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Clinical and Inflammatory Features of Exacerbation-Prone Asthma: A Cross-Sectional Study Using Multidimensional Assessment

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Keywords
Exacerbation-prone asthma · Eosinophils · Bronchodilator reversibility

Abstract

Background: Reducing asthma exacerbations is a major target of current clinical guidelines, but identifying features of exacerbation-prone asthma (EPA) using multidimensional assessment (MDA) is lacking. ***Objective:*** To systemically explore the clinical and inflammatory features of adults with EPA in a Chinese population. ***Methods:*** We designed a cross-sectional study using the Severe Asthma Web-based Database from the Australasian Severe Asthma Network (ASAN). Eligible Chinese adults with asthma (n = 546) were assessed using MDA. We stratified patients based on exacerbation frequency: none, few (1 or 2), and exacerbation prone (≥3). Univariate and multivariable negative binomial regression analyses were performed to investigate features associated with the frequency of exacerbations. ***Results:*** Of 546 participants, 61.9% had no exacerbations (n = 338), 29.6% had few exacerbations (n = 162), and 8.4% were exacerbation prone (n = 46) within the preceding year. EPA patients were characterized by elevated blood and sputum eosinophils but less atopy, with more controller therapies but worse asthma control and quality of life (all $p < 0.05$). In multivariable models, blood and sputum eosinophils (adjusted rate ratio = 2.23, 95% confidence interval = [1.26, 3.84] and 1.67 [1.27, 2.21], respectively), FEV_1 (0.90 [0.84, 0.96]), bronchodilator responsiveness (1.16 [1.05, 1.27]), COPD (2.22 [1.41, 3.51]), bronchiectasis (2.87 [1.69, 4.89]), anxiety (2.56 [1.10, 5.95]), and depression (1.94 [1.20, 3.13]) were found. Further, upper respiratory tract infection (1.83 [1.32, 2.54]) and food allergy (1.67 [1.23, 2.25]) were at high risk of asthma symptom triggers. ***Conclusion:*** EPA is a clinically recognizable phenotype associated with several recognizable traits that could be addressed by targeted treatment.

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Introduction

Asthma is a common chronic disease across the globe, affecting 4.2% of the adult population (about 45.7 million people) in China [1]. Frequent asthma exacerbations contribute to severe public health problems and a high burden from asthma-related costs [2]. Severe exacerbations occur in patients with severe disease as well as those with mild or well-controlled asthma [3]. Exacerbations are also a risk factor for the progression to severe disease [4]. As such, reducing the number of exacerbations is a major aim of current clinical guidelines in asthma [5]. Notably, the total exacerbation burden is experienced by only a fraction of patients who experience frequent exacerbations. It is reported that <5% of the patients with asthma are responsible for almost half of the total asthma exacerbation burden [6]. Understanding why this small group of asthma patients suffer from frequent exacerbations is crucial.

Several studies have investigated risk factors of exacerbations, including sex, age, race, lower income [7], smoking, lung function [8], and viral respiratory infections [9]. These studies however did not explore whether these risk factors are related to frequent exacerbations. Even though various endogenous and exogenous factors are implicated in asthma exacerbations, only a few studies were involved in multidimensional assessment (MDA) of patients with exacerbation-prone asthma (EPA) [10].

From 13 clinical and environmental factors, ten Brinke and colleagues [11] identified 2 specific comorbidities (severe chronic rhinosinusitis and psychological dysfunction) that were independently associated with frequent exacerbations in severe asthma patients, but inflammatory biomarkers and lung function were lacking. Recently, a cohort study of adults and children (60% of population with severe asthma) from the Severe Asthma Research Program (SARP) network described EPA as a phenotype which was independent of asthma severity [12]. They also identified several factors (gastroesophageal reflux disease [GERD], chronic rhinosinusitis, obesity, airway reversibility, and blood eosinophils) that were associated with frequent exacerbations. However, psychological health [13, 14] and smoking [13, 15] which had previously been reported as potentially modifiable clinical factors were not evaluated. Some further studies with smaller sample sizes reported no significant findings in inflammation or comorbid diseases on a limited basis [14, 16, 17]. Therefore, extensive MDA and in-depth biological profiling for EPA are still needed.

A more recently published study based on multiethnic individuals from 12 Asthma Clinical Research Network and Asthma Net trials showed that the risk factors of EPA differed according to race. Grossman et al. [18] identified chronic rhinosinusitis, allergic rhinitis, and GERD were only associated with increased exacerbation risk in Blacks rather than Caucasians. Since few studies focus on EPA in Asians and there are no available data from a Chinese population, it is unclear whether these risk factors contribute to frequent exacerbations in the Chinese population. Accordingly, it is urgently needed to identify predictors of frequent exacerbation in this unexplored population with EPA.

The aim of this study is to explore sociodemographic and clinical characteristics of Chinese adults with EPA and identify risk factors associated with frequent exacerbations using MDA. Some of the results of this study have previously been reported as an abstract [19].

Methods

Study Design and Participants

This was a cross-sectional study in which data were based on the Australasian Severe Asthma Network (ASAN) [20]. Participants were prospectively and consecutively recruited, and a standardized protocol was used for clinical data collection, acquisition, and detection of experimental samples (sputum and blood), and quality control of source data was provided by ASAN [20].

Adults (≥18 years old) diagnosed with asthma were from the asthma clinic of West China Hospital, Sichuan University, from March 2014 to December 2018. The diagnosis of asthma was confirmed by clinicians according to the Global Initiative for Asthma (GINA) guideline [5]. This included current episodic respiratory symptoms with the evidence of airway hyperresponsiveness or variable airflow limitation (decline in forced expiratory volume in 1 s [FEV_1] from baseline of ≥20% with methacholine <2.565 mg of provocative dose or increase in FEV_1 of >12% and >200 mL from baseline, 15 min after 400 μg of salbutamol). Severe asthma was defined as asthma that remained uncontrolled despite step 4 or 5 treatment, according to the GINA guideline [5]. All participants were recruited during a stable state defined as no exacerbation or respiratory tract infection for at least 1 month before enrollment. We excluded the subjects who were pregnant and breastfeeding women, those with chronic unstable diseases of other systems, and those with recent cardiac or thoracic surgery.

The institutional review board at West China Hospital, Sichuan University (Chengdu, China), reviewed and approved this study (No. 2014-244). All included participants gave written informed consents prior to participation.

Assessment and Definition of Exacerbation Frequency

A medical history intake questionnaire regarding exacerbation details was completed by participants. Then, the frequency of asthma exacerbations was determined by cross-checking process by clinical researchers based on records from the medical records system and self-reported number of exacerbations in the past 12 months. We excluded those if self-reported acute events were not

proved by their medical records. According to the frequency of severe exacerbations within the preceding year, all included participants were classified into 3 groups of patients with no exacerbation, few exacerbations (1 or 2), and exacerbation prone (EPA, 3 or more). Severe asthma exacerbations were defined by the use of systemic corticosteroid for acute asthma for at least 3 days according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) statement [21]. The criteria for severe asthma exacerbations also included hospitalization or emergency room or intensive care unit visits requiring systemic corticosteroids for asthma [21].

Data Collection and Clinical Assessments

MDAs were completed in participants and involved collection of demographic characteristics, medication use, comorbidities, and asthma symptom triggers. Asthma control was assessed using the Asthma Control Questionnaire (ACQ) [22], and health status was assessed using the Asthma Quality of Life Questionnaire (AQLQ) [23] and the Hospital Anxiety and Depression Scale (HADS) [24], previously described [20]. Participants also underwent spirometry, fractional exhaled nitric oxide (FeNO), skin-prick testing (SPT), and systemic and airway inflammation assessment in peripheral blood and induced sputum. Participants underwent standard measurement of FeNO by an airway inflammation monitor (NioxVero®; Aerocrine, Sweden). Atopy was confirmed by at least 1 positive SPT to common allergens including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), mold (*Alternaria tenuis* and *Aspergillus* species), dog hair, cat hair, pollen (ragweed, birch, and London plane), and cockroach as described previously [25]. Further, venous blood samples were collected either in ethylenediaminetetraacetic acid-treated tubes for total and differential blood cell counts or untreated tubes to obtain serum for measurement of total IgE level by immunoassay (Beckman Immage 800 immunoassay analyzer; Beckman Coulter Inc., USA), with a minimum detectable level of IgE of 5.0 IU/mL.

Lung Function and Bronchodilator Responsiveness

Participants were asked to withhold any long-acting β_2-agonists or anticholinergics for at least 24 h and short-acting β_2-agonists for ≥12 h prior to attendance. Spirometry was performed according to the ATS/ERS standards [26]. Baseline (pre) and postsalbutamol (post) FEV_1 and forced vital capacity (FVC) were assessed before and 15 min after the inhaled administration of 400-μg salbutamol (GSK, A vda de Extremadura, Spain) delivered by a metered-dose inhaler and spacer (150 mL, Wanbo Technology Corp., Shanghai, China) using a standardized spirometer (Med Graphics CPES/D USB, St. Paul, MN, USA). The largest FVC and the largest FEV_1 from 3 forced expiratory curves were used for analysis [26]. Predicted FEV_1 and FVC were calculated using data from the Chinese population [27, 28]. Reversibility in FEV_1 was defined as follows: change (Δ) FEV_1, % = (post-FEV_1 − pre-FEV_1)/pre-FEV_1 × 100.

Sputum Induction and Processing

Sputum induction was performed with routine standard methods as described in our previous studies [29]. In brief, sputum was induced after pretreatment with 400 μg of inhaled salbutamol administration through adopting a spacer device. A total of 15.5-min sputum induction was then performed using 4.5% saline nebulized by an ultrasonic nebulizer (Cumulus; HEYER Medical AG, Bad Ems, Germany). Sputum was induced with 0.9% saline for safety if FEV_1 was <40% of predicted at baseline. The procedure was stopped if FEV_1 declined >15% from baseline. Sputum samples were processed with plug selection and dithiothreitol treatment within 2 h. Cytospins were prepared using centrifugation smear (CYTOPRO 7620; WESCOR®, Inc., South Logan, UT, USA) and stained (May-Grunwald-Giemsa), and then differential cell counts (eosinophils, macrophages, neutrophils, and lymphocytes) were performed by 2 well-trained laboratory researchers independently, 1 from Australia and 1 from China, for accuracy.

Definitions of Clinical Phenotypes

We further classified participants within currently recognized phenotypes. Allergic asthma was defined as asthma with a positive SPT and documentation of symptoms in response to allergen exposure based on medical history [30]. Eosinophilic asthma was classified as sputum eosinophils >3% [31] or blood eosinophil count >300 cells/μL if induced sputum was unavailable [32]. Early-onset asthma was categorized as asthma onset before age 12 [33]. High T-helper (Th) type 2 asthma was defined as a total IgE level of >100 IU/mL and an eosinophil count of 0.14×10^9 cells/L or more [34]. Elderly asthma was defined as asthma in elderly patients (>65 years). Obese asthma was defined as asthma in a patient with BMI ≥30 kg/m^2.

Statistical Analyses

Descriptive analysis of variables is presented as *n* (%) for categorical data, and continuous data are presented as mean with standard deviations or median with interquartile range depending on distribution assessed by the Kolmogorov-Smirnov test. We compared continuous variables using 1-way ANOVA or Kruskal-Wallis H test appropriately and categorical variables using χ^2 tests among the participants in the 3 groups determined by exacerbation frequency. Two-tailed Fisher's exact χ^2 tests were used when small cell frequencies were observed. In addition, post hoc Bonferroni comparisons were performed to explore differences between groups, with the cutoff for significance set at α/n ($\alpha = 0.05$ and n is the number of comparisons).

We also examined exacerbation frequency as a discrete count in outcome. Univariate and multiple negative binomial regression models were established to investigate independent factors associated with exacerbation frequency. We examined the associations between each variable and exacerbations by univariate negative binomial regression models. Variables associated with exacerbations on univariate analysis (at $p < 0.10$) were included in adjusted multivariable models. The adjusted rate ratio (aRR) with 95% confidence interval (CI) was calculated. Age, sex, smoking status, asthma duration, and medication adherence were included in all models as potential confounders.

Data analyses were performed with SPSS software (version 23.0) for IBM Professional (SPSS, Inc., Chicago, IL, USA). Two-sided p value ≤0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

Among 546 participants included in our study, 338 (61.9%) had no exacerbations, 162 (29.6%) had few exac-

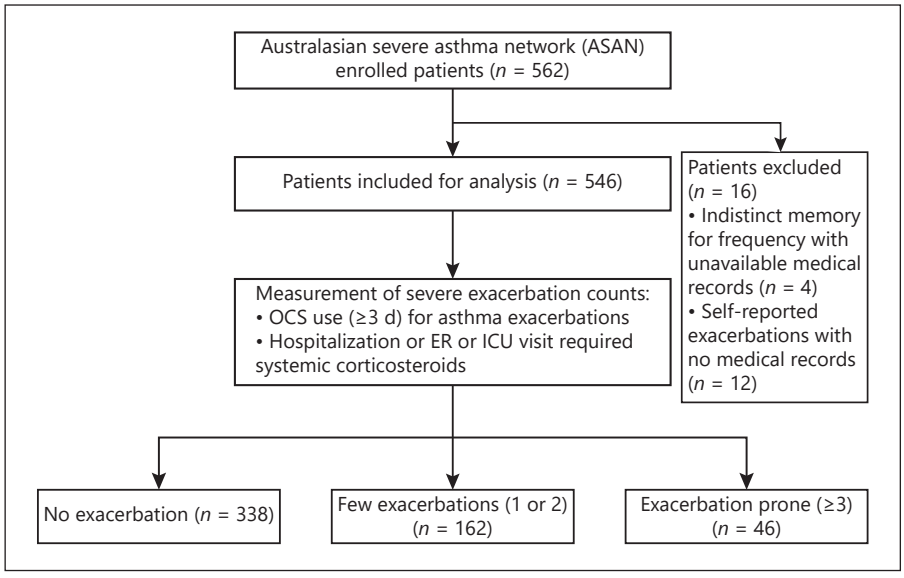

Fig. 1. Flowchart of asthma exacerbations classification. OCS, oral corticosteroid; ER, emergency room; ICU, intensive care unit.

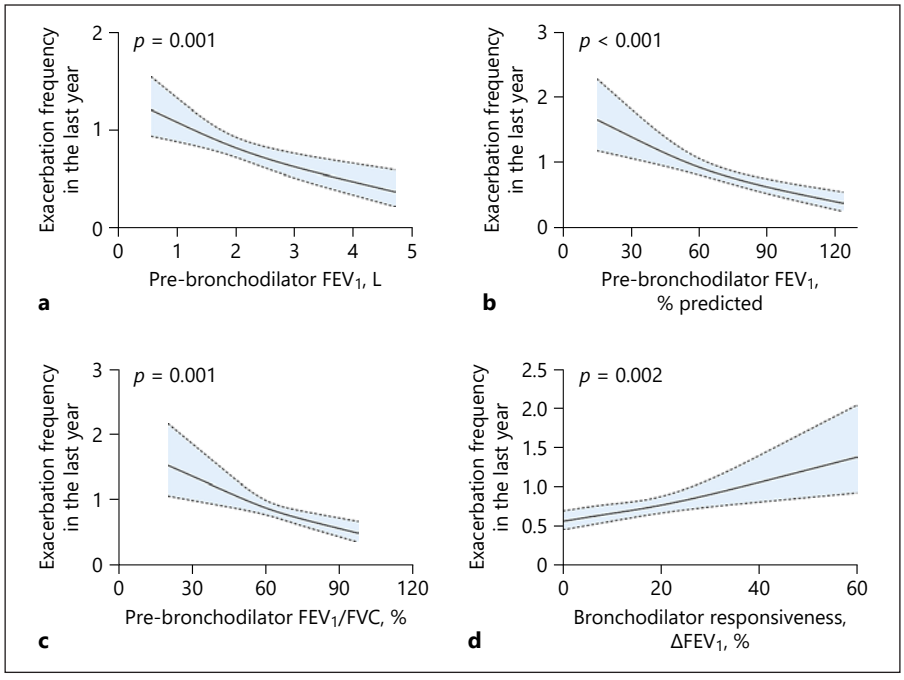

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Fig. 2. Regression curves of exacerbation frequency and lung function in unadjusted models. Negative binomial models were used to generate predicted number of exacerbation frequency (solid line) along with 95% CIs (dashed line) shaded with blue color. Four parts of the figure show unadjusted models of exacerbation frequency by FEV_1 (**a**), FEV_1% predicted (**b**), FEV_1/FVC (**c**), and ΔFEV_1 (**d**). Significance testing refers to the slope of the curve, and p values are labeled. FEV, forced expiratory volume; FVC, forced vital capacity.

erbations, and 46 (8.4%) were exacerbation prone in the previous year (Fig. 1). Sociodemographic and clinical characteristics of patients within the 3 groups are shown in Table 1. Age of the participants differed within groups (44.1 [35.2, 54.8] vs. 46.9 [38.2, 59.5] vs. 48.7 [36.6, 60.6] years, $p = 0.045$) for no, few, and exacerbation prone participants, respectively. Compared to the no exacerbation group (89.2%), a greater proportion of the patients with few exacerbations (95.4%) and those that were exacerbation prone (97.6%) had medical insurance ($p = 0.031$). The EPA patients contained lower proportion of atopy (30.4%) than other 2 groups (57.9 and 48.0%) ($p = 0.001$). As expected, severe asthma was enriched in the EPA group ($p = 0.027$). Although the participants with EPA were using more intensive controller therapies such as inhaled corticosteroids ($p = 0.016$), long-acting β-agonists ($p = 0.002$), theophylline ($p < 0.001$), and oral corticosteroids ($p = 0.001$), those with EPA had worse asthma con-

Table 1. Demographic and clinical characteristics of participants grouped by the frequency of asthma exacerbations in the preceding year

Variables	No exacerbation (0)	Few exacerbations (1 or 2)	Exacerbation prone (≥3)	χ^2/H/*t*	*p* value
N	338	162	46		
Male, *n* (%)	117 (34.6)	67 (41.4)	17 (30.37)	2.141	0.343
Age, years	44.14 (35.17, 54.83)	46.93 (38.17, 59.54)	48.72 (36.64, 60.62)	6.202	**0.045**
Asthma duration, years	7.66 (2.48, 18.84)	6.02 (2.88, 22.15)	9.09 (3.20, 22.45)	0.574	0.750
Asthma onset age, years	32.00 (20.00, 46.00)	36.00 (19.75, 46.00)	35.00 (21.50, 47.25)	1.801	0.406
BMI, kg/m^2	22.75 (20.83, 25.35)	22.64 (20.64, 24.80)	24.18 (22.00, 26.39)	4.444	0.108
Atopy, *n* (%)	186 (57.9)	73 (48.0)	14 (30.4)†††	14.016	**0.001**
Education, *n* (%)					
Uneducated	61 (19.6)	30 (20.4)	12 (30.8)	10.390	0.109
Primary	80 (25.6)	41 (27.9)	8 (20.5)		
Middle and high school	59 (18.9)	39 (26.5)	10 (25.6)		
College or above	112 (35.9)	37 (25.2)	9 (23.1)		
Family income, *n* (%)					
Low	84 (27.1)	48 (32.9)	14 (35.0)	7.555	0.109
Moderate	178 (57.4)	87 (59.6)	23 (57.4)		
High	48 (15.5)	11 (7.5)	3 (7.5)		
Medical insurance, *n* (%)	282 (89.2)	146 (95.4)†	40 (97.6)	12.326	**0.031**
Smoking status (ever/current/never), *n*	36/44/248	18/33/110	13/1/31†	11.435	**0.020**
Pack years	2.53±8.79	4.29±11.15	3.53±10.59	5.068	0.079
Asthma medications					
ICS daily dose (BPD), μg	400 (400, 1,000)	400 (400, 1,000)	1,000 (400, 1,000)††	−2.413	**0.016**
LABA, *n* (%)	180 (53.3)	95 (58.6)	37 (80.4)†††	12.426	**0.002**
LTRA, *n* (%)	106 (31.4)	56 (34.6)	18 (39.1)	1.373	0.503
Theophylline, *n* (%)	39 (11.5)	42 (25.9)†††	13 (28.3)†††	20.205	**<0.001**
OCS, *n* (%)	5 (1.5)	7 (4.3)	6 (13.0)††	13.701	**0.001**
Severe asthma, *n* (%)	35 (10.4)	23 (14.2)	11 (23.9)†	7.249	**0.027**
Medication adherence, %	88.37±12.84	90.89±5.00	91.13±8.57	2.132	0.317
ACQ	0.50 (0.00, 1.33)	1.00 (0.17, 1.67)†	1.08 (0.17, 2.38)††	15.219	**<0.001**
AQLQ	5.84 (5.16, 6.38)	5.63 (5.12, 6.13)	5.11 (4.13, 6.02)††	14.380	**0.001**
HADS-A scores	1.00 (0.00, 4.00)	1.00 (0.00, 4.00)	1.50 (0.00, 4.00)	1.187	0.552
HADS-D scores	1.00 (0.00, 3.25)	1.00 (0.00, 4.25)	2.00 (0.00, 4.00)	4.874	0.087

BMI, body mass index; BPD, beclomethasone dipropionate; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; HADS-A, anxiety symptom of the Hospital Anxiety and Depression Scale; HADS-D, depression symptom of the Hospital Anxiety and Depression Scale. Statistical significance is presented in bold. † $p < 0.017$. †† $p < 0.005$. ††† $p < 0.001$ versus the no exacerbation group, with the Bonferroni correction.

trol (1.08 [0.17, 2.38] vs. 0.50 [0.00, 1.33] vs. 1.00 [0.17, 1.67], $p < 0.001$ for ACQ) and quality of life (5.11 [4.13, 6.02] vs. 5.84 [5.16, 6.38] vs. 5.63 [5.12, 6.13], $p = 0.001$ for AQLQ) than other patients with no and few exacerbations.

Lung Function and Inflammation

Pre- and postbronchodilator lung function in patients with no, few, and EPA in the past year is shown in Table 2. Compared with the patients with no exacerbation, the EPA patients had more severe airway obstruction measured as FEV_1 (L) ($p = 0.002$ and $p = 0.004$, respectively), FEV_1 %predicted ($p = 0.007$ and $p = 0.001$, respectively) and FEV_1/FVC ($p = 0.011$ and $p = 0.001$, respectively), both at prebronchodilator and postbronchodilator. However, no statistical difference was found in ΔFEV_1 (%) across groups ($p = 0.312$). Unadjusted negative binomial models indicated a linear correlation between exacerbations in the previous year and FEV_1 (L) ($\beta = -0.27$, $p = 0.001$) (Fig. 2a), FEV_1 %predicted ($\beta = -0.01$, $p < 0.001$)

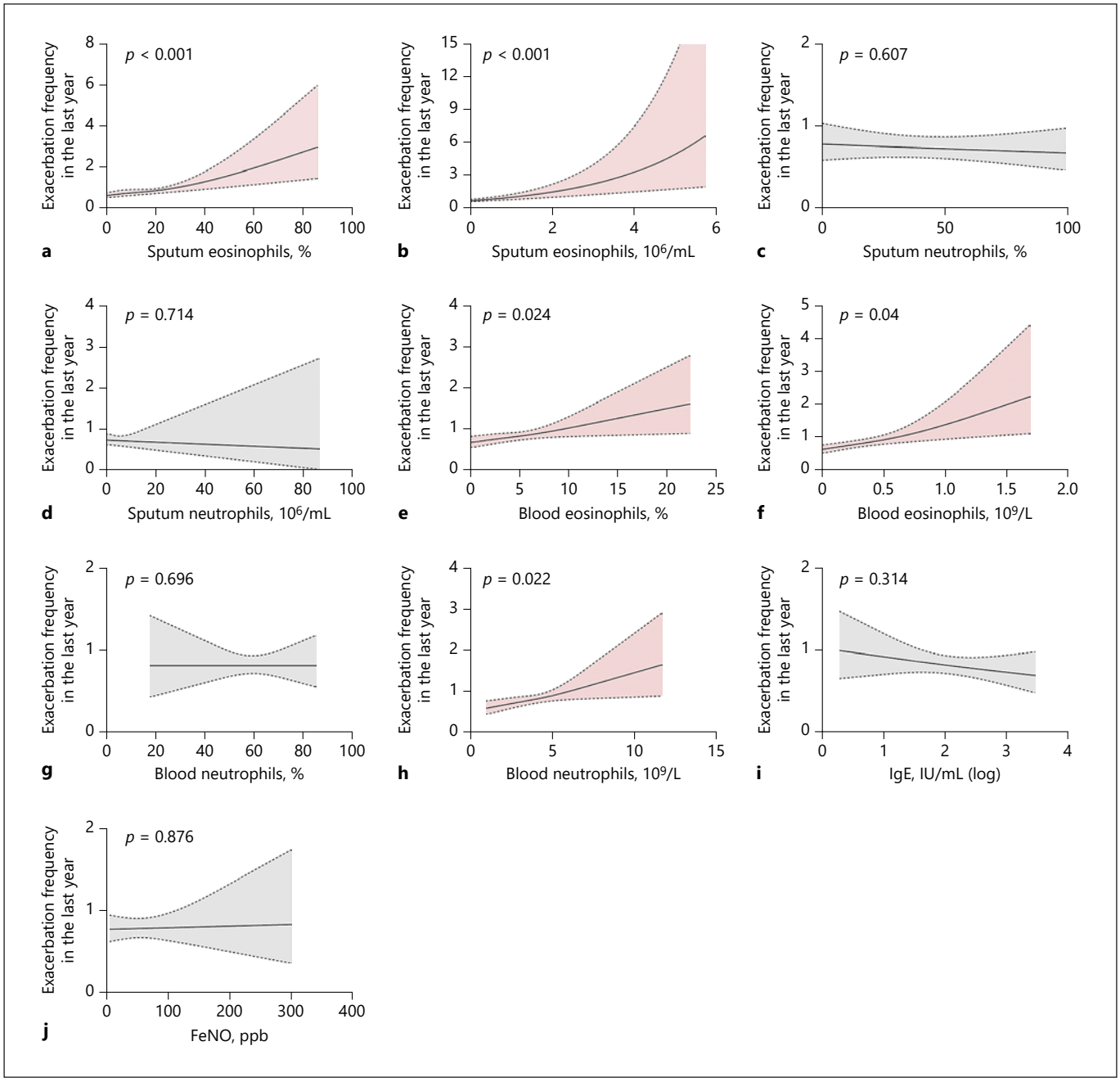
Table 2. Lung function and airway and systemic inflammatory cells and biomarkers grouped by the frequency of asthma exacerbations in the preceding year

Variable	No exacerbation (0)	Few exacerbations (1 or 2)	Exacerbation prone (≥3)	H/*t*	*p* value
Lung function					
N	338	162	46		
Prebronchodilator					
FEV_1, L[#]	2.18±0.75	2.09±0.83	1.83±0.85[††]	5.472	**0.004**
FEV_1, %predicted	74.62±18.49	71.27±22.28	64.46±24.01[†]	7.983	**0.018**
FEV_1/FVC, %	67.34±12.28	65.68±14.64	61.22±15.57[††]	4.470	**0.012**
Postbronchodilator					
FEV_1, L[#]	2.43±0.76	2.28±0.88	2.08±0.83[††]	5.761	**0.003**
FEV_1, %predicted[#]	83.48±17.39	78.52±22.31	72.38±21.08[††]	6.264	**0.002**
FEV_1/FVC, %	73.62 (63.07, 81.55)	69.78 (59.09, 79.35)	62.85 (55.77, 73.76)[††]	13.070	**0.001**
ΔFEV_1, %	15.4±11.55	14.52±11.17	21.95±21.68	2.332	0.312
Inflammation					
FeNO, ppb	34 (20, 62)	32 (20, 55)	42 (27, 89)	2.282	0.319
Sputum					
N	211	87	25		
Eosinophils, 10^6/mL	0.06 (0.00, 0.08)	0.06 (0.00, 0.34)	0.00 (0.03, 0.86)	−1.172	0.241
Eosinophils, %	0.25 (0.00, 1.75)	0.25 (0.00, 1.00)	1.50 (0.00, 31.75)	4.874	0.087
Neutrophils, 10^6/mL	0.96 (0.30, 2.88)	1.47 (0.36, 3.37)	0.69 (0.23, 1.92)	−0.498	0.618
Neutrophils, %	32.25 (14.88, 64.74)	45.50 (18.25, 76.50)	24.25 (8.75, 53.25)	5.576	0.062
Lymphocytes, 10^6/mL	0.02 (0.00, 0.05)	0.03 (0.01, 0.05)	0.01 (0.00, 0.02)	−0.817	0.414
Lymphocytes, %	0.50 (0.25, 1.50)	0.50 (0.25, 1.31)	0.25 (0.00, 0.63)	5.248	0.073
Monocytes, 10^6/mL	1.47 (0.74, 2.35)	1.44 (0.48, 2.37)	1.28 (0.58, 1.88)	−0.232	0.817
Monocytes, %	58.63 (28.06, 80.44)	48.50 (19.25, 69.75)	44.75 (17.75, 78.75)	1.607	0.448
Blood					
N	338	162	46		
Leukocytes, 10^9/L	5.77 (4.80, 6.96)	6.36 (4.97, 7.77)	6.46 (5.47, 8.09)	3.254	**0.039**
Neutrophils, 10^9/L	3.40 (2.73, 4.22)	3.60 (2.70, 4.94)	3.98 (3.26, 4.69)	6.529	**0.038**
Neutrophils, %	59.71 (53.41, 65.06)	59.30 (53.15, 65.53)	61.03 (54.43, 64.74)	−0.662	0.508
Lymphocytes, 10^9/L	1.69 (1.41, 2.05)	1.72 (1.43, 2.09)	1.71 (1.41, 2.25)	0.692	0.707
Lymphocytes, %	29.19 (24.85, 33.78)	28.74 (23.54, 33.87)	28.25 (24.57, 32.76)	−0.488	0.625
Monocytes, 10^9/L	0.33 (0.26, 0.43)	0.37 (0.29, 0.48)	0.35 (0.30, 0.47)	7.237	**0.027**
Monocytes, %	0.06 (0.05, 0.07)	0.06 (0.05, 0.07)	0.05 (0.05, 0.07)	−0.112	0.910
Eosinophils, 10^9/L	0.20 (0.11, 0.35)	0.25 (0.12, 0.41)	0.27 (0.11, 0.52)	2.632	0.268
Eosinophils, %	3.31 (2.08, 5.92)	4.00 (1.81, 7.26)	4.38 (2.00, 6.27)	−2.350	**0.019**
Basophils, 10^9/L	0.03 (0.02, 0.05)	0.03 (0.02, 0.05)	0.04 (0.02, 0.05)	1.415	0.493
Basophils, %	0.54 (0.38, 0.83)	0.56 (0.40, 0.78)	0.55 (0.33, 0.78)	−0.099	0.921
IgE (IU/mL)[#]	289.11±416.44	247.48±370.27	195.02±439.06	0.980	0.376

FEV_1, forced expiratory volume in 1 s; FVC, forced expiratory volume; Δ, change from the baseline; FeNO, fractional exhaled nitricoxide. Statistical significance is presented in bold. [#] Normal transformation in statistical disposal. [†] $p < 0.017$. [††] $p < 0.005$. [†††] $p < 0.001$ versus the no exacerbation group, with the Bonferroni correction.

(Fig. 2b), FEV_1/FVC (β = −0.02, $p = 0.001$), and ΔFEV_1 (%) (β = 0.015, $p = 0.002$) (Fig. 2c, d).

Airway and systemic inflammation in patients with no, few, and EPA is presented in Table 2. The EPA patients had increased sputum eosinophils (%) and reduced neutrophils (%) than patients with no and few exacerbations in the past year, but this did not reach statistical significance ($p = 0.087$ and $p = 0.062$). Unadjusted regression models indicated that sputum eosinophils (% and absolute counts) had a significant linear correlation with exacerbation frequency (β = 0.02, $p < 0.001$, and β = 0.41, $p < 0.001$, respectively) (Fig. 3a, b), but sputum neutrophils were not associated with exacerbation frequency ($p = 0.607$ and $p = 0.714$) (Fig. 3c, d).



Color version available online

Fig. 3. Regression curves of exacerbation frequency with inflammatory cells and biomarkers in unadjusted models. Negative binomial models were used to generate predicted number of exacerbation frequency (solid line) along with 95% CIs (dashed line) shaded with color (red and gray). This figure shows unadjusted models of exacerbation frequency by sputum eosinophils (**a**, **b**), sputum neutrophils (**c**, **d**), blood eosinophils (**e**, **f**), blood neutrophils (**g**, **h**), IgE (**i**), and FeNO (**j**). Significance testing refers to the slope of the curve, and *p* values are labeled. FeNo, fractional exhaled nitric oxide.

Correlation analyses between exacerbation frequency and measures of inflammatory biomarkers were also performed. In peripheral blood, the EPA patients exhibited elevated inflammatory cells such as leukocytes (6.46 [5.47, 8.09] × 10^9/L vs. 5.77 [4.80, 6.96] vs. 6.36 [4.97, 7.77], p = 0.039), neutrophils (3.98 [3.26, 4.69] vs. 3.40 [2.73, 4.22] vs. 3.60 [2.70, 4.94] × 10^9/L, p = 0.038), and the percentage of eosinophils (4.38 [2.00, 6.27] vs. 3.31 [2.08, 5.92]

Table 3. Asthma symptom triggers grouped by the frequency of asthma exacerbations in the preceding year

Variables	No exacerbation (0)	Few exacerbations (1 or 2)	Exacerbation prone (≥3)	χ^2	*p* value
N	338	162	46		
Seasons, *n* (%)	195 (57.9)	96 (59.3)	29 (63)	0.476	0.788
Exercise, *n* (%)	174 (51.8)	79 (48.8)	15 (32.6)	5.976	0.050
Upper respiratory tract infection, *n* (%)	231 (68.8)	131 (80.9)†	40 (87)††	12.759	**0.002**
Work, *n* (%)	54 (16.3)	27 (17)	7 (15.6)	0.755	0.967
Reflux, *n* (%)	27 (8)	15 (9.3)	5 (10.9)	0.755	0.702
Pets, *n* (%)	26 (7.8)	8 (4.9)	4 (8.9)	1.735	0.438
Food, *n* (%)	66 (19.6)	37 (22.8)	17 (37)†	7.204	**0.027**
Aspirin, *n* (%)	5 (1.5)	0 (0)	1 (2.2)	3.112	0.197
Fumes, *n* (%)	58 (17.2)	25 (15.4)	14 (30.4)	5.720	0.057
Rhinitis, *n* (%)	126 (37.4)	62 (38.3)	17 (37)	0.046	0.977

† $p < 0.017$. †† $p < 0.005$. ††† $p < 0.001$ versus the no exacerbation group, with the Bonferroni correction. Statistical significance is presented in bold.

Table 4. Comorbidities in participants with asthma grouped by the frequency of asthma exacerbations in the preceding year

Variables	No exacerbation (0)	Few exacerbations (1 or 2)	Exacerbation prone (≥3)	χ^2	*p* value
N	338	162	46		
Rhinitis, *n* (%)	179 (53.1)	89 (54.9)	22 (47.8)	0.731	0.694
Nasal polyps, *n* (%)	22 (6.5)	17 (10.5)	5 (10.9)	3.126	0.224
GERD, *n* (%)	16 (4.8)	11 (6.9)	5 (10.9)	3.329	0.197
Sleep apnea, *n* (%)	5 (1.5)	1 (0.6)	0 (0)	0.583	0.806
COPD, *n* (%)	14 (4.2)	19 (11.7)††	8 (17.4)††	15.971	<0.001
Bronchiectasis, *n* (%)	9 (2.7)	8 (4.9)	6 (13)††	11.068	**0.004**
Vocal cord dysfunction, *n* (%)	2 (0.6)	0 (0)	1 (2.2)	2.967	0.259
Anxiety, *n* (%)	2 (0.6)	5 (3.1)	2 (4.4)†	6.882	**0.018**
Depression, *n* (%)	1 (0.3)	2 (1.2)	1 (2.2)	3.534	0.108
Osteoporosis, *n* (%)	15 (4.5)	4 (2.5)	3 (6.5)	2.133	0.316
Aspirin sensitivity, *n* (%)	10 (3)	2 (1.2)	1 (2.2)	1.304	0.500
Anaphylaxis, *n* (%)	85 (25.3)	42 (25.9)	15 (32.6)	1.125	0.570
Hyperventilation dysfunctional breathing, *n* (%)	1 (0.3)	1 (0.6)	0 (0)	1.111	0.618
Allergic bronchopulmonary aspergillosis, *n* (%)	1 (0.3)	0 (0)	1 (2.2)	3.616	0.250

GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease. Statistical significance is presented in bold. † $p < 0.017$. †† $p < 0.005$. ††† $p < 0.001$ versus the no exacerbation group, with the Bonferroni correction.

vs. 4.00 [1.81, 7.26]%, $p = 0.019$) in comparison with patients with no and few exacerbations. However, the level of monocytes in blood significantly increased in patients with few exacerbations (0.37 [0.29, 0.48] × 10^9/L) than other 2 groups (0.33 [0.26, 0.43] and 0.35 [0.30, 0.47] × 10^9/L) ($p = 0.027$). The unadjusted regression models showed a linear correlation between exacerbation frequency and the percentage of eosinophils ($\beta = 0.04$, $p = 0.024$) (Fig. 3e) rather than neutrophils ($p = 0.696$) (Fig. 3g) in peripheral blood. The total IgE and FeNO levels did not significantly differ between categories of exacerbation frequency ($p = 0.376$ and $p = 0.319$, respectively) (Table 2) and had no correlation with exacerbation frequency in the regression model ($p = 0.314$ and $p = 0.876$, respectively) (Fig. 3i, j).

Table 5. Factors associated with frequent exacerbations in multivariable negative binomial models

Variables	Unit	aRR[a]	95% CI	*p* value
Lung function				
FEV_1, % predicted	10	0.90	(0.84–0.96)	0.001
Bronchodilator response (ΔFEV_1, %)	10	1.16	(1.05–1.27)	0.003
Inflammation cells				
Blood eosinophils, 10^9/L (log)	1	2.23	(1.26–3.84)	0.005
Sputum eosinophils, 10^6/L (log)	1	1.67	(1.27–2.21)	<0.001
Comorbidities				
COPD		2.22	(1.41–3.51)	0.001
Bronchiectasis		2.87	(1.69–4.89)	<0.001
Anxiety		2.56	(1.10–5.95)	0.029
Depression		1.94	(1.20–3.13)	0.007
Asthma triggers				
Upper respiratory tract infection		1.83	(1.32–2.54)	<0.001
Food		1.67	(1.23–2.25)	0.001
Atopy		0.61	(0.46–0.79)	<0.001

aRR, adjusted rate ratio; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease. [a] RR adjusted for age, sex, smoking status, asthma duration, and medication adherence.

Asthma Symptom Triggers and Comorbidities

Asthma symptom triggers and comorbidities across patients with no, few, and EPA participants are shown in Tables 3 and 4. A greater proportion of EPA participants had symptoms triggered by upper respiratory tract infection (87 vs. 69 vs. 81%, $p = 0.002$) and food (37 vs. 19 vs. 23%, $p = 0.027$) but a lower proportion triggered by exercise (32.6 vs. 51.8 vs. 48.8%, $p = 0.050$) compared with patients with no and few exacerbations. Within participants ($n = 100$) with asthma symptoms triggered by food, 33% ($n = 33$) reported being triggered by common food allergens (peanuts, eggs, mutton, pork, beans, seafood, and fruits) [35] as the cause, and 67% of participants were triggered by spice, pickled food, frozen food, and alcohol. In terms of comorbidities, the EPA participants had a greater proportion with COPD (17.4 vs. 4.2 vs. 11.7%, $p < 0.001$), bronchiectasis (13.0 vs. 2.7 vs. 4.9%, $p = 0.004$), and anxiety (4.4 vs. 0.6 vs. 3.1%, $p = 0.018$) compared with participants with no and few exacerbations (Table 4). Factors associated with exacerbation frequency were identified using multivariable negative binomial regression.

Multivariable negative binomial regression was performed to identify the features associated with exacerbation frequency after adjusting for age, sex, smoking status, asthma duration, and medication adherence (Table 5). The aRR for FEV1% and ΔFEV_1 was 0.90 (95% CI = [0.84–0.96], $p = 0.001$) and 1.16 (95% CI = [1.05–1.27], $p = 0.003$) for every 10% change. Further, eosinophils in sputum (aRR = 1.67, 95% CI = [1.27–2.21], $p < 0.001$ for every log unit) and blood (aRR = 2.23, 95% CI = [1.26–3.84], $p = 0.005$ for every log unit) were positively associated with exacerbation frequency. Atopy displayed a negative correlation (aRR = 0.61, 95% CI = [0.46–0.79], $p < 0.001$). The comorbidities of COPD (aRR = 2.22, 95% CI = [1.41, 3.51], $p = 0.001$), bronchiectasis (aRR = 2.87, 95% CI = [1.69, 4.89], $p < 0.001$), anxiety (aRR = 2.56, 95%

Table 6. Comparison of phenotypes in EPA versus non-EPA patients

Phenotypes	Non-EPA	EPA	χ^2	*p* value
N	500	46		
Eosinophilic asthma, *n* (%)	197 (40.0)	25 (55.6)	4.138	**0.042**
Allergic asthma, *n* (%)	286 (44.8)	14 (30.4)	9.947	**0.002**
Late-onset asthma, *n* (%)	417 (83.6)	38 (82.6)	0.028	0.867
Elderly asthma, *n* (%)	58 (11.6)	9 (19.6)	2.483	0.115
Th2-high asthma, *n* (%)	271 (54.2)	23 (50.0)	0.299	0.585
Obese asthma, *n* (%)	55 (11.0)	5 (10.9)	0.001	0.978

EPA, exacerbation-prone asthma; Th, T-helper. Statistical significance is presented in bold.

CI = [1.10, 5.95], $p = 0.029$), and depression (aRR = 1.94, 95% CI = [1.20, 3.13], $p = 0.007$) were all significantly associated with exacerbation frequency. Further, it was found that upper respiratory tract infection (aRR = 1.83, 95% CI = [1.32, 2.54], $p < 0.001$) and food (aRR = 1.67, 95% CI = [1.23, 2.25], $p = 0.001$) were at high risk of asthma symptom triggers (Table 5).

Differences of Phenotypes in EPA versus Non-EPA

Phenotypes in EPA and non-EPA patients are shown in Table 6. There was significantly more eosinophilic asthma in EPA compared with non-EPA (55.6 vs. 40.0%, $p = 0.042$) patients. The proportion of allergic asthma in patients in the EPA group was lesser than the non-EPA group (30.4 vs. 44.8%, $p = 0.002$). No significant differences were observed in late-onset, elderly, Th2-high, and obese asthma ($p = 0.867$, $p = 0.115$, $p = 0.585$, and $p = 0.987$, respectively).

Discussion

This study comprehensively explored the sociodemographic, clinical, and inflammatory characteristics, concomitant phenotypes of EPA, and the risk factors associated with exacerbation rates using MDA. Compared with precedent studies [12, 14, 36–41] in population enriched for severe asthma patients (>50%), this study was actually conducted in a real-world setting, including 12% severe asthma participants. It enabled the findings of more closely represented features of EPA in the general asthma patient population. Few studies [42, 43] explored features of EPA from the Asian area, and our data from 546 Chinese participants provided essential evidence to this field for the target population. As a result, we found that EPA was associated with severe asthma, worse asthma control and quality of life, airway obstruction, increased airway and systemic inflammation, and more comorbidities. The pathological features of EPA, such as elevated eosinophils reflecting airway and systemic inflammation, airway obstruction, and higher bronchodilator responsiveness, in our data were supported by precedent studies [12, 44]. Specifically, we found that EPA had particular asthma symptom triggers (upper respiratory tract infection and food allergy), distinct comorbidities (COPD, bronchiectasis, and anxiety), and concomitant phenotypes (eosinophilic asthma and nonallergic asthma). Further, the multivariable negative binomial regression models indicated that atopy, FEV_1 %pre, bronchodilator responsiveness, eosinophils either in sputum or blood, comorbidities (i.e., COPD, bronchiectasis, anxiety, and depression), and asthma symptom triggers such as upper respiratory tract infection and food allergy were independently associated with exacerbation frequency after adjusting for confounders.

Asthma exacerbation is considered a highly important outcome, and minimizing events is a major priority of asthma management. It highlights the importance of MDAs and precise treatment [45, 46] in the management of EPA. Agusti et al. proposed the "treatable traits" model of airway diseases, which identifies that key traits have potential treatment benefits. A small randomized controlled trial of a treatable traits model in stable severe asthma showed promising results in reducing primary care presentations for acute asthma and improving quality of life [47]. This approach may be useful in reducing exacerbations in patients who are most at risk. We have identified traits that could be targeted with this approach, and these include airway obstruction, bronchodilator responsiveness, eosinophilic airway inflammation, systemic inflammation, anxiety and depression, upper respiratory tract infection, and bronchiectasis.

We evaluated inflammatory biomarkers in the airway and peripheral blood in order to explore which biomarkers were likely to correlate with risk of frequent exacerbations, which implicated clinical relevance. It was found that EPA was associated with airway and systemic eosinophils despite treatment with glucocorticoids, which has potential implications for targeting eosinophils in those patients. Accordingly, monoclonal antibodies [48] targeting the essential cytokines for the development, recruitment, and survival of eosinophils, such as anti-IL-5 or anti-IL-5 receptor antibodies, would be a promising strategy in EPA. Atopy did not appear to be a prominent trait in EPA. In our study, it did not find a relationship between exacerbations and IgE, and on the contrary, there was a negative relationship of exacerbations with atopy. It has been demonstrated that previous experimental studies indicated that IgE could be easily suppressed in severe asthma [14, 49, 50]. Ilmarinen et al. [51] also showed patients with atopic asthma could be well controlled even with low ICS dose. Accordingly, the patients with atopic asthma in the non-EPA groups may have a better response to ICS and can be well controlled when symptoms fluctuated.

Previously, EPA was described as a phenotype that is independent of asthma severity [12]. Our study indicates that EPA was characterized by an overlap of multiple phenotypes, demonstrating that EPA could be a symptom-based phenotype driven by multiple inflammatory mech-

anisms. Th type 2 response was classically thought to play a central role in asthma, especially in the Th2-high phenotype pathophysiology. However, it was found that 50% of EPA patients had Th2-low/non-Th2 asthma phenotype. Intriguingly, 13% of EPA patients had an overlapping phenotype of eosinophilic and nonatopic asthma, which suggests that allergy may not be a prominent mechanism in those patients. Type 2 innate lymphoid cells in the airways which could contribute to airway eosinophilia might drive this nonatopic subgroup of eosinophilic inflammation in EPA [52].

The worsening airway obstruction in EPA and elevated variability of airway obstruction along with frequent exacerbations raise the question of whether EPA is related to diverse pathophysiologic features of airway remodeling or airway smooth muscle cell proliferation. Furthermore, a vicious circle between asthma exacerbations and increased airway obstruction may be an underlying feature of this phenotype. Bai et al. [53] reported that 1 severe exacerbation per year was associated with a 30.2 mL greater annual decline in FEV_1. Low FEV_1 (especially if <60% predicted) is also a risk factor for asthma exacerbation [8]. For the targeted treatment, Kerstjens and coworkers [54] reported a 21% reduction in the risk of asthma exacerbation associated with tiotropium, along with a significant improvement in FEV_1. However, whether tiotropium is beneficial to EPA remains unclear since a limited effect of tiotropium was observed among patients with high eosinophils [55].

Our study firstly assessed asthma triggers of episodic symptoms in EPA. The profound effect of upper respiratory tract infection was found in our study, which would be explained by impaired innate immunity in EPA [9]. Beyond that, complex categories of food symptom triggers were reported by EPA patients. Future studies may be needed to explore underlying mechanisms of food in triggering asthma symptom of EPA.

Comorbidities are highly prevalent among EPA patients. We did not find a correlation between EPA and rhinitis or GERD, which were previously reported to be associated with increased exacerbation risk in Blacks [18]. A possible reason is that the prevalence of GERD in East Asia (2.5–7.8%) is much lower than that in North America (18.1–27.8%), South America (23.0%), and Europe (8.8–25.9%) [56]. Instead, our data revealed that COPD, bronchiectasis, and anxiety were associated with EPA. It emphasized the necessity to raise awareness and make correct diagnosis of these comorbidities among clinicians to guide an appropriate treatment strategy in these patients with EPA [57, 58]. This suggests that comorbidity varies among races. The strength of the analysis on the relationship between anxiety and EPA might be limited because of the small number of patients with anxiety. We also found that depression was associated with exacerbation frequency at the time of assessment. As interaction effects between depression and asthma have been reported in previous studies [29, 59, 60] and also the association between psychological dysfunction with increased risk of frequent asthma exacerbations, targeted therapy for psychological dysfunction would be beneficial for reducing asthma exacerbations in EPA, but it needs further studies to validate in the future.

The major strength of this study was the MDA of EPA in an unexplored population and the identification of traits associated with exacerbation frequency by multivariable regression models. Importantly, most of these traits are potentially modifiable or "treatable." Clinical trials that explore the therapeutic effect of modifying these traits in EPA are now needed. Our study also has some potential limitations to be addressed. First, we recruited patients consecutively from the asthma clinic of a university hospital. As such, there were more mild-moderate asthma than other relevant studies enriched with severe asthma, such as SARP-3 which had 60% severe asthma in their cohort. Second, our findings only identified those associations of relevant traits with EPA in the cross-sectional design, but the potential causality may need further confirmation. Third, it is likely that work and occupational exposure can be a risk factor in specific phenotypes of work-exacerbated asthma and occupational asthma [61, 62] although we observed work exposures based on self-reports of a relationship between work setting and asthma symptoms.

Conclusion

We identified FEV_1 %pre, bronchodilator responsiveness, sputum and blood eosinophils, COPD, bronchiectasis, anxiety, and depression to be associated with exacerbation frequency in asthma. Furthermore, we found that upper respiratory tract infection and food allergy would be risk factors of symptom triggers for EPA. Most of these implicated traits are potentially modifiable or "treatable." EPA is underpinned by multiple phenotypes and enriched with eosinophilic and nonatopic asthma. This study suggests that EPA is a symptom-based clinical phenotype with implications of various traits requiring targeted treatments to reduce exacerbations.

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Statement of Ethics

The institutional review board at West China Hospital, Sichuan University (Chengdu, China), reviewed and approved this study (No. 2014-244). All included participants gave written informed consents prior to participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.W., L.W., and P.G. conceived the study and performed the data interpretation and manuscript revision. M.F. and X.Z. carried out the data analysis and drafted the manuscript. W.W.W. and P.M.H. conducted the participant recruitment and assisted in data interpretation. Z.H.C., M.X., Q.L., and J.Z. participated in data interpretation. B.O., W.M.L., and V.M. contributed to the manuscript revision. All authors approved the final manuscript.

References

1 Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394(10196):407–18.
2 Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol. 2012;129(5):1229–35.
3 Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003;361(9363):1071–6.
4 Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(2):405–13.
5 GINA report. Global strategy for asthma management and prevention. 2018. Available from: https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-V1.3-002.pdf
6 Loymans RJ, Sterk PJ. Exacerbation-prone asthma: a separate bioclinical phenotype? Am J Respir Crit Care Med. 2017;195(3):275–7.
7 Cardet JC, Louisias M, King TS, Castro M, Codispoti CD, Dunn R, et al. Income is an independent risk factor for worse asthma outcomes. J Allergy Clin Immunol. 2018;141(2):754–60.e3.
8 Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. Chest. 2007;132(4):1151–61.
9 Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet. 2010;376(9743):826–34.
10 Clark VL, Gibson PG, Genn G, Hiles SA, Pavord ID, McDonald VM. Multidimensional assessment of severe asthma: a systematic review and meta-analysis. Respirology. 2017;22(7):1262–75.
11 ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J. 2005;26(5):812–8.
12 Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med. 2017;195(3):302–13.
13 Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. J Asthma Allergy. 2016;9:1–12.
14 Tay TR, Radhakrishna N, Hore-Lacy F, Smith C, Hoy R, Dabscheck E, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. Respirology. 2016;21(8):1384–90.
15 Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chanez P, et al. Frequent exacerbators: a distinct phenotype of severe asthma. Clin Exp Allergy. 2014;44(2):212–21.
16 de Groot JC, Amelink M, de Nijs SB, Plaat R, Reitsma BH, Storm H, et al. Risk factors for frequent severe exacerbations in late-onset eosinophilic asthma. Am J Respir Crit Care Med. 2015;192(7):899–902.
17 Boulay MÈ, Pruneau-Pomerleau C, Villeneuve H, Deschesnes F, Ringuette L, Boulet LP. Comparative features of asthma with frequent or infrequent exacerbations: a longitudinal study of retrospective and prospective events. J Asthma. 2018;55(3):231–43.
18 Grossman NL, Ortega VE, King TS, Bleecker ER, Ampleford EA, Bacharier LB, et al. Exacerbation-prone asthma in the context of race and ancestry in Asthma Clinical Research Network trials. J Allergy Clin Immunol. 2019 Dec;144(6):1524–33. https://doi.org/10.1016/j.jaci.2019.08.033.
19 Zhang XFeng M,, Wang L, Zhang HP, Wang G. Clinical and inflammatory features of exacerbations-prone asthma in Chinese population: a cross-sectional study (abstract). Respirology. 2019;24(S2):273–4. https://doi.org/10.1111/resp.13706_30.
20 Wang G, Wang F, Gibson PG, Guo M, Zhang WJ, Gao P, et al. Severe and uncontrolled asthma in China: a cross-sectional survey from the Australasian Severe Asthma Network. J Thorac Dis. 2017;9(5):1333–44.

21 Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59–99.
22 Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553–8.
23 Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999;115(5):1265–70.
24 Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J. 1986;292(6516):344.
25 Zheng J, Zhang X, Zhang L, Zhang HP, Wang L, Wang G. Interactive effects between obesity and atopy on inflammation: a pilot study for asthma phenotypic overlap. Ann Allergy Asthma Immunol. 2016;117(6):716–7.
26 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
27 Zheng J, Zhong N. Normative values of pulmonary function testing in Chinese adults. Chin Med J. 2002;115(1):50–4.
28 Jian W, Gao Y, Hao C, Wang N, Ai T, Liu C, et al. Reference values for spirometry in Chinese aged 4–80 years. J Thorac Dis. 2017;9(11):4538–49.
29 Zhang L, Zhang X, Zheng J, Liu Y, Wang J, Wang G, et al. Depressive symptom-associated IL-1β and TNF-α release correlates with impaired bronchodilator response and neutrophilic airway inflammation in asthma. Clin Exp Allergy. 2019;49(6):770–80.
30 Schatz M, Rosenwasser L. The allergic asthma phenotype. J Allergy Clin Immunol Pract. 2014;2(6):645–9.
31 Lemiere C, Ernst P, Olivenstein R, Yamauchi Y, Govindaraju K, Ludwig MS, et al. Airway inflammation assessed by invasive and noninvasive means in severe asthma: eosinophilic and noneosinophilic phenotypes. J Allergy Clin Immunol. 2006;118(5):1033–9. https://doi.org/10.1016/j.jaci.2006.08.003.
32 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189–97.
33 Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004;113(1):101–8.
34 Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011;365(12):1088–98.
35 Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992–1007.
36 Soenjoyo KR, Nadkarni N, Koh MS. Comparison of exacerbation phenotypes among patients with severe asthma. Allergy Asthma Proc. 2020;41(4):e67–79.
37 Westerhof GA, de Groot JC, Amelink M, de Nijs SB, Ten Brinke A, Weersink EJ, et al. Predictors of frequent exacerbations in (ex) smoking and never smoking adults with severe asthma. Respir Med. 2016;118:122–7.
38 ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J. 2005;26(5):812–8.
39 Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, et al. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. Am J Respir Crit Care Med. 2020 Oct 1;202(7):973–82.
40 Boulay MÈ, Pruneau-Pomerleau C, Villeneuve H, Deschesnes F, Ringuette L, Boulet LP. Comparative features of asthma with frequent or infrequent exacerbations: a longitudinal study of retrospective and prospective events. J Asthma. 2018;55(3):231–43.
41 Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chanez P, et al. Frequent exacerbators: a distinct phenotype of severe asthma. Clin Exp Allergy. 2014;44(2):212–21.
42 Kim MA, Shin SW, Park JS, Uh ST, Chang HS, Bae DJ, et al. Clinical characteristics of exacerbation-prone adult asthmatics identified by cluster analysis. Allergy Asthma Immunol Res. 2017;9(6):483–90.
43 Koga T, Oshita Y, Kamimura T, Koga H, Aizawa H. Characterisation of patients with frequent exacerbation of asthma. Respir Med. 2006;100(2):273–8.
44 Janson C, Lisspers K, Ställberg B, Johansson G, Thuresson M, Telg G, et al. Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden (PACEHR). Eur Respir J. 2018;52(2).
45 Li W. Precision medicine: to cure and relieve more. Precis Clin Med. 2018;1(1):3–4.
46 Hong HG, Christiani DC, Li Y. Quantile regression for survival data in modern cancer research: expanding statistical tools for precision medicine. Precis Clin Med. 2019;2(2):90–9.
47 McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J. 2020;55(3):1901509.
48 Lommatzsch M. Immune modulation in asthma: current concepts and future strategies. Respiration. 2020;99(7):566–76. https://doi.org/10.1159/000506651.
49 Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, et al. Dedicated severe asthma services improve health-care use and quality of life. Chest. 2015;148(4):870–6.
50 van der Meer AN, Pasma H, Kempenaar-Okkema W, Pelinck JA, Schutten M, Storm H, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. Eur Respir J. 2016;48(3):726–33.
51 Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract. 2017;5(4):967–e3.
52 Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O'Byrne PM, et al. Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. J Allergy Clin Immunol. 2016;137(1):75–86.e8.
53 Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007;30(3):452–6.
54 Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367(13):1198–207.
55 Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med. 2019;380(21):2009–19.
56 El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871–80.
57 Crimi C, Ferri S, Campisi R, Crimi N. The link between asthma and bronchiectasis: state of the art. Respiration. 2020;99(6):463–76. https://doi.org/10.1159/000507228.
58 Romem A, Rokach A, Bohadana A, Babai P, Arish N, Azulai H, et al. Identification of asthma-COPD overlap, asthma, and chronic obstructive pulmonary disease phenotypes in patients with airway obstruction: influence on treatment approach. Respiration. 2020;99(1):35–42.
59 Park H-W, Song W-J, Cho S-H, McGeachie MJ, Martinez F, Mauger D, et al. Assessment of genetic factor and depression interactions for asthma symptom severity in cohorts of childhood and elderly asthmatics. Exp Mol Med. 2018;50(7):1.
60 Shanahan L, Copeland WE, Worthman CM, Angold A, Costello EJ. Children with both asthma and depression are at risk for heightened inflammation. J Pediatr. 2013;163(5):1443–7.
61 Lau A, Tarlo SM. Update on the management of occupational asthma and work-exacerbated asthma. Allergy Asthma Immunol Res. 2019;11(2):188–200.
62 Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemière C, Martin J, et al. An official American Thoracic Society statement: work-exacerbated asthma. Am J Respir Crit Care Med. 2011;184(3):368–78.