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Distinct phenotype and risk factor analysis of persistent airflow limitation among asthmatic children: a case-control study

Shiqiu Xiong[1,2,3], Xinyu Jia[1], Wei Chen[1] and Chuanhe Liu[1,2*]

Abstract

Background Persistent airflow limitation (PAL) in childhood asthma is associated with a poor prognosis. The aim of this study was to categorize asthmatic children with PAL into distinct phenotypes and investigate the risk factors associated with each phenotype.

Methods We conducted a case-control study with a total of 119 PAL patients and 120 non-PAL (NPAL) individuals. To classify the patients into appropriate clusters, unsupervised cluster analysis using K-means clustering was employed. The clusters were then compared to explore different PAL phenotypes. Univariate and multivariate logistic regression analyses were performed to identify risk factors for PAL and calculate odds ratios (ORs) with 95% confidence intervals (95%CIs).

Results K-means clustering divided patients into three clusters: Cluster 0 included 120 NPAL patients, Cluster 1 characterized by elevated blood neutrophils included 66 PAL patients, and Cluster 2 exhibited elevated blood eosinophils and FeNO levels, containing 53 PAL patients. Independent risk factors for PAL included older age in both Cluster 1 (9～11y: OR 12.67, 95%CI 3.30-55.74; ≥11y: OR 5.42, 95%CI 1.26-25.69) and Cluster 2 (9～11y: OR 7.25, 95%CI 1.70-33.35; ≥11y: OR 11.28, 95%CI 2.79-51.89), as well as pneumonia history, with an OR of 6.41(95%CI 1.34-33.41) in Cluster 1 and an OR of 7.92(95%CI 1.83-37.44) in Cluster 2. Furthermore, specific factors associated with Cluster 1 included BMI above 22 kg/m^2(OR 12.28, 95%CI 2.68-70.45), asthma duration exceeding three years (OR 4.77, 95%CI 1.60-15.94), and a blood neutrophil percentage between 0.4 and 0.5 (OR 4.13, 95%CI 1.17-16.6). In Cluster 2, independent risk factors included a blood eosinophil percentage greater than 0.07 (OR 4.36, 95%CI 1.16-19.73) and a high FeNO level (OR 3.94, 95%CI 1.35-11.97).

Conclusion Our study identified two phenotypes of PAL in asthmatic children: non-eosinophilic and eosinophilic inflammation. Older age and a history of pneumonia were independent risk factors for both phenotypes. For non-eosinophilic inflammation PAL, specific contributing factors included higher BMI, long duration of asthma, and a blood neutrophil percentage between 0.4 and 0.5. Elevated FeNO levels and blood eosinophilic percentage were independently associated with eosinophilic inflammation PAL.

Keywords Asthma, Persistent airflow limitation, Phenotype, Risk factors, Clustering analysis

*Correspondence:
Chuanhe Liu
liuchcip@126.com
Full list of author information is available at the end of the article

Background

Asthma is a prevalent chronic respiratory disease in children, characterized by reversible airflow obstruction [1]. While the majority of pediatric asthma cases experience symptom remission and regain normal lung function through spontaneous recovery or appropriate treatment, a small proportion of patients continue to face persistent airflow limitation (PAL) despite receiving optimal treatment [2–4].

Patients with PAL experience accelerated lung function decline, and children with abnormal lung function growth are at a high risk of developing chronic airflow obstruction in early adulthood [5, 6]. While the short-term effects of PAL in asthmatic children on quality of life, aerobic fitness, and peripheral muscle strength may not be significant, PAL due to asthma in adulthood is associated with frequent hospital admissions, higher mortality rates, and even shorter life expectancy [7–9]. Therefore, the early identification of characteristics and risk factors associated with PAL is crucial.

Most studies have generally described the characteristics of patients with PAL, including being male, older in age, having a longer duration of asthma, and exhibiting elevated sputum or blood inflammatory cells [10–13]. However, there has been limited exploration of the distinct phenotypes of PAL, despite their crucial importance, as distinct phenotypes of the disease may be underpinned by different mechanisms, thereby guiding clinical decisions more effectively [14]. Furthermore, while risk factors for PAL in asthmatic populations have been extensively studied [11–13], only a few investigations have focused on the pediatric population [4]. Whether the risk factors for PAL in asthmatic adults and children are similar remains unknown. In this study, we aimed to identify distinct PAL phenotypes in asthmatic children and explore the specific risk factors associated with each phenotype.

Methods

Study design

This case-control study has received approval from the Ethics Committee of the Children's Hospital Capital Institute of Pediatrics (Approval No: SHERLL 2014040) in Beijing, China. We collected data from asthmatic children with PAL who visited the hospital's allergy clinic between 1 January 2021 and 31 July 2023. A control group consisting of an equal number of patients without PAL (NPAL) was included, maintaining a 1:1 ratio between the groups. Unsupervised clustering analysis was performed to uncover distinct PAL phenotypes. Additionally, univariate and multivariate logistic regression (LR) analyses were conducted to identify risk factors associated with each PAL phenotype.

Participants

The diagnostic criteria for asthma used in this study were aligned with the criteria provided by the Global Initiative for Asthma (GINA) [2]. The inclusion criteria consisted of the following: (1) patients diagnosed with asthma; (2) individuals aged between 5 and 18 years; (3) patients who had visited our clinic for asthma at least three times. Exclusion criteria were: (1) missing medication data or spirometry records; (2) individuals with concurrent chronic conditions, including cardiovascular diseases, autoimmune diseases, and mental disorders.

Data collection

We collected data from the medical records of the participants in our study, including the following information:

(1) Demographic data: This included age, gender, weight, and height.
(2) Disease-related variables: We recorded asthma severity, history of asthma exacerbation, history of pneumonia, atopy, and allergic comorbidities. Asthma severity was defined in accordance with the GINA guidelines [2]. Asthma exacerbation was determined based on the criteria outlined in the Official American Thoracic Society/European Respiratory Society Statement [15]. Atopy was defined as having any positive Phadiatop test ($\geq$ 0.35 KU/L) or positive skin prick test.
(3) Treatment-related variables: We noted the daily dose of inhaled corticosteroids (ICS), medication adherence, and systemic steroid use. Good adherence was defined as patients using ICS in the prescribed dose and frequency and regularly visiting our allergy clinic every 3-6 months.
(4) Auxiliary examination: We recorded blood neutrophils and eosinophils, total serum immunoglobulin E (IgE) level, fraction of exhaled nitric oxide (FeNO), as well as baseline spirometry parameters such as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC), percentage of predicted FEV1(FEV1%pred), percentage of predicted FVC(FVC%pred), percentage of predicted peak expiratory flow (PEF%pred), and percentage of predicted forced expiratory flow at 25% to 75% of forced vital capacity(FEF25-75%pred).

Outcome definition

The definition of PAL has varied across different studies. Some have defined PAL based on pre-bronchodilation(BD) or post-BD FEV1/FVC with a threshold of 0.70 or the lower limit of the normal range [4, 10, 16, 17]. However, FEV1/FVC <0.7 may underestimate the presence of airflow limitation, and a ratio of

0.75 has been shown to achieve better sensitivity and specificity [18, 19]. Additionally, some studies have solely used a single post-BD FEV1/FVC to define PAL, which may not accurately reflect the persistent nature of airflow limitation [20]. In our study, we defined PAL as FEV1/FVC ratio below 0.75 in all completed spirometry measurements conducted within one year. Moreover, we differentiated between irreversible PAL(IPAL), characterized by an FEV1/FVC ratio below 0.75 for both pre-BD and post-BD measurements, and reversible PAL (RPAL), characterized by an FEV1/FVC ratio below 0.75 for the pre-BD measurement but above 0.75 for the post-BD measurement [21].

Data processing

Four variables exhibited missing values, with the missing rate ranging from 10.04% to 19.66%. Moreover, these missing values occurred at random (Figure S1). Thus, we employed multiple imputation to deal with missing data [22, 23]. The imputed values for these variables closely mirrored the empirical distribution observed in subjects for whom these variables were measured (Figure S2). Continuous variables were normalized, and categorical variables were encoded using one-hot encoding. The processed data was further subjected to principal component analysis. Components were selected for clustering analysis if their cumulative variance explained more than 70% of the total variance, and we finally chose seven components for further clustering analysis.

In univariate and multivariate LR analyses, we initially addressed missing values through multiple imputation techniques. Subsequently, we categorized continuous variables based on their interquartile range (IQR).

Clustering analysis

K-means clustering is widely recognized for its versatility, computational efficiency, and straightforward implementation, making it a popular choice in various research domains [24]. The critical consideration for K-means clustering lies in determining the optimal number of clusters. In our study, we explored a range of cluster numbers, spanning from three to six, and conducted an evaluation using validity indices to pinpoint the most appropriate number of clusters.

We applied the silhouette coefficient (SC), Davies-Bouldin Index(DBI), and Calinski-Harabasz Index(CHI) for performance estimation. The range of SC is from -1 to +1, and a higher SC indicates a better clustering effect. DBI and CHI were metrics for estimating the compactness and separation between clusters. DBI and CHI range from zero to positive infinity. A smaller DBI suggests a better clustering result. Conversely, a higher CHI indicated a better performance. All visualization and clustering analyses were conducted using Python 3 and Prism 9.

Sample size and statistical analysis

We utilized the software PASS 15 to calculate the sample size for our case-control study. Based on previous literature [4], an expected odds ratio of 4.0 and a proportion of control group exposure of 0.63 were determined. We selected a desired power of 0.90 and a significance level of 0.05 to ensure adequate power while controlling for false positive findings. The calculated minimum sample size of patients was 124, with 62 patients in the PAL group and 62 patients in the NPAL group.

Continuous variables were reported as either the mean ± standard deviation or the median with the IQR. Categorical variables were described using frequencies and percentages. For the comparison of continuous variables between two independent groups, we employed either the Student's t-test or the Mann-Whitney U test, depending on the data distribution. When comparing multiple independent groups, we utilized the Kruskal-Wallis test. Categorical variables were compared using either the Chi-square test or Fisher's exact test as appropriate. The univariate and multivariate LR were conducted to calculate the odds ratios (OR) and 95% confidence intervals (95%CI) for the variables. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using R (Version 4.0.2)

Results

Characteristics of PAL and NPAL patients

Our study included 119 patients with PAL and 120 patients with NPAL (Table 1 summarizes patient characteristics). Patients with PAL were significantly older than those in the NPAL group (median age 11.0 [9.0, 13.0] vs. 8.0 [7.0, 9.0], $P<0.001$). The BMI of patients with PAL (median 20.00 [16.63, 24.29]) was higher compared to patients with NPAL (median 16.69 [14.85, 18.98])($P<0.001$). The proportion of patients with asthma duration over three years in the PAL group was higher, with 76.5% compared to 61.7% in the NPAL group ($P = 0.020$). Furthermore, patients with PAL were more likely to have a history of systemic steroid use (11.7% vs. 3.3%, $P=0.026$), asthma exacerbation (16.8% vs. 6.7%, $P=0.025$), and pneumonia (13.4% vs. 4.2%, $P=0.021$) compared to the patients with NPAL. FeNO levels were also significantly higher in the PAL group. Conversely, the NPAL group had a higher percentage of patients with eczema or dermatitis than the PAL group (35.8% vs. 19.3%, $P=0.007$). All spirometry parameters except FVC%pred in the PAL group were significantly lower than those in the NPAL group ($P<0.001$). However, no statistically significant differences were observed in gender, asthma

Table 1 Characteristics of patients with or without persistent airflow limitation

Characterisitcs	N1	NPAL(*N*=120)	N2	PAL(*N*=119)	P
Female, n(%)	120	32(26.7)	119	22(18.5)	0.175
Age(y),median(IQR)	120	8.0[7.0, 9.0]	119	11.0[9.0, 13.0]	<0.001
BMI(kg/m^2),median(IQR)	120	16.69[14.85, 18.98]	119	20.00[16.63, 24.29]	<0.001
Duration(≥3y), n(%)	120	74(61.7)	119	91(76.5)	0.020
Severe asthma, n(%)	120	16(13.3)	119	9(7.5)	0.213
Poor adherence, n(%)	120	38(31.7)	119	53(44.5)	0.055
Systemic steroid use, n(%)	120	4(3.3)	119	14(11.7)	0.026[a]
Exacerbation, n(%)	120	8(6.7)	119	20(16.8)	0.025
Allergic rhinitis, n(%)	120	119(99.2)	119	117(98.3)	0.622
Allergic conjunctivitis, n(%)	120	16(13.3)	119	11(9.2)	0.427
Food allergy, n(%)	120	2(1.7)	119	1(0.8)	1.000[a]
Eczema or dermatitis, n(%)	120	43(35.8)	119	23(19.3)	0.007
Atopy, n(%)	109	95(87.2)	102	90(88.2)	0.977
Pneumonia, n(%)	120	5(4.2)	119	16(13.4)	0.021
Neu percentage, median(IQR)	101	0.48[0.40, 0.54]	91	0.51[0.44, 0.58]	0.940
Eos percentage, median(IQR)	101	0.045[0.021, 0.066]	91	0.050[0.024, 0.080]	0.978
FeNO(ppb), median(IQR)	109	20.0[10.0, 26.0]	106	29.0[13.0, 44.0]	<0.001
FEV1%pred, mean(IQR)	120	98.20[92.20, 104.47]	119	85.85[79.52, 92.50]	<0.001
FVC%pred, mean(IQR)	120	94.40[88.88, 99.90]	119	101.3[94.70, 108.60]	<0.001
FEV1/FVC,median(IQR)	120	88.05[84.73, 91.60]	119	71.28[69.64, 73.75]	<0.001
PEF%pred,median(IQR)	120	94.15[86.58, 103.47]	119	85.50[74.85, 93.15]	<0.001
FEF25-75%pred,median(IQR)	120	85.02[73.12, 99.55]	119	50.90[45.04, 57.45]	<0.001

[a] The Fisher's exact test was used for comparison

severity, medication adherence, allergic rhinitis, allergic conjunctivitis, food allergies, atopy, blood neutrophil percentage, and blood eosinophil percentage.

Distinct phenotypes of PAL

Based on the validity indices, we employed K-means clustering to partition the dataset into three distinct clusters (Fig. 1). Cluster 0 exclusively comprised patients with NPAL (n=120), while Cluster 1 (n=66) and Cluster 2 (n=53) encompassed patients with PAL. Cluster 1 included 32 patients with IPAL and 34 patients with RPAL, while Cluster 2 comprised 24 patients with IPAL and 29 patients with RPAL (Fig. 2A).

We conducted a comparative analysis of several key biomarkers, including blood neutrophils, blood eosinophils, and FeNO, identifying two distinct phenotypes within the PAL patient group (Fig. 2). Specifically, PAL patients in Cluster 1 exhibited elevated blood neutrophil counts and higher neutrophil percentages in comparison to the NPAL group (Cluster 0). In contrast, PAL patients in Cluster 2 displayed significantly increased blood eosinophil counts, eosinophil percentages, as well as elevated FeNO levels. In summary, PAL patients in Cluster 1 tended to exhibit characteristics associated with non-eosinophilic inflammation, whereas those in Cluster 2 were more likely to display features indicative of eosinophilic inflammation.

Characteristics of distinct PAL phenotypes

As illustrated in Table S1, PAL patients with non-eosinophilic inflammation (Cluster 1) tended towards older age, higher BMI, longer disease duration, and demonstrated good adherence to treatment regimens. On the other hand, PAL patients with eosinophilic inflammation (Cluster 2) tended to be relatively younger, had lower BMI values, shorter disease duration, and displayed poorer treatment adherence. Although a history of asthma exacerbation, systemic steroid use, and pneumonia showed significant differences among the three clusters, post hoc tests did not reveal any statistically significant differences between any two groups. This lack of statistical significance could potentially be attributed to the relatively small sample size in the study.

Risk factors of PAL

To identify the risk factors associated with each PAL phenotype, we initially performed a univariate LR analysis on the included variables (Table S2). Variables with a significance level of P<0.1 from the univariate LR analysis were subsequently included in the multivariate

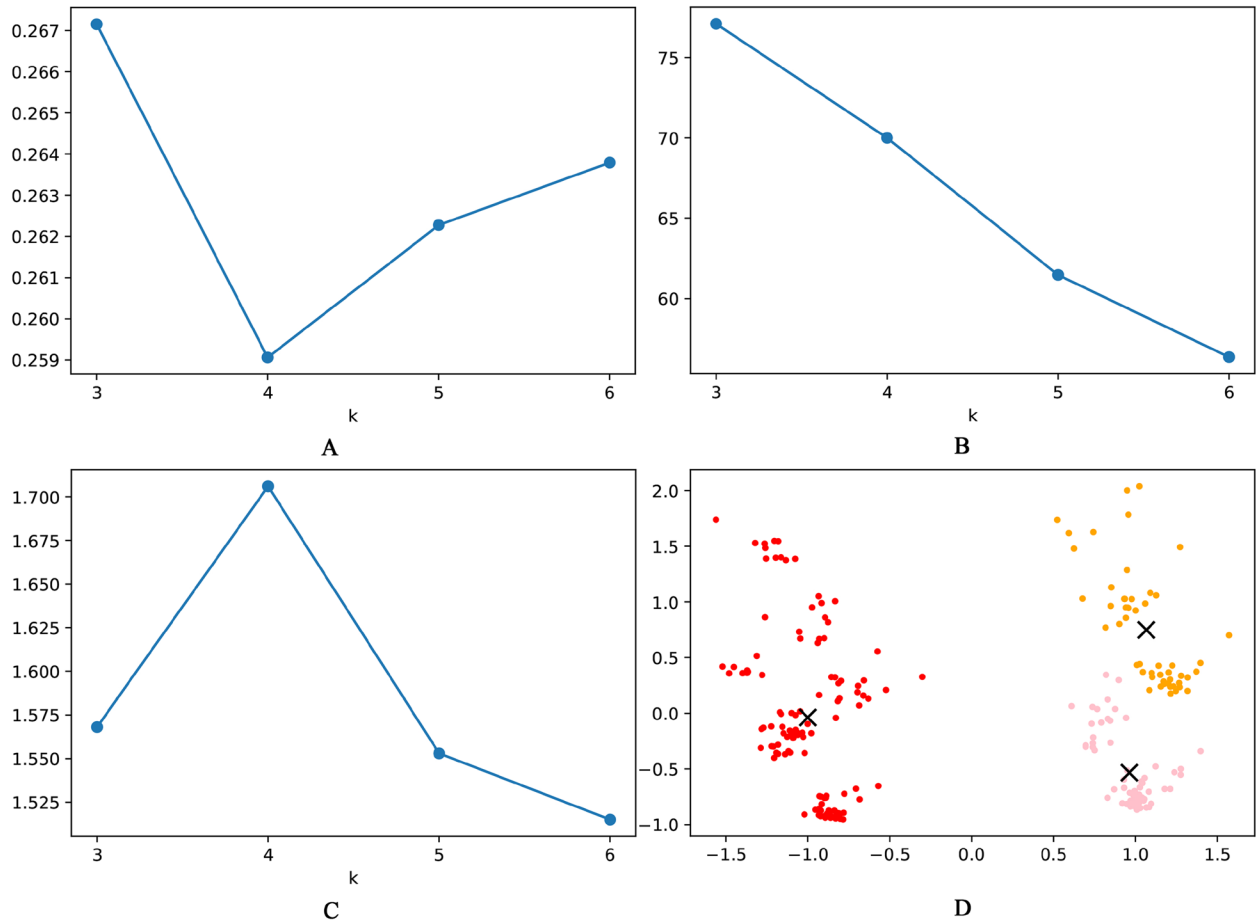

Fig. 1 Kmeans clustering results. **A** Silhouette coefficient with varying cluster numbers. **B** Calinski-Harabasz Index across different cluster counts. **C** Davies-Boudin Index under various cluster settings. **D** Cluster outcome with three clusters

LR analysis. For identifying variables significantly associated with PAL characterized by non-eosinophilic inflammation, we included the following variables in the multivariate LR analysis: age, BMI, disease duration, systemic steroid use, history of asthma exacerbation, allergic conjunctivitis, eczema or dermatitis, pneumonia, blood neutrophil percentage, and FeNO. For PAL characterized by eosinophilic inflammation, we included the following variables in the multivariate LR analysis: age, BMI, systemic steroids use, history of exacerbation, pneumonia, blood eosinophil percentage, and FeNO.

As presented in Table 2, we observed significant associations between age above nine years and both non-eosinophilic inflammation PAL (9~11y: OR 12.67, 95%CI 3.30-55.74; ≥11y: OR 5.42, 95%CI 1.26-25.69) as well as eosinophilic inflammation PAL (9~11y: OR 7.25, 95%CI 1.70-33.35; ≥11y: OR 11.28, 95%CI 2.79-51.89). Additionally, a history of pneumonia independently contributed to the risk of both non-eosinophilic phenotype (OR 6.41, 95%CI 1.34-33.41) and eosinophilic phenotype (OR 7.92, 95%CI 1.83-37.44).

Furthermore, specific risk factors were identified for PAL associated with non-eosinophilic inflammation. These included a BMI above 22 kg/m^2 (OR 12.28, 95%CI 2.68-70.45), an asthma duration exceeding three years (OR 4.77, 95%CI 1.60-15.94), and blood neutrophil percentage between 0.4 and 0.5 (OR 4.13, 95%CI 1.17-16.60). In the eosinophilic inflammation phenotype of PAL, blood eosinophil percentage greater than 0.07 (OR 4.36, 95%CI 1.16-19.73) and a high level of FeNO (OR 3.94, 95%CI 1.35-11.97) were found to be independent risk factors. Interestingly, a moderate level of FeNO demonstrated a protective effect with an OR of 0.10 (95%CI 0.02-0.41).

Discussion

Our study first explored phenotypes in asthmatic children with PAL and identified two distinct phenotypes: non-eosinophilic inflammation and eosinophilic

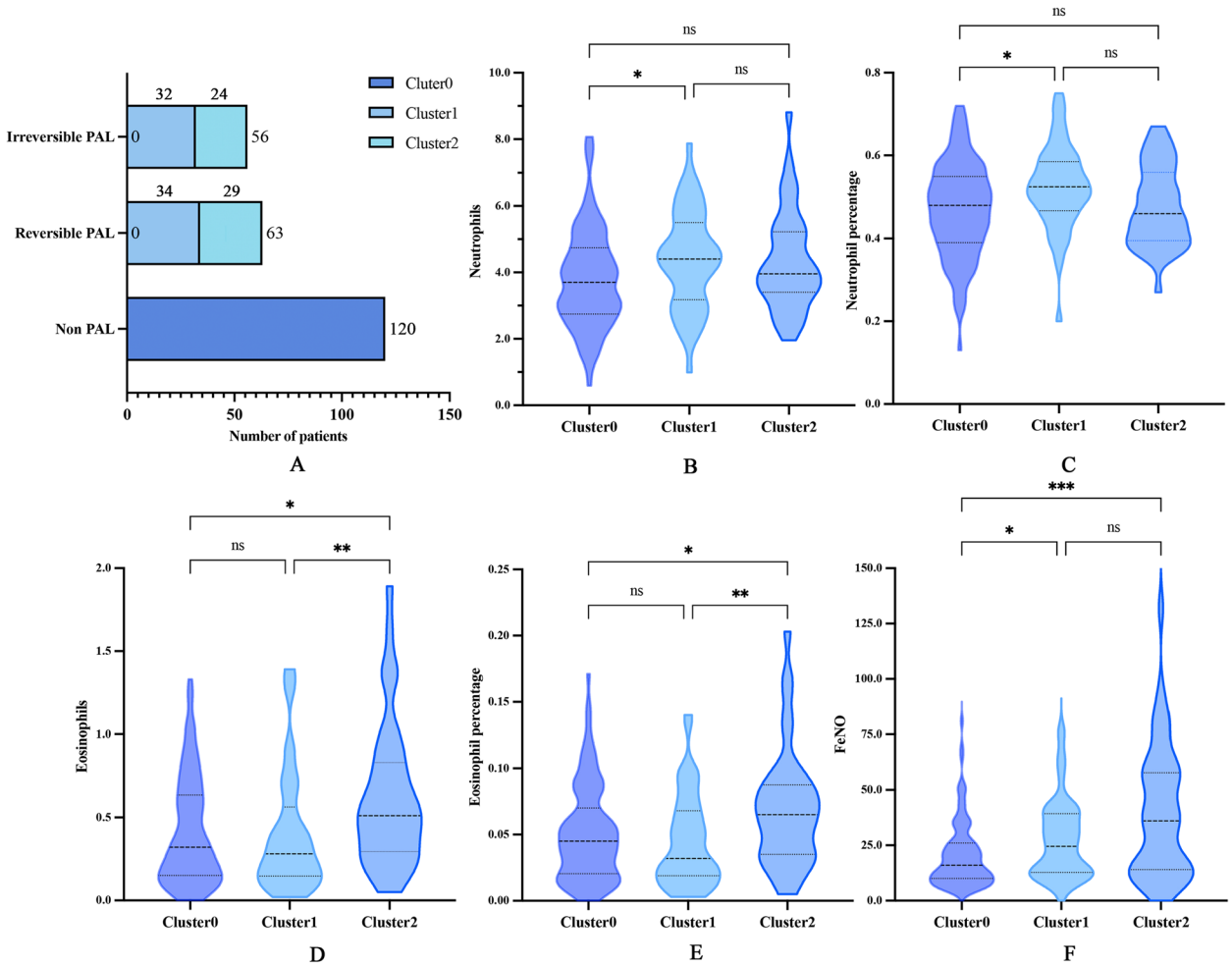

Fig. 2 Phenotype comparison of three clusters. **A** The distribution of patients with or without persistent airflow limitation among three clusters. **B** Blood neutrophil count. **C** Blood neutrophil percentage. **D** Blood eosinophil count. **E** Blood eosinophil percentage. **F** FeNO level

inflammation. We found that age above nine years and a history of pneumonia were independent risk factors for both phenotypes. In addition, we identified specific risk factors for each phenotype. A BMI above 22.0 kg/m^2, asthma duration exceeding three years, and a blood neutrophil percentage between 0.40 and 0.50 were significantly associated with PAL characterized by non-eosinophilic inflammation. On the other hand, high FeNO levels were found to be an independent risk factor for eosinophilic inflammation PAL.

Several studies have examined the phenotypes of PAL in adult asthmatic patients. Kanstantellou et al. [16] categorized asthmatic adults into three clusters, with only one cluster showing an association with PAL. This PAL cluster was characterized by elevated levels of FeNO and higher counts of sputum eosinophils and neutrophils. Similarly, Mogensen et al. [10] found that asthmatic adults with PAL tended to have higher FeNO levels, along with elevated blood eosinophil and neutrophil percentages. However, these studies did not further explore the specific phenotype of PAL. In our study, we further investigated the distribution of elevated blood eosinophils and neutrophils and identified two subgroups of asthma patients with PAL. One cluster of PAL patients exhibited higher blood neutrophils, while another cluster had higher blood eosinophils and elevated FeNO levels. Smith et al. [14] conducted a study that also identified two distinct phenotypes of PAL. Patients with long-term PAL (duration≥3 years) exhibited neutrophilic sputum inflammation and airway remodeling, while patients who developed PAL during the follow-up period displayed higher sputum eosinophil content. Due to challenges in collecting sputum samples in our study, we chose to identify inflammation patterns based on blood eosinophils and neutrophils.

Risk factors have been extensively investigated in asthmatic adults, with relatively limited attention given to asthmatic children. Numerous studies consistently

Table 2 Multivariate logistic regression of variables for distinct phenotype of persistent airflow limitation

Characteristics	Cluster1		Cluster2	
	OR(95%CI)	P	OR(95%CI)	P
Age(y)				
5~7	Ref			
7~9	1.08(0.28, 4.26)	0.914	1.61(0.48, 5.62)	0.442
9~11	12.67(3.30, 55.74)	<0.001	7.25(1.70, 33.35)	0.008
≥11	5.42(1.26, 25.69)	0.027	11.28(2.79, 51.89)	0.001
BMI(kg/m2)				
<15.0	Ref			
15.0~18.5	2.82(0.73, 13.11)	0.152	1.35(0.39, 5.00)	0.644
18.5~22.0	3.07(0.59, 18.27)	0.193	0.71(0.15, 3.23)	0.658
≥22.0	12.28(2.68, 70.45)	0.002	3.46(0.84, 15.27)	0.090
Duration(≥3y)	4.77(1.60, 15.94)	0.007	-	-
Pneumonia	6.41(1.34, 33.41)	0.021	7.92(1.83, 37.44)	0.006
FeNO(≤12y/>12y)				
<20/<25	Ref			
20~35/25~50	0.42(0.14, 1.15)	0.099	0.10(0.02, 0.41)	0.003
≥35/≥50	3.01(0.85, 11.49)	0.095	3.94(1.35, 11.97)	0.013
NEU percentage				
<0.4	Ref			
0.4~0.5	4.13(1.17, 16.60)	0.034	-	-
0.5~0.6	2.20(0.65, 8.06)	0.215	-	-
≥0.6	4.83(0.99, 26.16)	0.057	-	-
Eo percentage				
<0.02				
0.002~0.05	-	-	1.89(0.48, 8.60)	0.378
0.05~0.07	-	-	2.87(0.65, 14.50)	0.177
≥0.07	-	-	4.36(1.16, 19.73)	0.038

demonstrated that in adult patients, older age, smoking, and a longer duration of asthma independently increased the risk of PAL [11–13]. In our research, we discovered that children of older age and those with a duration of asthma exceeding three years also exhibited an elevated risk of PAL. Furthermore, evidence has suggested that maternal cigarette smoking during gestation was associated with abnormal lung function growth in children [6]. These findings collectively indicated that certain risk factors for PAL were shared between asthmatic adults and children.

A 4-year follow-up cohort study on asthmatic children demonstrated that frequent asthma exacerbations and severe asthma were independently associated with PAL [4]. Our research found that systemic steroid use and asthma exacerbations were associated with eosinophilic inflammation PAL in univariate LR analysis. Nonetheless, these associations did not remain significant in the multivariate LR analysis. Additionally, we did not observe any significant association with asthma severity. Similar to studies in adult patients, research on asthma exacerbations and asthma severity has produced conflicting results [11, 12, 25, 26]. These disparities could be attributed to variations in study design, sample size, diverse populations, and even different definitions of PAL. To enhance the confidence of these findings, further perspective cohort studies with larger sample sizes of asthmatic children and meta-analyses investigating the risk factors for PAL are necessary.

Many studies have detailed the characteristics of adult patients with PAL, such as being male, older, having a longer duration of asthma, and having a higher likelihood of a smoking history. Nevertheless, no significant differences were found in atopy status, BMI, or a history of asthma exacerbation [10–13]. Our study also observed that patients with PAL were older and had a higher proportion of long asthma duration, but there was no significant change in atopy status. Furthermore, in line with previous research on asthmatic children [4], we found that asthmatic patients with PAL exhibited higher BMI and a tendency towards asthma exacerbations. These characteristics appear to be specific to pediatric asthma cases. Interestingly, our findings showed children in cluster 2 had poor adherence, contrasting with cluster 1's good adherence. Although, elucidating the results of data-driven cluster analysis can be challenging. Several factors may account for this outcome. Suboptimal adherence is associated with elevated FeNO levels [27, 28], partially explaining why more patients with poor adherence were in cluster 2, characterized by the highest FeNO levels. Additionally, perception of airflow limitation is also related to adherence [29]. Research indicates that elevated FeNO levels and younger age are associated with poor perception [30, 31], a trend consistent with our observations that patients in cluster 2 exhibited higher FeNO levels and were younger in age. Nevertheless, direct evidence regarding the relationship between adherence and phenotypes was not explored. Further investigation is warranted to determine whether adherence is a consequence or a contributing factor to phenotypic characteristics.

Our study had several limitations. Firstly, being a case-control study based on medical records, we were unable to include broader factors potentially associated with PAL in our analysis, such as smoking exposure, air pollution, and economic status. Secondly, our study only focused on identifying the phenotype of PAL without delving into the underlying mechanisms. It would be beneficial to further investigate the specific mechanisms involved in the development of PAL, as different phenotypes of PAL may be associated with different underlying mechanisms. Thirdly, although we included all eligible

patients with PAL within three years in our study, the sample size was still relatively small. This limited the number of variables that could be included in the multivariate LR analysis. Despite these limitations, our study provides valuable insights into the distinct phenotypes and risk factors of PAL. Future research with larger sample sizes and a more comprehensive approach is warranted to further elucidate the complex nature of PAL and its underlying mechanisms.

Conclusion

Our study identified two phenotypes of PAL in asthmatic children: non-eosinophilic and eosinophilic inflammation. Older age and a history of pneumonia were independent risk factors for both phenotypes of PAL. For non-eosinophilic inflammation PAL, specific contributing factors included higher BMI, long duration of asthma, and a blood neutrophil percentage between 0.4 and 0.5. Higher FeNO levels and elevated blood eosinophilic percentages were independently associated with eosinophilic inflammation PAL.

Abbreviations

PAL	Persistent airflow limitation
NPAL	Non persistent airflow limitation
RPAL	Reversible persistent airflow limitation
IPAL	Irreversible persistent airflow limitation
GINA	The Global Initiative for Asthma
LR	Logistic regression
BD	Bronchodilation
IQR	Interquartile range
SC	Silhouette coefficient
DBI	Davies-Bouldin Index
CHI	Calinski-Harabasz Index
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05201-3.

Supplementary Material 1: Tables S1 and S2; Figures S1 and S2.

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Authors' contributions

Shiqiu Xiong contributed to the data collection, data processing and analysis, as well as manuscript drafting. Xinyu Jia contributed to data collection and data processing. Wei Chen contributed to data analysis and visualization. Chuanhe Liu supervised all aspects of data collection and revised the manuscript. All authors reviewed the manuscript.

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Data availability

The original data and code used in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This case-control study has been approved by the Ethics Committee of the Children's Hospital, Capital Institute of Pediatrics, Beijing, China (Approval No: SHERLL 2014040). All patient identities and private information have been rigorously protected in compliance with ethical guidelines. Consequently, a waiver of informed consent has been granted by the Ethics Committee of the Children's Hospital, Capital Institute of Pediatrics.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Allergy, Center for Asthma Prevention and Lung Function Laboratory, Children's Hospital of Capital Institute of Pediatrics, Beijing 100020, China. [2]Children's Hospital of Capital Institute of Pediatrics, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China. [3]Department of Pediatrics, Xi'an Children's hospital, Xi'an 710003, China.

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