

ORIGINAL ARTICLE

Screening instrument to identify skin prick test-negative patients with asthma and/or rhinitis

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Abstract

Introduction: To the best of our knowledge, there is no prediction tool for determining respiratory allergy in patients with asthma and/or rhinitis.

Objectives: As such, this study aimed to develop an instrument for identifying skin prick test (SPT)-negative patients with asthma and/or rhinitis.

Methods: This cross-sectional study screened 510 consecutive patients diagnosed with asthma and/or rhinitis between November 2009 and May 2011 in Ankara, Turkey. A structured questionnaire was the screening tool that was administered during the initial visit by the treating specialist and compared with a SPT result. All 15 variables were analysed using the logistic regression model to obtain β values (a score) for each variable. Each variable had a score, and scores were summed up to obtain final score for each patient.

Results: The study included 363 patients, of which 165 (45.5%) were SPT positive. The final model included 13 variables. The lowest and highest scores were -21 and 26. A total score of 5.5 had sensitivity of 63% and specificity of 80%. The area under the receiver operating characteristic curve was 0.78. The histogram of the total scores for the study population was bimodal.

Conclusions: We designed a highly specific 13-item instrument for identifying SPT-negative patients. It may be used in middle income countries where allergy testing is expensive, not reimbursed or few allergy clinics are available. We think that our idea is interesting, that needs further research.

KEYWORDS

allergen, allergic asthma, allergic rhinitis, asthma, rhinitis

1 | INTRODUCTION

The prevalence of asthma among adult males and females in urban areas in Turkey has been reported to be 6.2% and 7.5%; and the prevalence of allergic rhinitis among males and females in urban areas has been reported to be 11.7% and 17%, respectively.¹ Among 1149 asthmatic patients in Turkey, the atopy rate was reported to be 42%.² Although the prevalence of allergic rhinitis and asthma in the Turkish general population is high, not all cities in Turkey have an allergy clinic.

The skin prick test (SPT) is a diagnostic tool used in patients with a clinical history suggestive of allergic rhinitis and/or asthma to identify potential triggers of symptoms; however, treatment planning for such patients is usually made without performing a SPT.³ Strategies for allergen avoidance are either not provided or are non-specific.⁴ Phadiatop serologic test can be used as a screening tool to identify allergic sensitization.^{5,6} However, diagnostic accuracy of Phadiatop may vary not only with the prevalence of allergic sensitization in the studied population, but also with the aeroallergen

profile of a given area.⁵ Aeroallergen composition of it is fixed and not stated by the manufacturer. In studies that evaluate diagnostic accuracy of Phadiatop use SPT results as the reference standard.^{5,7} In Turkey, Phadiatop serological test cannot be performed in all clinical settings.

To the best of our knowledge, there is no alternative instrument to SPT for distinguishing the allergic status of patients with asthma and/or rhinitis that is based on patients' history. An accurate and effective instrument could reduce the cost of diagnostic work up, and the number of unnecessary referrals to allergy clinics from primary care centres or from otorhinolaryngology clinics.

An easy to use scoring system that can predict negative SPT results could aid clinical practice. The aim of the present study was to develop a highly specific instrument for identifying SPT-negative patients with asthma and/or rhinitis.

2 | MATERIALS AND METHODS

In this cross-sectional survey study 510 consecutive patients presenting for the first time to our allergy clinic between November 2009 and May 2011 and who were diagnosed with asthma and/or rhinitis were assessed for eligibility. Diagnosis of asthma and/or rhinitis was based on international guidelines.^{8,9}

Patients under daily antihistamine treatment, those with dermographism, and those that declined to participate were excluded. A structured allergy history was obtained from all the participants, each of who also underwent SPT. Among

510 consecutive patients assessed for eligibility, 464 were eligible. Patients with incomplete data ($n = 6$) and those that refused to participate ($n = 95$) were excluded; the remaining 363 patients were included in the final analysis (Figure 1).

2.1 | Structured allergy history

A structured survey was administered to each participant during their initial visit by the treating specialist at the tertiary care study centre. Patients were interviewed by the specialist. The survey collected demographic (age, sex, level of education) and clinical data (smoking status, diagnosis, disease duration, age at onset, seasonality of symptoms, presence of nasal itching, outdoor/indoor exacerbation of symptoms, pet ownership, family history of asthma/rhinitis). Table 1 shows the questions included in the survey.

2.2 | Skin prick tests

Following completion of the survey, all patients were skin prick tested. SPTs to common aeroallergens, including *Dermatophagoides pteronyssinus*, pollens (*Phleum pratense*, *Artemisia vulgaris*, *Parietaria officinalis*, *Corylus avellana*, *Olea europaea*, and *Betula verrucosa*), moulds (*Aspergillus fumigatus*, *Cladosporium herbarum* and *Alternaria alternata*), animal dander (dog and cat), latex and *Blatella orientalis*, were performed. Allergenic extracts were obtained from Allergopharma (Germany). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. SPTs were considered positive if mean wheal diameter

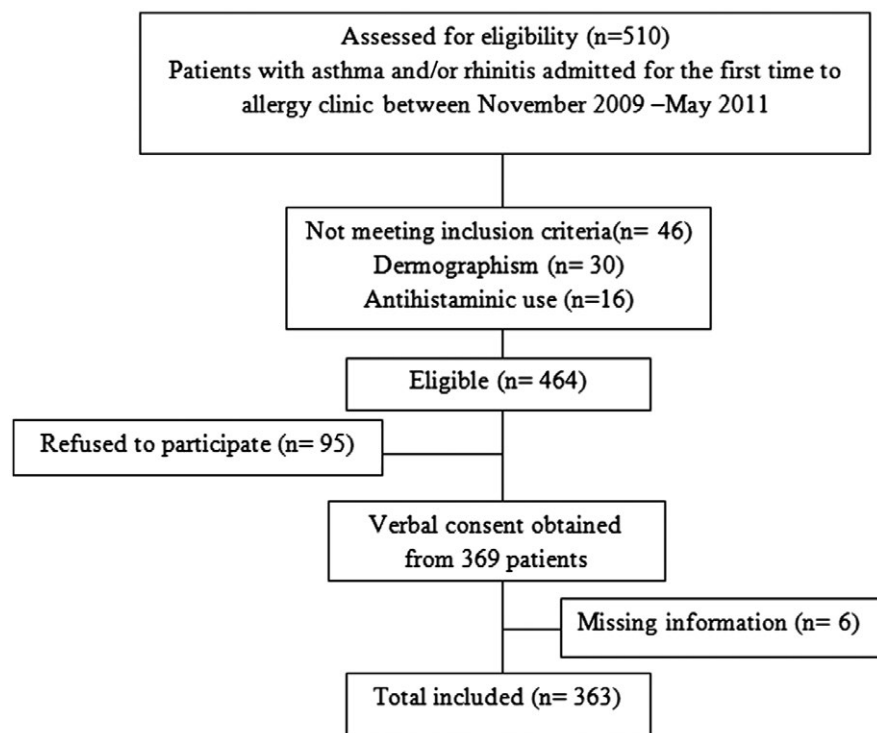


FIGURE 1 Consort diagram

TABLE 1 Questions in the survey

1	Which school did you last graduated from, and what is your current occupation?
2	Do you ever/never/currently smoke cigarettes? (how long/how many)
3	How old were you when your first symptoms started?
4	Do your symptoms show seasonal variation in intensity? (persistent, spring, spring and autumn, winter) ^a
5	Do outdoor or indoor environment effect the intensity of your symptoms? (symptoms worsen at outdoor/indoor environment/does not matter)
6	Is nasal itching one of your most prominent symptom? ^b
7	Do you ever/currently have a pet in your home?
8	Do you have any relatives with asthma and/or rhinitis? If yes, who?
9	Do you think you are allergic to something?
10	(if yes to previous question) What do you think you are allergic to? (Pollens, moulds, house dust mites, pets)

^a≥1 answer is possible.^bNasal itching is not applicable for patients who do not have rhinitis.

was ≥3 mm larger than the negative control.^{3,10} Values calculated for each allergen were recorded on a standardized data collection form.

2.3 | Statistical methods

A nomogram was used to calculate the sample size.¹¹ When we accepted the prevalence of SPT positivity among patients with asthma and/or rhinitis to be 45%, a test with sensitivity of 80% and absolute precision of 0.07 estimated that the required sample size was 280 patients; a test with specificity of 80% and absolute precision of 0.07 estimated that the required sample size was 230 patients.

SPSS v. 18.0 for Windows was used for data analysis. Variables were analysed using logistic regression model to obtain β values for each variable in the model. There were 15 variables in the model, and via multiplying each β value of each variable by 10, a score for each variable was calculated. Then, a total score for each patient was calculated. A receiver operating characteristic (ROC) curve for total scores was drawn and a cut-off value with specificity of 80% was determined based on the coordinates of the ROC curve. If the total score of a patient is equal to or greater than the cut-off value, the SPT result was presumed to be positive, if the total score of a patient is less than the cut-off value, the SPT result was presumed to be negative.

3 | RESULTS

The study included 363 patients. Mean age of the study population was 35.64 (SD 12.19, range 16-74), and 69% were women. Patient characteristics based on SPT results are shown in Table 2. Among 136 patients who had asthma (w/wo rhinitis), 58 (35.2%) were SPT positive (sensitisation to pollens, moulds, pets and mites were 27%, 1.5%, 10%, and 18%, respectively) and 154 (46%) patients with rhinitis

(w/wo asthma) were SPT positive (sensitisation to pollens, moulds, pets, and mites were 36%, 1.5%, 11% and 13%, respectively). Among patients who had both asthma and rhinitis ($n = 111$), 47 (42%) were SPT positive. When compared to SPT-negative group, SPT-positive patients were younger, and more of them had spring, and outdoor symptoms, nasal itching, and thought that they would be SPT positive.

Data collection survey included 10 questions and 15 variables were entered into logistic regression model (some questions had categorical answers). Variables included in the logistic regression model and β values for each variable are shown in Table 3. As having a first-degree relative with asthma/rhinitis, and pet ownership had a final score of 0, they were not included in the final scoring system. Final instrument included 13 items.

Interestingly, all seasonal variations weighed differently in the model, and nasal itching had a positive score. Symptom exacerbation during spring had the highest score (13), and 74.6% of patients with spring symptoms ($n = 126$) were SPT positive, whereas symptom exacerbation during winter had the lowest score (−13) and only 14% of patients with winter symptoms ($n = 34$) were SPT positive.

Figure 2 shows the distribution of total scores for patients in the study population. The shape of the histogram is bimodal with 2 humps; 1 hump mainly includes SPT-positive patients and the other SPT-negative patients. The total scores ranged between −21 and 26.

Figure 3 shows the ROC curve for total scores of the study population. The area under the curve was 0.78. Based on the coordinates of the ROC curve, a total score of 5.5 had sensitivity of 63% and specificity of 80%. Table 4 shows the sensitivity, specificity, false-positive and false-negative values of different cut-off values for SPT results. As the total score increased, the sensitivity of the instrument decreased and the specificity increased. Table 5 shows the performance of the 5.5 cut-off value.

TABLE 2 Characteristics of the study population based on SPT^a results

	Total (<i>n</i> = 363)	SPT positive (<i>n</i> = 165)	SPT negative (<i>n</i> = 198)	<i>P</i> ^c
	100%	100%	100%	
Age, mean (SD) years	35.64 (12.19)	34.05 (12.07)	36.97 (12.13)	0.02^d
Female	251 (69.1)	108 (65.5)	143 (72.2)	0.17
University graduate	184 (50.7)	91 (55.2)	93 (47.0)	0.12
Ever smoker	102 (28.1)	39 (23.6)	63 (31.8)	0.08
Presence of asthma ^b	136 (37.5)	58 (35.2)	78 (39.4)	0.41
Presence of rhinitis ^b	338 (93.1)	154 (93.3)	184 (92.9)	0.88
Disease onset age ≤18 years	94 (25.9)	54 (32.7)	40 (20.2)	0.007
Disease duration ≥3 years	262 (72.2)	131 (79.4)	131 (66.2)	0.005
Symptoms peak during spring	126 (34.7)	94 (57)	32 (16.2)	<0.001
Symptoms peak during winter	34 (9.4)	5 (3)	29 (14.6)	<0.001
Persistent symptoms	222 (61.2)	85 (51.5)	137 (69.2)	0.001
Symptoms peak during autumn and spring	24 (6.6)	13 (7.9)	11 (5.6)	0.38
Symptoms peak outdoors	98 (27)	70 (42.4)	28 (14.1)	<0.001
Symptoms peak indoors	80 (22)	22 (13.3)	58 (29.3)	<0.001
Nasal itching	221 (60.9)	118 (71.5)	103 (52)	<0.001
First-degree relative with asthma/rhinitis	190 (52.3)	87 (52.7)	103 (52)	0.89
Second-degree relative with asthma/rhinitis	84 (23.1)	36 (21.8)	48 (24.2)	0.59
Currently owns a pet	33 (9.1)	14 (8.5)	19 (9.6)	0.71
Patients predicting positive SPT results	240 (66.1)	124 (75.2)	116 (58.6)	0.001

^aSkin prick test.^bDiagnosis of asthma/rhinitis was confirmed by physicians at the study centre at study entry.^cChi-square test, except for age.^d*t* test.

The Bold values indicates lesser than 0.05.

4 | DISCUSSION

We developed a highly specific instrument comprised of 13 items that identifies SPT-negative asthma and/or rhinitis patients. The instrument identifies SPT-negative patients with 80% specificity at a cut-off value of 5.5. To the best of our knowledge, this is the first report of such an instrument in the literature. In the present study, the factors that were most probably associated with atopic status in patients with asthma and/or rhinitis were entered into a logistic regression model and a final score for each patient was obtained; this score was used to rule out allergy in an individual patient. This scoring system described herein can only be used in adult patients diagnosed with asthma and/or rhinitis.

Specificity is the proportion of people free of the disease who are correctly identified by a negative test result, and positive results from highly specific tests can rule a diagnosis in.¹² In the present study, the total score was <5.5 in 80% of SPT-negative patients. However, among SPT-positive

patients, total score was >5.5 in 63% of the cases. In other words, with a total score under 5.5, the instrument could be able to identify 80% of the SPT-negative patients with asthma and/or rhinitis.

This instrument is easy to apply. Sex, age, smoking history, disease onset age and duration, indoor/outdoor and seasonal changes in symptom intensity, presence of nasal itching, presence of a relative with asthma/rhinitis, and patients' opinion about being allergic to something were the variables needed to calculate the total score.

Pollens are outdoor seasonal allergens. Patients that are allergic only to pollens are expected to have seasonal and outdoor symptom exacerbation, especially during spring. Patients with non-allergic rhinitis have more persistent, but equally severe symptoms, than do patients with allergic rhinitis.¹³ It was reported that patients with allergic rhinitis more frequently sneeze, and have nasal itching.¹⁴ A previous study that investigated the key nasal symptoms predictive of positive SPT result in patients with allergic rhinitis reported that

there were not any predictive symptoms and that the characteristics in patients with positive and negative SPT results did not differ; however, they found that mean age of the SPT-positive patients was lower than that of the SPT-negative patients ($P < 0.05$) and severe nasal itching was more common among SPT-positive patients ($P = 0.04$).¹⁵ Based on our clinical experience and the literature, to differentiate between

TABLE 3 Variables included in the logistic regression model, and β value and score for each variable^a

	β value	Score
Female gender	-0.274	-3
Ever smoker	-0.174	-2
Disease onset age ≤ 18 years	0.300	3
Disease duration ≥ 3 years	0.421	4
Symptom peak during spring	1.286	13
Symptom peak during winter	-1.260	-13
Persistent symptom	-0.448	-4
Symptom peak during spring and autumn	0.368	4
Symptom peak outdoors	0.114	1
Symptom peak indoors	-0.550	-5
Nasal itching	0.292	3
First-degree relative with asthma/rhinitis	0.024	0 ^b
Second-degree relative with asthma/rhinitis	-0.235	-2
Currently owns a pet	-0.048	0 ^b
Patients predicting positive SPT results	0.193	2

^aAll the variables were entered together into the logistic regression model.

^bThese variables do not weigh in the model.

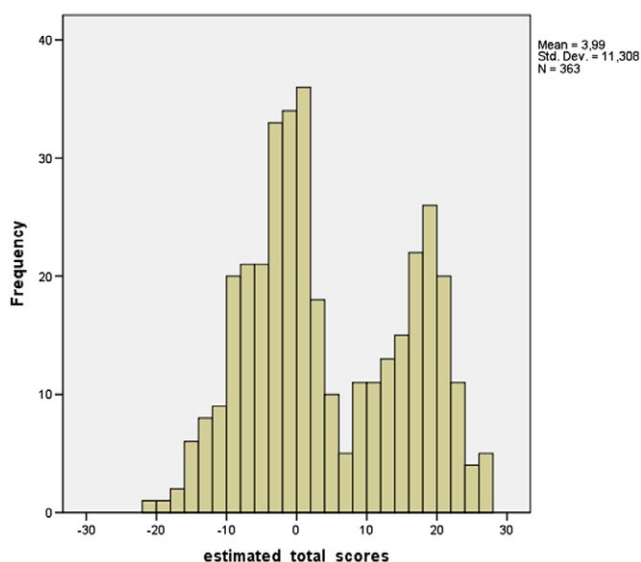


FIGURE 2 Histogram of patients' total scores

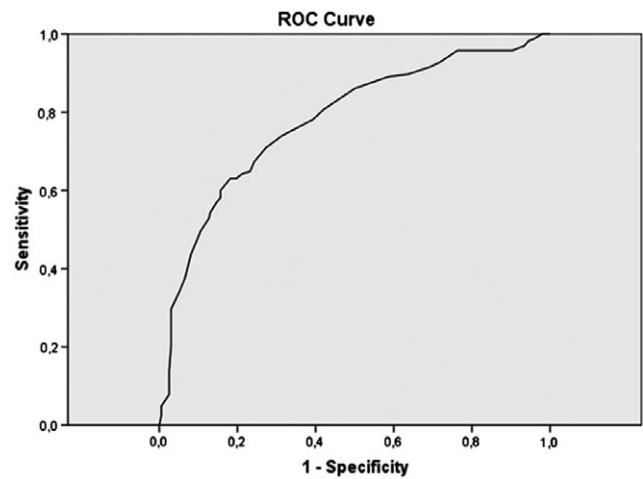


FIGURE 3 ROCs curve for patients' total scores (area under the curve is 0.78)

SPT-positive and -negative patients, we asked our patients “Do your symptoms show seasonal variation in intensity? (persistent, spring, spring and autumn, winter)” and “Is nasal itching one of your most prominent symptom?” Symptoms peak during winter had the lowest score (-13), meaning that if the patients' symptoms peak or exclusively present during cold winter season than the patient has high probability of having nonallergic asthma and/or rhinitis. In our study population, only 3% of SPT-positive patients had winter symptom exacerbation. In contrast symptom peak during spring had the highest score (13), and 57% of SPT-positive patients had spring time symptom exacerbation.

Li et al asked 73 patients with asthma and/or rhinitis, “Do you expect the skin tests to be positive or negative?” and “What do you expect the allergy tests to be positive for?” They concluded that patients have limited ability to correctly predict positive skin tests to aeroallergens, and patients are able to predict negative skin tests with reasonable accuracy.¹⁶ Smith et al reported that the combination of SPTs and a structured allergy history is markedly superior to patients' own assessments of their allergic status or the structured history alone.⁴ In the present study, 75% of SPT-positive patients predicted the test result to be positive.

A previous study of ours aimed to determine if allergy specialists could predict positive SPT results based on detailed allergy history; however, the questionnaire used did not include questions concerning nasal itching, seasonality of symptoms and indoor/outdoor symptom exacerbation, which have proven to be important correlates in this study. Assessment of atopy based on detailed allergy history was reported to be inefficient, and the specialist could be able to identify non-atopic patients.¹⁷ Those previous studies were based on specialists' opinion, and/or patients' self-report of allergic status.^{4,16,17}

One limitation of the present study is that, it was not conducted at a primary care setting, which could limit the

TABLE 4 Sensitivity, specificity, false-positive and false-negative values of different cut-off values for SPT results^a

Cut-off value ^b	Sensitivity (%)	Specificity (%)	False negative	False positive
			<i>n</i> (%)	<i>n</i> (%)
−7.5	96	24	7 (1.9)	151 (41.6)
−1.5	80	58	83 (22.9)	32 (8.8)
2.5	67	76	48 (13.2)	54 (14.9)
5.5	63	80	39 (10.7)	61 (16.8)
8.5	60	84	31 (8.5)	66 (18.2)
14.5	47	90	19 (5.2)	87 (24)

^aTotal scores ranges from −21 to 26.

^bIf the total score of a patient is equal to or greater than the cut-off value the skin prick test result is presumed to be positive, if the total score of a patient is less than the cut-off value the SPT result is presumed to be negative.

The Bold values indicates lesser than 0.05.

TABLE 5 Performance of the 5.5 cut-off value

	SPT negative (%)	SPT positive (%)
Score < 5.5	80.3	37
Score ≥ 5.5	19.7	63

generalizability of our tertiary care centre findings. However, patients directly seek medical care from allergy centres in Turkey without referral. Therefore, our patient population is generalizable to population of patients with asthma and/or rhinitis for our country. Nevertheless, the scoring system will be validated in a primary care setting.

In conclusion, the 13-item instrument described herein was highly specific for identifying SPT-negative patients with asthma and/or rhinitis. It provides a simple and quick method to define nonallergic patients. The instrument may be used especially in middle income countries where allergy testing is expensive or not reimbursed or few allergy clinics available. We think that our idea is interesting, that needs further research.

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CONFLICT OF INTEREST

All authors declare no conflict of interest relevant to this study. No financial support for the research was received.

AUTHOR CONTRIBUTIONS

Corresponding author (Ebru Celebioglu) took the responsibility for the content of the manuscript. All listed authors made important contributions to conception and design of the study,

acquisition and analysis of data, and revised the manuscript for intellectual content and provide final approval of the version to be published. The data analysis was performed at American Thoracic Society (ATS), Methods in Epidemiologic, Clinical and Operations Research (MECOR) level 3 course in Turkey.

ETHICS

The study protocol was approved by Medical Ethics Committee of Hacettepe University.

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