Dilek Karadoğan[1, 2], Vehbi Ayhan[2, 3], Adile Berna Dursun[2, 3]

[1]Department od Chest Diseases, Recep Tayyip Erdoğan University, School of Medicine, Rize, Turkey
[2]Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey
[3]Department of Immunology and Allergic Diseases, Recep Tayyip Erdoğan University, Rize, Turkey

The effects of mold sensitivity on the clinical characteristics of adult asthmatic patients

Abstract

Introduction: The effects of mold sensitivity on the development and course of asthma have been researched previously, although study results vary. We sought to evaluate the characteristics of our mold-sensitive patients in comparison with those of other adult asthmatic patients.

Materials and methods: Data were collected retrospectively from adult asthmatic patients who underwent regular follow-ups at our tertiary care outpatient clinic for immunology and allergic diseases. Patients were grouped and compared according to three categories of aeroallergen sensitivity status determined via a skin prick test. The study variables were demographic data, asthma-onset age, comorbid conditions, asthma-related emergency department visits and hospitalizations, systemic corticosteroid burst, asthma control assessment tests, and pulmonary function tests.

Results: In total, 242 patients' data were evaluated. Their mean age was 48.6 ± 15.4 years, with female predominance (81.4%). Mold-sensitive asthmatics composed 34.7%, while the aeroallergen-sensitive group without molds (33.1%) and the non-sensitized group (32.2%) composed the rest. The mold-sensitive group had a higher rate of polysensitization (92.8%) than the sensitized group without molds. In multinomial logistic regression analysis, mold sensitivity was positively associated with shorter asthma duration, absence of sinonasal polyposis, presence of allergic rhinitis, and generally well-controlled asthma compared to the non-sensitized group. Also, mold sensitivity was positively associated with shorter asthma duration, drug allergy, and absence of systemic corticosteroid bursts compared to the sensitized group without molds in logistic regression analysis.

Conclusion: Our mold-sensitive asthmatic patients demonstrated better asthma symptom control. It should be considered that mold sensitization in adult asthmatics is not always a poor prognostic factor.

Key words: adult asthma, mold sensitivity, asthma control

Adv Respir Med. 2020; 88: 99–107

Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation [1]. There are many factors that have a role in the development and control of asthma [1]. Mold exposure and sensitization to molds constitute a significant trigger factor. Mold sensitizations and their role in asthma have been previously evaluated in many studies [2]. Most of these investigations have found that mold sensitivity has an effect not only on the development of asthma, but also in the success of asthma control efforts and the severity of asthma [2] by way of inducing type I allergic reactions in susceptible individuals [3].

Direct associations between increased fungal exposure and a loss of asthma control are numerous [4]. Previous studies have suggested an increased risk of asthma development after mold exposure at an early age [2, 5]. McSharry *et al.* found that high environmental mold exposure was associated with poor lung function [6]. Besides the impact on asthma development, fungal sensitization was also found to have an effect on the persistence and activation of asthma symptoms, and on the severity of asthma [2, 7].

Mold species including *Penicillium*, *Aspergillus* and *Cladosporium* have been studied in conjunction with asthma. *Alternaria* species have been found to increase the risk of asthma symp-

Address for correspondence: Dilek Karadoğan, Department od Chest Diseases, Recep Tayyip Erdoğan University, School of Medicine, Rize, Turkey; e-mail: cakmakcidilek@yahoo.com
DOI: 10.5603/ARM.2020.0083
Received: 07.10.2019
Copyright © 2020 PTChP
ISSN 2451–4934

tom exacerbation [8]. In previous research, sensitization to *Alternaria* and *Cladosporium* had been associated with severe asthma [4]. The European Community Respiratory Health Survey also showed that *Alternaria* and *Cladosporium* were significantly associated with asthma severity [9]. In one study, patients admitted to the intensive care unit for a severe asthma attack were found to have a positive skin prick test for *A. alternata* and *C. herbarum* [10].

Notably, climate change has been labelled as a potential contributing factor in aeroallergens due to the risk of accelerated mold sporulation in environments with increased CO_2 [11, 12]. The effects of the existing climate on fungal sensitization also impact characteristics of various aeroallergens, including mold sporulation patterns [11, 12]. Turkey's diverse regions have significantly different climates because of the country's irregular topography. For example, the coastal areas of Turkey bordering the Black Sea have a temperate oceanic climate with warm, wet summers and cool-to-cold, wet winters. The Turkish Black Sea coast is the only region of Turkey that receives such high precipitation throughout the year. Thus, inhabitants in this region face the possibility of indoor and outdoor mold exposure throughout the year more so than their neighbors.

The effects of mold sensitization have been thoroughly reported in severe asthmatics [2]; however, in general asthmatic patients, the link is not as definite. Although mold sensitization and asthma outcomes are generally associated with poor prognoses [2], research from various geographical areas has indicated the opposite [13]. Therefore, in this study, we sought to explore the percentage and pattern of mold sensitization among adult asthmatics and to reveal the similarities and/or differences between mold-sensitized asthmatics and non-sensitized patients. To our knowledge, this study is the first to evaluate the clinical characteristics of adult asthmatics according to their mold sensitivity status in Turkey.

Materials and methods

Study design

A retrospective case–control study was conducted after obtaining local ethics committee approval on June 20, 2018 (approval no. 40465587-120).

Setting and participants

Patients meeting relevant criteria who were admitted to the department of immunology and allergic diseases in the outpatient clinic between June 2013 and June 2018, and having an asthma diagnosis according to Global Initiative for Asthma (GINA) guidelines [1] were retrospectively evaluated from their paper files. The hospital has electronic records for all patients. In this department, doctors also collected and filed separate paper files for each patient. These files contained demographic characteristics, past medical history, comorbid conditions, anamnesis regarding asthma-related admissions, and patient symptoms. Laboratory data, skin prick test (SPT) and acceptable pulmonary function test (PFT) results of the patients were also recorded to that file by the doctors, along with records of follow-up evaluations. In the follow-ups, which were made at 3 or 6 month intervals, patients were questioned about symptoms, exacerbations, and all prescribed medications. Physical examinations and required test results, such as PFT, were also recorded at that time.

All data regarding the allergic status of patients was pulled from tests administered in our hospital. Previous records or patients' anamnesis regarding allergic diseases were confirmed by test results. In patients with symptoms of allergic rhinitis (AR), the diagnosis was confirmed by nasal endoscopic examination by ear-nose-throat experts, regardless of patient SPT results. Sinonasal polyposis (SNP) diagnoses were also confirmed by nasal endoscopic examination.

Among all relevant patients, 242 adult asthmatics met the inclusion criteria and were therefore included in this study. Inclusion criteria were as follows: asthmatics older than 18 years of age who participated in regular follow-up visits at least once a year who had SPT results and acceptable PFT results (14). Exclusion criteria were being younger than 18 years of age, having irregular follow-ups or follow-up periods being under a year, missing patient file information, and patients who had respiratory comorbidities such as bronchiectasis and/or allergic bronchopulmonary aspergillosis, among others.

Data collection

Patients' demographics, smoking history, body mass index (BMI), asthma history, asthma duration, age at asthma diagnosis, comorbidities, presence of allergic rhinitis, sinonasal polyposis, drug allergies, systemic corticosteroid use, and lifetime hospitalization/emergency department visits were obtained from manually filled records. PFT and SPT results performed concurrently on the same day were recorded.

Records of SPTs were obtained from patient follow-up records. For each patient, an SPT had

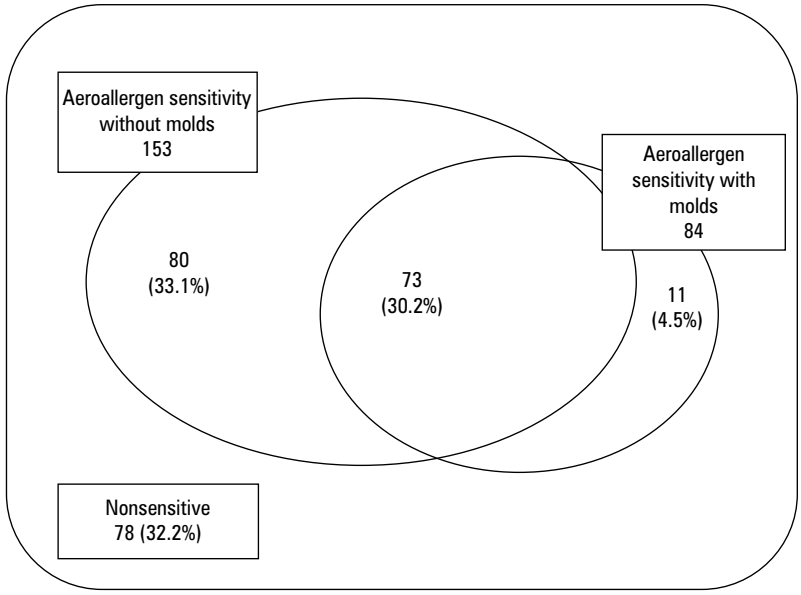

Figure 1. Aeroallergen sensitization pattern of the patients

been performed involving common inhalant allergens including *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (dust mites); *Aspergillus*, *Alternaria*, *Cladosporium*, and *Penicillium* (molds); cat and dog dander; latex; pollens from grass, trees, and weeds; and cockroaches (Allergopharma, Reinbek, Germany). SPTs were performed on the volar forearm and were read after 20 minutes. A wheal reaction with a mean diameter of 3 mm greater than the negative control was considered to indicate allergen positivity.

PFT was performed according to recommendations (14) using a pulmonary spirometer (CareFusion, Germany, 234 GmbH). The best of three attempts was recorded. Postbronchodilator forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$) values were obtained from the study participants' files. Our procedures for SPT and PFT are thoroughly described in our previous studies' methods section [14, 15].

For evaluating asthma symptom control, the GINA assessment of asthma control in adults was used [1, 15].

Statistical analysis

Patients were grouped into three categories according to SPT results: non-sensitized patients, sensitized patients without molds, and sensitized patients with molds (Figure 1).

For data analysis, the Statistical Package for the Social Sciences version 22 (IBM Corp., Armonk, NY, USA) was used. Categorical variables are expressed as absolute and relative frequencies, whereas quantitative variables are expressed as means and standard deviations. To evaluate the relationship between independent variables (i.e. demographic variables, asthma history, asthma clinical course, and PFT) and dependent variables, Pearson's chi-squared test was used. For categorical variables and numerical variables, one-way analysis of a variance test was used with a post-hoc Tukey test. Associations were considered significant at $p < 0.05$. Multinomial logistic regression was used to find differences among the three groups. A multivariate logistic regression analysis was performed by the backward likelihood ratio test to find differences between the mold-sensitive group and the sensitized group without molds.

Results

In total, 242 adult asthmatic patients' data were evaluated. The mean age of the study participants was 48.6 ± 15.4 years. Most study subjects were female (81.4%), homemakers (68.6%), had never smoked (81.8%), had comorbid diseases (56.6%), had AR (81.4%), and were on less than five medications for asthma (81.4%) (Table 1).

Figure shows the sensitization patterns of patients according to SPTs. Out of 242, the non-sensitized patient rate was 32.2%. Of them, 33.1% had aeroallergen sensitivity without molds, 30.2% had mold sensitivity plus at least one other aeroallergen sensitivity, and 4.5% had only mold sensitivity. Therefore, most of the patients in the mold-sensitive group were also sensitized to other aeroallergens.

Table 1. Demographic characteristics of patients and comparison of them among groups

Variables	Total (242)	SPT negative (n = 78, 32.2%)	SPT positivity without mold sensitization (n = 80, 33.1%)	SPT positivity with mold sensitization (n = 84, 34.7%)
Age (mean ± SD)	48.6 ± 15.4	59.9 ± 14.1[#¶]	45.8 ± 14.9	44.5 ± 14.7
Gender				
Female	197 (81.4)	65 (33.0)	64 (32.5)	68 (34.5)
Male	45 (18.6)	13 (28.9)	16 (35.6)	16 (35.6)
Job**				
Housewife	166 (68.6)	63 (38.0)*	49 (29.5)	54 (32.5)
Occupational risk	52 (21.5)	3 (12.5)	13 (54.2)	8 (33.3)
No occupational risk	24 (9.9)	12 (23.1)	18 (34.6)	22 (42.3)
Smoking status				
Non-smoker	198 (81.8)	65 (32.8)	64 (32.3)	69 (34.8)
Former smoker	22 (9.1)	9 (40.9)	9 (40.9)	4 (18.2)
Current smoker	22 (9.1)	4 (18.2)	7 (31.8)	11 (50.0)
Smoking (pack/year)	3.69 ± 8.4	3.37 ± 7.71	4.75 ± 10.5	3.1 ± 7.1
BMI (kg/m^2)	30.0 ± 6.4	32.1 ± 7.5[#¶]	29.5 ± 5.4	28.6 ± 5.6
Comorbid disease				
Present	137 (56.6)	52 (38.0)[#]	48 (35.0)[#]	37 (27.0)
Absent	105 (43.4)	26 (24.8)	32 (30.5)	47 (44.8)
AR				
Present	197 (81.4)	52 (26.4)[#¶]	68 (34.5)	77 (39.1)
Absent	45 (18.6)	26 (57.8)	12 (26.7)	7 (15.6)
SNP				
Present	36 (14.9)	18 (50.0)[#]	11 (30.6)	7 (19.4)
Absent	206 (85.1)	60 (29.1)	69 (33.5)	77 (37.4)
Drug allergy				
Present	18 (7.4)	10 (55.6)[¶]	2 (11.1)	6 (33.3)
Absent	224 (92.6)	68 (30.4)	78 (34.8)	78 (34.8)
Number of medications used for asthma and/or rhinitis symptoms				
≥ 5 [n%]	45 (18.6)	9 (20.0)[#¶]	22 (48.9)	14 (31.1)
≤ 4 [n%]	197 (81.4)	69 (35.0)	58 (29.4)	70 (35.5)
Mean (± SD)	2.93 ± 1.32	2.74 ± 1.19	3.20 ± 1.42	2.85 ± 1.30
Omalizumab use				
Present	21 (8.7)	5 (23.8)***	9 (42.9)	7 (33.3)
Absent	221 (91.3)	73 (33.0)	71 (32.1)	77 (34.8)
FEV_1%	88.0 ± 13.8	86.4 ± 15.3[¶]	94.3 ± 16.0	90.0 ± 14.9
$FEV_{25–75}$	68.3 ± 30.1	64.2 ± 30.2	74.0 ± 28.9	71.1 ± 30.6
FEV_1/FVC	76.4 ± 8.77	75.5 ± 9.99	76.9 ± 7.82	77.0 ± 9.45

[#]Compared to the group that had have prick test positivity with mold sensitization; [¶]Compared to the group that had prick test positivity without mold sensitization; *Among housewives, normal prick test was significantly higher than the group with occupational risk, Patients that have jobs with occupational risk factor; [*, #, ¶]Show the statistical significance between groups, $p < 0.05$; **Job was classified according to presence of occupational risk factors for asthma; ***5 patients who used omalizumab and had a negative skin prick test were found to have specific IgE positivitiy for perennial allergens.
AR — allergic rhinitis; BMI — body mass index; FEV_1 — forced expiratory volume in first second; FEF_{25-75} — forced vital capacity and forced expiratory flow at 25–75% of forced vital capacity; SPT — skin prick test

Table 2 shows data relating to the asthma characteristics of the included patients. The mean age at asthma diagnosis was 39.3 ± 15.2, and 50.4% of patients were younger than 40 years of age at the time of asthma onset. The majority of patients had experienced no hospitalization (80.6%), no emergency department admission (63.6%), and had no systemic steroid (SS) use (71.1%) during their disease course. According to GINA Asthma Control Test scores, most patients had "well-controlled" asthma (59.9%); the rest had either "partially controlled" (20.2%) or "uncontrolled" asthma (20.2%).

When considering aeroallergen sensitization patterns, 32.2% of our adult asthmatic patients were non-sensitized, 33.1% had sensitivity to

Table 2. Comparison of patients' characteristics according to asthma course

Variables	Total (242)	SPT negative (n = 78, 32.2%)	SPT positivity without mold sensitization (n = 80, 33.1%)	SPT positivity with mold sensitization (n = 84, 34.7%)
Asthma diagnosis age (years)	39.3±15.2	44.9 ± 14.5[#¶]	36.1 ± 15.6	37.3 ± 14.1
Asthma onset age				
< 40 [n%]	122 (50.4)	28 (23.0)[#¶]	47 (38.5)	47 (38.5)
≥ 40 [n%]	120 (49.6)	50 (41.7)	33 (27.5)	37 (30.8)
Asthma duration (years)	9.36 ± 8.9	11.2 ± 10.9[#]	9.7 ± 8.5	7.3 ± 6.7
Lifetime hospitalization due to asthma				
Present	47 (19.4)	23 (48.9)[#]	14 (29.8)	10 (21.3)
Absent	195 (80.6)	55 (28.2)	66 (33.8)	74 (37.9)
Mean (± SD)	0.77 ± 2.7	1.53 ± 4.26[#¶]	0.34 ± 1.06	0.49 ± 1.76
Emergency department visits				
Present [n%]	88 (36.4)	38 (43.2)[#¶]	25 (28.4)	25 (28.4)
Absent [n%]	154 (63.6)	40 (26.0)	55 (35.7)	59 (38.3)
Mean (± SD)	2.68 ± 6.52	4.33 ± 9.7[¶]	1.8 ± 3.73	1.99 ± 4.33
Systemic steroid use				
Present [n%]	70 (28.9)	29 (41.4)[#]	25 (35.7)	16 (22.9)
Absent [n%]	172 (71.1)	49 (28.5)	55 (32.0)	68 (39.5)
Mean (± SD)	1.76 ± 5.28	2.55 ± 7.53	1.71 ± 4.45	1.07 ± 2.87
Asthma control status				
Well controlled	144 (59.5)	43 (29.9)	50 (34.7)	51 (35.4)
Partially controlled	49 (20.2)	18 (36.7)	17 (34.7)	14 (28.6)
Uncontrolled	49 (20.2)	17 (34.7)	13 (26.5)	19 (38.8)

Note: R2 = 0.31 (Cox–Snell), 0.35 (Nagelkerke). Model $\chi 2 = 91.122$, $p < 0.0001$; goodness of fit; deviance-p = 0.402; pearson-p = 0.183. [#]Compared to the group that had have prick test positivity with mold sensitization; [¶]Compared to the group that had prick test positivity without mold sensitization. SPT — skin prick test

aeroallergens without molds, and 34.7% demonstrated mold sensitivity with or without other common aeroallergens. While those with mold sensitivity were mostly polysensitized (60.9%), those without mold sensitivity were mostly mono-sensitized (83.3%; $p < 0.05$). Identified sensitized mold species included *Cladosporium* (48.2%), *Aspergillus* (43.4%), *Penicillium* (38.6%), and *Alternaria* (21.7%).

In univariate analysis, the mean age and mean BMI of non-sensitized patients were higher than those of the sensitized groups ($p < 0.05$). In addition, the number of patients with a high number of medications used (5 or more medications) was lower in the non-sensitized group. The presences of comorbidities, SNP, and drug allergies were also higher among non-sensitized patients. The mean FEV_1% was lower in the non-sensitized group, compared with sensitized patients without mold sensitization ($p < 0.05$) (Table 1).

Furthermore, univariate analysis revealed that the mean age of asthma diagnosis, prevalence of late-onset asthma (≥ 40 years), mean number of hospitalizations, and number of patients who experienced emergency department (ED) admission were higher in the non-sensitized group ($p < 0.05$). Finally, asthma duration and presence of SS bursts were higher in the non-sensitized group when compared with the mold-sensitive group ($p < 0.05$) (Table 2).

Table 3 shows the multinomial logistic regression analysis findings of other groups in comparison with the non-sensitized group. The absence of drug allergies [odds ratio (OR): 8.794, 95% confidence interval (CI): 1.499–51.603], absence of ED admission (OR: 3.351, 95% CI: 1.116–10.065), and presence of occupational exposure (OR: 7.943 CI: 1.383–45.608) were more associated with sensitization without molds as compared to patients with non-sensitization. Separately, shorter asthma duration (OR: 1.795, 95% CI: 0.829–3.890), absence of SNP (OR: 3.791, CI: 1.207–11.903), presence of AR (OR: 4.132, 95% CI: 1.436–11.886), and well-controlled asthma (OR: 2.647, CI: 1.096–6.392) were more associated with mold sensitivity than with non-sensitization.

Table 4 shows the differences identified between mold-sensitive patients and sensitized patients without following logistic regression analysis. Shorter asthma duration (OR:2.170,

Table 3. Associations between groups compared to nonsensitive group in multinominal analysis

	SPT positivity without mold sensitization	SPT positivity with mold sensitization
Gender (male gender compared to female)	3.534 (0.914–13.672)	2.997 (0.782–11.488)
Age group (< 65 vs ≥ 65)	1.294 (0.444–0.637)	2.511 (0.756–8.348)
Asthma duration (shorter than 10 years vs longer than 10 years)	0.977 (0.461–2.068)	1.795 (0.829–3.890)*
Asthma onset age (< 40 age vs ≥ 40 age)	1.633 (0.717–3.720)	1.135 (0.497–2.595)
BMI (< 30 vs ≥ 30)	1.228 (0.564–2.675)	1.581 (0.706–3.541)
Comorbidity (presence vs absence)	1.004 (0.436–2.315)	0.523 (0.224–1.221)
SNP (absence vs presence)	1.972 (0.707–5.501)	3.791 (1.207–11.903)*
AR (presence vs absence)	2.036 (0.818–5.068)	4.132 (1.436–11.886)*
Drug allergy (absence vs presence)	8.794 (1.499–51.603)*	1.293 (0.347–4.825)
Hospitalization (absence vs presence)	2.071 (0.705–6.080)	2.746 (0.900–8.372)
Emergency admission (absence vs presence)	3.351 (1.116–10.065)*	1.758 (0.636–4.858)
Systemic steroid burst (absence vs presence)	2.747 (0.858–8.793)	0.686 (0.222–2.114)
Omalizumab use (presence vs absence)	3.348 (0.766–14.631)	3.610 (0.808–16.129)
Asthma control (well controlled vs other)	1.219 (0.511–2.912)	2.647 (1.096–6.392)*
Number of medications using for asthma and/or rhinitis symptoms (≥ 5 vs ≤ 4)	1.944 (0.734–5.153)	1.048 (0.366–2.999)
Job		
Housewife	1	1
No occupational risk group	2.722 (0.866–8.555)	1.918 (0.607–6.066)
Occupational risk group	7.943 (1.383–45.608)*	3.899 (0.667–22.787)
Smoking status		
Never smoker	1	1
Former smoker	0.673 (0.184–2.459)	0.299 (0.065–1.369)
Current smoker	0.863 (0.186–4.008)	1.461 (0.0355–6.018)
FEV_1% predicted (< 80 vs ≥ 80)	0.260 (0.651–1.628)	1.019 (0.419–2.478)

Note: R2 = 0.31 (Cox–Snell); 0.35 (Nagelkerke). Model χ^2 = 91.122, p < 0.0001; goodness of fit; deviance-p = 0.402; pearson-p = 0.183. *p < 0.05, shows the statistically significant difference. BMI — body mass index; FEV_1 — forced expiratory volume in first second; SPT — skin prick test

95% CI: 1.028–4.583), presence of drug allergy (OR:7.462, 95% CI:1.053–52.887), and absence of SS (OR:3.647, 95% CI:1.108–12.006) were more associated with the mold-sensitive group in comparison to the sensitized group without mold-sensitization.

Discussion

This study revealed that nearly one-third of adult asthmatic patients treated at this clinic are mold-sensitive; most of that group have polysensitization but well-controlled asthma. When compared with the non-sensitized group, patients in the mold-sensitive group were positively associated with shorter asthma duration, the presence of AR, an absence of SNP, and the presence of well-controlled asthma. Additionally, mold sensitivity was positively associated with the presence of drug allergies and an absence of SS bursts in comparison with sensitized patients without mold-sensitivity. In this study, we evaluated our population using two models. Firstly, univariate analysis was used to compare the three groups (non-sensitized, sensitized without molds, and sensitized with molds). Secondly, a multivariate analysis and logistic regression analysis of factors associated with mold sensitivity, in comparison with other groups, were performed. Due to the existence of confounding variables, we will discuss our findings according to the results of the logistic regression analysis, but also consider univariate analysis results in our comments.

The relationship between mold sensitivity status and asthma has been previously studied. Many prior studies showed that mold had a negative impact on asthma symptoms and asthma control [2]. A recent study that evaluated the relationship between mold burden in house dust and asthma control found that the concentrations of some molds detected in dust samples from the homes of asthma patients were negatively associ-

Table 4. Factors associated with mold sensitivity compared to non-mold sensitive group

	Mold sensitive group
Gender (female vs male)	1.026 (0.304–3.466)
Age groups (< 65 vs ≥ 65 age)	1.728 (0.413–7.221)
Asthma duration (< 10 vs ≥ 10 years)	2.170 (1.028–4.583)*
Asthma onset age (≥ 40 vs < 40 years)	1.421 (0.634–3.182)
BMI (< 30 vs > 30 kg/m^2)	1.327 (0.597–2.950)
Comorbidity (absence vs presence)	1.992 (0.868–4.576)
SNP (absence vs presence)	1.716 (0.469–6.275)
AR (presence vs absence)	2.096 (0.623–7.058)
Drug allergy (presence vs absence)	7.462(1.053–52.887)*
Hospitalization (absence vs presence)	1.489 (0.455–4.876)
Emergency admission (presence vs absence)	1.587 (0.533–4.717)
Systemic steroid use (absence vs presence)	3.647(1.108–12.006)*
Omalizumab (absence vs presence)	1.086(0.292–4.041)
Asthma control (others vs well controlled)	2.513 (1.086–5.816)
Number of medications used for asthma and/or rhinitis symptoms (≤ 5 vs ≥ 5)	2.126 (0.878–5.164)
Job	
Occupational risk group	1
No occupational risk group	1.588 (0.419–6.028)
Housewife	1.878 (0.460–7.665)
Smoking status	
Never smoker	1
Current smoker	1.720 (0.484–6.119)
Former smoker	0.592 (0.147–2.379)
FEV$_1$% predicted (< 80 vs ≥ 80)	1.380 (0.551–3.459)

Note: R2(Cox–Snell: 0.174, Nagelkerke:0.233) model $p < 0.05$. *$p < 0.05$, shows the statistically significant difference.
AR — allergic rhinitis; BMI — body mass index; FEV$_1$ — forced expiratory volume in first second; SPT — skin prick test

ated with parameters of asthma control in male subjects, but not in female ones. The researchers attributed their finding to males demonstrating a stronger immunoglobulin (Ig) E response following exposure to some molds. This speculation was also supported by the higher IgE concentrations of males in population studies and the higher capability of males to produce stronger allergic responses to fungal infections. Also, potentially due to the protective effects of sex hormones, women were expected to have a stronger immune response than that of men [7]. In our study, only 18.6% of our study population was male. The fact that the majority of our study population was female may be one of the explanations for finding a reverse relationship between mold sensitivity and asthma control. In another study from China, mold-sensitive asthmatics appeared to have higher asthma severity scores than those of the sensitized group without mold-sensitization, but they had lower FEV$_1$ values than those of the non-sensitized group [16]. These authors, however, excluded asthmatics with smoking histories; all of their participants were nonsmokers. In this study, our findings showed a positive impact on patients' asthma control status as well as SS bursts. We included asthmatics who smoke, but neither the univariate nor multivariate results differed with respect to smoking status.

In a cohort study, the effects of mold or dampness exposure during infancy on the risk of asthma, rhinitis, or IgE sensitization was evaluated in children followed from birth to 16 years of age. During this investigation, sensitization was assessed using blood samples in 3,293 children. Exposure to any mold or dampness was associated with asthma in patients up to 16 years of age, while exposure to mold odor and visible mold were associated with rhinitis. Increased risks were observed for nonallergic asthma and rhinitis [17]. Considering this study, it is possible that mold exposure also adversely affects nonallergic/ /nonatopic asthmatics rather than only mold-sensitive cases. In our study, data on environmental mold exposure could not be measured due to the experimental design; therefore, this confounding factor should be considered in future research.

In a recent review article [2], the authors considered studies that measured mold exposure both by qualitative and quantitative methods in order to evaluate the association between asthma, asthma development, asthma exacerbation, and rhinitis. Exposure to molds by using a qualitative metrics approach (i.e. observation of visible mold or smell) was found to have an association with asthma development. In the same review, it is also mentioned that there is currently insufficient evidence to determine whether an association exists between quantitatively measured mold species/ /components and the occurrence of asthma. In our study, we did not evaluate the indoor or outdoor mold exposure status of our study population. This is because it was previously reported that, regardless of sensitization patterns, asthma control was worse in a high-mold exposure group [18].

There are other dissenting studies in the literature to consider when analyzing the findings of this study. Al-Ahmad et al. did not find molds to have a significant triggering role, despite the

high rate of sensitization leading to asthma exacerbation in the desert environment. These authors evaluated asthma exacerbations and mold concentrations across the four seasons and found a higher average concentration of *Alternaria* and *Cladosporium* during September and November. Among the asthmatic participants, the mold-sensitive patients had higher rates of asthma exacerbations in that season. They additionally suggested that the climate and season can affect the presence of molds and asthma exacerbation [19]. Our region, the Eastern Black Sea of Turkey, has an oceanic climate with a narrow annual temperature range. This makes indoor mold growth and the outdoor mold rate similar during all four seasons.

Based on our findings, it is obvious that the mold-sensitive patients had shorter asthma durations. Younger mean age and younger mean asthma diagnosis age, and thus a higher rate of early-onset asthma, were also determined in univariate analysis in the mold-sensitive group. Previous studies have suggested a link between new-onset asthma and mold exposure; prolonged exposure to molds was also found to have an effect on new-onset asthma [20]. Further, it was concluded elsewhere that exposure to damp and moldy work places can induce new-onset adult asthma [21]. Mold exposure in early childhood was found to have an effect on asthma-related symptoms and the development of asthma at earlier ages [22]. Severe asthma with fungal sensitization was also found to be characterized by an early onset of the disease [23]. The mold-sensitive patients' shorter asthma durations and younger ages in this study could be related to the new-onset and early-onset effects of mold exposure in light of these prior investigations. However, Thacher *et al.* evaluated the effects of mold exposure on the development of asthma and rhinitis from birth to the age of 16 years in a cohort study and concluded that exposure to mold and dampness during infancy increased the odds of asthma and rhinitis. Further, exposure was associated with persistent asthma but not with early-transient or late-onset asthma [17].

The mold-sensitive group in our study had higher rates of AR. The effect of mold sensitivity on allergic rhinitis has been presented in previous studies [24]. Exposure to mold is associated with the development of asthma in occupants of damp buildings, and rhinitis is known to be a risk factor for asthma. However, there is little information about the degree of risk for the progression of rhinosinusitis to asthma owing to mold exposures in damp buildings [25]. Another study, from Poland, suggested AR patients' clinical distinctness. They found elevated nasal nitric oxide levels during seasons when the air concentrations of grass pollen and *Alternaria* spores were very high but there was no correlation during or after the pollen season [26]. The presence of a lower rate of SNP in our mold-sensitive group compared to the non-sensitized group is thus in line with the literature. It was previously reported that the SNP is more prevalent among nonatopic asthmatics than atopic asthmatics. Also, late-onset asthma was thought to have an association with the development of nasal polyposis [27].

Strengths and limitations

This study allows us to compare asthma patients' characteristics according to their mold sensitivity status, tested via SPT during their regular follow-ups. Data was gleaned from files from an expert ear-nose-throat outpatient clinic. Beside its ability to address a gap in the literature, there are some limitations that should be mentioned. The retrospective design of the study, as well as the heterogenous distribution of patients regarding gender and occupation, is a limiting factor. Another confounding factor is the sensitivity level of SPT, which limits the ability to determine the exact sensitization status of patients. Sensitivity of SPT in determining aeroallergen sensitization could be an issue. Therefore, future studies should consider using more specific tests. Of our patients, 5 who were treated with Omalizumab had negative SPT results. This may be due to steroid use or use of other medications that can produce false negative SPT results. Also, 26.4% of our asthmatics with an AR diagnosis had negative SPTs. In a previous national study, that rate was found to be 43.7% [28]. Evaluating all of the asthmatics that meet our broad inclusion criteria helped to make the groups more diverse. However, it also led to more confounding factors that could affect the evaluation of the direct effects of mold sensitivity. The lack of evaluation of indoor and outdoor mold exposure in the study design is another limiting factor.

In conclusion, asthmatic patients determined to be mold-sensitive by SPTs were found to have better asthma symptom control. The measurement of the mold exposure that patients encounter in their unique environments can lead to better accuracy regarding the effects of mold on asthma control and comorbidities. Based on the findings of this study, it should be kept in mind that mold sensitization in adult asthmatics is not always a poor prognostic factor.

Conflict of interest

None declared.

References:

1. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma. 2019 update. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. [Access: 27.03.2020].
2. Caillaud D, Leynaert B, Keirsbulck M, et al. Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies. Eur Respir Rev. 2018; 27(148), doi: 10.1183/16000617.0137-2017, indexed in Pubmed: 29769295.
3. Simon-Nobbe B, Denk U, Pöll V, et al. The spectrum of fungal allergy. Int Arch Allergy Immunol. 2008; 145(1): 58–86, doi: 10.1159/000107578, indexed in Pubmed: 17709917.
4. Denning DW, O'Driscoll BR, Hogaboam CM, et al. The link between fungi and severe asthma: a summary of the evidence. Eur Respir J. 2006; 27(3): 615–626, doi: 10.1183/09031936.06.00074705, indexed in Pubmed: 16507864.
5. Oluwole O, Kirychuk SP, Lawson JA, et al. Indoor mold levels and current asthma among school-aged children in Saskatchewan, Canada. Indoor Air. 2017; 27(2): 311–319, doi: 10.1111/ina.12304, indexed in Pubmed: 27108895.
6. McSharry C, Vesper S, Wymer L, et al. Decreased FEV_1% in asthmatic adults in Scottish homes with high Environmental Relative Moldiness Index values. Clin Exp Allergy. 2015; 45(5): 902–907, doi: 10.1111/cea.12482, indexed in Pubmed: 25580663.
7. Segura-Medina P, Vargas MH, Aguilar-Romero JM, et al. Mold burden in house dust and its relationship with asthma control. Respir Med. 2019; 150: 74–80, doi: 10.1016/j.rmed.2019.02.014, indexed in Pubmed: 30961954.
8. Sharpe RA, Bearman N, Thornton CR, et al. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. J Allergy Clin Immunol. 2015; 135(1): 110–122, doi: 10.1016/j.jaci.2014.07.002, indexed in Pubmed: 25159468.
9. Zureik M, Neukirch C, Leynaert B, et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. BMJ. 2002; 325(7361): 411–414, doi: 10.1136/bmj.325.7361.411, indexed in Pubmed: 12193354.
10. Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk factor for life-threatening asthma. Allergy. 2000; 55(5): 501–504, doi: 10.1034/j.1398-9995.2000.00293.x, indexed in Pubmed: 10843433.
11. Shea KM, Truckner RT, Weber RW, et al. Climate change and allergic disease. J Allergy Clin Immunol. 2008; 122(3): 443–53; quiz 454, doi: 10.1016/j.jaci.2008.06.032, indexed in Pubmed: 18774380.
12. Ziska LH, Epstein PR, Schlesinger WH. Rising CO(2), climate change, and public health: exploring the links to plant biology. Environ Health Perspect. 2009; 117(2): 155–158, doi: 10.1289/ehp.11501, indexed in Pubmed: 19270781.
13. Knutsen AP, Bush RK, Demain JG, et al. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol. 2012; 129(2): 280–91; quiz 292, doi: 10.1016/j.jaci.2011.12.970, indexed in Pubmed: 22284927.
14. Moore VC. Spirometry: step by step. Breathe. 2012; 8(3): 232–240, doi: 10.1183/20734735.0021711.
15. Cakmakci Karadoğan D, Ayhan V, Dursun AB. What are the difference between elderly and non-elderly asthma patients? Turkish Journal of Geriatrics 2017; 20(3): 194–203.
16. Ma Y, Tian G, Tang F, et al. The link between mold sensitivity and asthma severity in a cohort of northern Chinese patients. J Thorac Dis. 2015; 7(4): 585–590, doi: 10.3978/j.issn.2072-1439.2015.01.04, indexed in Pubmed: 25973223.
17. Thacher JD, Gruzieva O, Pershagen G, et al. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. Allergy. 2017; 72(6): 967–974, doi: 10.1111/all.13102, indexed in Pubmed: 27925656.
18. Vincent M, Corazza F, Chasseur C, et al. Relationship between mold exposure, specific IgE sensitization, and clinical asthma: A case-control study. Ann Allergy Asthma Immunol. 2018; 121(3): 333–339, doi: 10.1016/j.anai.2018.06.016, indexed in Pubmed: 29944956.
19. Al-Ahmad M, Jusufovic E, Arifhodzic N, et al. Association of molds and metrological parameters to frequency of severe asthma exacerbation. Allergy Asthma Clin Immunol. 2019; 15: 29, doi: 10.1186/s13223-019-0323-8, indexed in Pubmed: 31168304.
20. Karvala K, Toskala E, Luukkonen R, et al. Prolonged exposure to damp and moldy workplaces and new-onset asthma. Int Arch Occup Environ Health. 2011; 84(7): 713–721, doi: 10.1007/s00420-011-0677-9, indexed in Pubmed: 21769455.
21. Karvala K, Toskala E, Luukkonen R, et al. New-onset adult asthma in relation to damp and moldy workplaces. Int Arch Occup Environ Health. 2010; 83(8): 855–865, doi: 10.1007/s00420-010-0507-5, indexed in Pubmed: 20127354.
22. Sheehan WJ, Phipatanakul W. Indoor allergen exposure and asthma outcomes. Curr Opin Pediatr. 2016; 28(6): 772–777, doi: 10.1097/MOP.0000000000000421, indexed in Pubmed: 27653703.
23. Masaki K, Fukunaga K, Matsusaka M, et al. Characteristics of severe asthma with fungal sensitization. Ann Allergy Asthma Immunol. 2017; 119(3): 253–257, doi: 10.1016/j.anai.2017.07.008, indexed in Pubmed: 28801088.
24. Codispoti CD, Bernstein DI, Levin L, et al. Early-life mold and tree sensitivity is associated with allergic eosinophilic rhinitis at 4 years of age. Ann Allergy Asthma Immunol. 2015; 114(3): 193–198.e4, doi: 10.1016/j.anai.2014.12.008, indexed in Pubmed: 25744905.
25. Park JH, Kreiss K, Cox-Ganser JM. Rhinosinusitis and mold as risk factors for asthma symptoms in occupants of a water-damaged building. Indoor Air. 2012; 22(5): 396–404, doi: 10.1111/j.1600-0668.2012.00775.x, indexed in Pubmed: 22385263.
26. Kołodziejczyk K, Bozek A. Clinical distinctness of allergic rhinitis in patients with allergy to molds. Biomed Res Int. 2016; 2016: 3171594, doi: 10.1155/2016/3171594, indexed in Pubmed: 27340656.
27. Bachert C, Patou J, Van Cauwenberge P. The role of sinus disease in asthma. Curr Opin Allergy Clin Immunol. 2006; 6(1): 29–36, doi: 10.1097/01.all.0000200504.54425.0e, indexed in Pubmed: 16505609.
28. Keles E, Karlıdağ T, Alpay HC, Akyiğit A, et al. The symptoms in patient with allergic rhinitis and distribution of allergens detected by skin test. KBB-Forum 2010; 9(2). Available from: www.kbbforum.net/journal/abstract.php?lang=en&id=249. [Access: 27.03.2020].