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ORIGINAL RESEARCH

Changes in the "U-Shaped" Distribution of Airway Hyperresponsiveness and Characterization of Inflammatory Phenotypes in Different Age Groups

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Objective: This study investigated age-related variations in airway hyperresponsiveness (AHR) based on pulmonary function, fractional exhaled nitric oxide (FeNO), total immunoglobulin E (IgE), eosinophils, basophils, neutrophils, monocytes, and lymphocytes.

Methods: A total of 1,500 patients treated at the Second Hospital of Shanxi Medical University from 2021 to July–September 2023 were enrolled and stratified into four age groups. General information, smoking history, pulmonary function, FeNO (including FeNO50, FeNO200, and CaNO), and blood biomarkers (total IgE, eosinophils, basophils, neutrophils, monocytes, lymphocytes) were collected. Intergroup comparisons and correlation analyses were performed.

Results: Pulmonary function: The positive rate of bronchial provocation test and the decline rate of FEV1 were higher in adolescents and the elderly, exhibiting a "U-shaped" distribution. FEV1, FVC, MEF50, and MEF25 increased with age until 18 years old and then declined. FEV1/FVC showed an overall decline with age. Exhaled nitric oxide test: The positive rate of type 2 inflammation in small airways showed a "U-shaped" distribution. CaNO was highest in the elderly group, overall displaying a "U-shaped" trend. No age-related differences were observed in FeNO50 and FeNO200. Laboratory indicators: Eosinophils, total IgE, and lymphocytes decreased with age. Basophils were highest in the young adult group. Neutrophils were lower in adolescents and higher in the elderly. Monocytes were elevated in both adolescent and elderly groups.

Conclusion: AHR is more prominent in adolescents and the elderly, showing a "U-shaped" age distribution. Adolescents exhibited Th2-type inflammation (mainly eosinophil-driven), while the elderly showed non-Th2-type inflammation (mainly neutrophil- and monocyte-driven). Pulmonary function peaks in young adulthood and declines more rapidly after middle age, with small airway obstruction worsening in the elderly. The elevated CaNO in the elderly group dissociated from decreased blood eosinophils, suggesting localized eosinophilic inflammation or impaired migration, potentially indicating an eosinophil non-dependent inflammatory phenotype.

Keywords: age-dependent, airway hyperresponsiveness, lung function, inflammatory phenotype

Introduction

Airway Hyperresponsiveness (AHR) is a core pathological feature of respiratory diseases such as asthma, allergic rhinitis, and chronic obstructive pulmonary disease,[1] resulting in bronchoconstriction caused by nonspecific stimuli.[2] The mechanism of AHR is still uncertain, but it may be related to airway narrowing due to increased release of mediators from inflammatory cells (especially mast cells), increased contractility of airway smooth muscle, and increased sensitivity of airway sensory nerves.[3] It has been shown that with age, lung function gradually declines and airway diastolic and constrictive functions are compromised, thus exacerbating AHR.[4]

Airway hyperresponsiveness (AHR) is a major contributing factor to the development of bronchial asthma. As a common respiratory disease, asthma causes approximately 250,000 deaths annually and has become a significant medical, social, and economic burden.[5] This disease has a high incidence across all age groups, and its occurrence and progression substantially impact population health.[6] Asthma is a heterogeneous condition affecting both children and

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adults. Factors such as allergens, infections, and tobacco smoke can increase an individual's risk of developing chronic airway inflammation, leading to airflow obstruction and airway hyperresponsiveness.[7]

Studies have shown that airway hyperresponsiveness is independently associated with a reduced rate of lung function growth and exerts an independent adverse effect on lung function development in individuals aged 7 to 37 years. This is manifested as a decline in the maximum attained level of lung function and a continued decrease after the peak is reached.[8] Furthermore, rapid lung function growth during adolescence is associated with the remission of atopic asthma. Since airway responsiveness is inversely correlated with airway caliber, the improvement in airway development during adolescence leads to a decrease in airway responsiveness in patients experiencing asthma remission, suggesting that airway growth contributes to the alleviation of asthma symptoms.[9]

The prevalence of airway hyperresponsiveness increases with age. Older populations generally have a higher cumulative exposure to smoking, which can be considered a key factor influencing the relationship between airway responsiveness and aging, with the duration of exposure playing a critical role. Age-related enhancement of airway inflammatory responses may contribute to elevated nonspecific airway responsiveness. Concurrently, the decline in lung elastic recoil in the elderly may exacerbate the degree of bronchoconstriction. Additionally, age-related decreases in lung function and structural abnormalities in the lungs can also promote an increase in airway hyperresponsiveness.[10]

Currently, there are many studies on AHR and asthma at home and abroad, however, most of the existing studies focus on a single disease or a specific age stage, and lack analysis of the distribution of AHR across the entire age spectrum. In this study, we analyzed airway hyperresponsiveness across the entire age spectrum from adolescence to old age, broke through the limitations of the traditional single disease (eg, asthma, COPD) or a single age stage, and proposed the "U-shape" distribution of airway hyperresponsiveness with age. The "U-shaped" distribution of airway hyperresponsiveness with age was proposed, and the phenotypic characteristics of inflammation in different age groups were also found, with Th2 inflammation dominating in adolescence and neutrophilic inflammation dominating in old age. Meanwhile, the age-specific injury pattern was also hypothesized by the indexes of lung function: the lung function of adolescents matured gradually and reached a peak in youth, and then the decline of the small airway function accelerated in middle age. The degree of small airway obstruction increases in old age. Finally, we analyzed the paradoxical phenomenon of elevated CaNO and decreased peripheral blood eosinophils in the elderly group, and explored the underlying mechanism.

Methods

Study Design and Patients

This study retrospectively analyzed the clinical data of patients who visited the outpatient clinics of the Department of Respiratory and Critical Care Medicine and the Department of Otorhinolaryngology at the Second Hospital of Shanxi Medical University during July–September of 2021, 2022, and 2023. Using stratified sampling by year, 500 patients were randomly selected from each year, yielding a total of 1500 patients. The sample comprised 1057 patients who underwent provocation tests, 253 who underwent dilation procedures, and 190 who received ventilation-only management. Inclusion Criteria: (1) Patients who visited the outpatient departments of Respiratory and Critical Care Medicine or Otolaryngology at the Second Hospital of Shanxi Medical University during July to September in 2021, 2022, and 2023. (2) Patients who had undergone pulmonary function tests, complete blood count tests, or serum IgE tests. Exclusion Criteria: (1) Patients with missing key clinical information, such as age. (2) For patients with multiple visits, only the first visit record was retained. (Note:provocation tests means Bronchoprovocation Test: Following the inhalation of methacholine, lung function is reassessed. A decrease in FEV1 of ≥20% is considered a positive result. Dilation procedures means Bronchodilation Test: Following the administration of terbutaline, lung function is reassessed within 15–30 minutes. An increase in FEV1 of ≥12% compared to the pre-bronchodilator value, along with an absolute increase of ≥200 mL, is diagnostic of a positive result. Ventilation-only management means Pulmonary Ventilation Function Test). The Ethics Committee of the Second Hospital of Shanxi Medical University approved the study with the approval number (2023)YX No. (131), and informed consent was obtained from all subjects.

The patients were divided into four groups according to age grouping: adolescents (<18 years old), young adults (18–39 years old), middle-aged (40–64 years old), and elderly (≥65 years old); all data were extracted by two

independent researchers using a uniform method. Clinical data of the four groups were collected from the outpatient system of the Second Hospital of Shanxi Medical University, including general information, smoking history, pulmonary function test results, nitric oxide breath test (FeNO), blood cell analysis, and total IgE. Among them, FeNO included exhaled breath nitric oxide concentration at an expiratory flow rate of 50 mL/s (FeNO50), exhaled breath nitric oxide concentration at an expiratory flow rate of 200 mL/s (FeNO200), and alveolar nitric oxide concentration (CaNO).

A positive bronchial provocation test indicates airway hyperresponsiveness. In fractional exhaled nitric oxide (FeNO) testing, FeNO50 primarily reflects inflammation in the large airways, whereas FeNO200 is more indicative of inflammation in the small airways. Alveolar nitric oxide (CaNO) serves as a marker of inflammation in the peripheral airways and alveoli. Given that asthma and chronic obstructive pulmonary disease (COPD) are frequently associated with impaired small airway function, FeNO200 was used to evaluate small airway inflammation. A FeNO200 value exceeding 25 ppb suggests the presence of inflammatory activity in the small airways, indicating a positive result for inflammation.

Statistical Analysis

Statistical analysis was performed using SPSS 27.0.1 statistical software. The normality of the distribution of the measurement data was assessed using the Shapiro–Wilk test. Descriptive statistics of normally distributed quantitative variables were expressed as means and standard deviations, while non-normally distributed data were described in terms of Median and Interquartile Range (IQR) ie M(Q1, Q3). Pearson correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for non-normally distributed data; the values of three or more groups of normally distributed data were compared by One-way Analysis of Variance (One-way ANOVA). Continuous data from three or more non-normally distributed groups were compared using the Kruskal–Wallis test. Categorical variables were expressed as frequency distributions and percentages. The data of categorical variables were compared using the chi-square test. The difference was considered statistically significant at $P < 0.05$.

Result

General Information About the Study Subjects

Stratified sampling was used to retrospectively collect general information on the age, gender, and smoking history of patients attending the Respiratory and Critical Care Unit and ENT clinics in July-September for a total of three years, 2021, 2022, and 2023, as shown in Table 1.

Age and Lung Function

The population was divided into four groups according to age. There were a total of 1057 cases of excitation test, of which the total number and percentage of positive excitation test were 196 (18.54%) cases, of which the positive and percentage of each group were: 16 cases (28.57%) in the adolescent group, 57 cases (20.14%) in the youth group, 86 cases (15.52%) in the middle-aged group, and 37 cases (22.56%) in the elderly group. The difference between the groups analyzed by chi-square test was $\chi^2(3, N = 196) = 9.304$, $P = 0.026$. The stimulated positivity rate showed that the adolescent group and the elderly group were significantly higher than that of the youth group and the middle-aged group, and the trend showed a "U"-shaped distribution.

After Shapiro–Wilk test of normality, the rate of decline of FEV1 in the four groups of variables was nonnormally distributed, and the observations of the rate of decline of FEV1 in different age groups were described by the median

Table 1 Comparison of General Information of Each Group

	Teenager Group N = 70	Youth Group N = 334	Middle-Aged Group N = 777	Senior Group N = 319	F/χ^2	P
Age, years	13.67±2.63	29.97± 6.11	53.28± 6.71	70.66± 5.01	F=3314.381	P=0.00
The male sex, n (%)	42(60.0%)	148(44.3%)	345(44.4%)	185(58.0%)	χ^2=93.337	P< 0.001
Smoke, n (%)	0(0%)	73(21.9%)	276(35.5%)	158(49.5%)	χ^2=55.689	P< 0.001

Notes: Quantitative variables are shown as mean ± SD and categorical variables are shown as n (%).

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Table 2 Correlation Analysis Between FEV1 Decline Rate and Age Spearman

Age Stratification	Sample Capacity (n)	Correlation (ρ)	P	Directional Interpretation
ensemble	1057	0.036	P=0.236	Age stratification masks bidirectional associations
< 40 years old	339	−0.123	P=0.023	The rate of FEV1 decline decreased with age
≥ 40 years old	718	0.147	P< 0.001	The rate of FEV1 decline increased with age

Abbreviation: FEV1, Forced Expiratory Volume in the first second.

(P25,P75), 10.77 (6.08,21.25) in the adolescent group, 9.04 (5.31,15.85) in the youth group, middle-aged group 8.39 (5.23, 13.52), and older group 10.17 (6.04, 19.38). A anonparametric Kruskal–Wallis test showed a statistically significant difference in the rate of decline in FEV1, H(3) = 11.875, P = 0.008. Post hoc pairwise comparisons revealed that the adolescent group scored significantly higher than the youth group (p = 0.038) and the middle-aged group (p = 0.011). Additionally, the older group scored significantly higher than the middle-aged group (p = 0.008). In contrast, no significant differences were observed between the youth group and middle-aged groups (p = 0.483), the adolescent and older groups (p = 0.441), or the older group and youth groups (p = 0.060).

Spearman correlation analysis was performed and the results are shown in Table 2 below, which revealed that age <40 years old had a significant weak negative correlation between age and the rate of FEV1 decline (ρ=−0.123, P=0.023), and age ≥40 years old had a significant weak positive correlation between age and the rate of FEV1 decline (r=0.147, P<0.001).

The rate of positive excitation and the rate of decline of FEV1 in patients with bronchial asthma showed a "U-shaped" distribution of decreasing and then increasing with age. To represent it more intuitively, the rate of positive excitation was shown in a line graph as in Figure 1, and the rate of decline of FEV1 was shown in a boxed plot as in Figure 2.

After the Shapiro–Wilk test for normality, FEV1, FVC, FEV1/FVC, MEF50, and MEF25 were non-normally distributed. The results of the non-parametric Kruskal–Wallis test for different age groups are shown in Table 3 below. The paired comparisons of FEV1 showed that the adolescent group was significantly smaller than the youth group (P=0.032), the youth group was significantly larger than the middle-aged group (P=0.00), and the middle-aged group was significantly larger than the elderly group (P<0.001). FVC pairwise comparisons showed that the adolescent group was significantly smaller than the youth group (P<0.001), the youth group was significantly larger than the middle-aged group (P=0.00), and the middle-aged group was significantly larger than the elderly group (P<0.001). Pairwise comparisons of FEV1/FVC showed that the adolescent group was significantly larger than the youth group (P=0.005), the youth group was significantly larger than the middle-aged group (P<0.001), and the middle-aged group was significantly larger than the elderly group (P<0.001).MEF50 pairwise comparisons showed that the adolescent group did not differ significantly from the youth group (P=0.378), the youth

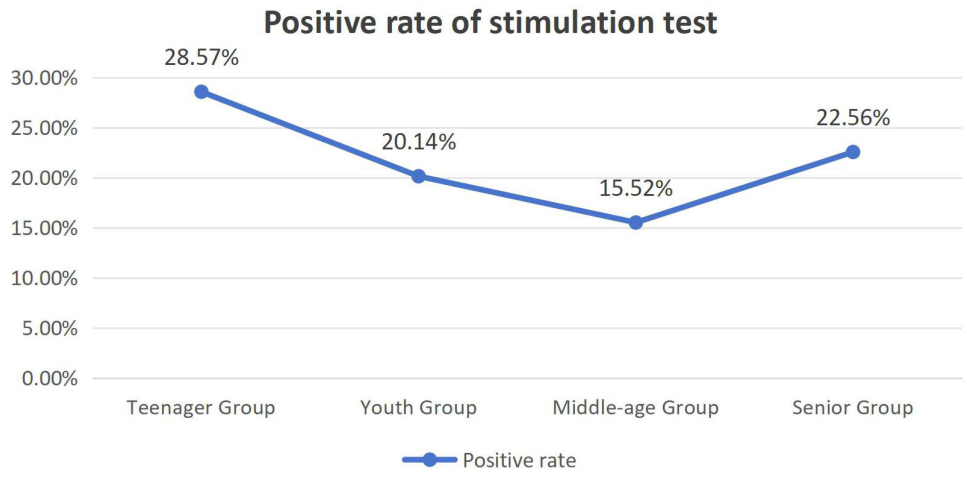

Figure 1 The variation of positive rate of stimulation test in different age groups.
Notes: In the figure, each point indicates the rate of positive excitation tests for each group. It can be seen from the figure that the rate of stimulus positivity and the rate of FEV1 decline in patients with bronchial asthma show a "U-shaped" distribution that first decreases and then increases with age.

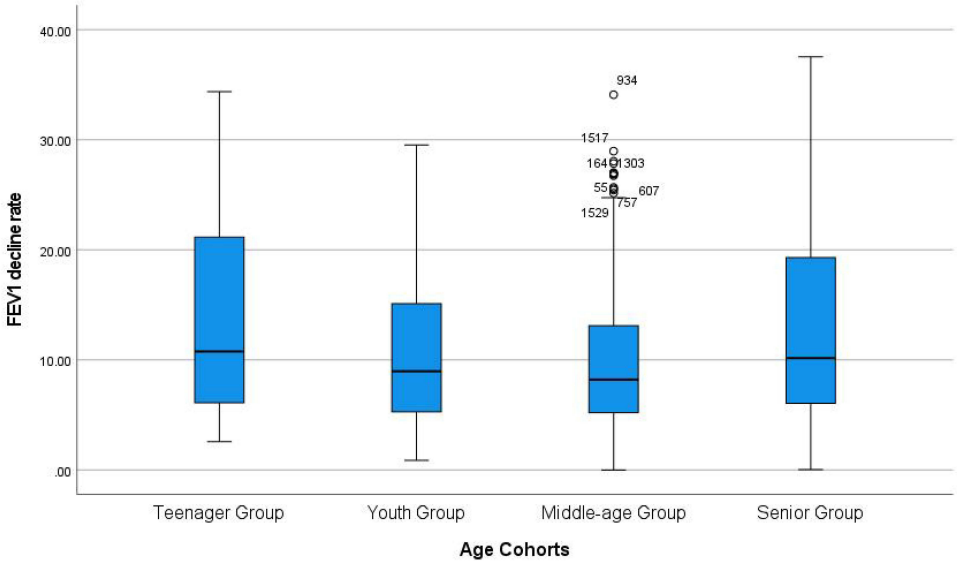

Figure 2 Box plot of the decline rate of FEV1 with age.
Notes: The horizontal lines in the blue box plots indicate the median FEV1 decline rate in each group. It can be seen that the FEV1 decline rate shows a "U-shaped" distribution that first decreases and then increases with age.

group was significantly larger than the middle-aged group (P<0.001), and the middle-aged group was significantly larger than the elderly group (P<0.001). MEF25 pairwise comparisons showed that the adolescent group did not differ significantly from the youth group (P=0.189), the youth group was significantly greater than the middle-aged group (P=0.00), and the middle-aged group was significantly greater than the elderly group (P<0.001).

Since FEV1, FVC, FEV1/FVC, MEF50, and MEF25 did not conform to a normal distribution, Spearman correlation analysis was chosen to be performed. The results are shown in Tables 4 below, which revealed that age < 18 years old had a significant positive correlation with FEV1, FVC, MEF50, and MEF25, and age ≥ 18 years old had a significant negative correlation with FEV1, FVC, MEF50, and MEF25; whereas age <18 years FEV1/FVC was not significantly correlated with age (P = 0.458), and age ≥18 years was significantly negatively correlated ($\rho = -0.442$, P < 0.001).

Age and Nitric Oxide Breath Test

FeNO50, FeNO200, and CaNO were non-normally distributed. The probability of small airway type 2 inflammatory response was greater in the adolescent and elderly groups than in the youth and middle-aged groups, and there was no significant difference in the changes of FENO50 and FeNO200 with age, the results of which are shown in Table 5. The nonparametric Kruskal–Wallis test of CaNO concluded that CaNO H(3) = 18.845, P < 0.01, the difference was statistically significant. Pairwise comparisons revealed that the older group was significantly larger than the adolescent

Table 3 Results of Nonparametric Kruskal–Wallis Test on Changes in Lung Function with Age

	Teenager Group N=56	Youth Group N=283	Middle-Age Group N=554	Senior Group N=164	Difference Between Group H	p
FEV 1, L	3.08 (2.59,3.79)	3.29 (2.85,3.82)	2.64 (2.31,3.08)	2.19 (1.83,2.61)	H = 255.995	P < 0.001
FVC, L	3.59 (2.90,4.70)	4.06 (3.55,4.84)	3.45 (2.97,4.11)	3.02 (2.45,3.61)	H = 166.027	P < 0.001
FEV1/FVC, %	83.02 (78.48,89.84)	80.69 (76.48,84.25)	77.52 (73.65,80.92)	74.54 (68.61,79.32)	H = 130.202	P < 0.001
MEF 50, L/s	3.58 (2.80,4.50)	3.77 (3.04,4.50)	2.97 (2.28,3.80)	2.11 (1.57,3.17)	H = 159.318	P < 0.001
MEF 25, L/s	1.57 (1.16,2.18)	1.32 (1.02,1.74)	0.79 (0.59,1.03)	0.50 (0.38,0.73)	H = 395.304	P < 0.001

Notes: The data in the table are described in terms of Median and Interquartile Range (IQR) ie M(Q1,Q3).
Abbreviations: FEV1, Forced Expiratory Volume in the first second, FVC, Forced Vital Capacity, FEV1/FVC, The ratio of expiratory volume at first second of exertion to expiratory lung capacity, ie, the one-second rate; MEF50, Maximal Expiratory Flow After 50% of the FVC Has Not Been Exhaled; MEF25, Maximal Expiratory Flow After 25% of the FVC Has Not Been Exhaled. H: The H statistic is used to characterize the degree of difference between groups. A higher H value indicates greater intergroup differences, thereby providing more substantial grounds for rejecting the null hypothesis that "the population medians of all groups are equal.".

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Table 4 Correlation Analysis of Lung Function Indexes with Age Spearman

	Age Lamination	Sample Capacity (n)	Correlation (ρ)	P	Directional Interpretation
FEV1	Population	1057	−0.512	P< 0.001	Age increase, FEV1 decreased (negatively correlated)
	<18 years old	56	0.686	P< 0.001	Age increase, FEV1 increased (positive correlation)
	≥18 years old	1001	−0.540	P< 0.001	Age increase, FEV1 decreased (negatively correlated)
F VC	Population	1057	−0.399	P< 0.001	Age increase, FVC decreased (negatively correlated)
	<18 years old	56	0.6 49	P< 0.001	Age increase, FVC increased (positive correlation)
	≥18 years old	1001	−0.442	P< 0.001	Age increase, FVC decreased (negatively correlated)
FEV1/FVC	Population	1057	−0.370	P< 0.001	Age increase, FEV1/FVC decreased (negatively correlated)
	<18 years old	56	0.101	P=0.458	There was no significant relationship between age and FEV1/FVC
	≥18 years old	1001	−0.442	P< 0.001	Age increase, FEV1/FVC decreased (negatively correlated)
MEF50	Population	1057	−0.407	P< 0.001	As age increases, MEF50 decreases (negatively correlated)
	<18 years old	56	0.576	P< 0.001	As age increases, MEF50 increases (positively correlated)
	≥18 years old	1001	−0.419	P< 0.001	As age increases, MEF50 decreases (negatively correlated)
MEF25	Population	1057	−0.651	P< 0.001	As age increases, MEF50 decreases (negatively correlated)
	<18 years old	56	0.600	P< 0.001	As age increases, MEF50 increases (positively correlated)
	≥18 years old	1001	−0.638	P< 0.001	As age increases, MEF50 decreases (negatively correlated)

Abbreviations: FEV1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; FEV1/FVC, The ratio of expiratory volume at first second of exertion to expiratory lung capacity; ie, the one-second rate;, MEF50, Maximal Expiratory Flow After 50% of the FVC Has Not Been Exhaled; MEF25, Maximal Expiratory Flow After 25% of the FVC Has Not Been Exhaled.

Table 5 The Positive Rate of Type 2 Inflammation in Small Airways and the Relationship Between FeNO and Age Stage

	Teenager Group N=91	Youth Group N=487	Middle-Aged Group N=716	Senior Group N=206	Difference Between Group H/χ^2	P
Inflammatory positive n(%)	21(23.1%)	78(16.0%)	120(6.8%)	43(20.9%)	χ^2=4.60	P=0.20
FeNO50 (ppd)	25(14,57)	26(16,52)	25(18,43)	27(18,41.25)	H=0.321	P=0.96
FeNO200 (ppd)	13(8,24)	13(8,21)	13(8.25,19.75)	13(9,22)	H=3.392	P=0.34
CaNO (ppd)	5.6(2.5,8.8)	4.8(2.5,8.1)	5.5(2.6,9.5)	6.6(3.2,13.2)	H=18.845	P< 0.01

Notes: The data in the table are described in terms of Median and Interquartile Range (IQR) ie M(Q1,Q3).
Abbreviations: FeNO50, Fractional Exhaled Nitric Oxide at 50 mL/s; FeNO200, Fractional Exhaled Nitric Oxide at 200 mL/s; CaNO, Concentration of Alveolar Nitric Oxide. H: The H statistic is used to characterize the degree of difference between groups. A higher H value indicates greater intergroup differences, thereby providing more substantial grounds for rejecting the null hypothesis that "the population medians of all groups are equal.".

group (P = 0.041), the youth group (P < 0.001), and the middle-aged group (P = 0.002) and that the middle-aged group was significantly larger than the youth group (P = 0.047), whereas there was no significant difference between the adolescent and youth groups (P = 0.365).

Spearman correlation analysis of FeNO rows, the results are shown in Table 6, FeNO50, FeNO200 with the age stage of the change is not much difference, CaNO row correlation analysis, age <18 years with age change is negatively correlated, while for age ≥18 years with age change is positively correlated.

Age and Peripheral Blood Chemistries Blood Count, Total IgE

By Shapiro–Wilk Test (Shapiro–Wilk Test) normality test eosinophils, basophils, neutrophils, monocytes and lymphocytes laboratory indicators are non-normal distribution. Line non-parametric Kruskal–Wallis test concluded that the results are shown in Table 7. The specific analysis is as follows: leukocytes H(3) = 7.825, P = 0.05, there is no significant difference between the four groups of leukocytes; eosinophils H(3) = 77.129, P < 0.001, the difference between the four groups is statistically significant. The pairwise comparison revealed that the adolescent group > youth group (P = 0.005), youth group > middle-aged group (P < 0.001), middle-aged group > old age group (P = 0.034); basophilic granulocyte H(3) = 21.173, P < 0.001, the difference between the four groups was statistically significant. The pairwise comparison revealed that there was no significant difference between the adolescent group and the youth group (P = 0.711), the youth group > the middle-

Table 6 The Spearman Correlation Analysis Results of FeNo

	Age Stratification	Sample Capacity (n)	Correlation Index (ρ)	P
FeNO50 (ppd)	Population	1500	0.021	0.424
	<18 years old	91	0.124	0.242
	≥18 years old	1409	0.020	0.460
FeNO200 (ppd)	Population	1500	0.045	0.079
	<18 years old	91	0.085	0.424
	≥18 years old	1409	0.055	0.038
CaNO(ppd)	Population	1499	0.111	P<0.001
	<18 years old	91	−0.137	P=0.195
	≥18 years old	1408	0.125	P<0.001

Abbreviations: FeNO50, Fractional Exhaled Nitric Oxide at 50 mL/s; FeNO200, Fractional Exhaled Nitric Oxide at 200 mL/s; CaNO, Concentration of Alveolar Nitric Oxide.

Table 7 Blood Cell Analysis Kruskal–Wallis Test Results

Chemical Examination	Teenager Group	Youth Group	Middle-Aged Group	Senior Group	H	P
White blood cell count ($\times10^9$/L)	7.21 (5.79,8.76)	6.92 (5.46,8.42)	6.68 (5.37,8.18)	6.90 (5.51,8.26)	7.825	P=0.05
Absolute eosinophil count ($\times10^9$/L)	0.19 (0.1,0.39)	0.16 (0.08,0.34)	0.12 (0.05,0.23)	0.09 (0.05,0.18)	77.129	P< 0.001
Absolute eosinophil count ($\times10^9$/L)	0.02 (0.02,0.04)	0.03 (0.02,0.04)	0.02 (0.01,0.03)	0.02 (0.01,0.03)	21.173	P< 0.001
Absolute neutrophils ($\times10^9$/L)	3.57 (2.74,4.95)	4.07 (3.01,5.41)	4.00 (3.10,5.50)	4.30 (3.19,5.87)	16.854	P< 0.001
Absolute monocytes ($\times10^9$/L)	0.42 (0.34,0.55)	0.40 (0.32,0.54)	0.39 (0.31,0.51)	0.44 (0.34,0.58)	17.489	P< 0.001
Absolute lymphocyte count ($\times10^9$/L)	2.44 (2.00,3.13)	1.96 (1.58,2.40)	1.82 (1.40,2.27)	1.66 (1.25,2.07)	156.181	P< 0.001

Notes: The data in the table are described in terms of Median and Interquartile Range (IQR) ie M(Q1,Q3) H: The H statistic is used to characterize the degree of difference between groups. A higher H value indicates greater intergroup differences, thereby providing more substantial grounds for rejecting the null hypothesis that "the population medians of all groups are equal.".

aged group (P < 0.04), and the middle-aged group > the old-aged group (P = 0.005); neutrophils H(3) = 16.854, p < 0.001, the difference between the four groups was statistically significant, pairwise comparisons revealed that the adolescent group <youth group (P=0.006), no significant difference between the youth group and middle-aged group (P=0.844), and the middle-aged group <elderly group (P=0.050) was borderline significant; monocyte H(3) =17.489, P<0.001, the difference between the four groups was statistically significant, and pairwise comparisons revealed that the elderly group >middle-aged group (P<0.001), the elderly group > the youth group (P = 0.017), the adolescent group > the middle-aged group (P = 0.005). There was no significant difference between the adolescent group and the youth group (P = 0.176), and between the youth group and the middle-aged group (P = 0.054); Lymphocytes H(3) = 156.181, P < 0.001, the difference between the four groups was statistically significant, and the rows into pairwise comparisons revealed that the adolescent group > the youth group (P < 0.001), youth group > middle-aged group (P = 0.002), middle-aged group > elderly group (P < 0.001).

In order to further visualize the changes in the distribution of hemocyte analysis results with age, a plot of the mean values of hemocyte analysis was performed, and the results are shown in Figure 3.

After the Shapiro–Wilk test of normality, the total IgE assay indexes were non-normally distributed. The results of the Kruskal–Wallis test were shown in Table 8, which were analyzed as follows: IgE H(3) = 69.735, P < 0.001, with significant differences in the comparison of the four groups, and pairwise comparisons revealed that the adolescent group > young group (P < 0.001), the young group > middle-aged group (P = 0.012), and the middle-aged group > elderly group (P = 0.009).

To further clearly compare and describe the trend of peripheral blood total IgE and hemocyte analysis with age, SPSS software was used to form a mean line graph, and the results are shown below in Figure 4. Overall, With the exception of neutrophils and monocytes, there is a gradual decline with age. Whereas the neutrophils increased year by year with the change of the age stage, and the monocytes showed a trend of decreasing and then increasing. Both reached a maximum at the older age stages.

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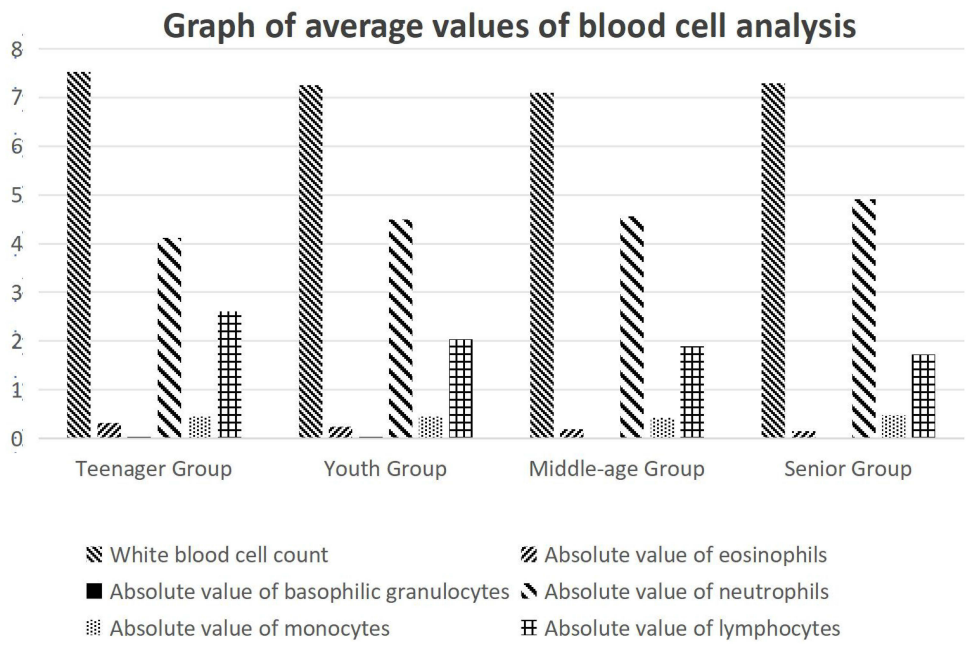

Figure 3 Graph of average values of blood cell analysis.
Notes: In the graph, which shows the mean values of various cell counts in *109/L, it is possible to see how the distribution of the results of blood cell analysis changes with age.

Discussion

The Effect of Age on Airway Hyperresponsiveness Has a "U-Shaped" Distribution

Airway hyperresponsiveness is an important feature of asthma, which is a serious global health problem affecting all age groups and whose prevalence has increased in many countries, especially among children.[11] Parental history of asthma is the most prominent risk factor. Genetically influenced, children with relatives who have airway hyperresponsiveness have a significantly increased risk of developing asthma, which puts adolescents at a significantly increased risk of developing asthma.[12,13] Chronic cough is a cause of airway hyperresponsiveness in children. In an analysis of the clinical morbidity characteristics and etiological components of 226 cases of chronic wet cough in children, it was found that most of the children have idiosyncratic responses. When in respiratory tract infections, spring and fall season environmental sensitizers increased exposure, the sinuses, adenoids in the preschool and school-age development is rapid. Postnasal drip, direct stimulation of the nasal mucosa, inflammation of the upper and lower airways and cough reflex sensitivity and other mechanisms are prone to cause chronic wet cough.[14] This is more likely to cause airway hyperreactivity. Inflammatory reactions in the airways of children with allergic cough are associated with eosinophil accumulation and infiltration in the airways.[15] For the elderly, relevant studies have also shown that the occurrence of asthma is becoming more and more prevalent, due to the changes in immune and respiratory physiology caused by aging make elderly asthmatics more susceptible to instability.[16] The various changes in the structure and function of the lungs are related to aging. With age, the lung function of the elderly patients becomes worse. When faced with respiratory and systemic diseases, the lungs become more vulnerable and less resilient. Impaired lung function increases the risk of lung cancer as well as the risk of death in the elderly.[17]

Table 8 Results of Kruskal–Wallis Test on Total IgE Changes with Age

Chemical Examination	Teenager Group	Youth Group	Middle-Aged Group	Senior Group	Difference Between Group H	P
Overall IgE	136.45 (97.32,227.72)	105.11 (76.17,186.31)	99.95 (56.74,183.08)	53.29 (17.53,99.26)	69.735	P< 0.001

Notes: The data in the table are described in terms of Median and Interquartile Range (IQR) ie M(Q1,Q3).
Abbreviation: IgE, Immunoglobulin E.

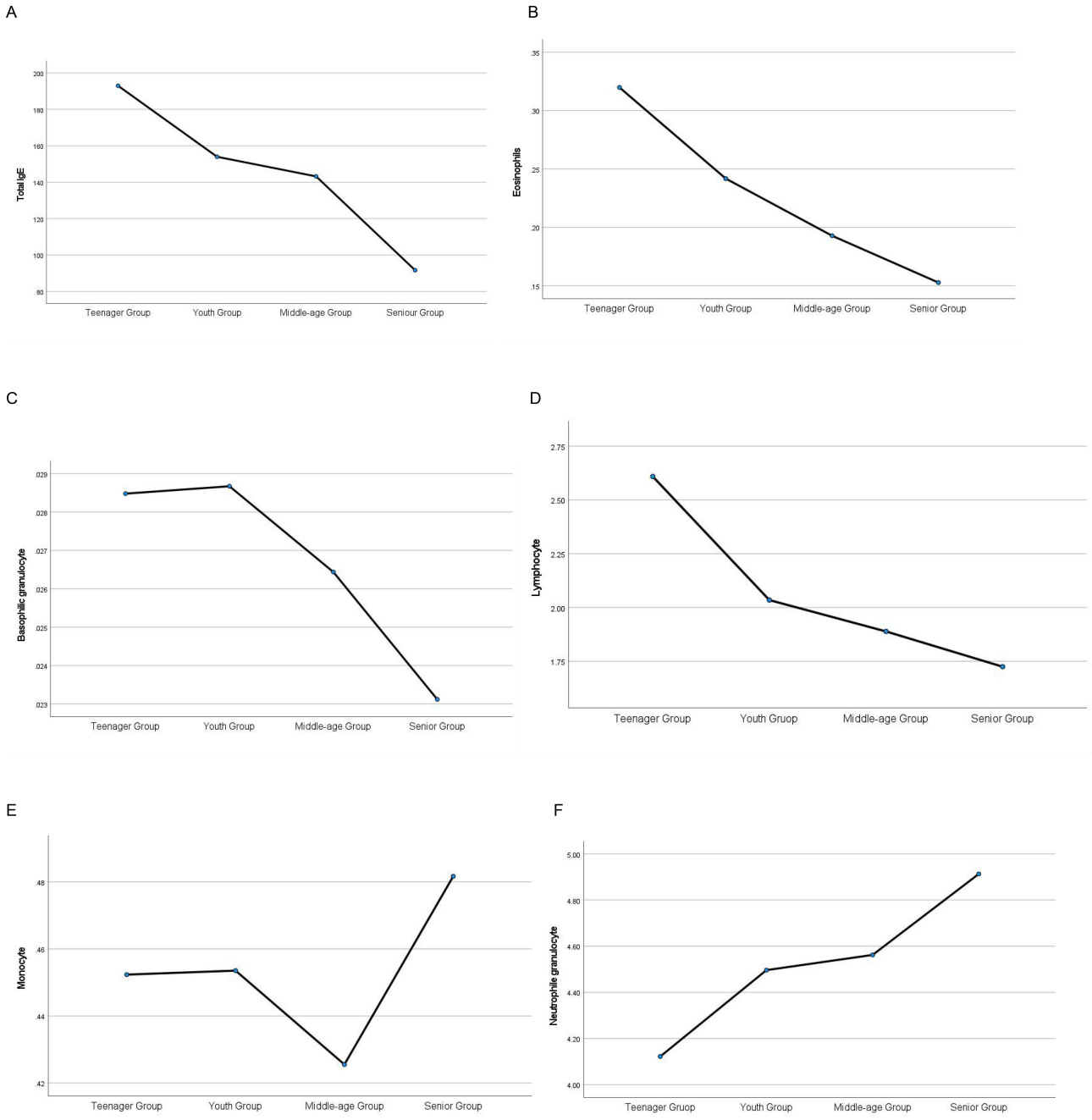

Figure 4 Mean peripheral blood total IgE and hematocrit graphs. (**A**) Median total IgE count per age group; (**B**) Mean eosinophils count per age group; (**C**) Mean basophilic granulocyte count per age group; (**D**) Mean lymphocyte count per age group; (**E**) Mean monocyte count per age group; (**F**) Mean neutrophile granulocyte count per age group.
Notes: With the exception of neutrophils and monocytes, there is a gradual decline with age. Whereas the neutrophils increased year by year with the change of the age stage, and the monocytes showed a trend of decreasing and then increasing. Both reached a maximum at the older age stages.

In the present study, the results of lung function, FeNO, blood cell analysis, and total IgE in all age groups showed that the positive rate of provocation test and the decline rate of FEV1 were significantly higher in the adolescent group and the elderly group than in the young group and the middle-aged group. The decline rate of CaNO started from the adolescent group, increased in the middle-aged group, and reached the highest in the elderly group. All of the above suggests that airway hyperresponsiveness is stronger in the adolescent and elderly age groups and that the effect of age on airway hyperresponsiveness shows a "U-shaped" distribution.

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Different Age Groups Have Different Inflammatory Phenotypes

AHR-induced asthma is a common disease that affects the respiratory health of approximately 300 million people worldwide. There are large numbers of eosinophils in the airways of patients with mild asthma, which is a class of specific immune cells in asthmatic airway inflammation, and which is also considered to be one of the most critical effector cells in causing asthmatic inflammation, and has been confirmed through the data from mouse models. Asthma has long been recognized as a hallmark T helper 2 cell (Th2) disease of the airways.[18,19] The existence of a Th1/Th2 imbalance was mentioned in a study of bronchoalveolar lavage cell counts in patients with cough-variant asthma, which was manifested as a Th2-dominant immune response. Th2 cell-dependent inflammation facilitation of IgE production. Recruitment of associated airway inflammatory mediators by mast cells and eosinophils, including interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin interleukin-13 (IL-13), and interleukin-25 (IL-25), leads to localized airway inflammatory cell infiltration, which increases airway sensitization and contributes to asthma attacks.[20,21] High IgE, eosinophil, and FeNO levels suggest a predominance of Th2-type inflammation, and IL-5-mediated eosinophil activation may directly damage the airway epithelium through the release of granulin.[18] FeNO is a well-known indicator of eosinophilic airway inflammation and correlates with the severity of inflammation in asthma. Despite the presence of a large number of inflammatory phenotypes in asthma, several studies have identified a FeNO and Th2 immune response link.[16]

Adolescence is a critical stage in the maturation of the immune system, where the thymus outputs functional T cells at its peak, but immune tolerance mechanisms are not yet fully established.[22] With age, degenerative atrophy of the thymus, decline in T-cell receptor function, accumulation of memory T cells, and mitochondrial damage occur,[23] which in turn results in a diminished adaptive immune response. Frequent exposure to environmental allergens (eg, dust mites, pollen) activates the differentiation of initial CD4+ T cells to Th2 via dendritic cells, which secrete IL-4, IL-5, and IL-13, forming a pathological loop:[18] IL-4 induces B cells to produce IgE and sensitize mast cells,[20] IL-5 promotes eosinophilia and survival, and IL-13 stimulates airway epithelial secretion of mucins and elevates FeNO.[18]

Related studies suggest that the airway inflammatory phenotype in older asthmatics may differ from that of younger patients. Asthma endophenotypes or phenotypes containing biological markers and severity have not been determined. Theoretically, the neutrophil phenotype may explain more of the increased airway severity among older adults. It is well known that neutrophils in normal lungs increase with age, but the clinical significance of increased airway neutrophilia in elderly asthmatics is unclear.[24] It has been established that asthma is a mechanistically complex and heterogeneous disease that is classified into different subtypes based on immunological characteristics, of which neutrophilic asthma is considered to be a subtype with a longer duration, greater severity, and resistance to corticosteroids, with higher rates of hospitalization and mortality among patients. Mainstream therapies usually being ineffective in neutrophilic asthma.[25] Bone Marrow Hematopoietic Stem Cells give rise to circulating monocytes, which can differentiate into macrophages in tissues.[26] Removal of intact neutrophils occurs through specific receptors phagocytosed by macrophages, which sequester and degrade neutrophil granule contents and prevent them from further tissue damage. Decreased function of apoptotic mechanisms of macrophage phagocytosis and degradation of neutrophils may lead to the accumulation of neutrophils in bronchoalveolar lavage of aging human lungs.[17]

In the present study, the results of eosinophils and IgE showed that the adolescent group > young group > middle-aged group > old group, which was consistent with the attenuation of the Th2 response with age. While the change of neutrophil level with age showed that the old group > middle-aged group ≈ young group > adolescent group ($P<0.05$). Monocyte level indicated that the old group was significantly higher ($P<0.05$), which might be involved in tissue repair and chronic inflammation. Overall, the adolescent period showed a change in the immune pattern from Th2-type immunity represented by eosinophils to an immune phenotype characterized by neutrophils and monocytes with age. There are also cutting-edge studies that have shown that iron death inducers have been demonstrated to trigger eosinophilic cell death and attenuate airway inflammation in eosinophilic asthma mice or cellular models and that fat stilbene attenuates neutrophilic asthma in mice by inhibiting iron death, among others,[25] arguing side by side for the characterization of these two inflammatory phenotypes. In summary, the adolescent group exhibited an immune pattern characterized by Th2-type immunity represented by eosinophils, while a portion of the elderly group displayed a non-Th2 -type immune phenotype dominated by neutrophils and monocytes.

Age-Specific Impairment Patterns

In this study, we found that FEV1 and FVC showed age-dependent changes with age stage, and correlation analysis indicated that a trend of first increase occurred in the adolescent stage (less than 18 years old), which was presumed to be related to the maturation of adolescent lung growth and development, and that the expansion of lung volume, the enhancement of respiratory muscles, and the increase in ventilation efficiency with the growth and development of adolescence reached the peak in youth, and gradually declined after middle-age. This decay trajectory may reflect degenerative pathophysiological processes such as decreased elastic retraction of lung parenchyma and changes in thoracic compliance. FEV1/FVC continued to decrease and was lowest in the older age group ($P<0.05$), suggesting that the degree of airflow limitation of the small airways gradually increased with age, which is consistent with the characteristics of COPD.[27] MEF50 and MEF25 changes in response to small airway obstruction, associated with risk factors such as COPD, and can reflect the prognosis of future chronic airflow obstruction.[28] The present study showed that MEF50 and MEF25 for the adolescents and youth group did not differ ($P>0.05$), while after middle age a significant decline ($P<0.05$), reflecting the accelerated decline of small airway function in middle age. Overall, aging has a specific pattern of damage to the lungs, with gradual maturation of the lungs in adolescents, reaching a peak in youth, accelerated decline of the small airways after middle age, and increased small airway obstruction in old age.

Dissociated Paradoxical Phenomenon and Potential Mechanism of Elevated FeNO and Reduced Blood EOS

In recent years, the effect of age on AHR has received increasing attention. Adolescent asthma is characterized by Th2-type inflammation and eosinophilic infiltration. Th2-type cytokines orchestrats the allergic-inflammatory cascade of responses that occur in asthma including Th2 cell survival, B-cell isotype switching to IgE synthesis, mast cell differentiation and maturation, eosinophil maturation and survival, and basophil recruitment.[20] However, some studies have shown that eosinophils are not necessary for the development of asthma. Elimination of eosinophilic inflammation has been found to neither halt the progression of asthma nor alter the decline in lung function. There are disconnect between eosinophilic inflammation and remodeling.[29] It has been found that sputum eosinophils and neutrophils are increased in elderly patients and that inadequate asthma control in the elderly is strongly associated with eosinophilic and neutrophilic inflammation.[24] Another related study showed that the number of neutrophils increased in bronchoalveolar lavage fluid of elderly healthy subjects and found that neutrophils and monocytes may migrate from capillaries to air cavities through matrix-degrading proteases leading to inflammation.[17] The decrease in peripheral blood eosinophils and the increase in neutrophils and monocytes in the elderly may be related to aging and the body's immunity to non-Th2 type (neutrophils as well as monocytes) shift associated with aging.

Eosinophils are granulocytes that develop in the bone marrow from pluripotent progenitor cells in response to cytokines such as IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Mature eosinophils are released into the peripheral blood.[30] Eosinophils play an important role in the eosinophilic inflammatory response in asthma. In allergic inflammatory response, secretion of relevant chemokine ligands can recruit eosinophils from bone marrow to the lungs and further recruit Th2 cells and cell death in asthma.[31] Thymic stromal lymphocytic and interleukin-33 (IL-33) are considered important initiators of type 2 immunity. In asthmatics, allergic inflammatory responses are associated with increased pulmonary homing of bone marrow-derived CD34(+) hematopoietic progenitors, including those of the eosinophil lineage. In the airway mucosa of elderly asthmatics, IL-33 and thymic stromal lymphopoietin (TSLP)-activated type 2 intrinsic lymphocytes may substitute for T cells in the sustained secretion of IL-5 and IL-13 to maintain localized eosinophilic inflammation,[32] which tends to a coexist of localized airway Th2 inflammation (elevation of CaNO reflecting small airway and alveolar eosinophil status) and peripheral blood eosinophilic migration blocked (decreased bone marrow production, tissue retention). That may lead to a decrease in eosinophils in the peripheral blood with age, whereas eosinophils locally in the lungs do not necessarily decrease with it.

Asthma can be categorized into eosinophilic and non-eosinophilic asthma based on the pattern of inflammatory cells in airway secretions. Eosinophilic asthma is the most severe case of asthma, but neutrophilic asthma or a mixture of the two types may also present a severe asthma phenotype. Clinical studies have shown that patients with non-eosinophilic

asthma do not have eosinophilic symptoms and are usually older at the time of the attack,[7] so it is also suggested that an "eosinophil-independent" inflammatory phenotype may be present in older patients.

Advantages and Limitations

In this study, we found that the occurrence of airway hyperresponsiveness may be age biphasic, with Th2-type allergic inflammation dominating in adolescence, a shift to neutrophil/monocyte-mediated chronic inflammation in old age, and a relatively stable period in the intermediate age group (youth-middle age), where the decline in lung function and the shift in inflammatory pattern together form a "U-shaped" age risk curve. Then, for clinical medication guidance, differentiated airway management strategies can be developed according to different age groups: focusing on allergy prevention and control in adolescents, chronic inflammation suppression in the elderly, and strengthening lung function monitoring and early intervention in middle age. There are also some limitations. This study is a single-center cross-sectional study. It is difficult to distinguish the cohort effect. Further longitudinal studies are needed to verify. The sample size of this study is relatively small due to resource constraints, and the region of the study is Shanxi Province, China, which may be affected by the regional population's physical condition. The effects of confounding factors, such as air pollution, smoking history, body mass index, etc., were not controlled. It was not possible to incorporate bronchial biopsy, alveolar lavage and inflammatory markers into the study. The study also failed to combine bronchial biopsy, alveolar lavage, and inflammatory markers to analyze the molecular mechanisms of age-related airway remodeling.

Conclusion

This study demonstrates that airway hyperresponsiveness (AHR) follows a distinct "U-shaped" age-dependent distribution, being more prominent in adolescents and the elderly, and less so in young and middle-aged adults. Accompanying this distribution are age-specific inflammatory phenotypes: adolescents exhibit a predominance of Th2-driven eosinophilic inflammation, whereas the elderly display a non-Th2 pattern characterized by neutrophilic and monocytic inflammation. Lung function parameters further reveal an age-related trajectory—peak function is attained in young adulthood, followed by an accelerated decline in small airway function after middle age, and increased obstruction in the elderly.

These findings have important implications for clinical practice. They support the adoption of age-stratified management strategies for airway diseases, such as emphasizing allergen control and anti-eosinophilic therapies in adolescents, targeting neutrophilic inflammation and enhancing small airway protection in the elderly, and prioritizing lung function preservation through mid-life monitoring. From a public health perspective, these results underscore the need for age-tailored prevention programs and resource allocation to mitigate the burden of respiratory diseases across the lifespan. Future research should focus on longitudinal validation and exploring molecular mechanisms underlying age-associated airway remodeling to further refine personalized treatment approaches.

Abbreviation

AHR, Airway Hyperresponsiveness; FEV1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; FEV1/FVC, The ratio of expiratory volume at first second of exertion to expiratory lung capacity, ie, the one-second rate; CV, Closing Volume; RV, Residual Volume; FRC, Functional Residual Capacity, MEF50, Maximal Expiratory Flow After 50% of the FVC Has Not Been Exhaled; MEF25, Maximal Expiratory Flow After 25% of the FVC Has Not Been Exhaled; FeNO, Fractional Exhaled Nitric Oxide; FeNO50, Fractional Exhaled Nitric Oxide at 50 mL/s; FeNO200, Fractional Exhaled Nitric Oxide at 200 mL/s; CaNO, Concentration of Alveolar Nitric Oxide; IgE, Immunoglobulin E; Eos, Eosinophil; Th2, T helper 2 cell.

Data Sharing Statement

All the data of this article are available from the corresponding author upon reasonable request.

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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.

Statement of Informed Consent

All procedures conducted in the study involving human subjects were by the ethical standards of the Ethics Committee of the Second Hospital of Shanxi Medical University (approval number 2023 YX 131) and the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards. Written informed consent was obtained from all volunteers and the anonymity of each participant was strictly preserved. Participants under the age of 18 have had their informed consent forms signed by their legal guardians.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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