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Four subtypes of childhood allergic rhinitis identified by latent class analysis

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Abstract

Background: Childhood allergic rhinitis (AR) is clinically heterogenous. We aimed to identify distinct phenotypes among children with AR using data-driven techniques and to ascertain their association with patterns of symptoms, allergic sensitization, and comorbidities.

Methods: We recruited 510 children with physician-diagnosed AR, of whom 205 (40%) had asthma. Latent class analysis (LCA) was performed to identify latent structure within the data set using 17 variables (allergic conjunctivitis, eczema, asthma, family history of asthma, family history of allergic rhinitis, skin sensitization to 8 common allergens, tonsillectomy, adenoidectomy).

Results: A four-class solution was selected as the optimal model based on statistical fit. We labeled latent classes as: (1) AR with grass mono-sensitization and conjunctivitis ($n = 361$, 70.8%); (2) AR with house dust mite sensitization and asthma ($n = 75$, 14.7%); (3) AR with pet and grass polysensitization and conjunctivitis ($n = 35$, 6.9%); and (4) AR among children with tonsils and adenoids removed ($n = 39$, 7.6%). Perennial AR was significantly more common among children in Class 2 (OR 5.83, 95% CI 3.42–9.94, $p < .001$) and Class 3 (OR 2.88, 95% CI 1.36–6.13, $p = .006$). Mild and intermittent AR symptoms were significantly more common in children in Class 2 compared to those in Class 1. AR was more severe in Class 1 compared to other 3 classes, indicating that upper respiratory symptoms are more severe among children with isolated seasonal rhinitis, than in those with rhinitis and coexisting asthma.

Conclusion: We have identified 4 phenotypes in school-age children with AR, which were associated with different patterns of clinical symptoms and comorbidities.

KEYWORDS
allergic rhinitis, allergy, asthma, children, phenotype

1 | INTRODUCTION

Allergic rhinitis (AR) is common in childhood,[1] and its symptoms can have a major adverse impact on quality of life, emotional well-being, sleep, daily activities, and productivity of children and adolescents, especially when they are poorly controlled.[2] Traditionally, classification of AR is based on the temporal pattern of symptoms (as seasonal and perennial). Several other approaches to classify patients

according to sensitization patterns and comorbidities have also been proposed.[3–5] Since the introduction of ARIA guidelines, the classification has mainly been based on symptom severity and persistence.[6] ARIA guidelines have additionally emphasized the link between AR and asthma, and introduced the concept of "one airway, one disease".[6]

In addition to these mainly consensus-driven classifications, novel approaches utilizing data-driven approaches have recently emerged to identify "phenotypes" of allergic diseases.[7] These methods allow analyses of large datasets without prior hypotheses and identify latent (i.e., hidden) structures within such datasets. This approach has been successfully used to identify subtypes of childhood wheezing,[8] asthma,[9] allergic sensitization,[10,11] atopic dermatitis,[12] and AR in adults.[13,14] We hypothesized that there are different patterns of AR during childhood and that uncovering such patterns ("phenotypes") may help determine whether they are underpinned by distinct mechanisms. To address our hypothesis, we applied data-driven methodology to phenotypically well-defined group of children with AR to identify distinct subgroups and ascertain their association with clinical patterns of symptoms, allergic sensitization, and concomitant physician-diagnosed asthma.

Key Message

We have identified four different subgroups of children with allergic rhinitis using latent class analysis, which were associated with different patterns of clinical symptoms and comorbidities.

2 | METHODS

2.1 | Study design, setting, and participants

The Gulhane Asthma and Allergic Rhinitis Study (GAARS) is a cross-sectional study established in 2011 in Ankara, Turkey. We recruited 510 consecutive children aged 5–17 years who presented to the Pediatric Allergy and Asthma Unit of Gulhane Military School of Medicine (GMCM) between 2011 and 2017 and were diagnosed with AR by pediatric allergist. The study was approved by the institutional review board of GMCM, and written informed consent was obtained from parents. Details of the study protocol can be found elsewhere.[15]

2.2 | Data sources

Symptoms, medication use, doctor's diagnoses of allergic diseases, and environmental exposures were assessed using interviewer-administered questionnaires. Information on sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, and presence of troublesome symptoms was collected to define the severity of AR. Data regarding tonsillectomy and adenoidectomy were confirmed from the medical records.

All children underwent skin prick testing (SPT) to common aeroallergens for our region,[16] including house dust mites (HDM, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (Phleum pratense, Poa pratensis, Dactylis glomerata, Lolium perenne, Festuca pratensis, and Avena eliator), weed pollen mix (Artemisia, Urtica, Taraxacum, Plantago), tree pollen mix (Alnus glutinosa, Corylus avellane, Populus alba, Ulmus minor, Betula alba), molds (Alternaria, Cladosporium, Penicillium, and Aspergillus), and animal dander (cat and dog). Histamine (10 mg/ml of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Total serum IgE level was measured using ImmunoCAP (Phadia AB).

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter) leucocyte measurements.

Pulmonary function tests were performed using Zan 100 spirometer (Nspire Health) according to recommendations by the European Respiratory Society.[17] Three best efforts were recorded, and the highest value (presented as percent predicted according to age, gender, weight, and height[18]) was used in the analysis.

2.3 | Definitions of outcomes

Allergic rhinitis was diagnosed by a pediatric allergy specialist using the following criteria: (1) Current upper respiratory symptoms (nasal blockage, rhinorrhea, nasal itching, and sneezing after allergen exposure); and (2) at least one positive SPT to common inhalant allergens.

The symptoms were classified as *"seasonal"* when they were limited to a certain period or a season, and as *"perennial"* when they occurred throughout the year. The duration of the symptoms was classified according to ARIA guidelines[6] as "*Intermittent*" (the symptoms present less than 4 days a week or for less than 4 consecutive weeks) or "*Persistent*" (present more than 4 days a week and for more than 4 consecutive weeks).

Allergic rhinitis was classified as "*mild*" when none of the severity items (sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, and presence of troublesome symptoms) was present, and as "*moderate/severe*" in patients with one or more of the aforementioned severity indicators.

2.3.1 | Allergic conjunctivitis

It is defined as the presence of current ocular symptoms (tearing, burning, itching, and redness in the eyes) and positive SPT.

2.3.2 | Physician-diagnosed asthma

It is defined as current symptoms (wheeze and cough) and positive bronchodilator responsiveness (improvement of FEV_1 by 12%

or more following administration of 200 mcg salbutamol), and/or a positive response to a trial of therapy with inhaled or oral corticosteroids.[19]

2.3.3 | Atopic dermatitis

Current pruritus and a relapsing eczematous rash typically found over flexor surfaces.

2.3.4 | Allergic sensitization

Skin prick testing means wheal diameter at least 3 mm greater compared to the negative control.

Parental asthma and *parental allergic rhinitis* were determined by questionnaire at enrollment.

2.4 | Statistical analysis

Normally distributed continuous data (age, age at diagnosis, lung function measures) were expressed as mean and standard deviation, and non-normally distributed continuous data (eosinophil counts and total IgE titers) as median and interquartile ranges (IQR). Group comparisons carried out using Student's *t*-test, Mann–Whitney *U* test, ANOVA, or Kruskal–Wallis test as appropriate for the continuous, and the chi-square test or Fisher test for categorical variables.

Latent class analysis (LCA) was performed to identify latent classes of AR using 17 variables (allergic conjunctivitis, eczema, asthma, family history of asthma, family history of allergic rhinitis, skin sensitization to 8 common allergens, tonsillectomy, adenoidectomy). Starting with a latent model including 2 classes, we compared models with increasing numbers of classes using the Bayesian information criterion (BIC). The expectation maximization algorithm was used to estimate relevant parameters, with 100,000 iterations and 500 replications. The optimal number of classes was selected based on the lowest BIC and interpretability.

Association of LCA-derived classes with clinical outcomes was examined using regression models adjusted for potential confounders, including gender and maternal history of AR. The odds ratio (OR) and 95% confidence interval (CI) were reported. Data-driven analyses were performed using MPlus 8 and R (http://www.r-project.org/), and association analyses using Stata 16 (StataCorp) and SPSS v21.0 (IBM).

3 | RESULTS

3.1 | Descriptive statistics

We recruited a total of 510 children with AR (352 male [69%]; mean age [±SD] 10.5 [±3.1] years). Of these, 117 (22.9%) had mild intermittent, 92 (18.0%) mild persistent, 63 (12.4%) moderate-severe intermittent, and 238 (46.7%) moderate-severe persistent AR. A total of 205 children (40% of study population; 35 female and 180 male patients; 9.8 ± 2.9 years) had asthma. Table 1 summarizes the demographic and clinical characteristics of all participants, and among those with and without coexisting asthma. Persistent (52% vs. 73%, $p < .001$) and moderate-severe AR (48% vs. 67%, $p < .001$), coexisting conjunctivitis (71% vs. 80%, $p = .012$), and grass pollen sensitization (81% vs. 90%, $p = .005$) were more frequent in children without asthma, whereas HDM (26.8% vs. 17.4%, $p = .01$) and mold sensitization (13% vs. 5%, $p = .001$) were more common (13.2% vs. 4.9%, $p = .001$) in those with asthma.

All measures of lung function were significantly lower among children with asthma (Table 1).

3.2 | Latent classes of children with AR

Figure 1 shows assignment of children and changes in their allocation into AR latent classes (phenotypes) over a sequence of LCA models with two to five classes (based on most likely membership class). A four-class solution was selected as the optimal model based on statistical fit (Table 2). Figure 2 shows the distribution of variables across classes. Based on this and clinical interpretation, the latent classes were labeled as: (1) AR with grass mono-sensitization and conjunctivitis ($n = 361$, 70.8%); (2) AR with HDM sensitization and asthma ($n = 75$, 14.7%); (3) AR with pet and grass polysensitization and conjunctivitis ($n = 35$, 6.9%); and (4) AR among children with tonsils and adenoids removed ($n = 39$, 7.6%).

3.3 | Clinical characteristics of latent classes

Table 3 shows the clinical features of patients in each latent class. The results of the multinomial logistic regression analysis comparing the temporal pattern of AR, its duration, and severity, as well as the family history of allergic diseases between different classes, are shown in Table 4. We found significant differences in the duration, severity and temporal patterns of AR, and allergic conjunctivitis between the four latent classes. Boys were more likely to be in Class 3 (AR with pet and grass polysensitization and conjunctivitis; OR 2.51, 95% CI 1.08–5.80, $p = .03$). Perennial AR was markedly and significantly more common among children in Class 2 (AR with HDM sensitization and asthma; OR 5.83, 95% CI 3.42–9.94, $p < .001$) and Class 3 (AR with pet and grass polysensitization and conjunctivitis; OR 2.88, 95% CI 1.36–6.13, $p = .006$). Mild and intermittent AR symptoms were significantly more common in children in Class 3 compared to those in Class 1. Maternal history of AR was significantly more common among children in Class 1, compared to children assigned to other clusters. AR was more severe in Class 1, compared to other 3 classes, indicating that upper respiratory symptoms are more severe among children with isolated seasonal rhinitis than in those with rhinitis and coexisting asthma.

TABLE 1 Demographic data of the study population and comparison according to asthma

	Study population ($n = 510$)	Children with asthma ($n = 205$)	Children without asthma ($n = 305$)	p*
Age (y)	10.5 ± 3.1	9.8 ± 2.9	11.0 ± 3.1	<.001
Sex (male)	69.0	72.2	66.9	.20
Age at AR symptoms start (y)	7.0 ± 3.1	6.2 ± 2.9	7.4 ± 3.2	<.001
Temporal pattern				.25
Seasonal	77.2	74.6	79.0	
Perennial	22.8	25.4	21.0	
Duration				<.001
Intermittent	35.3	47.5	27.1	
Persistent	64.7	52.5	72.9	
Severity				<.001
Mild	40.9	52.0	33.1	
Moderate/severe	59.1	48.0	66.9	
Environmental characteristics				
Pet exposure	11.7	10.3	12.7	.41
ETS exposure	39.9	42.9	37.9	.27
Family history of allergic disease				
Maternal asthma	9.8	12.3	8.2	.13
Paternal asthma	5.1	6.4	4.3	.29
Maternal allergic rhinitis	25.1	23.5	26.2	.49
Paternal allergic rhinitis	17.7	16.7	18.4	.62
Comorbid conditions				
Allergic conjunctivitis	76.5	70.7	80.3	.012
Atopic dermatitis	11.8	14.1	10.2	.17
Tonsillectomy	8.6	8.8	8.5	.92
Adenoidectomy	14.1	14.1	14.1	.98
Tonsillectomy and Adenoidectomy	7.8	7.8	7.9	.98
Sensitization				
Grass pollens	86.7	81.5	90.2	.005
Tree pollens	8.4	8.3	8.5	.93
Weed pollens	6.1	3.9	7.5	.09
House dust mites	21.1	26.8	17.4	.01
Cat	15.3	16.1	14.8	.68
Dog	8.4	8.8	8.2	.82
Molds	2.9	13.2	4.9	.001
Mono-sensitization	62.4	58.5	64.9	.15
Total IgE (kU/L)	92 (34–183)	88 (37–202)	96 (34–170)	.70
Blood eosinophils (%)	4.3 (2.7–7–0)	4.0 (2.3–7.4)	4.5 (2.8–6.9)	.12
Blood eosinophils (/mm^3)	290 (180–497)	295 (173–518)	290 (190–485)	.86
FEV_1% predicted	97 ± 15	87 ± 13	104 ± 11	<.001
FVC % predicted	94 ± 13	89 ± 14	98 ± 11	<.001
FEV_1/FVC %	90 ± 7	87 ± 8	91 ± 6	<.001
PEF % predicted	90 ± 17	82 ± 16	95 ± 16	<.001
FEF_{25-75}% predicted	94 ± 21	77 ± 19	108 ± 20	<.001

Note: Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%).
Abbreviation: ETS, Environmental tobacco smoke.

*The p value denoted the difference between children with and without asthma.

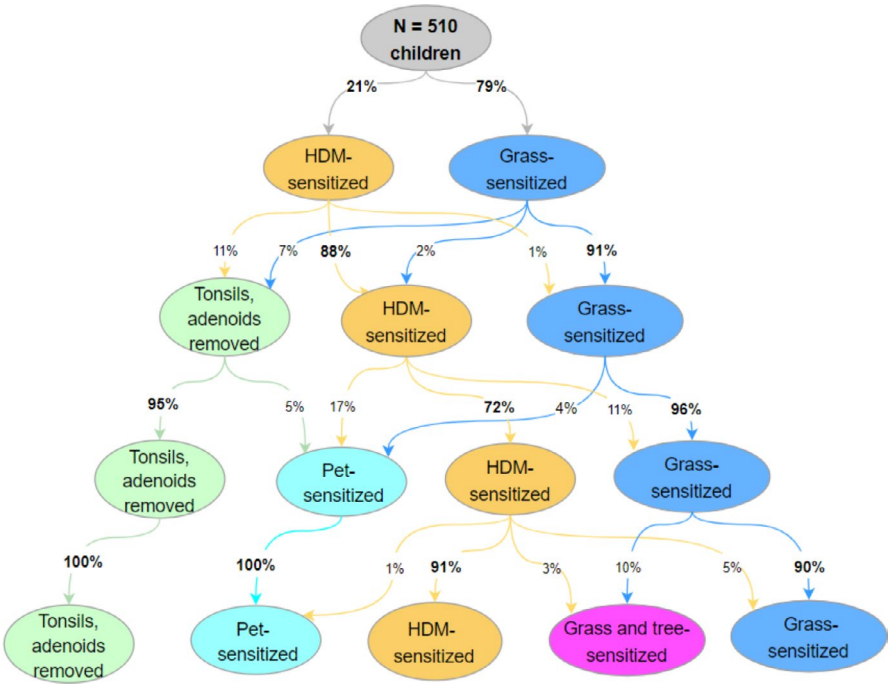

FIGURE 1 Assignment of 510 children into distinct classes over a sequence of latent class model with two, three, four, and five classes based on most likely class membership. Ellipse nodes show class membership whilst the values along the arrow represent the % of children moving from one class to another in models with an increasing number of classes

TABLE 2 Model fit statistics

K-Class	AIC	BIC	Entropy	Lo-Mendell-Rubin *p* Value (k−1 vs. k classes)	Parametric Bootstrapped LRT *p* Value (k−1 vs. k classes)
2	6404	6552	0.729	.0004	<.0001
3	6288	6512	0.832	.0814	<.0001
4	6195	**6496**	0.912	<.0001	<.0001
5	6191	6568	0.913	.7813	<.0001

Note: LCA models with 2 to 5 classes were developed using 17 categorical variables and the BIC selected a 4-class model as the optimal option which is indicated in bold.

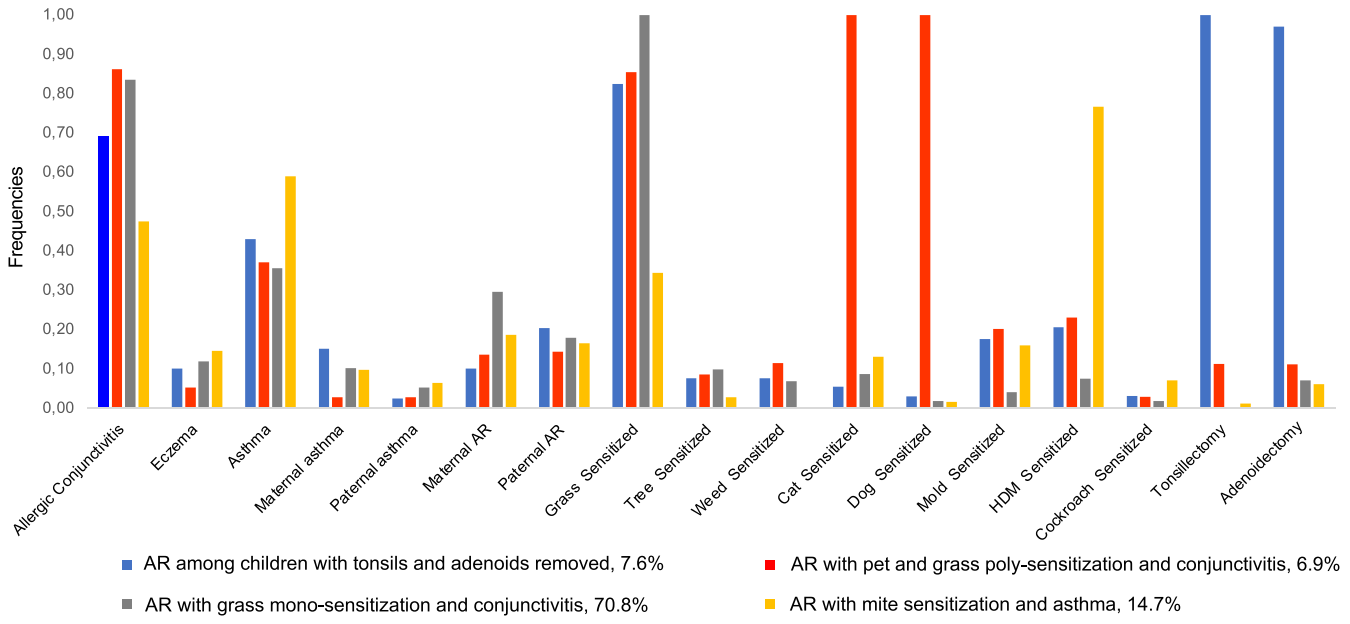

FIGURE 2 AR subtypes identified by latent class analysis in 510 children. Class proportions shown in the figure are computed based on most likely class membership

TABLE 3 Clinical features of patients according to classes

	C1: AR with grass mono-sensitization and conjunctivitis (70.8%)	C2: AR with house dust mite sensitization and asthma (14.7%)	C3: AR with pet and grass polysensitization and conjunctivitis (6.9%)	C4: AR among children with tonsils and adenoids removed (7.6%)	*p**
N	361	75	35	39	
Age (y)	10.5 ± 3.1	10.2 ± 2.9	11.2 ± 2.9	11.1 ± 3.2	.31
Sex (male)	66.8	72.0	82.9	71.8	.22
Age at AR symptoms start (y)	7.0 ± 3.1	6.8 ± 3.2	6.8 ± 2.7	7.2 ± 3.4	.89
Temporal pattern					<.001
Seasonal	85.0	48.0	65.7	71.8	
Perennial	15.0	52.0	34.3	28.2	
Duration					<.001
Intermittent	30.8	60.0	40.0	25.6	
Persistent	69.2	40.0	60.0	74.4	
Severity					.04
Mild	37.6	53.3	42.9	43.6	
Moderate/severe	62.4	46.7	57.1	56.4	
Environmental characteristics					
Pet exposure	10.4	18.9	14.3	8.1	.21
ETS exposure	38.5	35.1	55.9	48.6	.12
Family history of allergic disease					
Maternal asthma	10.3	8.0	2.9	15.4	.23
Paternal asthma	5.3	6.7	2.9	2.6	.83
Maternal allergic rhinitis	29.4	17.3	14.3	10.3	.005
Paternal allergic rhinitis	18.1	16.0	14.3	20.5	.88
Comorbid conditions					
Asthma	36.0	60.0	37.1	43.6	.002
Allergic conjunctivitis	83.7	41.3	85.7	69.2	<.001
Atopic dermatitis	11.9	14.7	5.7	10.3	.59
Tonsillectomy	0	1.3	11.4	100	<.001
Adenoidectomy	7.2	5.3	11.4	100	<.001
Tonsillectomy and Adenoidectomy	0	0	5.2	100	<.001
Sensitization					
Grass pollens	100.0	25.3	85.7	82.1	<.001
Tree pollens	9.7	2.7	8.6	7.7	.26
Weed pollens	6.6	0.0	11.4	7.7	.07
House dust mites	8.3	82.7	22.9	20.5	<.001
Cat	8.0	16.0	100.0	5.1	<.001
Dog	1.7	1.3	100.0	2.6	<.001
Molds	4.2	17.3	20.0	17.9	<.001
Mono-sensitization	67.3	65.3	0.0	66.7	<.001
Total IgE (kU/L)	91 (35–196)	85 (31–184)	118 (59–203)	58 (27–160)	.39
Blood eosinophils (%)	4.3 (2.7–7.6)	4.1 (2.7–6.2)	4.2 (2.5–6.2)	4.3 (2.3–5.7)	.77
Blood eosinophils (/mm^3)	290 (180–540)	300 (185–465)	300 (190–380)	255 (163–390)	.71
FEV_1% predicted	97 ± 15	93 ± 14	99 ± 14	100 ± 15	.08
FVC % predicted	94 ± 13	93 ± 12	95 ± 11	98 ± 13	.24
FEV_1/FVC %	90 ± 7	89 ± 7	89 ± 6	89 ± 8	.48
PEF % predicted	90 ± 17	88 ± 17	90 ± 15	91 ± 23	.72
FEF_{25-75}% predicted	95 ± 25	89 ± 23	95 ± 24	96 ± 27	.38

Note: Continuous variables are given as mean and standard deviation, and binary variables are given as frequency (%).

**p*-Values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal–Wallis for continuous variables.

TABLE 4 Univariate multinomial logistic regression results (reference category: AR with grass mono-sensitization and conjunctivitis)

	Latent classes (phenotypes)					
	AR with house dust mite sensitization and asthma		AR with pet and grass polysensitization and conjunctivitis		AR among children with tonsils and adenoids removed	
	Relative Risk Ratio (95% CI)	*p*	Relative Risk Ratio (95% CI)	*p*	Relative Risk Ratio (95% CI)	*p*
Sex						
Male gender	1.30 (0.75–2.25)	.35	2.51 (1.08–5.80)	.03	1.26 (0.61–2.62)	.53
AR Temporal pattern (reference: Seasonal)						
Perennial	5.83 (3.42–9.94)	<.001	2.88 (1.36–6.13)	.006	1.91 (0.88–4.13)	.10
AR Duration (reference: Intermittent)						
Persistent	0.29 (0.17–0.48)	<.001	0.66 (0.32–1.35)	.26	1.28 (0.60–2.72)	.52
AR Severity (reference: Mild)						
Moderate/severe	0.55 (0.33–0.90)	.02	0.81 (0.40–1–64)	.56	0.79 (0.40–1.54)	.49
Family history of allergic disease						
Maternal allergic rhinitis	0.71 (0.52–0.98)	.04	0.51 (0.33–0.85)	.03	0.28 (0.09–0.79)	.02

4 | DISCUSSION

4.1 | Key findings

In this cross-sectional study, we performed latent class analysis to identify distinct subgroups of children with physician-diagnosed AR in a large number of clinically well-defined patients. The optimal solution identified four latent classes characterized by different patterns of allergic sensitization, clinical presentation, and comorbidities. The largest class consisted of 361 children (70.8% of the study population) who were predominantly mono-sensitized to grass pollens and had concomitant ocular symptoms. Although upper airway symptoms were the most severe in this latent class (albeit seasonal), the prevalence of coexisting asthma was significantly lower compared to all other classes. 75 children (14.7%) were allocated to the AR class characterized by predominantly HDM sensitization and coexisting asthma. In this group, AR symptoms were significantly milder, intermittent, and perennial. In the third cluster, there were 39 children (7.6%) who underwent tonsillectomy and adenoidectomy. The fourth cluster included 35 children (6.9%) sensitized to cats and/or dogs along with grass pollens. This pattern was associated with male gender and seasonal symptoms.

4.2 | Limitations and strengths

We acknowledge that our definitions of symptoms, medication use, and environmental exposures are based on parental reporting using interviewer-administered questionnaires, and that this may introduce bias (e.g., through inaccurate recall, misreported information, and/or interaction between respondent and interviewer). A further limitation is the absence of longitudinal evaluation that would allow investigation of the phenotype-specific trends in disease progression over time. We analyzed the data among children recruited from the specialist referral center, and our results are likely not generalizable to other contexts. One important strength of our study is the availability of data from a large number of children with accurate clinical diagnosis and objective measures of allergic sensitization and lung function.

4.3 | Interpretation

It is well established that allergic diseases are more frequent in prepubertal boys. In contrast to asthma and eczema in which higher prevalence tend to shift toward females in adolescence, AR continues to affect more males up to the age of 20 years.[20] In our study, boys outnumbered the girls (69% vs. 31%). However, male gender was not associated with AR severity or concomitant asthma. In agreement with previous childhood studies, allergic conjunctivitis was the most frequent comorbidity among our patients with AR (76.5%). Zicari et al.[3] have studied 1200 Italian children with AR, and conjunctivitis was present in 51.7%, whereas Ibanez et al.[21] have reported a prevalence of 53.6% in 1275 Spanish children. The prevalence of conjunctivitis in our cohort was considerably higher. We note that the proportion of patients with moderate-severe persistent AR was also substantially higher in our cohort compared to previous childhood studies,[3,21] and this may account for a higher proportion of those with ocular symptoms.

According to the united airway disease concept, AR and asthma frequently occur together and share common pathophysiological mechanisms.[6] Consistent with previous data, asthma was present in 40% of our patients.[3,19,21] Previous epidemiological studies have predominantly emphasized the adverse impact of AR on asthma severity, and it has been shown that co-occurrence of rhinitis is associated with more severe and uncontrolled asthma in children and adolescents.[22,23] However, the impact of contemporaneous asthma

on the severity and persistence of AR symptoms in children and adolescents has rarely been investigated. In our study, in contrast with the asthma-oriented studies,[24] among children with AR, the upper airway symptoms were more severe and persistent in children without asthma diagnosis.

Results of several studies indicated aeroallergen sensitization, particularly to HDM and Aspergillus, as one of the independent risk factors for asthma in children.[25,26] In a recent study, Chiu et al. have reported a significant association between HDM sensitization and various urinary metabolites which were associated with childhood asthma development.[27] In our study, the prevalence of HDM and mold sensitizations was significantly higher in children with asthma, whereas grass pollen sensitization was lower in this group. In the cross-sectional study by Bousquet et al.,[24] which included 591 adults with AR, HDM sensitization was associated with perennial and milder symptoms (consistent with our results), and, in contrast to our data, persistent rhinitis. In the study by Zicari et al. which included 2319 Spanish children with AR, no difference was found in terms of temporal pattern and severity between HDM and grass pollen-sensitized children.[3] The results of these studies are based on investigator-led assignments, whilst our sensitization patterns are data-driven. Boulet et al.[28] have reported that patients with HDM sensitizations are more prone to have asthma as a comorbidity than those sensitized to outdoor allergens. Bertelsen et al.[4] have speculated that perennial exposure to allergens can be more related to asthma, when compared to pollen exposure which occurs only during a limited time period. These data are consistent with our data-driven analysis, which identified a class of children with AR with HDM sensitization and asthma, among whom lung function parameters were significantly diminished.

Sensitization to domestic pets is associated with asthma severity,[29] and sensitization to major cat allergen Fel d 1 in preschool age predicts subsequent asthma development.[30] However, the number of the studies that investigated the features of pet allergy in children with AR is limited. Zicari et al.[3] reported pet sensitization only in 2.5% of AR patients, with little impact on symptom severity. However, in the Environment and Childhood Asthma birth cohort study, pet allergens (dog and cat) were the second most prevalent sensitizing agents in children with AR, and the investigators documented two major sensitization groups (grass pollen mono-sensitization vs. grass pollen/furry pets polysensitization).[4] Similar to our findings, pet sensitization was associated with milder and perennial AR symptoms, whilst asthma prevalence and severity were greater in children with pet sensitization.[4]

Adenoid hypertrophy (AH) is one of the most frequent comorbidities in children with AR.[21,31] Previous studies have reported mold sensitization as a risk factor for AH in children with AR.[32,33] In agreement with this finding, sensitization to molds was significantly higher in our cluster, which included children who underwent tonsillectomy and adenoidectomy when compared with patients in Cluster 1 (AR with grass mono-sensitization and conjunctivitis). Dogru et al.[33] have reported an association between AH and the severity of AR in children. However, this relationship was not demonstrated in our study. The plausible explanation for the lack of this association may be that the children in this cluster already has surgery, which might have contributed to the improvement in symptoms.

Our findings may have potentially important clinical implications. Given that asthma is more strongly associated with specific phenotypes of rhinitis, our results emphasize the importance of careful assessment of asthma symptoms and lung function among children with rhinitis who are sensitized to HDM and molds. Furthermore, as severe and persistent symptoms should be expected in children with grass pollen mono-sensitization, physicians may consider early initiation of allergen immunotherapy in such children.

In conclusion, we have identified four different phenotypes of children with AR using data-driven techniques in a cross-sectional study, which were associated with different patterns of clinical symptoms and comorbidities.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Suleyman Tolga Yavuz: Conceptualization (lead); Data curation (lead); Investigation (lead); Methodology (equal); Project administration (equal); Writing-original draft (lead). **Ceyda Oksel Karakus:** Formal analysis (lead); Methodology (supporting); Software (lead); Validation (lead); Writing-review & editing (supporting). **Adnan Custovic:** Conceptualization (supporting); Investigation (equal); Methodology (supporting); Project administration (supporting); Resources (lead); Supervision (equal); Writing-review & editing (equal). **Ömer Kalayci:** Conceptualization (supporting); Formal analysis (equal); Investigation (equal); Methodology (supporting); Project administration (lead); Supervision (lead); Writing-review & editing (equal).

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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

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