

Differences in Type 2 Phenotype and Clinical Characteristics of Adult Asthma Patients with Different Severity, Across GINA Step 1 to 5 Asthma

Wang Chun Kwok, Julie Kwan Ling Wang, Terence Chi Chun Tam, James Chung Man Ho, David Chi Leung Lam, Mary Sau Man Ip

Department of Medicine, the University of Hong Kong, Hong Kong, SAR, People's Republic of China

Correspondence: Mary Sau Man Ip, Department of Medicine, the University of Hong Kong, Hong Kong, SAR, People's Republic of China, Tel +85222553111, Email msmip@hku.hk

Background: The prevalence and clinical characteristics of asthma phenotypes are less studied in mild asthma than in severe asthma. This study aims to assess the prevalence and clinical features of different phenotypes in patients with asthma with different severity.

Methods: A cross-sectional study was conducted in Hong Kong. Adult patients with mild, moderate and severe asthma based on GINA steps (1 to 5) were included. The prevalence of eosinophil phenotype, elevated IgE, overlapping eosinophil phenotype with elevated IgE levels and type 2 phenotype in mild and moderate/severe asthma were compared. The clinical features of different phenotypes in patients with mild or moderate/severe asthma were also compared.

Results: A total of 152 patients were recruited. The mild asthma group had significantly fewer patients with type 2 phenotype (49.0% vs 69.3%, $p = 0.015$), eosinophilic phenotype (25.5% vs 43.6%, $p = 0.030$), elevated IgE (41.2% vs 59.4%, $p = 0.033$), and overlapping eosinophilic phenotype with elevated IgE (17.6% vs 33.7%, $p = 0.038$). Those with mild eosinophilic phenotype had better lung function than their non-eosinophilic counterparts (2.67 ± 0.75 L vs 2.18 ± 0.62 L, $p = 0.045$), in contrast to the comparatively poorer lung function of those with eosinophilic moderate/severe asthma ($87.87 \pm 19.54\%$ vs $98.10 \pm 19.77\%$, $p = 0.018$). The eosinophilic phenotype and a higher blood eosinophil count were only associated with an increased risk of exacerbation in moderate/severe asthma.

Conclusion: The prevalence of the type 2 phenotype is lower in patients with mild asthma than in patients with moderate/severe asthma. Eosinophilic phenotype in the mild and moderate/severe asthma group showed differences in spirometry findings and exacerbation risks. The heterogeneity in the phenotype across asthma of different severity suggests that risk stratification based on blood-based biomarkers alone may be inadequate and other clinical factors should also be considered.

Keywords: asthma, clinical severity, phenotype, eosinophils

Introduction

Asthma is defined by having the history of respiratory symptoms (wheeze, dyspnoea, chest tightness and cough) which vary over time and in intensity and also variable expiratory airflow limitation.¹ As a common respiratory condition, asthma affects between 1% and 29% of the population across various studies.^{2,3} Studies have suggested that there are around 339 million people suffering from asthma worldwide.⁴ In Hong Kong, more than 330,000 people are suffering from asthma in Hong Kong.⁵⁻⁷ The severity of asthma can be categorized from mild to severe based on the treatment steps by Global Initiative for Asthma (GINA) recommendations, in which there are 5 treatment steps (step 1 to 5).⁸

Phenotyping by distinct clinical features and biomarkers in chronic airway diseases is the key to personalized treatment.⁹⁻¹⁴ One of the most commonly used methods to classify asthma into different phenotypes is based on the underlying inflammatory mechanisms indicated by different biomarkers.¹⁵ Broadly speaking, asthma can be classified into type 2 asthma and non-type 2 asthma. Type 2 asthma is triggered by type 2 inflammation, mediated by eosinophils, basophils, mast cells, T helper 2 lymphocytes that secrete interleukin [IL]-4, IL-5 and IL-13, group 2 innate lymphoid

cells and immunoglobulin E (IgE)-producing B cells.¹⁶ In non-type 2 asthma, the pathophysiology mainly involves neutrophils, smooth muscle, or metabolic-related processes. Cytokines that mediate non-type 2 asthma include IL-1 β , IL-6, IL-17, IL-18, interferon (IFN)- γ , and tumour necrosis factor (TNF)- α .^{17–22} There have been phenotype studies conducted previously, focusing on patients with moderate or severe asthma patients. According to these studies, the prevalence of type 2 phenotype ranges from 50 to 70% in patients with moderate to severe asthma.²³

The epidemiology of phenotypes also varies in different populations. Data from the International Severe Asthma Registry suggested that the proportion of severe asthma with elevated IgE, blood eosinophil count and fractional exhaled nitric oxide (FeNO) differs across patients from the United States (USA), United Kingdom (UK), Italy, Australia and South Korea.²⁴ According to this multi-national study, a total of 49.4% of the patients had elevated IgE (cut-off at 150 IU/mL), with lowest percentage noted in the USA (42.2%) and highest percentage in Italy (67.5%). About 48.5% of the patients with elevated blood eosinophil count (cut-off at 300 cells/ μ L), with lowest percentage noted in the South Korea (40.9%) and highest percentage in UK (64.5%). This suggested possible ethnic differences in asthma phenotypes. Asthma phenotypes (type 2 and non-type 2) were also reported to impact the prevalence of co-morbidities, such as rhinitis, chronic rhinosinusitis and nasal polyps.²⁵

The phenotyping carries important implications in asthma treatment. For example, while inhaled corticosteroid (ICS) is indicated in asthma of all severities, patients with obesity associated asthma, which are typically of non-type 2 phenotype, respond poorly to ICS treatment.²⁶ In the recent years, the availability of biologics has revolutionized the treatment of severe asthma but the choices of biologics depend heavily on the phenotype as most of them only work in type 2 asthma.^{27,28} As such, it is crucial to have in-depth understanding of asthma phenotypes.

The presence of biomarkers and phenotypes has also been associated with differences in allergic sensitization and the coexistence of nasal polyposis.²⁹ One study reported that allergic sensitization was most prevalent in the patients who had with elevated total serum IgE.²⁹ Concomitant elevation of 2 or more biomarkers (IgE, blood eosinophil count, FeNO) was reported in the same study to be associated with a higher prevalence of nasal polyposis. Other reported differences related to asthma phenotypes include a history of smoking, the presence of allergic rhinitis and chronic rhinosinusitis.²⁵

Unlike severe asthma, where the phenotypes and their associations with prognosis and therapeutic implications are well known,³⁰ the prevalence and clinical characteristics of type 2 and non-type 2 phenotypes in mild asthma are less well investigated. While a recently published population-based study did report the prevalence of the phenotypes in patients with asthma of different severity, mild asthma patients only contributed to around 20% of the patients only.³¹ In that study, there were 185 patients with mild asthma on ICS only and among them, 87.0% had type 2 asthma. But the prevalence of mild asthma in the whole population was reported to be up to 70% in other studies.³² These suggested that mild asthma was under-represented in previous study and there is a need for proper evaluation. In type 2 asthma, various biologics have showed promising results while the blood eosinophil count, FeNO and serum IgE level will influence the biologics of choice.³³ In non-type 2 asthma, most biologics except tezepelumab are not effective.³⁴ Among non-type 2 asthma, there is a distinct entity known as obesity associated asthma which is well reported to respond poorly to ICS but glucagon-like peptide-1 receptor agonists (GLP1-RA) have been assessed and have showed potential benefits in this phenotype.³⁵ We conducted this study to investigate the prevalence and clinical characteristics of type 2 and non-type 2 phenotypes in asthma patients with varying degrees of severity, from mild to severe asthma.

Material and Methods

This was a cross-sectional study conducted at Queen Mary Hospital (QMH), in Hong Kong. Adult patients with asthma of varying severity who were treated at the asthma clinic of QMH from January 8th, 2023, to November 7th, 2023, were included. Asthma severity was defined according to the 2024 Global Initiative for Asthma (GINA) recommendation, with patients in step 1 to 2 of treatment level classified as mild asthma, patients in step 3 to 4 treatment level as moderate asthma and step 5 treatment level as severe asthma.⁸ Patients were followed up until November 15th 2024 to observe the development of clinical outcomes (asthma exacerbation, hospitalized asthma exacerbation and increase in asthma maintenance treatment) during the follow-up period. The follow up were arranged at every 24 to 28 weeks with additional appointment allowed if deemed clinically necessary. Phenotypes were defined as follows: type 2 phenotype was defined by a blood eosinophil count ≥ 300 cells/ mm^3 or total serum IgE ≥ 100 IU/mL, eosinophilic phenotype was

defined by a blood eosinophil count ≥ 300 cells/mm³, elevated IgE asthma was defined by a total serum IgE ≥ 100 UI/mL and an overlapping eosinophilic phenotype with elevated total serum IgE (overlapping phenotype) was defined by a blood eosinophil count of ≥ 300 cells/mm³ and a total serum IgE of ≥ 100 UI/mL. The cut-off for eosinophilic phenotype adopted in this study was chosen for consistency with previous studies.^{36–40} Although there was no standard cut-off for high total serum IgE formally defined, a cut-off at 100 IU/mL was chosen as it was the commonly used reference value for normal IgE levels applied by pathology laboratories, which was also adopted in other asthma studies conducted in Hong Kong.⁴⁰

The inclusion criteria were adult patients aged 18 years old or above with a diagnosis of asthma, confirmed by symptoms typical of asthma with demonstration of variable expiratory airflow limitation, preferably by spirometry and exclusion of alternative diagnoses. Patients with predominant diagnosis of chronic respiratory conditions other than asthma that may dominate the clinical picture of respiratory status, active malignancy, benign or malignant lung tumor, pregnant patients, patients with recent respiratory tract infections, patients with poor asthma medication compliance or poor inhaler technique were excluded from the study. Patients receiving biologics and systemic corticosteroids (both as long term maintenance and ad hoc prescription in past 30 days) that could interfere with biomarker values at their recruitment visit were also excluded.

At the screening visits, patients underwent a detailed assessment that included a history of asthma and comorbidities, a measurement of body mass index, an asthma control test (ACT) questionnaire and blood sampling to determine eosinophil and total IgE levels. Patients were also assessed by a nurse specializing in respiratory diseases to determine whether they were compliant with their asthma medication. Patients then underwent spirometry with a bronchodilator reversibility test within 4 weeks of screening. Spirometry was performed using the CareFusion Vmax[®] Encore 22 system in accordance with the American Thoracic Society standard,⁴¹ and was performed both before and after administration of 400ug of Salbutamol by inhalation via a spacer.

The primary outcome was the prevalence of different asthma phenotypes in patients with varying severity, and secondary outcomes included the clinical features of patients with type 2 asthma and non-type 2 asthma of varying levels of severity, any development of clinical outcomes within the follow-up period such as asthma exacerbation, hospitalization due to asthma exacerbation and increase in asthma maintenance treatment by escalating in treatment in GINA steps. The association between type 2 biomarkers level and risk of exacerbation was also assessed. This study was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority/Hong Kong West Cluster (UW 23–180).

Statistical Analysis

Numerical data based on demographic features and laboratory results were presented as mean, and standard deviation (SD), as most of these variables were normally distributed. Unpaired t-tests or Wilcoxon Mann–Whitney *U*-tests were applied for continuous variables with normally or non-normally distributed data. ANOVA and Kruskal–Wallis were used to compare continuous variables in more than 2 groups, for data that was normally and not normally distributed. Categorical variables such as sex and stratified variables were presented in frequencies and percentages. Categorical data were compared by Chi-square test. As the data on mild asthma phenotyping is lacking, which is considered to be the knowledge gap, we compared this group with those having moderate to severe asthma. Prevalence of asthma phenotype in mild or moderate to severe asthma was compared by chi-square test. Univariate and multi-variable logistic regression was performed to assess the relationship between phenotypes and biomarkers with the risk of asthma exacerbation (as expressed in categorical outcome). Covariates such as age, sex, asthma severity, baseline FEV₁ and smoking status were adjusted in the multivariable analysis, using backward stepwise selection. The statistical significance was determined at the level of $p < 0.05$. All statistical analyses were completed using the 28th version of the SPSS statistical package.

Results

A total of 152 adult patients with asthma treated at QMH were recruited. The mean follow up duration was 16.1 ± 1.9 months. Among these patients, 102 (67.1%) were females, with a mean age of 58.6 ± 14.5 years. Of the cohort, 125 (82.2%)

were non-smokers, 15 (9.9%) were ex-smokers, and 12 (7.9%) were current smokers. Regarding asthma severity, 51 (33.6%) patients had mild asthma (GINA step 1–2) [30 GINA step 1 and 29 GINA step 2], 50 (32.9%) had moderate asthma (GINA step 3–4) [21 GINA step 3 and 29 GINA step 4] and 51 (33.6%) had severe asthma (GINA step 5). Overall, 95 (62.5%) patients exhibited a type 2 phenotype; 57 (37.5%) had an eosinophilic phenotype, 81 (53.3%) had elevated IgE levels and 43 (28.3%) had overlapping phenotypes. There was no statistically significant difference between mild and moderate/severe asthma in the degree of eosinophilia or IgE elevation among those with type 2 phenotype, although their mean values were numerically lower and individual variation was high. The results are summarized in [Table 1](#).

Prevalence of Asthma Phenotype in Asthma of Different Severities

Various type 2 inflammation-related phenotypes (type 2 ($p = 0.015$), eosinophilic ($p = 0.030$), elevated IgE ($p = 0.033$) and overlapping phenotypes ($p = 0.038$)) were more common among patients with moderate to severe asthma. The prevalence of these phenotypes across mild, moderate and severe asthma is summarized in [Table 2](#).

Table 1 Baseline Demographic and Clinical Characteristics

	Mild Asthma (n = 51)	Moderate to Severe Asthma (n = 101)	p-values
Sex (Female) (%)	31 (60.8%)	71 (70.3%)	0.24
Age (years)*	55.9 ± 15.7	59.9 ± 1.37	0.12
Non-smoker (%)	41 (80.4%)	84 (83.2%)	0.82
Ex-smoker (%)	5 (9.8%)	10 (9.9%)	
Current smoker (%)	5 (9.8%)	7 (6.9%)	
Body weight (kg)*	66.5 ± 15.6	63.5 ± 12.8	0.24
BMI (kg/m ²) *	25.5 ± 5.5	25.0 ± 4.0	0.49
Symptom onset age (years)*	32.2 ± 23.3	33.5 ± 21.7	0.74
Age of first clinician attendance for asthma (years)*	35.9 ± 23.2	35.9 ± 20.9	0.39
Age of initiation of maintenance therapy (years)*	38.8 ± 20.9	38.7 ± 19.0	0.99
ACT score*	22.3 ± 2.5	19.4 ± 4.7	<0.001 [^]
Post-bronchodilator FEV ₁ (L)*	2.31 ± 0.68	1.96 ± 0.50	0.005*
Post-bronchodilator FEV ₁ (% predicted) *	98.1 ± 17.4	93.5 ± 20.2	<0.001*
Post-bronchodilator FVC (L)*	3.10 ± 0.89	2.91 ± 0.71	0.17
Post-bronchodilator FVC (% predicted), mean ± SD	103.4 ± 13.3	107.2 ± 16.7	0.16
Post-bronchodilator FEV ₁ /FVC ratio*	74.7 ± 7.9	66.3 ± 12.6	<0.001 [^]
Bronchodilator reversibility (mL)*	130 ± 159	114 ± 154	0.56
Bronchodilator reversibility (%)*	6.7 ± 8.6	7.2 ± 9.5	0.77
Baseline eosinophil count (cells/μL) *	252 ± 236	331 ± 269	0.07
Baseline eosinophil percentage*	3.78 ± 3.70	4.49 ± 3.37	0.25
Serum IgE level*	291 ± 794	776 ± 2643	0.10

Note: *Expressed in mean ± standard deviation; [^] statistically significant.

Abbreviations: m, meter; kg, kilogram; mL, milliliter; BMI, body mass index; ACT, asthma control test; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; μL, microliter.

Table 2 Prevalence of Different Asthma Phenotypes Among Mild and Moderate to Severe Asthma

Eosinophilic Phenotype		p-value*
Mild asthma	25.5%	0.030
Moderate to severe asthma	43.6%	
Elevated IgE asthma		
Mild asthma	41.2%	0.033
Moderate to severe asthma	59.4%	
Overlapping eosinophilic phenotype with elevated total serum IgE level		
Mild asthma	17.6%	0.038
Moderate to severe asthma	33.7%	
Th2 phenotype		
Mild asthma	49.0%	0.015
Moderate to severe asthma	69.3%	
Eosinophilic phenotype with normal IgE		
Mild asthma	7.8%	0.68
Moderate to severe asthma	9.9%	
Elevated IgE with normal blood eosinophil count		
Mild asthma	23.5%	0.77
Moderate to severe asthma	25.7%	

Note: *The prevalence was compared by Chi-square test.

Abbreviation: IgE, Immunoglobulin E.

Association Between Clinical Characteristics and Phenotypes in Patients with Mild Asthma

Eosinophilic Phenotype

Demographics

Among patients with mild asthma, there were more males with eosinophilic phenotype, while more females exhibited the non-eosinophilic phenotype (68.4% of non-eosinophilic patients were female, 61.5% of eosinophilic patients were male, $p = 0.05$). There were more non-smokers with the non-eosinophilic phenotype (89.5% vs 53.8%, $p = 0.02$). Mild asthma patients with eosinophilic phenotype were younger compared to their non-eosinophilic phenotype counterparts (47.1 ± 14.9 vs 58.9 ± 15.0 years, $p = 0.02$).

Clinical Aspects and Lung Function

Patients with eosinophilic phenotype had a higher post-bronchodilator FEV₁ (2.67 ± 0.75 L vs 2.18 ± 0.62 L, $p = 0.05$) and post-bronchodilator FVC (3.69 ± 1.00 L vs 2.89 ± 0.75 L, $p = 0.0$). Additionally, patients with eosinophilic phenotype had a shorter time from initial clinic attendance to starting controller therapy (1.00 ± 2.45 years vs 7.95 ± 15.65 years, $p = 0.01$).

Overlapping Eosinophilic Phenotype with Elevated Total Serum IgE Level

Patients with this phenotype were statistically more likely to have nasal polyps (33.3% vs 4.8%, $p = 0.01$). They also had a higher incidence of prior intensive care unit admission for severe asthma exacerbation compared to the other phenotype counterparts (11.1% vs 0%, $p = 0.03$).

Type 2 Phenotype (Blood Eosinophil Count ≥ 300 Cells/mm³ or Total Serum IgE ≥ 100 IU/mL)

Mild asthma patients with type 2 phenotype were younger compared with their non-type 2 phenotype counterparts (49.8 ± 15.0 vs 61.7 ± 14.4 years, $p = 0.01$).

The results were summarized in Table 3.

Association Between Clinical Characteristics and Phenotypes of Patients with Moderate to Severe Asthma Eosinophilic Phenotype

Differences in the co-morbidities and lung function parameters were observed. More patients with eosinophilic phenotype had nasal polyps (20.5% vs 1.8%, $p < 0.01$).

Patients with eosinophilic phenotype also had lower post-bronchodilator FEV₁ ($87.87 \pm 19.54\%$ vs $98.10 \pm 19.77\%$, $p = 0.02$) and post-bronchodilator FEV₁/FVC ratio ($63.97 \pm 11.67\%$ vs $71.77 \pm 12.44\%$, $p < 0.01$).

There were also differences in the time from disease onset to asthma care noted. Patients with eosinophilic phenotype had shorter time from disease onset to controller therapy (2.09 ± 4.31 years vs 7.75 ± 14.73 years, $p = 0.02$) and disease onset to clinician attendance (0.39 ± 1.87 years vs 4.10 ± 11.99 years, $p = 0.04$).

Table 3 Clinical Characteristics and Phenotypes of Patients with Mild Asthma

	Eosinophilic Phenotype	Non-Eosinophilic Phenotype	p-value
Male sex (%)	61.5%	31.6%	0.05
Non-smoker (%)	53.8%	89.5%	0.02
Age (Years), mean $\pm$ SD	47.1 $\pm$ 14.9	58.9 $\pm$ 15.0	0.02
Post-bronchodilator FEV ₁ (L), mean $\pm$ SD	2.67 $\pm$ 0.75	2.18 $\pm$ 0.62	0.05
Post-bronchodilator FVC (L), mean $\pm$ SD	3.69 $\pm$ 1.00	2.89 $\pm$ 0.75	0.02
Time from initial clinic attendance to starting controller therapy (Years), mean $\pm$ SD	1.00 $\pm$ 2.45	7.95 $\pm$ 15.65	0.01
	Overlapping eosinophilic phenotype with elevated total serum IgE level	Non-overlapping eosinophilic phenotype with elevated total serum IgE level	
Nasal polyps (%)	33.3%	4.8%	0.01
Prior ICU admission for severe asthma exacerbation (%)	11.1%	0%	0.03
	Type 2 phenotype	Non-type 2 phenotype	p-value
Age (Years), mean $\pm$ SD	49.8 $\pm$ 15.0	61.7 $\pm$ 14.4	0.01

Note: The prevalence was compared by Chi-square test.

Abbreviations: SD, standard deviation; FEV₁, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; ICU, Intensive Care Unit.

Overlapping Eosinophilic Phenotype with Elevated Total Serum IgE Level

There were more male patients (47.1% vs 20.9%, $p = 0.01$), patients with atopic dermatitis (58.8% vs 34.3%, $p = 0.02$) and nasal polyps (26.5% vs 1.5%, $p < 0.01$) among those with this phenotype.

Elevated IgE Asthma

There were more patients with nasal polyps in those with IgE elevated asthma (16.7 vs 0%, $p = 0.01$).

Type 2 Phenotype

There were more patients with nasal polyps among those type 2 phenotype (14.3% vs 0%, $p = <0.01$).

The results were summarized in [Table 4](#).

Association Between Phenotypes and Clinical Outcomes in Follow Up Period

Whole Cohort

The annual number of all asthma exacerbations was higher in patients with the eosinophilic phenotype (0.44 ± 0.91 per year vs 0.21 ± 0.44 per year, $p = 0.038$), elevated IgE asthma (0.40 ± 0.82 per year vs 0.19 ± 0.40 per year, $p = 0.05$) and overlapping phenotype (0.54 ± 1.02 per year vs 0.21 ± 0.43 per year, $p = 0.006$).

Higher blood eosinophil levels, as a continuous variable, were associated with increased risks of having all asthma exacerbation during the follow-up period, with odds ratios (OR) of 1.14 (95% confidence interval [CI] = 1.14–1.30, $p = 0.049$) and adjusted OR (aOR) of 1.23 (95% CI = 1.02–1.48, $p = 0.044$), when assessed as per 100-unit increase. When assessed in per 1 SD increase in blood eosinophil level, the OR was 1.41 (95% CI = 1.00–1.98, $p = 0.049$), and the aOR was 1.45 (95% CI = 1.01–2.10, $p = 0.044$).

Table 4 Clinical Characteristics and Phenotypes of Patients with Moderate to Severe Asthma

	Eosinophilic Phenotype	Non-Eosinophilic Phenotype	p-value
Nasal polyps (%)	20.5%	1.8%	<0.01
Post-bronchodilator FEV ₁ (L), mean $\pm$ SD	87.87 $\pm$ 19.54%	98.10 $\pm$ 19.77%	0.02
Post-bronchodilator FVC (L), mean $\pm$ SD	63.97 $\pm$ 11.67%	71.77 $\pm$ 12.44%	<0.01
Time from disease onset to controller therapy (Years), mean $\pm$ SD	2.09 $\pm$ 4.31	7.75 $\pm$ 14.73	0.02
Time from disease onset to clinician attendance (Years), mean $\pm$ SD	0.39 $\pm$ 1.87	4.10 $\pm$ 11.99	0.04
	Overlapping eosinophilic phenotype with elevated total serum IgE level	Non- overlapping eosinophilic phenotype with elevated total serum IgE level	
Male sex (%)	47.1%	20.9%	0.01
Nasal polyps (%)	26.5%	1.5%	<0.01
Atopic dermatitis (%)	58.8%	34.3%	0.02
	Elevated IgE phenotype	Non-IgE elevated phenotype	
Nasal polyps (%)	16.7%	0%	0.01
	Type 2 phenotype	Non-type 2 phenotype	p-value
Nasal polyps (%)	14.3%	0%	<0.01

Abbreviations: SD, standard deviation; FEV₁, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; IgE, Immunoglobulin E.

Similarly, higher blood eosinophil levels were associated with increased risks of hospitalized asthma exacerbations during follow up, with ORs of 1.21 (95% CI = 1.03–1.42, $p = 0.022$) and an aOR of 1.22 (95% CI = 1.03–1.44, $p = 0.036$), when assessed as per 100-unit increase. When assessed in per 1 SD increase in blood eosinophil level, the OR was 1.64 for (95% CI = 1.07–2.50, $p = 0.022$) and aOR was 1.69 (95% CI = 1.06–2.70, $p = 0.036$).

Moderate to Severe Asthma

Among patients with moderate to severe asthma, 25% of those with IgE-elevated asthma had an increase in their asthma maintenance treatment, while only 9.8% with non-IgE elevated asthma had an increase in asthma maintenance treatment ($p = 0.05$). Also, 29.4% and 13.4% with overlapping and non-overlapping phenotype had increase in asthma maintenance treatment during follow up ($p = 0.05$).

The annual number of asthma exacerbations was higher in patients with eosinophilic phenotype (0.56 ± 1.00 per year vs 0.24 ± 0.47 per year, $p = 0.037$) and in those with overlapping phenotype (0.65 ± 1.11 per year vs 0.24 ± 0.45 per year, $p = 0.009$).

Within this group, a higher blood eosinophil level as a continuous variable was associated with increased risk of exacerbations in the follow-up period, with ORs of 1.19 (95% CI = 1.01–1.34, $p = 0.034$) and an aOR of 1.21 (95% CI = 1.03–1.43, $p = 0.017$), when assessed as per 100-unit increase. When assessed in per 1 SD increase in blood eosinophil level, the OR was 1.58 (95% CI = 1.03–2.42, $p = 0.034$) and the aOR was 1.74 (95% CI = 1.10–2.74, $p = 0.017$).

Moreover, the risks of having all asthma exacerbation in the follow-up period was also increased among those with baseline blood eosinophil count in 4th quartile (Q1: <130 cells/ μ L, Q2: 130–250 cells/ μ L, Q3: 250.1–425 cells/ μ L, Q4: >425 cells/ μ L) with an OR of 5.35 (95% CI = 1.52–18.75, $p = 0.009$) and an OR of 5.12 (95% CI = 1.36–19.22, $p = 0.016$).

Subgroup Analysis in Patients with Type 2 Phenotype

Subgroup analysis was performed among patients with type 2 phenotype which consisted of 95 patients (25 mild asthma patients, 70 moderate to severe asthma patients). Patients with moderate to severe type 2 asthma were older (59.5 ± 13.5 years vs 49.8 ± 15.0 years, $p = 0.007$), had a longer duration of asthma (26.9 ± 17.7 years vs 15.7 ± 17.5 years, $p = 0.009$), and exhibited lower post-bronchodilator FEV₁/FVC ratios ($66.8 \pm 12.3\%$ vs $74.3\% \pm 8.7\%$, $p = 0.009$) than those with mild type 2 asthma. They were also more likely to have a history of intensive care unit care for severe asthma exacerbation compared to those with mild type 2 asthma (40.0% vs 12.0%, $p = 0.01$); co-existing hypertension (48.6% vs 20.0%, $p = 0.013$) and hyperlipidaemia (47.1% vs 24.0%, $p = 0.043$) than those with mild type 2 asthma.

Discussion

In this study, we describe the phenotypes and their distinctive clinical features across the spectrum of asthma severity. Consistent with the literature, the type 2 phenotype was more prevalent among patients with moderate to severe asthma, whereas the non-type 2 phenotype was more common among those with mild asthma. There was notable heterogeneity in asthma phenotypes, especially among patients with different severity levels, with the proportions of various type 2 biomarkers in the mild asthma group differing from those in the more severe asthma group. The blood eosinophil count and serum IgE level were numerically lower in patients with mild asthma compared to those with moderate to severe asthma, but this difference did not reach statistical significance. Throughout the range of asthma severity, the type 2 phenotype was associated with significantly more exacerbations, with blood eosinophil count serving as a predictor of exacerbation risk.

While the asthma phenotype has been extensively studied in severe asthma,^{11,14,42,43} partly because it guides biologic treatment,^{44–48} the knowledge on the prevalence and related clinical characteristics among mild asthma is less well understood. Reports suggest that the type 2 phenotype is predominant in severe asthma. A Caucasian study suggested that 70% of the patients with severe asthma had at least one type 2 biomarker, while 39% had two or more elevated biomarkers.¹⁶ A local study conducted in Hong Kong reported that 72.8% of Chinese asthma patients on GINA step 4/5 treatment had the type 2 phenotype, 43% had an eosinophilic phenotype (blood eosinophil count ≥ 300 cell/mm³), while 59% had high total IgE levels of >100 IU/mL (overlapping with eosinophilic phenotype in 30%) and 44% had IgE levels

of >150 IU/mL (overlapping with eosinophilic phenotype in 22%).⁴⁰ Patients with eosinophilic phenotype and IgE >150 IU/mL had a 1.8-fold higher rate of uncontrolled asthma compared to those without this combination.

In studies involving mild asthma, the reported prevalence of type 2 phenotypes varies. In our study, patients with mild asthma, unlike their severe asthma counterparts, showed no predominance of the eosinophilic and type 2 phenotype. The literature suggested that eosinophilic or type 2 phenotypes can contribute to more than two-third or even 90% of the cases in severe asthma.^{38,49} A recent publication from Austria suggested the prevalence of eosinophilic asthma contributed to 32.0% of the cases, which is close to the findings we reported.⁵⁰ However, that study also reported that using FeNO with blood eosinophil count could reclassify a further 13.7% of patients into eosinophilic subgroup. Meanwhile, elevated IgE was the most common biomarker in the type 2 biomarker subgroup. Similar findings have been reported in an American study, suggesting that approximately half of patients with mild-to-moderate asthma have persistently non-eosinophilic disease,⁵¹ while another clinic/birth cohort in England reported a type 2 prevalence of 41% among mild asthma patients.⁵² Conversely, some studies, such as one conducted in a Severe Asthma Centre in Italy, reported that 81.9% of their patients on step 1 to 2 medication exhibited a type 2 phenotype.²⁵ Overall, this suggests that the prevalence of the type 2 phenotype among mild asthma remains controversial. While most of the reported studies were among Caucasian population, there seems to lack consistency in the prevalence of the phenotype. There is also a lack of data in Chinese population focusing on the inflammatory phenotype in mild asthma and the current study provided important information in this regard. As many of these studies involve asthma patients in specialist clinics, findings can be skewed due to referral bias.

While type 2 asthma is the predominant type among asthma patients, especially among severe asthma patients as reported in the current study and in the literature, they are also easier to treat as ICS and biologics are effective in this phenotype. Non-type 2 asthma is well reported to be treatment resistant and contributes to significant symptom burden. There is lack of effective treatment for this phenotype. Among non-type 2 asthma, a distinct subgroup known as “obesity-associated asthma” has been proposed.^{53–55} A European multi-cohort study of more than 500,000 subjects reported that adult-onset or late-onset asthma patients (comprising >85% of the cohort) had higher risks for being overweight/obese.⁵⁶ Another European study conducted by Moitra et al highlighted that among 7500 participants, the risk of developing obesity was higher among those with asthma than those without.⁵⁷ There are no FDA-regulated medications specifically with an indication for non-type 2 or obesity-associated asthma. Anti-thymic stromal lymphopoietin receptor, tezepelumab is the only biologics shown to have clinical efficacy for non-type 2 asthma, though the efficacy in non-type 2 asthma is not as pronounced as in type 2 counterparts.⁵⁸ For obesity-associated asthma, GLP-1RA have been evaluated as a potential therapeutic target. Meta-analysis also suggested a modest reduction in the incidence of asthma in patients with type 2 diabetes or obesity using GLP-1 receptor-based agonist treatments.⁵⁹

Beyond prevalence, other clinical features associated with different asthma severities and phenotypes are also worth assessing, one of which is the association with nasal polyposis. Literature indicates that severe asthma often coexists with nasal polyposis.²⁹ In our cohort-comprising the entire spectrum of asthma severity per treatment criteria-patients with eosinophilic, overlap, and type 2 phenotypes, regardless of asthma severity, were more significantly likely to have nasal polyposis.

Lung function impairment is another clinical feature that is of clinical importance in asthma. Interestingly, among mild asthma patients, those with eosinophilic phenotypes exhibited significantly better lung function as measured by post-bronchodilator FEV1 and post-bronchodilator FVC, as opposed to previous reports linking worse lung function and more severe airflow obstruction with the eosinophilic phenotype in severe asthma patients.⁶⁰ We also found no correlation between absolute eosinophilic counts or eosinophilic phenotypes and spirometric performance either in the mild asthma group or overall. Whether this phenomenon can be explained by the fact that eosinophilic inflammation might not be the only driver for persistent airflow obstruction is worth confirming with a larger cohort, preferably incorporating any histopathological and ultrastructural changes if available.

Furthermore, our study also revealed a significant difference in the time from first clinician attendance to initiation of controller therapy in relation to their phenotype. Patients with eosinophilic phenotype tended to receive treatment earlier by controller regardless of severity, likely due to earlier asthma diagnosis for those presenting with eosinophilia. The presence of eosinophilia and co-existing diseases such as atopic conditions allows asthma to be recognized earlier, with subsequent earlier initiation of controller therapy, whereas non-specific initial symptoms at initial presentation may delay diagnosis in the non-eosinophilic counterpart. On the other hand, those with moderate and severe asthma presented to the

clinician significantly earlier from the time of symptom onset, and also had earlier initiation of controller therapy, but they still had significantly poorer lung function compared to their non-eosinophilic counterparts. While it is tempting to speculate that earlier use of controller therapy preserves lung function, other unidentified factors might influence these outcomes.

The prognostic value of phenotyping and exacerbation risks by eosinophilic phenotype was once again demonstrated among patients with moderate to severe asthma. However, such associations were not observed in the mild asthma group, likely due to a smaller sample size.

In summary, our study demonstrated differences in the prevalence of type 2 related phenotypes among patients with asthma of different severity levels and demonstrated how different asthma phenotypes can be linked to various clinical features.

Among the type 2 phenotypes, apart from eosinophilic, elevated IgE and overlapping phenotypes we described, these patients can also be further stratified into elevated eosinophil with normal IgE and elevated IgE with normal eosinophil subgroups which were presented in Table 2. Due to small patient number in these subgroups, we did not perform additional analyses, but it will be important to assess these phenotypes with a larger cohort.

In this study, we first reported the prevalence of different asthma phenotypes in mild and moderate to severe asthma in the Chinese population which is not reported in the literature. Secondly, we reported the differences in the clinical characteristics among mild and moderate to severe asthma which is not only limited to demographics and co-morbidities, but also lung function and time from disease onset to medical care, in which the latter is seldom reported. Among non-eosinophilic asthma, regardless of disease severity, the time to diagnosis and proper treatment is significantly longer than the eosinophilic counterparts. This could be related to the lower prevalence of co-morbidities in patients with non-eosinophilic asthma and lack of reliable biomarkers. This may pose diagnostic challenges and inertia in treatment initiation. The research and discovery of reliable biomarkers in patients with non-eosinophilic asthma is warranted.

The strength and novelty of this study is that it comprehensively assesses asthma of different severity and phenotypes, with a wide range of clinical parameters assessed. Among these, some of the parameters such as time from disease onset to diagnosis and treatment were not well reported and we provided information on this aspect and its association with asthma phenotypes.

There are a few limitations in our study. First, it involved only a single asthma clinic patient pool with a limited sample size. The participants were all Chinese, which may affect the generalizability of the findings. Also, the short prospective follow-up duration precluded accurate documentation of long-term outcomes, such as serial changes in lung function over time. A longer follow-up of the patients would be meaningful to observe their trajectory. Another limitation is the lack of confirmation of atopic sensitization by specific serum IgE and/or skin prick tests in this study. As such, we cannot properly define a group as allergic asthma, and we reported a subgroup with elevated IgE only. Ideally, confirmation with atopic sensitization should be performed, and the allergic asthma subgroup should be separately analyzed. However, IgE is a much cheaper test with higher availability that allows even general practitioners to use it in daily practice. Also, total serum IgE was reported to be able to function as a proxy of atopic sensitization.^{61,62} We compared mild asthma patients with those having moderate to severe asthma as there is limited data on phenotyping among mild asthma patients and this is the knowledge gap that we would like to examine for. Ideally, we can separate the patients into 3 (mild, moderate, severe) or 5 (GINA step 1–5) groups but the limited sample size for each group which impacts the statistical power is the concern here. A larger scale study is warranted to examine the patients among more subgroups. Our study also lacks a healthy control group for comparison. By including a healthy control group, it can allow us to determine if the biomarkers for type 2 asthma (blood eosinophils and IgE levels) were also elevated in healthy subjects and whether the level of these biomarkers will be different from asthma patients with different severity. However, as a study focusing on phenotyping in asthma patients, lacking a healthy control group will not heavily impact the reliability of the study findings.

Conclusion

In this asthma cohort with a spectrum of clinical severity categorized according to the maintenance treatment required, those with mild asthma had a lower prevalence of the type 2 phenotype, as defined by blood eosinophils and IgE levels, compared with those with moderate/severe asthma. With comprehensive assessment of various clinical domains, the

distinct clinical features among asthma of different phenotypes and severities were assessed, in which some are not reported in literature. The type 2 phenotype was associated with nasal polyposis irrespective of asthma severity. The eosinophilic phenotype in the mild asthma group showed less airways obstruction on lung function testing and did not have an increased risk of exacerbations compared with their non-eosinophilic counterparts, which contrasts with the worse lung function and higher exacerbation risk seen in those with eosinophilic phenotype among the moderate/severe asthma group. The mean absolute eosinophil count of those with mild asthma was numerically lower, but not statistically significant, than that in patients with moderate /severe asthma, likely due to substantial individual variation. The differing clinical behaviors of the eosinophilic phenotype in asthma warrants further investigation. Linking the clinical features with biomarkers in non-type 2 asthma also worth future research.

Data Sharing Statements

All available data are presented in the manuscript, and no additional data will be provided. Due to the ethical restrictions imposed by the Institutional Review Board (IRB) regulations and rules on patient data privacy in this study, the supporting research data is not available upon request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 23-180). Informed consents were obtained from all participants. The study was conducted in accordance with the declaration of Helsinki. The University of Hong Kong and Hospital Authority is responsible for the governance of the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB), which oversees the ethics and scientific aspects of clinical studies of the University of Hong Kong conducted under their jurisdiction. The name of this approving IRB match all author affiliations with “the University of Hong Kong”).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was supported by Hong Kong Institute of Allergy Research Grant.

Disclosure

Mary Sau Man Ip reports grants from HK Allergy Institute, during the conduct of the study; grants, personal fees from Sanofi, personal fees from Astra Zeneca, outside the submitted work. The authors declare no other conflicts of interest in this work.

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