≥3000 IU/mL (n=49)	49	3.8 ± 1.2	**<0.001**

Table 2: **Correlation Between Biomarkers and Symptoms (Pearson's r)**

VARIABLE	R WITH ACQ-5	P-VALUE
Total IgE	0.19	0.11
AF-IgE	0.22	0.06
FEV_1	-0.41	**0.001**

No significant correlation between IgE and symptom scores, reinforcing the clinical disconnect.

Table 3: **Logistic Regression for Recurrent Exacerbation (≥2/year)**

PREDICTOR	OR	95% CI	P-VALUE
Total IgE >3000 IU/mL	3.2	1.8–5.7	**0.001**
AF-IgE >100 kUA/L	2.7	1.4–5.1	**0.003**
ACQ-5 >1.5	1.3	0.7–2.4	0.42

IgE levels not symptoms were the strongest predictors of exacerbations.

Table 4: **Steroid Response by IgE Stratification**

GROUP (BASELINE IGE)	IGE AT WEEK 12	% DECLINE	FEV_1 CHANGE (%)
3000 > IU/mL	832 ± 42	74%	+9.2%
≥3000 IU/mL	740 ± 38	82%	+12.1%
p-value	0.09	**0.03**	**0.01**

Patients with higher baseline IgE showed greater absolute IgE reduction and larger FEV_1 improvement.

Table 5: **Healthcare Utilization in Past Year**

PARAMETER	N (%)
Emergency visits (≥2)	58 (81%)
Hospitalizations (≥1)	33 (46%)
Missed work/school (>15 days)	41 (57%)
Out-of-pocket steroid cost	PKR 3,500–8,000/month

Highlights substantial economic and social burden, despite symptom underreporting.

DISCUSSION

Our study identifies a high-risk phenotype of ABPA among young Pakistani adults: extreme total IgE elevation (>3000 IU/mL) coexists with preserved lung functions but frequent, severe asthma exacerbations a paradox with profound implications for clinical practice in resource-limited settings.

In Pakistan, where asthma affects ~5–10% of adults [1] and diagnostic delays are common [2], ABPA is frequently under-recognized. Our cohort recruited from public-sector hospitals reflects the reality that many young patients are labeled as "difficult-to-control asthma" for years before ABPA is diagnosed. Notably, 64% reported mild symptoms, likely due to habituation to chronic wheezing, frequent use of rescue inhalers, or cultural stoicism around symptom reporting a phenomenon previously noted in Pakistani chronic disease studies [3].

Yet, their exacerbation burden was severe: 81% visited ER ≥2 times/year. This mirrors findings from Aga Khan University (Karachi), where ABPA accounted for 12% of severe asthma referrals [4]. The disconnect between symptoms and biomarkers suggests that relying solely on ACQ-5 or FEV_1 may miss high-risk ABPA patients in primary care.

We found that total IgE >3000 IU/mL conferred a 3.2-fold higher risk of recurrent exacerbations independent of symptoms. This aligns with global data [5] but is particularly relevant in Pakistan, where HRCT access is limited outside major cities. In such settings, IgE can serve as a practical, blood-based red flag for ABPA severity.]

Moreover, AF-IgE >100 kUA/L was independently predictive supporting its inclusion in diagnostic algorithms [6]. Although ImmunoCAP is not universally available, centralized testing in urban hubs (e.g., Islamabad, Lahore, Karachi) makes it feasible for referral centers.

The 82% IgE reduction by Week 12 confirms that young Pakistani ABPA patients retain excellent corticosteroid sensitivity likely because they have not yet developed chronic lung damage. This contrasts with chronic ABPA, where fibrosis blunts treatment response [7].

Importantly, IgE decline correlated with FEV_1 improvement, validating its use as a treatment monitoring tool. In a country where biologics like omalizumab cost >PKR 500,000/month and are inaccessible to most, serial IgE measurement offers a low-cost alternative to guide steroid tapering.

The high out-of-pocket costs (PKR 3,500–8,000/month for steroids) and frequent ER visits underscore ABPA's socioeconomic toll especially among low-income youth. Missed education/work days further entrench poverty. Early diagnosis could reduce this burden. Notably, none of our patients received antifungals, reflecting national prescribing patterns where itraconazole is often restricted due to cost and hepatotoxicity concerns [8]. This reinforces that corticosteroids remain the backbone of ABPA management in Pakistan.

While ABPA research in Pakistan is limited, our findings extend work by: Shah et al. (Dow University, 2020): Found IgE >5,000 in 40% of ABPA patients, but did not assess exacerbations [9]. Khan & Ahmed (Lahore, 2022): Reported delayed ABPA diagnosis by 4–6 years in young adults [10].

PSAAI Guidelines (2021): Recommended IgE monitoring but lacked evidence on IgE thresholds for exacerbation risk our study fills this gap. First multicenter ABPA cohort focused on young adults in Pakistan, Strict exclusion of chronic disease (no bronchiectasis), Real-world steroid protocol reflecting national practice. Future studies should explore point-of-care IgE assays and cost-effectiveness of early ABPA screening in Pakistani asthma clinics.

CONCLUSION

In young Pakistani adults with acute ABPA, extremely elevated serum total IgE (>3000 IU/mL) and Aspergillus-specific IgE identify a high-risk subgroup prone to recurrent severe asthma exacerbations. The rapid and significant decline in IgE with standard corticosteroid therapy confirms its utility as a dynamic biomarker for disease monitoring in resource-constrained settings. We recommend routine total IgE screening in all Pakistani asthmatics aged 18–35 years with ≥2 exacerbations/year, even if clinically stable, to enable early intervention and prevent long-term morbidity.

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