

# A Multi-Center Study of the Prevalence and Characteristics of Eosinophilic Phenotype and High IgE Levels Among Chinese Patients with Severe Asthma

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**Background:** Patients with severe asthma have higher total- and asthma-related health burden than those whose disease is not severe. Recent medical advances in biologic therapies allow better control of asthma characterized by type 2 inflammation.

**Objective:** To study the prevalence of eosinophilic phenotype and IgE levels in Chinese with severe asthma, and the relationship of these type 2 characteristics with asthma control, exacerbations and lung function.

**Methods:** This was a multicenter cross-sectional observational study in Hong Kong, in Chinese adults with asthma on Step 4 or 5 of GINA treatment. Their blood eosinophil counts and total IgE levels were measured, and the relationship of these phenotypic parameters to the number of exacerbations in the past 12 months, and to symptom control in the past 4 weeks, were investigated.

**Results:** A total of 232 subjects were recruited from 6 centers. The mean age was 53.9±12.9 years, with 86 (37.1%) male, and the duration of diagnosed asthma was 26.2±15.7 years. A T-helper 2 (Th2) phenotype indicated by elevated eosinophils and/or IgE was present in 169 (72.8%) of patients. Of 232 patients, 43% had an eosinophilic phenotype (blood eosinophil count ≥300 cell/mm<sup>3</sup>), while 59% had high total IgE levels of >100 IU/mL (overlap with eosinophilic phenotype in 30%) and 44% had IgE levels of >150 IU/mL (overlap with eosinophilic phenotype in 22%). Subjects with eosinophilic phenotype and IgE >150 IU/mL had a higher rate (1.8 times) of uncontrolled asthma compared with those without such a combination.

**Conclusion:** In Chinese adults with severe asthma defined by the use of conventional maintenance medication regimens, the prevalence of Th2 inflammation is comparable to that reported from other ethnic populations. Those with both eosinophil count ≥300 cell/mm<sup>3</sup> and high IgE levels >150 IU/mL had a higher rate of uncontrolled asthma compared with those without a combination of these features.

**Keywords:** asthma, Chinese, cross-sectional, eosinophils, Hong Kong, immunoglobulin E

## Introduction

Asthma is a leading cause of morbidity with an estimated global prevalence of 300 million patients,<sup>1</sup> of which approximately 5–10% have severe disease.<sup>2</sup> Patients with severe disease have higher total- and asthma-related outpatient visits, inpatient days, emergency room visits and costs per patient-year than those whose asthma is not severe.<sup>3,4</sup>

Asthma is a heterogeneous disease with different phenotypes. Severe eosinophilic asthma is associated with poor asthma control,<sup>5,6</sup> more frequent exacerbations,<sup>4,6–8</sup> reduced lung function<sup>6,9</sup> and impaired quality of life.<sup>6,10</sup> In a systematic review of studies on patients with asthma receiving Global Initiative of Asthma (GINA) Step 4 or 5

treatment,<sup>11</sup> subjects with severe uncontrolled asthma had 3-times greater health-care costs than those with severe, but controlled, asthma.<sup>12</sup> Among all subjects with asthma in a study from Finland, severe eosinophilic asthma was associated with the highest healthcare resource utilization.<sup>3</sup>

Type 2 inflammation plays an important role in pathogenesis of asthma, and thus T-helper 2 (Th2) cells, cytokines, and immunoglobulin E (IgE) – the main orchestrators of type 2 inflammation – are treatment targets in patients with asthma.<sup>13,14</sup> Following the presentation of antigens to naïve T cells, complex signaling pathways drive Th2 chemotaxis and stimulate type 2 inflammatory cytokine production at the airway epithelial cells, which in turn induce eosinophilic inflammation with eosinophil recruitment and activation at the site of inflammation.<sup>15,16</sup> Interleukin-4 (IL-4) promotes the differentiation of naïve Th cells into Th2 cells and plays a role in stimulating isotype class switching of B cells to produce IgE. IgE antibodies further escalate the immune response by sensitizing basophils and mast cells.<sup>15–17</sup> The emergence of biologics targeting IL-5, IL-4, IL-13 and IgE<sup>18</sup> have provoked clinical interest in the characterization of patients who may potentially derive benefit for better disease control and outcomes.

While the presence of eosinophilia and elevated IgE levels are commonly observed in asthma in clinical practice, systematic data on the phenotype pattern and related characteristics among Chinese patients are limited.<sup>19</sup>

This study aimed to evaluate the prevalence of eosinophilic asthma in a cohort of adult Chinese patients in Hong Kong with severe asthma. In addition, the study assessed if an overlapping eosinophilic phenotype and high serum IgE levels affect asthma control, exacerbations and lung function.

## Methods

### Study Design

This multicenter, cross-sectional, observational study assessed the prevalence of eosinophilic phenotypes and high IgE levels in Chinese patients with asthma in Hong Kong who were treated with medications at Step 4 or 5 of the GINA recommendations as part of the PRevalence of the Eosinophilic Phenotype Among Severe Asthma Patients (PREPARE) Study (ClinicalTrials.gov number: NCT03931954).

### Ethical Statements

Ethical approval was obtained from all six participating centers in Hong Kong: Prince of Wales Hospital [CREC2019.510], Princess Margaret Hospital [KW/EX-19-108 (142–11)], Queen Elizabeth Hospital [KC/KE-19-0230/ER-2], Queen Mary Hospital [UW-19-686], Tuen Mun Hospital [NTWC/REC/19117] and United Christian Hospital [KC/KE-19-0227/ER-2]. All participants provided informed written consent prior to enrolment. The manuscript complies with the Declaration of Helsinki.

### Population

Eligible patients were aged >18 years old, had severe asthma as defined in the 2018 GINA guidelines<sup>11</sup> for at least 1 year, ie, patients requiring Step 4 or 5 treatment (at least medium-dose inhaled corticosteroid [ICS]–long-acting beta agonist [LABA] to prevent asthma from becoming “uncontrolled” or asthma that remains “uncontrolled” despite this treatment). Patients receiving biologic therapy for asthma were excluded from this study, as well as those diagnosed with: chronic obstructive pulmonary disease, chronic respiratory conditions other than severe asthma (eg, bronchiectasis, interstitial lung disease, lung malignancies, history of lung resection), or an acute or chronic condition that, in the investigator’s opinion, would limit the patient’s ability to participate in this study (eg, severe renal failure, active malignancies). Consecutive patients attending routine clinical visits at participating centers were invited to participate in the study.

### Assessments

During the study visit, demographic characteristics, including the history of asthma onset, were recorded. Patients were asked about their asthma control in the past 4 weeks and classified as having levels of control according to criteria defined in the GINA guidelines (based on daytime symptoms more than twice/week, any night waking due to asthma, use of short-acting bronchodilator [SABA] reliever for symptoms more than twice/week, and any activity limitation due to

asthma; in which none, 1–2 and 3–4 of these indicated well controlled, partly controlled and uncontrolled asthma, respectively).<sup>11</sup> Medication history and exacerbation history in the past 12 months (exacerbations requiring systemic corticosteroid [CS] or hospitalization) were obtained from the patients and their medical records. The number of CS bursts (use of an intravenous CS or oral CS [OCS] for at least 3 days or the use of a single intramuscular CS dose; for patients on maintenance OCS, at least double the existing maintenance dose for at least 3 days) in the last 12 months were recorded. History of rhinitis, nasal polyps, atopic dermatitis were also recorded. A venous blood sample was taken for measurement of total serum IgE and complete blood count with differential white blood cell count. The most recent spirometry assessments within the past 12 months were also recorded.

The primary objective of the study was to assess the proportion of patients with an eosinophilic phenotype, defined by blood eosinophils  $\geq 300$  cells/ $\text{mm}^3$ . The definition of an eosinophilic phenotype of asthma in this study at  $\geq 300$  cells/ $\text{mm}^3$  was chosen for consistency with previous studies.<sup>3,9,20,21</sup> The secondary objectives were the prevalence of a high level of total serum IgE, defined as  $>100$  IU/mL or  $>150$  IU/mL. No standard cut-off for high total serum IgE has been formally defined, so we applied a cut-off of 150 IU/mL for this study, which was the 95th percentile of total IgE reference values for non-smokers in a study of young Europeans.<sup>22</sup> We also analyzed outcomes using a cut-off of  $>100$  IU/mL because this is the commonly used reference value for “normal” IgE levels applied by pathology laboratories. The prevalence of overlapping eosinophilic phenotype ( $\geq 300$  cells/ $\text{mm}^3$ ) and high IgE levels ( $>100$  IU/mL or  $>150$  IU/mL) were also assessed. Furthermore, associations between phenotypes and demographic characteristics, asthma control, exacerbation, and lung function were studied.

## Statistical methods

Descriptive statistics for numerical variables were reported. *T*-test (for normally distributed variables) or Wilcoxon signed-rank test (for non-normally distributed variables) were used to assess the differences in means or medians of continuous variables between groups. One-way analysis of variance or Kruskal–Wallis rank sum test was used to analyze the mean differences when there were more than two groups. Proportions were compared between groups using the Fisher’s exact test or Chi-square test, as appropriate. All statistical tests were two-sided and used a 5% significance level. R software (Version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

## Results

### Demographic Data

In total, 232 subjects from Hong Kong with severe asthma were enrolled between December 2019 and May 2020. The demographic characteristics of the study population are shown in Table 1. The mean $\pm$ standard deviation (SD) age of the subjects was 53.9 $\pm$ 12.9 (range, 24–84) years, with 146 (62.9%) being female. Mean $\pm$ SD duration of diagnosed asthma was 26.2 $\pm$ 15.7 years. The majority of the subjects were never smokers. There were 19 (8%) active smokers (smoking within the past 12 months) and 48 (21%) ex-smokers (quitted for at least 12 months). The most common comorbidity was rhinitis (156 [93.4%] subjects).

All patients were prescribed ICS/LABA for asthma control (74 [32%] on medium dose and 158 [68%] on high dose).<sup>11</sup> Eight (3.4%) subjects were being treated with long-term OCS therapy for asthma, at a mean $\pm$ SD dose of 16.8 $\pm$ 12.8 mg/day of prednisolone equivalent. Short bursts of systemic CS as defined were prescribed to 62 (26.7%) subjects in the past 12 months (1, 2, 3 and  $>3$  courses in 22, 11, 14 and 9 subjects, respectively; data was missing for 6 subjects). Sixty-seven (29%), 92 (40%), and 73 (31%) of the cohort had well-controlled, partly controlled, and uncontrolled asthma, respectively.

### Phenotype by Blood Eosinophils and IgE

Peripheral blood eosinophilia of  $\geq 300$  and 150–300 cells/ $\text{mm}^3$  was observed in 100 (43%) and 56 (24%) of the subjects, respectively. Total IgE levels of  $>100$  IU/mL and  $>150$  IU/mL were observed in 138 (59%) and 102 (44%) subjects, respectively. Th2 phenotype indicated by elevated eosinophils and/or IgE was present in 169 (72.8%) of patients. An

**Table I** Demographic Characteristics of the Subjects from Hong Kong Participating in the PREPARE Study

| Characteristic                                                   | N=232      |
|------------------------------------------------------------------|------------|
| Age, years, mean±SD                                              | 53.9±12.9  |
| Sex, male, n (%)                                                 | 86 (37.1)  |
| Height, cm, mean±SD                                              | 161.3±8.7  |
| Weight, kg, mean±SD                                              | 66.5±14.9  |
| Body mass index, kg/m <sup>2</sup> , mean±SD                     | 25.5±5.3   |
| Smoking history, n (%)                                           |            |
| Active smoker                                                    | 19 (8.2)   |
| Former smoker                                                    | 48 (20.7)  |
| Never smoker                                                     | 165 (71.1) |
| Duration of diagnosed asthma, years, mean±SD                     | 26.2±15.7  |
| Asthma diagnosed at <12 years of age, n (%) <sup>a</sup>         | 71 (30.7)  |
| Skin prick test, positive, n (%) <sup>b</sup>                    | 34 (73.9)  |
| Comorbidities, n (%)                                             |            |
| Rhinitis                                                         | 156 (93.4) |
| Nasal polyps                                                     | 17 (10.2)  |
| Sinusitis                                                        | 2 (1.2)    |
| Atopic dermatitis                                                | 30 (18.0)  |
| Asthma associated with NSAIDs                                    | 0 (0)      |
| Aspergillosis                                                    | 0 (0)      |
| Eczema                                                           | 13 (7.8)   |
| Treatment, n (%)                                                 |            |
| ICS/LABA                                                         | 232 (100)  |
| LAMA                                                             | 75 (39)    |
| LTRA                                                             | 154 (81)   |
| Chronic OCS                                                      | 8 (3.4)    |
| Level of asthma symptom control, n (%)                           |            |
| Well-controlled                                                  | 67 (29)    |
| Partly controlled                                                | 92 (40)    |
| Uncontrolled                                                     | 73 (31)    |
| Number of severe exacerbations in the last year, n (%)           |            |
| 0                                                                | 175 (75)   |
| 1                                                                | 28 (12)    |
| 2                                                                | 10 (4)     |
| 3                                                                | 9 (4)      |
| >3                                                               | 10 (4)     |
| Lung function test <sup>c</sup>                                  |            |
| Pre-bronchodilator FEV <sub>1</sub> , L                          | 2.0±0.8    |
| Post-bronchodilator FEV <sub>1</sub> , L                         | 2.0±0.6    |
| Pre-bronchodilator % of the predicted FEV <sub>1</sub> value, %  | 79.7±22.8  |
| Post-bronchodilator % of the predicted FEV <sub>1</sub> value, % | 83.8±18.4  |
| Pre-bronchodilator FEV <sub>1</sub> / FVC, %                     | 68.2±15.0  |
| Post-bronchodilator FEV <sub>1</sub> / FVC, %                    | 71.0±13.2  |

(Continued)

**Table 1** (Continued).

| Characteristic                            | N=232               |
|-------------------------------------------|---------------------|
| Eosinophil count, cells/mm <sup>3</sup>   |                     |
| Mean±SD                                   | 312.7±281.6         |
| Median (IQR)                              | 3.2 (1.7, 6.0)      |
| % Eosinophil count, cells/mm <sup>3</sup> |                     |
| Mean±SD                                   | 4.3±3.7             |
| Median (IQR)                              | 3.2 (1.7, 6.0)      |
| Total serum IgE, IU/mL                    |                     |
| Mean±SD                                   | 390.5±912.2         |
| Median (IQR)                              | 123.0 (40.8, 371.5) |

**Note:** <sup>a</sup>n=231; <sup>b</sup>n=46; <sup>c</sup>n=57.

**Abbreviations:** ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting  $\beta_2$  agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SD, standard deviation.

overlapping eosinophilic phenotype and total serum IgE level of >100 IU/mL was observed in 69 (29.7%) subjects, and a total serum IgE level of >150 IU/mL was present in 50 (22%) subjects (Table 1).

## Phenotype and Asthma Control

Interactions between phenotype and asthma control are shown in Table 2 and Figure 1. Among the four Th2 subtypes, a significant difference in asthma control was observed in the group with both eosinophils >300 cells/mm<sup>3</sup> and an IgE level >150 IU/mL, with subjects in this group being more likely to have uncontrolled asthma compared with those

**Table 2** Association of Asthma Control and Asthma Phenotypes

| Subjects, n (%)                                                                                                                            | Overall<br>(N = 232) | Well-Controlled<br>(N = 67) | Partly Controlled<br>(N = 92) | Uncontrolled<br>(N = 73) | p value <sup>a</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------------|-------------------------------|--------------------------|----------------------|
| <b>Eosinophilic phenotype (Blood eosinophils <math>\geq 300</math> cells/mm<sup>3</sup>)</b>                                               |                      |                             |                               |                          | 0.257                |
| Yes <sup>a</sup>                                                                                                                           | 100                  | 28 (28)                     | 35 (35)                       | 37 (37)                  |                      |
| No                                                                                                                                         | 132                  | 39 (30)                     | 57 (43)                       | 36 (27)                  |                      |
| <b>Total serum IgE &gt;100 IU/mL</b>                                                                                                       |                      |                             |                               |                          | 0.416                |
| Yes                                                                                                                                        | 138                  | 44 (32)                     | 54 (39)                       | 40 (29)                  |                      |
| No                                                                                                                                         | 94                   | 23 (24)                     | 38 (40)                       | 33 (35)                  |                      |
| <b>Total serum IgE &gt;150 IU/mL</b>                                                                                                       |                      |                             |                               |                          | 0.967                |
| Yes                                                                                                                                        | 102                  | 29 (28)                     | 40 (39)                       | 33 (32)                  |                      |
| No                                                                                                                                         | 130                  | 38 (29)                     | 52 (40)                       | 40 (31)                  |                      |
| <b>Overlapping eosinophilic phenotype (Blood eosinophils <math>\geq 300</math> cells/mm<sup>3</sup>) and total serum IgE &gt;100 IU/mL</b> |                      |                             |                               |                          | 0.126                |
| Yes                                                                                                                                        | 69                   | 19 (28)                     | 22 (32)                       | 28 (41)                  |                      |
| No                                                                                                                                         | 163                  | 48 (29)                     | 70 (43)                       | 45 (28)                  |                      |
| <b>Overlapping eosinophilic phenotype (Blood eosinophils <math>\geq 300</math> cells/mm<sup>3</sup>) and total serum IgE &gt;150 IU/mL</b> |                      |                             |                               |                          | <b>0.016</b>         |
| Yes                                                                                                                                        | 50                   | 10 (20)                     | 16 (32)                       | 24 (48)                  |                      |
| No                                                                                                                                         | 182                  | 57 (31)                     | 76 (42)                       | 49 (27)                  |                      |

**Notes:** <sup>a</sup>p value from chi-square analysis of ordinal composite variables between each group (Yes/No). p value <0.05 is highlighted in bold.

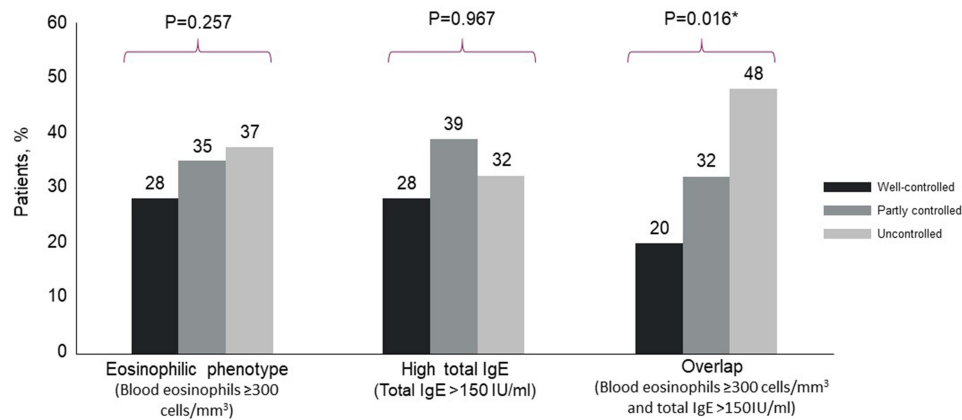


Figure 1 Association between asthma control levels and asthma phenotype \*P ≤ 0.05.

without an overlapping phenotype (1.8 times, 48% vs 27%; p = 0.016). No difference was observed among the 4 phenotype subgroups for asthma exacerbations (Supplementary Table 1).

Phenotype and Patient Characteristics

While there were more females among this cohort of subjects with severe asthma, Th2 phenotypes were more prevalent in male subjects. There was a difference in the sex distribution for those with and without an eosinophilic phenotype (male sex, 48.0% vs 28.8%, female sex, 52.0 vs 71.2%; p = 0.004) and those with and without an overlapping phenotype of eosinophilia and IgE level >150 IU/mL (male, 52.0 vs 33.0%, female 48.0 vs 67%; p = 0.021).

Among the 57 subjects with lung function data available, a lower predicted percentage of forced expiratory volume in 1 second (FEV<sub>1</sub>%) was observed for subjects with eosinophilic phenotype, IgE levels >150 IU/mL, IgE levels >100 IU/mL, or an overlapping eosinophilic phenotype with high IgE levels, compared with their respective counterparts (Table 3).

Table 3 Lung Function Parameters According to Asthma Phenotype Characteristics n=57

| Subjects, n (%)                                                                                      |                                | Eosinophilic Phenotype (Blood Eosinophils ≥300 Cells/mm <sup>3</sup> ) |               |              | Serum Total IgE >150 IU/mL |               |              | Overlapping Blood Eosinophils ≥300 Cells/mm <sup>3</sup> and Serum Total IgE >150 IU/mL |               |              |
|------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------------------|---------------|--------------|----------------------------|---------------|--------------|-----------------------------------------------------------------------------------------|---------------|--------------|
|                                                                                                      |                                | Yes                                                                    | No            | p value      | Yes                        | No            | p value      | Yes                                                                                     | No            | p value      |
| Total number of patients in the study<br>Lung function test with results n (%)<br>Pre-bronchodilator |                                | 100                                                                    | 132           |              | 102                        | 130           |              | 50                                                                                      | 182           |              |
|                                                                                                      |                                | 30 (30.0)                                                              | 27 (20.5)     | 0.129        | 21 (20.6)                  | 36 (27.7)     | 0.274        | 14 (28.0)                                                                               | 43 (23.6)     | 0.652        |
|                                                                                                      | FEV <sub>1</sub> , L           | 1.84 (0.74)                                                            | 2.06 (0.77)   | 0.307        | 1.78 (0.65)                | 2.05 (0.79)   | 0.370        | 1.66 (0.71)                                                                             | 2.04 (0.75)   | 0.151        |
|                                                                                                      | Predicted FEV <sub>1</sub> %   | 72.71 (21.40)                                                          | 86.06 (22.55) | <b>0.006</b> | 72.14 (19.85)              | 83.69 (23.53) | 0.068        | 67.04 (17.33)                                                                           | 83.18 (23.06) | <b>0.015</b> |
|                                                                                                      | FVC, L                         | 2.88 (1.07)                                                            | 2.89 (0.94)   | 0.901        | 2.71 (0.83)                | 2.97 (1.07)   | 0.570        | 2.56 (0.95)                                                                             | 2.97 (1.00)   | 0.335        |
|                                                                                                      | Predicted FVC%                 | 91.10 (22.27)                                                          | 96.36 (17.82) | 0.367        | 88.81 (13.68)              | 96.53 (22.44) | 0.226        | 85.68 (16.64)                                                                           | 96.11 (20.48) | 0.170        |
|                                                                                                      | FEV <sub>1</sub> /FVC ratio, % | 64.80 (14.25)                                                          | 71.40 (15.27) | 0.085        | 66.35 (17.44)              | 69.18 (13.84) | 0.607        | 64.71 (15.12)                                                                           | 69.17 (15.04) | 0.381        |
|                                                                                                      | Post-bronchodilator            |                                                                        |               |              |                            |               |              |                                                                                         |               |              |
|                                                                                                      | FEV <sub>1</sub> , L           | 1.94 (0.64)                                                            | 1.97 (0.48)   | 0.638        | 1.82 (0.45)                | 2.01 (0.60)   | 0.425        | 1.70 (0.45)                                                                             | 2.02 (0.57)   | 0.162        |
|                                                                                                      | Predicted FEV <sub>1</sub> %   | 78.80 (14.97)                                                          | 88.41 (20.22) | <b>0.043</b> | 75.26 (15.23)              | 87.26 (18.59) | <b>0.032</b> | 73.76 (13.88)                                                                           | 86.20 (18.63) | <b>0.032</b> |
|                                                                                                      | FVC, L                         | 2.87 (0.95)                                                            | 2.74 (0.67)   | 0.879        | 2.77 (0.73)                | 2.83 (0.87)   | 0.949        | 2.53 (0.69)                                                                             | 2.88 (0.85)   | 0.282        |
|                                                                                                      | Predicted FVC%                 | 90.76 (16.89)                                                          | 94.70 (16.53) | 0.348        | 88.12 (10.47)              | 94.71 (18.39) | 0.099        | 85.00 (11.68)                                                                           | 94.67 (17.21) | 0.065        |
|                                                                                                      | FEV <sub>1</sub> /FVC ratio, % | 68.47 (12.05)                                                          | 73.58 (14.05) | 0.177        | 66.57 (12.85)              | 72.75 (13.07) | 0.184        | 67.52 (11.50)                                                                           | 71.83 (13.56) | 0.349        |

Notes: p value from one-way analysis of variance, those with p values <0.05 are highlighted in bold. Data are presented in mean (standard deviation).

Abbreviation: IgE, immunoglobulin E.

## Discussion

Among this cohort of Chinese patients with asthma who were prescribed GINA Step 4 or 5 therapy, 72% had a Th2-driven phenotype defined by elevated eosinophils and/or IgE levels, 43% had an eosinophilic phenotype, while 59% had total serum IgE levels >100 IU/mL and 44% had IgE levels >150 IU/mL. An overlapping eosinophilic phenotype and high IgE at the two total serum IgE cut-off levels of 100 IU/mL and >150 IU/mL were observed in 30% and 22% of subjects, respectively. We also found that subjects with an overlap of eosinophilia and IgE >150 IU/mL had a 1.8 times higher rate of uncontrolled asthma compared with those who did not. In addition, lung function measured by predicted FEV<sub>1</sub>% was lower in patients with an eosinophilic phenotype compared with their counterparts in the same IgE subgroup without eosinophilia.

The prevalence of eosinophilic phenotype at 43% among Chinese patients with severe asthma in Hong Kong was comparable to that reported in studies performed in other populations of differing ethnicity: 47% in Finland,<sup>3</sup> 34% in Japan,<sup>20</sup> 41% in Canada,<sup>23</sup> and 57% in the International Severe Asthma Registry which comprised predominantly of patients from Europe and North America.<sup>24</sup> Data on Chinese patients from a study in Taiwan<sup>25</sup> showed an eosinophilic phenotype in 31% of 132 patients with severe asthma.

We identified 30% of subjects in this cohort of severe asthma as having overlapping features of elevated eosinophils ( $\geq 300$  cells/mm<sup>3</sup>) and high IgE (>100 IU/mL). A previous study from the United States reported that different cut-offs of blood eosinophil count, specific IgE levels and total IgE level would have differing degrees of overlap in a general population of asthma, with 22% having eosinophils of  $\geq 300$  cells/mm<sup>3</sup> and total IgE of  $\geq 100$  IU/mL.<sup>26</sup> However, there has been sparse information on whether overlapping eosinophilia and high total serum IgE levels affect asthma outcomes.

Various inflammatory cells are involved in airway inflammation of asthma, including eosinophils, basophils and mast cells. In a study obtaining bronchial biopsies in patients with asthma, it was observed that airway inflammation and asthma severity were associated with reduced apoptosis and enhanced survival of cells such as eosinophils and macrophages.<sup>27</sup> In a mice model, the depletion of basophils resulted in a significant reduction of inflammatory cells in the airways and eosinophil recruitment, suggesting that basophils also played a role in the inflammatory pathway of asthma.<sup>28</sup> Marked rise in IgE level together with an increase in airway mast cells was observed in mice with inhalation of *Aspergillus fumigatus* extract. On the other hand, mast cell expansion and activation and recruitment of eosinophils were markedly attenuated in mice not capable of producing IgE (IgE<sup>-/-</sup> animals) in response to *Aspergillus fumigatus*.<sup>29</sup> These findings suggested that eosinophils and raised IgE were involved in some patients with asthma, and the homeostasis of eosinophils and IgE is modulated by other cells, including basophils and mast cells. It is possible that overlapping of eosinophilic and high IgE phenotype drives more inflammation compared to those subjects without these characteristics.

In this cross-sectional study, we did not observe any association between blood eosinophil count and recent poor asthma control or exacerbations, while the combination of eosinophilic asthma with a high serum total IgE level increased the risk of uncontrolled asthma, but not exacerbations. In the study from Taiwan,<sup>25</sup> the exacerbator group had a higher proportion of eosinophilic phenotype and higher FeNO levels, compared to the non-exacerbator group, while there was no difference in IgE levels in the two groups, and the combination of high eosinophils and FeNO predicted exacerbations. From a pooled analysis of placebo data from seven randomized controlled trials, factors including exacerbation history, maintenance CS use, nasal polyposis, Asian race, geographic region and elevations in blood eosinophil counts and FeNO concentrations were associated with increased exacerbation risk in those with severe, uncontrolled asthma.<sup>30</sup> A study from New Zealand also reported that the mean number of exacerbations in patients with severe eosinophilic asthma having at least two exacerbations at baseline was four times that of patients with non-severe eosinophilic asthma patients after 1 year of follow up.<sup>4</sup> Therefore, multiple factors are likely contributing to exacerbations in patients with asthma.

We also observed that pre-bronchodilator predicted FEV<sub>1</sub>% was lower in subjects with eosinophilic asthma compared with non-eosinophilic asthma, and in those subjects with overlapping eosinophilic asthma and high IgE compared with those without overlap. Airway remodeling is mediated by many cells and cytokines. In particular, eosinophils have been implicated in airway remodelling.<sup>31–34</sup> Sputum eosinophils, sputum eosinophilic cationic protein and airway wall



eosinophil number all correlating with basement membrane thickness<sup>31</sup> On the other hand, IgE antibody-mediated mast cell degranulation plays a role in allergen-related asthma. For non-atopic asthma, there is greater involvement of innate immune cells, such as basophils, group 2 innate lymphoid cells, and eosinophils, but not allergen-specific IgE. It is not clear if IgE levels are related to airway remodeling and lung function decline.<sup>15</sup> Previous studies have reported that in patients with stable asthma, despite optimal treatment, those with sputum eosinophilia had lower lung function.<sup>35,36</sup> Therefore, it is likely that eosinophils, rather than serum IgE levels, are driving changes in lung function.

In this study, Th2 phenotypes were more prevalent in male subjects. A study on sex steroid hormones and asthma found that in women, low free testosterone levels, while in non-obese men, elevated serum estradiol, was associated with lower odds of current asthma.<sup>37</sup> The Severe Asthma Network registry of Italy involving over 1000 subjects observed that blood eosinophils, exhaled nitric oxide and serum IgE levels were significantly higher in male than female subjects. However, multi-variate analyses found that late-onset asthma and normal body mass index, but not male sex and age, had independent associations with these type 2 biomarkers.<sup>38</sup> It is likely that many factors apart from gender and sex hormones are involved in increased T2 inflammation in men, including gene polymorphisms and environmental factors, such as organic dust exposure and consequential DNA methylation.<sup>39</sup>

This study collected data on demographics, recent asthma control, blood eosinophils and IgE levels at the time of recruitment, while their previous medical records are available on the territory-wide electronic health administration record for public health-care visits in Hong Kong. Nonetheless, it has several limitations. Serum-specific IgE levels and exhaled nitric oxide levels were not included in the assessment of type 2 inflammation and atopy, and lung function test within the past year was only available in a proportion of patients. While high eosinophil counts and IgE levels may be caused by parasitic infection which has not been investigated in this study, we deem this unlikely given the very low prevalence of parasitic infections in Hong Kong. Finally, Hong Kong is an urbanized city and the data may not be generalizable to those residing in more rural areas.

In conclusion, this multi-center study in Hong Kong systematically demonstrated the phenotype pattern in Chinese patients with severe asthma, which is comparable with the Th2 phenotype dominance seen in many other ethnic populations. It appears that phenotype pattern of asthma is similar across different ethnicities. Subjects with features of both an eosinophilic phenotype (blood eosinophils  $\geq 300$  cells/mm<sup>3</sup>) and a high total serum IgE ( $>150$  IU/mL), found in 22% of the cohort, had a higher rate of poor asthma control. More aggressive therapy may be needed for patients with a combination of eosinophilic phenotype and high serum IgE levels.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Disclosure

MSM Ip has received honoraria for participating in advisory board meetings or expert panel meetings regarding asthma management for Astra Zeneca and Glaxo-Smith-Kline, and has received grants for clinical studies on asthma and COPD from Sanofi, Astra Zeneca, and Boehringer Ingelheim. Other authors have no conflict of interest to declare in relation to this manuscript.

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