Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Monosensitization vs Polysensitization in Severe Asthma: Implications for Disease Severity

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Aim: The impact of sensitization on asthma outcomes in adults is still being discussed. This study aims to describe the sensitization profiles and allergic comorbidities of patients with severe asthma, and to analyze their association with asthma severity.

Patients and Methods: This retrospective study included adult patients, evaluated at the Severe Asthma Clinic of Bichat University Hospital (Paris, France) during a 1-day hospital stay between May 2022 and January 2024. Sensitization, defined by a positive skin prick test and/or allergen-specific IgE levels greater than 0.10 kUA/L, was analysed alongside allergic comorbidities. The ASSESS score was used to grade asthma severity.

Results: Of the 201 patients included, 142 (70.6%) exhibited at least one sensitization to an aeroallergen, of whom 38 (26.8%) were monosensitized, and 104 (73.2%) were polysensitized. Compared to polysensitized patients, monosensitized patients were older at diagnosis (years: 30.6 ± 20.1 vs 21.7 ± 17.6, p = 0.01), had a higher ASSESS score (median (Q1; Q3); 13 (11; 15) vs 11 (9; 14), p = 0.02), a lower pre-bronchodilator forced expiratory volume in 1 second (%pred: 70.3 ± 23.2 vs 79.3 ± 21.8, p = 0.03), and experienced a greater burden of exacerbations (p = 0.03). There were significantly more polysensitized patients with at least three allergic comorbidities, but the number of allergic comorbidities did not correlate with asthma severity.

Conclusion: Monosensitized patients exhibited more severe disease and greater airway obstruction compared to polysensitized individuals. These findings suggest that allergies, especially in cases of late-onset asthma, may not be a significant determinant of asthma severity in adults.

Keywords: severe asthma, sensitization, aeroallergens, allergy, ASSESS

Introduction

Atopic sensitization to airborne allergens is an important risk factor for asthma, in both children and adults. However, the contribution of allergy to the disease severity differs between children and adults. In children, early sensitization is associated with a higher risk of persistent asthma in adulthood.[1] The number of allergens to which the patient is sensitized seems to influence the severity of asthma in children. Polysensitization[2] or high level of atopic sensitization (defined by the sum of IgE level and/or summative size of skin prick test (SPT) wheals) are associated with more severe outcomes, including poorer lung function and more severe exacerbations.[3,4]

In adults, this relationship between allergic sensitization and asthma severity is debated.[5] In the Severe Asthma Research Program cohort,[6] early-onset disease and allergic sensitization are common, especially in the less severe subgroups. Recently, in a French cohort of severe asthma,[7] no correlation was found between allergic sensitization (defined by yes/no) and asthma severity. However, the accumulation of allergic comorbidities (rhino conjunctivitis, atopic dermatitis, food allergy) significantly increased the risk of asthma exacerbations, long-term use of oral corticosteroids

Received: 23 October 2024
Accepted: 18 March 2025
Published: 2 May 2025

and reduced asthma control.[8,9] This highlights the importance of how the concept of allergy and sensitization is assessed in understanding the relationship between allergy and asthma severity. Moreover, severe asthma has been an evolving concept over the years until the ATS-ERS definition.[10] The definition of asthma severity includes several dimensions: symptoms control, exacerbation, lung function, therapeutic burden. All are interconnected, but their relationship with allergy can vary. For example, exacerbations can be triggered by exposure to aeroallergens. Additionally, lung function may be more significantly impacted by certain allergens, such as house dust mites[11] and fungi.[12] Therefore, assessing asthma severity requires a multidimensional approach rather than a binary one, supporting the development of the Asthma Severity Scoring System (ASSESS).[13]

The aim of the study is to describe both the sensitization profile and allergic comorbidities of patients with severe asthma and to investigate their association with asthma severity, quantitatively measured by the ASSESS score.

Materials and Methods

Data Sources and Population

This retrospective study includes patients aged 18 years and over who were consecutively explored for severe asthma at the Severe Asthma Clinic in Bichat University Hospital (Paris, France) during a 1-day hospital stay with multidisciplinary assessment between May 1st, 2022, and January 31st, 2024. All underwent a systematic medical evaluation, including allergy investigations, as previously described.[14] Most of them received step 5 asthma treatment according to GINA 2023 (combination of high doses inhaled corticosteroids and long acting beta2-agonist and tiotropium or biological treatment).[15] Late-onset asthma was defined by asthma diagnosis after 12 years old.[3] All patients underwent SPT and/or specific IgE blood tests for aeroallergens (*Dermatophagoides pteronyssinus* and *farina*e (house dust mite (HDM)), *Blomia tropicalis* (dust mite storage), cockroaches, pollens (trees birch, plane tree, olive tree, cypress, timothy grass, plantain, mugwort, and ragweed), cat, dog and molds (*Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum, Penicillium notatum*). The fractional exhaled nitric oxide (FeNO) value and blood eosinophil count were collected on the same day of the allergological assessment.

Outcome

Sensitization was defined by a positive SPT and/or airborne allergen-specific IgE of more than 0.10 kUA/L.[16] Patients were considered as monosensitized if they tested positive for a single allergen and polysensitized if they tested positive for two or more allergens. Anaphylaxis was defined as an immediate hypersensitivity reaction (minutes to several hours) with involvement of the skin, mucosal tissue, or both, and at least one of the following: severe gastrointestinal symptoms or acute onset of hypotension or bronchospasm or laryngeal involvement following the exposure to an allergen.[17,18] Type 2 (T2) phenotype was defined by blood eosinophil count ≥150 cells/µL and/or fractional exhaled nitric oxide (FeNO) ≥20 ppb. Allergic comorbidities included rhinoconjunctivitis, atopic dermatitis, food allergy, urticaria, and anaphylaxis.[8] Allergic comorbidities were categorized into major groups as follows: none, one, two and three or more. The multidimensional ASSESS score, ranging from 0 to 20, was used to assess asthma severity, taking into account symptoms with the Asthma Control Test (ACT), lung function (Forced Expiratory Volume in 1 second, FEV1), current medications (inhaled corticosteroids, oral corticosteroids, long acting anti muscarinic (LAMA), leukotriene receptor antagonists, biologics), and exacerbations hospitalized or not (Suppl Table 1).[13]

Ethics and Statistics

This retrospective study was approved by the French Pulmonology Society ethic committee (CEPRO 2024–041) and complies with the Declaration of Helsinki. This work complies to the protection of personal health data and privacy with the framework of application provided for by article 65–2 of the amended Data Protection Act and the general data protection regulations. The study was designed according to the STROBE guidelines.

Categorial variables are compared by Chi-square and Fisher's exact tests. Continuous variables are summarized as mean ± standard deviation and are compared by ANOVA. For non-normal data, variables are summarized as median and Q1, Q3 and compared with Kruskal Wallis test. Bonferroni corrected post hoc analysis based on residuals[19] of chi-square

test was performed if case of significant omnibus chi-square test. Significance was set at $p \leq 0.05$. Analyses were performed using Microsoft Excel, GraphPad Prism 9.0 and R (v4.3.3) software.

Results

Global Population

From the 261 patients referred to the Severe Asthma Clinic between May 1st, 2022, and January 31st, 2024, 201 patients with severe asthma were included (Figure 1). Patients' characteristics are described in Table 1. Briefly, most of them were females (71.1%), with a mean age of 49.3 ± 14.9 years, and 129 (64.2%) had late-onset asthma. T2 phenotype concerned 154 (76.6%) patients with a mean blood eosinophil count of 310.6 cells/mm3 and a mean FeNO of 44.8 ppb. Median ASSESS score was 12 (Q1, Q3; 11,14) with median ACT of 14 (10,14), mean post bronchodilator FEV1 of 79.4 ± 20.7% predicted and median exacerbation number in the previous year of 3(1,4). At the time of evaluation, 66 patients (32.8%) were treated by a biologic (dupilumab: 28.8%; omalizumab: 27.3%, mepolizumab: 18.2%, tezepelumab: 15.2% and benralizumab: 10.6% of the treated patients, respectively). Lastly, 15.9% of the patients were receiving daily oral corticosteroids.

Allergic Sensitization Profile and Asthma Severity

Among the 201 patients, 59 (29.4%) were not sensitized to any aeroallergen, and 142 (70.6%) had at least one sensitization. The latter had significantly higher total IgE levels (517.5 ± 725.4 KU/L versus 122.9 ± 217.6, $p < 0.01$), a higher mean basal tryptase level (4.7 ± 2.9 versus 3.8 ± 2.2, $p = 0.08$) and were less likely to receive daily oral corticosteroids (12.0% versus 25.4%, $p = 0.02$). No significant difference was found regarding ASSESS score between sensitized and non-sensitized patients (Table 1).

Among sensitized patients, 38 (26.8%) were monosensitized and 104 (73.2%) were polysensitized to a mean of 4.3 ± 2.1 allergens (Figure 1 and Table 2). The number of sensitizations was negatively correlated with age at asthma onset ($r = -0.3373$, $p < 0.01$) (Figure 2A). Monosensitized patients, compared to the polysensitized ones, were diagnosed at a later age (30.6 ± 20.1 versus 21.7 ± 17.6, $p = 0.01$), were more likely to have an obstructive ventilatory disorder, and had a lower pre-bronchodilator FEV1 (70.3 ± 23.2 versus 79.3 ± 21.8, $p = 0.03$) (Table 2). According to ASSESS score, monosensitized patients had more severe asthma (median (Q1, Q3); 13 (11,15) versus 11 (9,14), $p = 0.02$). The components of the ASSESS score that significantly differed between monosensitized and polysensitized patients were FEV1 ($p = 0.02$) and the exacerbation score ($p = 0.03$) (Table 2). Finally, polysensitized

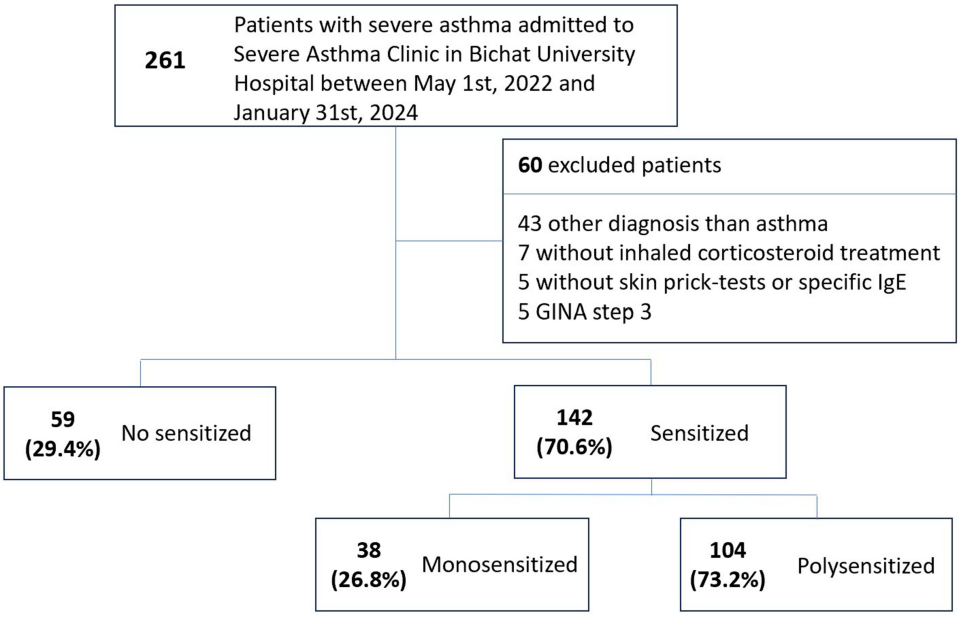

Figure 1 Flow chart.

https://doi.org/10.2147/JAA.S502442

Table 1 Patients' Characteristics

	Whole cohort (N=201)		No sensitized (N=59)		Sensitized (N=142)		p-value
	N	%	N	%	N	%	
Female	143	71.1	43	72.9	100	70.4	0. 73
Age (years), mean ± SD	49.3 ± 14.9		47.9 ± 13.5		49.9 ± 15.5		0.37
BMI kg/m² mean ± SD	27.8 ± 6.1		27.1 ± 5.7		28.0 ± 6.2		0.36
Ex smokers	60	29.9	21	35.6	39	27.5	0.25
Age at asthma diagnosis (years), mean ± SD	24.5 ± 17.9		25.6 ± 16.1		24.0 ± 18.6		0.59
Spirometry							
FEV1/FVC mean ± SD	69.5 ± 13.1		70.3 ± 13.2		69.2 ± 13.1		0.58
FEV1 (% pre BD) mean ± SD	78.0 ± 22.5		80.6 ± 22.6		76.9 ± 22.5		0.28
FEV1 (% post BD) mean ± SD	79.4 ± 20.7		78.8 ± 21.1		79.6 ± 20.6		0.81
Asthma inhaled treatment							
GINA step 4	40	19.9	10	16.9	30	21.1	0.50
GINA step 5	161	80.1	49	83.1	112	78.9	
Current biologics	66	32.8	16	27.1	50	35.2	0.27
Omalizumab	*18*	*27.3*	*1*	*6.3*	*17*	*34*	
Mepolizumab	*12*	*18.2*	*4*	*25.0*	*8*	*16*	
Benralizumab	*7*	*10.6*	*2*	*12.5*	*5*	*10*	
Dupilumab	*19*	*28.8*	*5*	*31.3*	*14*	*28*	
Tezepelumab	*10*	*15.2*	*4*	*25.0*	*6*	*12*	
Oral corticosteroids	32	15.9	15	25.4	17	12.0	0.02
LTRA	53	26.4	14	23.7	39	27.5	0.58
LAMA	141	70.1	43	72.9	98	69.0	0.59
Antihistamin drugs	117	58.2	26	44.1	91	64.1	<0.01
Phenotype							
BEC (cells/mm3) mean ± SD	310.5 ± 329.7		278.3 ± 291.5		324.0 ± 344.5		0.37
IgE (kUA/L) mean ± SD	401.1 ± 645.4		122.9 ± 217.6		517.5 ± 725.4		<0.01
FeNO (ppb) mean ± SD	44.8 ± 47.4		42.8 ± 46.1		45.7 ± 48.1		0.73
T2 phenotype [(a)]	154	76.6	43	72.9	111	78.2	0.47
Asthma control							
ACT, median (Q1;Q3)	14 (10;19)		15 (10;18)		14 (10;19)		0.93
Number of exacerbations in the previous year, median (Q1;Q3)	3 (1;4)		3 (2;5)		3 (1;4)		0.58
ASSESS score, median (Q1;Q3)	12 (10;14)		11 (10;13)		12 (10;14)		0.75
Asthma comorbidities							
Nasal polyposis	74	36.8	20	33.9	54	38.0	0.58
Gastroesophageal reflux	101	50.2	31	52.5	70	49.3	0.68

(*Continued*)

Table 1 (Continued).

	Whole cohort (N=201)		No sensitized (N=59)		Sensitized (N=142)		p-value
	N	%	N	%	N	%	
Sleep apnea syndrome	34	17.0	10	16.9	24	17.0	>0.99
Depression	22	10.9	9	15.3	13	9.2	0.21
Obesity	68	33.8	16	27.1	52	36.6	0.19
Allergic comorbidities							
Rhinoconjunctivitis	134	66.7	30	50.8	104	73.2	<0.01
Atopic dermatitis/eczema	55	27.4	10	16.9	45	31.7	0.03
Food allergy	25	12.4	1	1.7	24	16.9	<0.01
Urticaria	18	9.0	3	5.1	15	10.6	0.22
Anaphylaxis	32	15.9	9	15.3	23	16.2	0.87
Basal tryptase, mean ± SD	4.4 ± 2.8		3.8 ± 2.2		4.7 ± 2.9		0.08

Note: (a) T2 phenotype is defined by blood eosinophils count ≥ 150 cells/mm^3 or FeNO ≥ 20 ppb.
Abbreviations: ACT, Asthma Control Test; BD, bronchodilators; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; LAMA, long acting anti muscarinic; LTRA, leukotriene receptor antagonists.

Table 2 Patients' Characteristics According Sensitization

	Monosensitized		Polysensitized		p value
	N=38	%	N=104	%	
Female	23	60.5	77	74.0	0. 12
Age (years), mean ± SD	53.3 ± 16.0		48.8 ± 15.2		0.15
Age at asthma diagnosis (years), mean ± SD	30.6 ± 20.1		21.7 ± 17.6		0.01
Ex smokers	13	34.2	26	25.0	0.28
Spirometry					
FEV1/FVC mean ± SD	63.3 ± 14.6		71.3 ± 11.9		<0.01
FEV1 (% pre BD) mean ± SD	70.3 ± 23.2		79.3 ± 21.8		0.03
FEV1 (% post BD) mean ± SD	75.0 ± 22.1		81.3 ± 19.9		0.12
Asthma inhaled treatment					
GINA step 4	5	13.2	25	24.0	0.16
GINA step 5	33	86.8	79	76.0	
Current biologics	12	31.6	38	36.5	0.58
Omalizumab	*2*	*16.7*	*15*	*39.5*	
Mepolizumab	*1*	*8.3*	*7*	*18.4*	
Benralizumab	*2*	*16.7*	*3*	*7.9*	
Dupilumab	*6*	*50.0*	*8*	*21.1*	

(*Continued*)

https://doi.org/10.2147/JAA.S502442

Table 2 (Continued).

	Monosensitized		Polysensitized		p value
	N=38	%	N=104	%	
Tezepelumab	*1*	*8.3*	*5*	*13.2*	
Oral corticosteroids	10	26.3	7	6.7	<0.01
Phenotype					
BEC (cells/mm3) mean ± SD	288.9 ± 278.9		337.0 ± 366.1		0.46
IgE (kUA/L) mean ± SD	157.0 ± 137.3		650.4 ± 805.7		<0.01
FeNO (ppb) mean ± SD	34.3 ± 35.3		50.2 ± 51.9		0.12
T2 phenotype[(a)]	30	78.9	81	77.9	1.00
Asthma control and severity					
ACT, median (Q1;Q3)	13 (9;19)		15 (10;19)		0.38
Number of exacerbations in the previous year median (Q1;Q3)	2.5 (1;4)		3 (1.8;4)		0.93
ASSESS score, median (Q1;Q3)	13 (11;15)		11 (9;14)		0.02
ACT (points), median (Q1;Q3)	4 (2;5)		3 (2;5)		0.28
FEV1 (%predicted) (points), median (Q1;Q3)	1 (0;3)		0 (0;2)		0.02
Treatments (points), median (Q1;Q3)	5 (5;6.8)		5 (5;6)		0.18
Exacerbations (points), median (Q1;Q3)	2 (2;2)		2 (2;2)		0.03
Asthma comorbidities					
Nasal polyposis	16	42.1	38	36.5	0.55
Gastroesophageal reflux	25	65.8	45	43.3	0.02
Sleep apnea syndrome	7	18.4	17	16.5	0.79
Depression	4	10.5	9	8.7	0.75
Obesity	17	44.7	35	33.7	0.22
Current smoking	3	7.9	6	5.8	0.70
Allergic comorbidities					
Rhinoconjunctivitis	23	60.5	81	77.9	0.04
Atopic dermatitis/eczema	10	26.3	35	33.7	0.41
Food allergy	4	10.5	20	19.2	0.22
Urticaria	4	10.5	11	10.6	1.00
Anaphylaxis	5	13.2	18	17.3	0.55
Sensitized to aeroallergens					
House dust mite/cockroach	17	44.7	82	21.2	<0.01
Pollen	7	18.4	73	70.2	<0.01

(*Continued*)

Table 2 (Continued).

	Monosensitized		Polysensitized		p value
	N=38	%	N=104	%	
Dog/Cat	4	10.5	66	63.5	<0.01
Aspergillus fumigatus	10	23.7	40	38.5	0.02
Other molds	0	0.0	33	31.7	0.02
Basal tryptase mean ± SD	4.7 ± 2.6		4.6 ± 3.1		0.85

Note: (a) T2 phenotype is defined by blood eosinophils count ≥ 150 cells/µL or FeNO ≥ 20 ppb.
Abbreviations: ACT, Asthma Control Test; BD, bronchodilators; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma.

patients were significantly more sensitized to pollens ($p < 0.01$), dogs or cats ($p < 0.01$) and other molds than *Aspergillus fumigatus* ($p = 0.02$) but less often against house dust mite and cockroach ($p < 0.01$). No significant differences were found regarding anaphylaxis or mean basal tryptase rate (Table 2).

Allergic Comorbidities and Asthma Severity

The most represented allergic comorbidities were rhino conjunctivitis, atopic dermatitis and anaphylaxis with a frequency of 66.6%, 27.4%, and 15.9%, respectively (Table 1). Their number was negatively correlated with age at asthma onset ($r = -0.2119$, $p = 0.0025$) (Figure 2B).

Compared to non-sensitized patients, sensitized ones had significantly more rhino conjunctivitis (73.2% versus 50.8%, $p < 0.01$), atopic dermatitis (31.7% versus 16.9%, $p = 0.03$) and food allergy (16.9% versus 1.7%, $p < 0.01$) (Table 1 and Figure 3). No differences were found regarding urticaria and anaphylaxis.

Among sensitized patients, those who were polysensitized were also more likely to have at least 3 comorbidities (post-hoc analysis: $p < 0.01$). An increased number of allergic comorbidities was not associated with severity according to ASSESS score nor with biomarkers such as basal tryptase level nor with blood eosinophil count (Table 3).

Discussion

This study is the first to provide a full description of both sensitization profile and allergic comorbidities in adults with severe asthma in the era of biologics. We identified the subgroup of monosensitized patients characterized by a late-onset

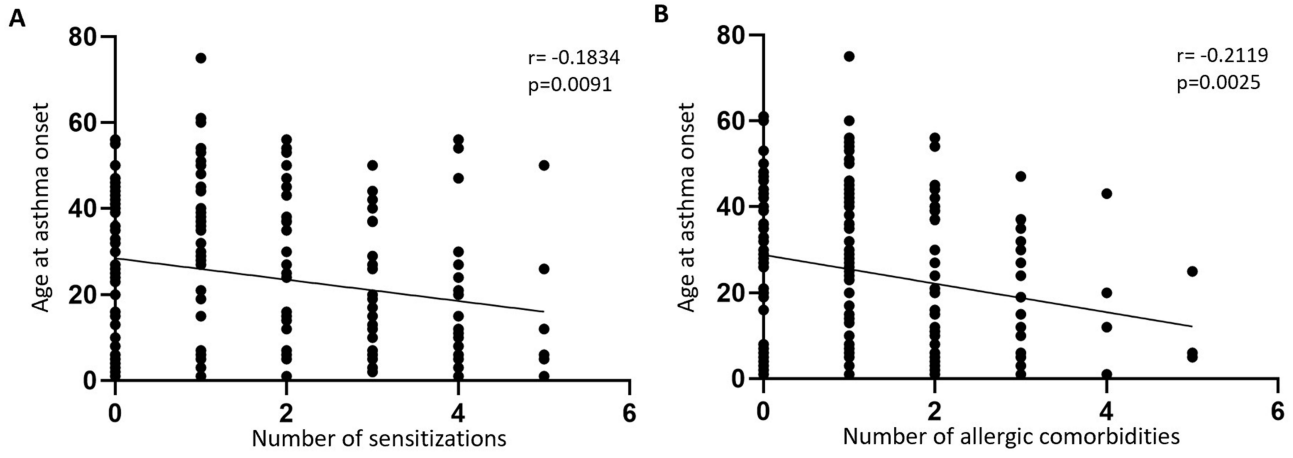

Figure 2 Correlation between age at asthma onset and number of inhalant allergen sensitizations (**A**) and allergic comorbidities (**B**).

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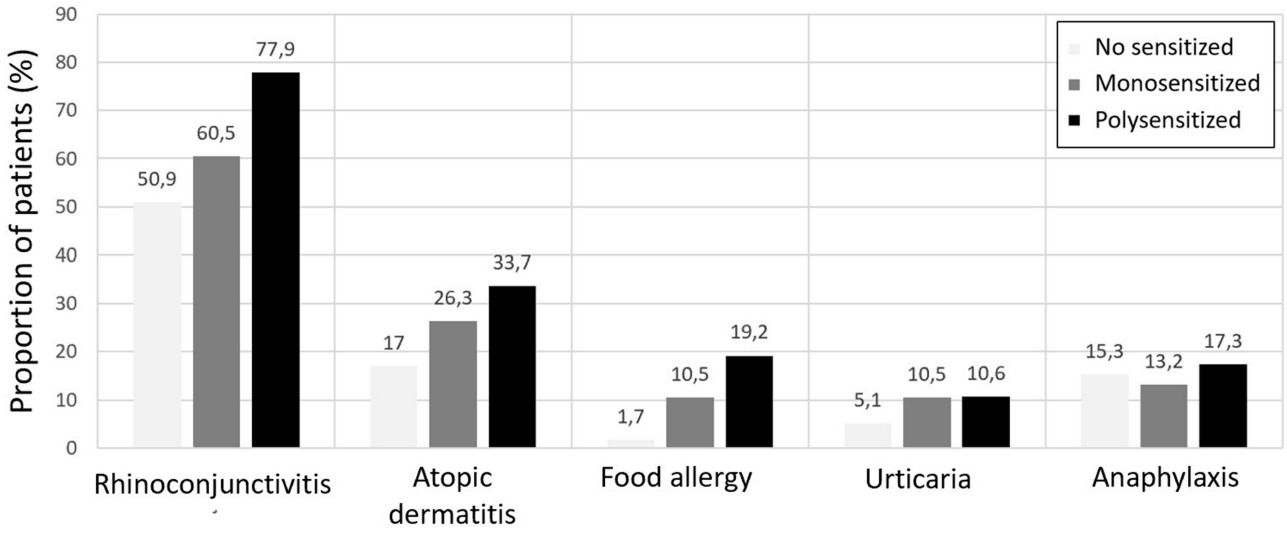

Figure 3 Proportion of allergic comorbidities according to inhalant allergen sensitization.

and more severe disease in addition to a more significant airway obstructive pattern. Contrary to what is described in children, the polyallergic phenotype is relatively underrepresented and is not linked to disease severity.

The characteristics of patients included in our cohort were similar to those of severe asthmatics described in larger cohorts[9]: the majority were female (71.1%), middle-aged, with late-onset asthma (24.5 ± 17.9) and had a T2 phenotype (76.6%). We found a global sensitization prevalence of 70.6%, which was in line with other large cohorts.[9,20] However, in the present study, the rates of allergic rhino conjunctivitis (66.6%), atopic dermatitis (27.4%) and food allergy (12.4%) were higher, compared with recent large severe asthma registries.[7,9] This discrepancy may be due to the systematic

Table 3 Burden of Allergic Comorbidities Including Allergic Rhinoconjunctivitis Atopic Dermatitis, Food Allergy, Urticaria and Anaphylaxis Among Patients with Severe Asthma

Number of allergic comorbidities	0		1		2		≥3		p-value
	N=50	%	N=78	%	N=43	%	N=30	%	
Age mean ± SD	50.2 ± 14.1		50.0 ± 16.2		48.3 ± 15.2		47.6 ± 12.6		0.81
Age at asthma onset mean ± SD	28.9 ± 16.8		26.3 ± 19.2		19.6 ± 17.7		19.4 ± 14.2		0.02
Sensitization									
No sensitized	22	44.0	23	29.5	12	29.7	2	6.7	<0.01
Monosensitized	10	20.0	14	17.9	11	25.6	3	10.0	
Polysensitized	18	36.0	41	52.6	20	46.5	25	83.3	
Allergic comorbidities									
Rhinoconjunctivitis	0	0	64	82.1	41	95.3	29	96.7	
Atopic dermatitis	0	0	2	2.6	28	65.1	25	83.3	
Food allergy	0	0	2	2.6	5	11.6	18	60.0	
Urticaria	0	0	4	5.1	3	7.0	11	36.7	
Anaphylaxis	0	0	6	7.7	9	20.9	17	56.7	

(*Continued*)

Table 3 (Continued).

Number of allergic comorbidities	0		1		2		≥3		p-value
	N=50	%	N=78	%	N=43	%	N=30	%	
ASSESS score, median (Q1;Q3)	11 (10;13.2)		12 (10;14)		11 (10;14)		11.5 (10;13)		0.53
BEC (cells/mm3) mean ± SD	249.6 ± 264.2		338.9 ± 375.8		352.6 ± 365.9		276.3 ± 221.8		0.35
FeNO (ppb)	51.2 ± 54.7		44.7 ± 48.9		42.1 ± 39.5		38.6 ± 43.0		0.77
Tryptase mean ± SD	3.9 ± 2.1		4.5 ± 2.4		4.4 ± 2.1		5.0 ± 4.7		0.55

Abbreviation: BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide.

evaluation by an allergist in our study. Indeed, in France, the proportion of severe asthma patients explored with skin prick tests was notably low, as observed in two large cohorts recently published.[21,22]

Interestingly, among our population of patients with severe asthma, we found no difference in the ASSESS score between nonsensitized and sensitized patients. However, within the sensitized group, monosensitized patients exhibited more severe asthma than polysensitized ones, this increased severity is mainly linked to a greater impairment of respiratory function. These findings are consistent with a previous study indicating that monosensitized patients had poorer asthma symptom control than polysensitized patients, had a lower pre-bronchodilator FEV1 and higher number of exacerbations.[23] The greater impairment in lung function may be surprising, given the later onset of the disease in this group, as airway obstruction is generally correlated with asthma duration.[24] This could be linked to a significantly higher prevalence of sensitization to house dust mites. Indeed, house dust mites were found to be an independent risk factor for asthma-related symptoms (Odds ratio (OR) = 7.9, 95% confidence interval (CI) 1.2–55) and nocturnal breathlessness (OR = 6.2; 95% CI 1.3–30) ($p < 0.05$) in adults after adjustment for age, sex, smoking, indoor temperature and air humidity.[25] Also, the analysis of high-resolution computed tomography scans from 88 patients with severe asthma revealed that those with house dust mite sensitization had a greater airway remodelling with significantly thicker airway walls than those with pollen sensitization ($p < 0.01$).[26] HDM, as other common airborne indoor allergens, contain damaging protease activities involved in epithelial barrier dysfunction, inflammation and remodelling.[27] As an ubiquitous allergen, with a year round presence, its eviction is challenging, therefore providing an explanation for its association with increased asthma severity.

Therefore, the similar rate of sensitization to *Aspergillus fumigatus* between monosensitized and polysensitized patients and the higher rate of sensitization to other molds in poly-sensitized patients were a surprising finding in the present study. Indeed, several fungi, both non-thermotolerant fungi and thermotolerant species, are ubiquitous and contribute to inflammation and remodelling.[27] Moreover, patients sensitized to fungi generally have poorer asthma control compared to those who are not sensitized,[28] defining multiple clinical, biological, and imaging entities.[29] However, in our cohort of patients with severe asthma, fungal sensitization, although similar to rates typically observed in European countries, does not appear to influence a specific phenotype of severe asthma.

As previously described, older age at asthma onset was inversely correlated with the rate of allergic sensitization and allergic comorbidities.[5,30,31] Usually, late-onset asthma is characterized by less frequent atopic sensitization. In these cases, type 2 inflammation is more likely linked to the activation of the innate lymphoid cells type 2 by alarmins, such as IL-25, IL-33, and thymic stromal lymphopoietin, which are released from bronchial epithelial cells in response to allergen-independent stimuli.[5,32] Immunosenescence and the remission of allergic sensitization among elderly people can also explain this observation.[32,33]

Regarding allergic comorbidities, as expected, rhino conjunctivitis, atopic dermatitis and food allergy were significantly more frequent among sensitized patients. Similar to children with severe asthma, allergic comorbidities may coexist within the same individual in adulthood.[31] Indeed, several multimorbid atopic trajectories are now recognized, with or without prior early atopic dermatitis, influenced by genetic, epigenetic and environmental factors.[34]

In our study, the number of allergic comorbidities was not associated with asthma severity according to ASSESS score and was inversely correlated with age at asthma onset. This suggests that while allergy likely contributes to the development and persistence of asthma, it is not a major factor in poor asthma control in adults.[30,35] Of course, this does not exclude the possibility that allergens can trigger exacerbations in patients with severe allergic asthma. In any case, from a clinical perspective, it remains essential to investigate allergic comorbidities, as they are associated with greater healthcare resources utilization, increased costs, and lower productivity compared to non-allergic asthmatic patients.[36] Proper characterization of allergic diseases, including the identification of both respiratory and non-respiratory allergies, though skin prick tests and specific and total IgE measurements, is crucial for distinguishing true allergy from mere sensitization and for implementing effective allergen avoidance measures. Moreover, our study revealed an unexpected proportion of food allergies and anaphylaxis, which may be responsible for severe manifestations and which require specific investigations and management, including education program and the prescription of emergency kits with adrenaline.[5,37] Allergy diagnosis is also important for guiding the choice of appropriate biologic treatment for severe asthma. For example, omalizumab and dupilumab have demonstrated efficacy not only in allergic asthma symptoms but also in food allergies, atopic dermatitis, and urticaria.[38]

One of the strengths of our study is the inclusion of all patients with severe asthma referred to an expert asthma centre for a specific systematic multidisciplinary assessment including allergic evaluation over an 18-months period. Since the population was severely affected, the ASSESS score proved to be a useful tool for grading severity. The ASSESS score has the advantage of incorporating distinct dimensions of asthma such as medication use, lung function, symptoms, and exacerbations. It has been shown to be correlated with patients' quality of life.[39] In our study, we found the same ASSESS score (11.8 ± 2.8) as another French cohort (11.2 ± 3.4) which included patients with severe asthma from secondary care hospitals.[7]

It seems important to acknowledge that variations in the distribution of inhalant allergens and sensitization patterns between countries, or even within the same country, may limit the generalizability of our findings.[40,41] Also, despite its retrospective design, our study offers a unique description of both sensitization profiles and allergic characteristics of patients with severe asthma, both being frequently confounded. Also, we observed a significant proportion of patients with rhino-conjunctivitis in our population of non-sensitized patients, which may be related to local allergic rhinitis.[42] However, nasal allergen tests are not performed routinely as they represent a time-consuming procedure that requires technical resources and qualified operators.

Conclusion

In conclusion, unlike observations in children, polyallergic or polysensitized phenotypes in adults were not associated with increased asthma severity. Moreover, allergy does not seem to be a major determinant of asthma severity in adults, especially for late onset asthma. Our findings underscore the complexity of allergic sensitization in severe asthma and the necessity for a nuanced approach to diagnosis and management.

Abbreviation

ACT, Asthma Control Test; ASSESS, Asthma Severity Scoring System; FeNO, Fractional Exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in 1 second; HDM, House Dust Mite; LAMA, Long Acting Muscarinic Antagonist; OR, Odds ratio; SPT, Skin Prick-Test; T2, Type 2.

Author Contributions

AD supervised the statistical analysis, contributed to interpretation of the results, revised the article and gave final approval. 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.

Disclosure

CTDM has received grants or contracts from LFB Biomedicaments, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from GSK and AstraZeneca, support for attending meetings and/or travel from ALK and AstraZeneca. LB has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, GSK and support for attending meetings and/or travel from Sanofi. FL has received support for attending meetings and/or travel from ALK, Stallergènes, GSK, Sanofi, Novartis. CN has received in past 36 months honoraria for being a speaker or advisory board from AstraZeneca, Sanofi, ALK Abello, Stallergenes Greer, GSK, Viatris. CT has received lecture or advisory board fees and grants from AstraZeneca, Sanofi, GSK, Chiesi, Stallergenes Greer and Novartis. CD reports personal fees, non-financial support from Astra Zeneca, personal fees, non-financial support from Chiesi, personal fees, non-financial support from GSK, personal fees, non-financial support from Novartis, personal fees, non-financial support from Sanofi, outside the submitted work. Dr Catherine Neukirch reports personal fees from Viatris, personal fees from Stallergenes Greer, personal fees from ALK Abello, personal fees from AstraZeneca, personal fees from Sanofi, personal fees from GSK, personal fees from Zambon, outside the submitted work. The authors declare that they have no other conflicts of interest.

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