

Analysis of a database to predict the result of allergy testing *in vivo* in patients with chronic nasal symptoms

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ABSTRACT

Background: This article uses the logistic regression model for diagnostic decision making in patients with chronic nasal symptoms. We studied the ability of the logistic regression model, obtained by the evaluation of a database, to detect patients with positive allergy skin-prick test (SPT) and patients with negative SPT. The model developed was validated using the data set obtained from another medical institution.

Methods: The analysis was performed using a database obtained from a questionnaire administered to the patients with nasal symptoms containing personal data, clinical data, and results of allergy testing (SPT). All variables found to be significantly different between patients with positive and negative SPT ($p < 0.05$) were selected for the logistic regression models and were analyzed with backward stepwise logistic regression, evaluated with area under the curve of the receiver operating characteristic curve. A second set of patients from another institution was used to prove the model.

Results: The accuracy of the model in identifying, over the second set, both patients whose SPT will be positive and negative was high. The model detected 96% of patients with nasal symptoms and positive SPT and classified 94% of those with negative SPT.

Conclusion: This study is preliminary to the creation of a software that could help the primary care doctors in a diagnostic decision making process (need of allergy testing) in patients complaining of chronic nasal symptoms.

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Chronic rhinitis is typically classified as allergic rhinitis (AR) if the symptoms and triggers correlate with a specific IgE-mediated response or as nonallergic rhinitis if symptoms are induced by irritant triggers in the absence of specific IgE-mediated responses.^{1–5} AR is a common condition affecting 5–40% of the general population and there is evidence that its prevalence is increasing.³ Rhinitis is an inflammation of the nasal membrane that causes periods of nasal discharge, sneezing, and congestion that persist for at least 2 hr/day.^{1,2,6–8} Rhinitis is considered allergic when allergen-specific IgE initiates the immunologic reaction that causes symptoms, whereas it is nonallergic if allergen-specific IgE is negative.^{9,10}

Diagnostic allergy tests attempt to detect specific IgE, which cause the nasal symptoms, binding common allergens, such as house-dust mites, pollens, animal proteins, and mold spores.¹¹ Primary care doctors are usually the first to encounter patients with chronic nasal symptoms, but they are often uncertain about how to differentiate between allergic and nonallergic forms of the disease.¹² They normally require a consultation with an allergy specialist if nasal symptoms have been present for >2 years and they occur cyclically.¹³ Rhinitis is a common problem in primary care, which is often managed suboptimally and causes considerable morbidity. As with many other long-term conditions, good communication between primary and secondary care in terms of timely and appropriate referral is a key factor for success.^{14,15}

The availability of a short questionnaire for the diagnostic decision, which correlates with the positive or negative allergy test, may serve to modify and rationalize the current approach taken by primary care doctors to evaluate patients with chronic nasal symptoms. In other words, we will try to answer the question, is it necessary for patients

to undergo allergy testing? This decision will be made considering their demographic and clinical characteristics. Because of its simplicity, high sensitivity (Se), rapid interpretation, and a relatively low cost skin-prick test (SPT) was, until recently, often recommended by primary care doctors; however, because of the current state of the economy and health care system problems, health care expenditure has fallen. In the Italian health care system, the total cost of an allergy test and *in vivo* testing is €44, considering the cost of the allergy extract and the allergist's charge (allergist's time for the medical history, clinical examination, and SPT¹⁶). This is paid by the patient, who possibly does not need an allergy test.

An important contribution to the rhinitis diagnostic decision process can be provided by the examination of a database performed on a wide sample of patients with chronic nasal symptoms. The crucial point is how to examine the data obtained from the database to assemble a questionnaire that will facilitate the diagnostic decision process of primary care doctors for new patients with chronic nasal symptoms.

A considerable amount of scientific production is directed at the exploitation of databases or questionnaires to implement models and algorithms useful to the assessment, assistance in medical diagnosis, and treatment of AR and respiratory diseases. In the early 1980s Pantin and Merrett¹⁷ applied a computer system to predict the IgE-mediated allergies of patients who answer a standard allergy questionnaire by referring to a database compiled from previous patients' answers and their IgE antibody profiles. Subsequently, other computer systems have been published.^{18–21} However, none have been used in the clinical practice.

Our objective was to evaluate accuracy of SPT results, by analysis, through a logistic regression model, of a database of 1359 patients with chronic nasal symptoms. The logistic regression model is a standard classification method used in statistics and machine learning.²²

The performance of the model was validated through a data set obtained from another medical institution of the center of Italy. Between the south (Palermo, Sicily) and center (Rome, Lazio) of Italy there are very different aerobiological realities and then different Se's in allergic patients.^{23,24} The results of this model could be useful for primary care doctors to start the correct diagnostic process, without interfering with the role of the doctor who, in our opinion, can not be replaced by a computer.

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PATIENTS AND METHODS

Description of the Database

The original database consists of 1511 patients, consecutively seen and evaluated in the outpatient allergy office of the 'Dipartimento BioMedico di Medicina Interna e Specialistica' (Di.Bi.M.I.S.; ex Dipartimento di Medicina Clinica e delle Patologie Emergenti) of the University of Palermo, Italy. The database was previously used to analyze the characteristics of AR disease.⁹ Of the 1511 patients with nasal symptoms reported in the previous study, we performed the current analysis evaluating 1359 patients who had completed the diagnostic process. The data were obtained from a questionnaire administered to the patients and containing their personal information, the main features about nasal symptoms, and the results of allergy testing. All questionnaires were administered by two allergists, who, if necessary, clarified to patients the meaning of the questions. All patients performed *in vivo* allergy testing: SPT, using a standard panel of allergens.^{9,24} Each patient underwent SPT on the volar aspect of the forearm, using a standard panel of aeroallergens present in our geographic area (Alk Abellò, Milan, Italy). The panel consisted of the following extracts: grass (*Phleum pratense*, *Dactylis glomerata*, *Festuca elatior*, *Lolium perenne*, and *Poa pratensis*), weeds (mugwort [*Artemisia vulgaris*]), pellitory of the wall or sticky weed (*Parietaria judaica* and *Salsola kali*), trees (birch [*Olea europaea* and *Cupressus*]), house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Alternaria alternata*, *Cladosporium herbarum*, and *Aspergillus fumigatus*), animal dander (cat and dog), negative control (glycerinated saline), and positive control (histamine, 10 mg/mL).

Positive responses were defined as any wheal with a diameter 3 mm greater than the negative control, 15 minutes after application. The diameter was assessed by measuring the minimal + maximal diameter/2. The wheal diameters were reported for each patient.

Results of the SPT were confirmed by the assay of serum-specific IgE. We analyzed the data of 25 different input variables for each patient of which 3/25 were continuous variables, 4/25 were ordinal variables, and, finally, 18/25 were dichotomous variables.

Statistical Analysis

We compared each input variable between SPT⁺ and SPT⁻ output variable, using the Student's *t*-test or Mann-Whitney test for continuous variables, depending on the distribution of the data, the χ^2 -test for the dichotomous variables, and, finally, the Mann-Whitney test for the ordinal variables.²⁵

All variables found to be significantly different between patients with positive SPT and negative SPT ($p < 0.05$) were selected for the logistic regression model and analyzed with backward stepwise logistic regression. The goodness of fit of the logistic models was assessed using the Hosmer and Lemeshow test.²⁶ Several multiple logistic regression models were tested to determine the most significant and simplest model with the best available fit for the available data. Based on the regression coefficients obtained for each significant factor chosen by the logistic regression, a predictive probability equation was used to generate predicted probability of positive SPT for each individual. The probability of having a positive SPT in patients with nasal symptoms (p) was then calculated using the following equation:

$$P = \frac{e^y}{1 + e^y}$$

where $y = \text{constant} + x_1 \text{ variable}_1 + x_2 \text{ variable}_2 + x_3 \text{ variable}_3 + \dots$

The area under curve of the receiver operating characteristic (ROC)²⁷ has been evaluated applying the equations indicated by Fletcher and Fletcher.²⁸ We then assessed the performance of the algorithm by calculating its Se, specificity (Sp), positive predictive value, negative predictive value, positive likelihood ratio (LR⁺), neg-

Table 1 Demographic and clinical characteristics of the population

Variable	SPT ⁺ (961)	SPT ⁻ (398)	<i>p</i> Value
Age* (yr)	32.83 (11.50)	39.88 (15.06)	<0.0001
Male#	488 (50.78)	131 (32.91)	<0.0001
Years of nasal symptoms*	7.11 (6.63)	7.5 (8.09)	0.35
Age of onset nasal symptoms* (yr)	25.81 (11.42)	32.52 (15.69)	<0.0001
Family history#	336 (34.96)	103 (25.90)	0.0011
Smoker#	187 (19.46)	78 (19.60)	0.95
Ex smokers#	82 (8.53)	36 (9.05)	0.76
Passive smoker#	216 (22.48)	102 (25.63)	0.21
Trigger of nasal symptoms#	929 (96.67)	296 (74.37)	<0.0001
Presence of pet#	109 (11.34)	6 (1.51)	<0.0001
Nasal symptoms outdoors#	442 (45.99)	74 (18.58)	<0.0001
Perennial nasal symptoms#	802 (83.45)	328 (82.41)	0.64
Sneezing#	953 (99.16)	150 (37.69)	<0.0001
Severity of sneezing§	3 (2–3)	0 (0–1)	<0.0001
Rhinorrhea#	891 (92.72)	372 (93.47)	0.62
Severity of rhinorrhea§	2 (1–3)	2 (1–2)	<0.0001
Nasal itching#	910 (94.70)	182 (45.73)	<0.0001
Severity of nasal itching§	2 (1–3)	0 (0–1)	<0.0001
Nasal obstruction#	856 (89.07)	386 (96.98)	<0.0001
Severity of nasal obstruction§	2 (1–3)	2 (2–3)	<0.0001
Conjunctivitis#	356 (37.04)	50 (12.56)	<0.0001
Duration of nasal symptoms (persistent)#	370 (38.50)	173 (43.47)	0.08
Severity of nasal symptoms (severe)#	644 (67.01)	129 (32.41)	<0.0001
Clinical response to antihistamines#	499 (51.93)	43 (10.80)	<0.0001

*Means (SDs); confidence level 99%, equal variances hypothesis.

#Frequencies of the value 1 (yes; relative percentages).

§Medians (25th–75th percentiles).

SPT = skin-prick test.

Table 2 Variables that significantly distinguish subjects who are SPT⁺ from subjects who are SPT⁻ by backward stepwise logistic regression

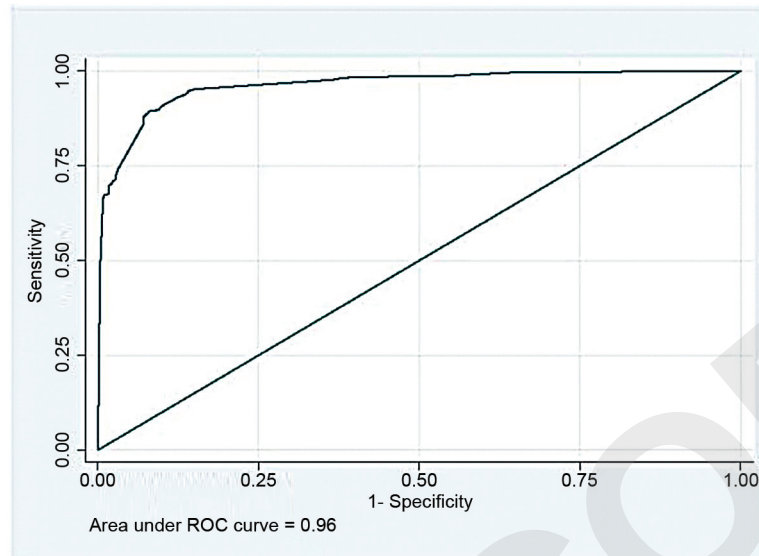
Variable	OR	95% CI	<i>p</i> Value
Age (yr)	0.96	0.94–0.96	<0.0001
Sex	1.70	1.13–2.56	0.01
Family history	1.71	1.10–2.64	0.02
Trigger of nasal symptoms	6.08	3.22–11.49	<0.0001
Presence of pet	7.24	2.40–21.81	0.0004
Nasal symptoms outdoors	1.96	1.23–3.14	0.005
Sneezing	1.13	2.66–6.43	<0.0001
Nasal itching	5.20	3.32–8.14	<0.0001
Nasal obstruction	0.19	0.07–0.51	0.0009
Conjunctivitis	3.88	2.32–6.48	<0.0001
Severity of nasal symptoms	18.82	10.98–32.28	<0.0001
Clinical response to antihistamines	10.37	21.68–75.17	<0.0001

SPT = skin-prick test; OR = odds ratio.

ative LR (LR⁻), accuracy, geometric mean of the identified true rates of positive SPT (Se) and negative SPT (Sp), and diagnostic odds ratio.

Validation of the Logistic Regression Model

To evaluate the probability of the previous obtained logistic model to identify correctly patients with positive or negative SPT,²⁸ we



Metric values of logistic regression model

Metric	Value	95% CI
Sensitivity	0.90	0.87 to 0.92
Specificity	0.87	0.83 to 0.91
Prevalence	0.70	0.67 to 0.73
Positive predictive value	0.94	0.92 to 0.96
Negative predictive value	0.78	0.73 to 0.83
Positive likelihood ratios	7.33	4.70 to 10.29
Negative likelihood ratios	0.11	0.08 to 0.14
Accuracy	0.89	0.87 to 0.91
Geometric mean of the individuated <i>Se</i> and <i>Sp</i>	0.89	0.86 to 0.91
Diagnostic odds ratio	65.69	34.5 to 100.91

Figure 1. ROC curve of the logistic regression model.

analyzed the data of 88 adult patients with chronic nasal symptoms, consecutively seen and evaluated in the outpatient allergy office of the Dipartimento di Pediatria Ospedaliera G.B. Grassi of Rome, Italy. The data consisted of patients' personal information, main features of nasal symptoms, and results of SPT. This was a blind performed evaluation: The physicians of Palermo did not know the results of the SPT performed in Rome and the physician in Rome did not know the results obtained from the responses to the questionnaire, examined with the algorithm obtained from logistic model of the database of Palermo.

ETHIC COMMITTEE

The study was approved by the Institutional Review Board of the Dipartimento di Medicina Interna e Specialistica (now Dipartimento BioMedico di Medicina Interna e Specialistica [Di.Bi.M.I.S.]) of the University of Palermo, Italy, and it was conducted according to the Declaration of Helsinki. Authorization of the study was not required according to our institutional policy and the Ethical Committee of our institution, because procedures performed were part of routine diagnostic testing. However, written informed consent for the study was obtained from each patient in compliance with our institutional policy.

RESULTS

Statistical Analysis of Database of Palermo

Based on the analysis reported in the previous section, we selected the variables used to make the logistic regression model. Seventy-one percent of the subjects, present in the Palermo database, were positive on SPT ($n = 961$). The clinical characteristics of the study population divided into positive and negative SPT subgroups are summarized in Table 1. The best logistic model included the following variables: age, sex, presence of family history of IgE-mediated allergic disease, if nasal symptoms were related to allergens, if the subject is in contact with pets, where the nasal symptoms occur, presence of sneezing, presence of nasal itching, presence of nasal obstruction, presence of conjunctivitis, severity of nasal symptoms, and presence of a clinical response to antihistamines. Table 2 shows the results of logistic regression retaining only the significant covariates in this model. The presence of a clinical response to antihistamines, severity of nasal symptoms, contact with pets, nasal symptoms related to allergens, presence of nasal itching, presence of sneezing, presence of conjunctivitis, nasal symptoms occurring outdoor, and male gender were associ-

Table 3 Contingency table of the results of the logistic regression model

From Logistic Model	From Allergy Testing <i>In Vivo</i>		Total
	SPT ⁺	SPT ⁻	
Predicted positive SPT	53	2	55
Predicted negative SPT	2	31	33
Total	55	33	88

SPT = skin-prick test.

Table 4 Allergy testing in patients of Rome and metric values

Metric	Value	95% CI
Sensitivity	0.96	0.87–0.99
Specificity	0.93	0.80–0.99
Prevalence	0.62	0.51–0.72
Positive predictive value	0.96	0.87–0.99
Negative predictive value	0.93	0.79–0.99
Positive LR	15.90	4.91–57.17
Negative LR	0.03	0.01–0.13
Accuracy	0.95	0.91–0.99
Geometric mean of the individuated Se and Sp	0.95	0.83–0.99
Diagnostic odds ratio	410.75	45.27–4801.20

LR = likelihood ratio; Se = sensitivity; Sp = specificity.

ated with positive SPT, whereas older age and presence of nasal obstruction were associated with negative SPT.

We performed ROC analysis for all variables that were found to be independently associated with SPT⁺ and SPT⁻ to identify the optimal cutoff point useful in predicting positive SPT. For the optimal cutoff point useful in predicting positive SPT, based on the aforementioned logistic regression model, the following equation was generated and used to calculate predicted probability (*pi*) of having patient who is SPT⁺: ($pi/1 - pi$) = (-3.32) + (-0.05 [age]) + (0.53[sex]) + (0.54 [presence of family history of IgE-mediated allergic disease]) + (1.80 [if nasal symptoms were related to allergens]) + (1.98 [if the subject is in contact with pets]) + (0.67 [nasal symptoms occur outdoor]) + (1.42 [presence of sneezing]) + (1.65 [presence of nasal itching]) + (-1.64 [presence of nasal obstruction]) + (1.36 [presence of conjunctivitis]) + (2.94 [severity of nasal symptoms]) + (3.70 [clinical response to antihistamines]). This algorithm resulted in high predictive accuracy, considering as the best cutoff >0.70: Se, 0.90 (95% CI [0.87, 0.92]); Sp, 0.88 (95% CI [0.83, 0.92]); positive LR, 7.33 (95% CI [4.70, 10.30]); negative LR, 0.11 (95% CI [0.09, 0.14]); and area under curve, 0.96 (95% CI [0.94, 0.97]), with a significance level <0.0001. We reported in Fig. 1 the performance of the ROC curve of the model based on SPT results present in the database of Palermo and the patients classified with the algorithm.^{27,28} Our results confirmed that the model can be considered as a diagnostic decision-making tool.

Validation of the Logistic Regression Model

We analyzed a new database obtained from 88 adult patients with chronic nasal symptoms, consecutively seen and evaluated clinically and with SPT, in the outpatient allergy office of the Dipartimento di Pediatria Ospedaliera (Pediatric Department) G.B. Grassi of Rome, Italy. We used the input variables of logistic model, obtained from the Palermo database. In this way we evaluated how many patients with chronic nasal symptoms in Rome would be classified correctly by the logistic model, comparing the results with the results of SPT performed on these patients. We then evaluated the probability of the

Table 5 Positive and negative probabilities of the predictive logistic regression model

	Value	95% CI
p_{post}^{+}	0.96	0.84–0.99
p_{post}^{-}	0.94	0.74–0.99

logistic model to identify correctly patients with positive or negative SPT. The results of SPT performed on these patients and the predicted SPT with the logistic model are reported in Tables 3 and 4. The logistic regression model is 96% sensitive and 94% specific. It will detect 96% of patients with nasal symptoms and positive SPT and classify 94% of patients with negative SPT (Table 5).

CONCLUSIONS

The model performed well in predicting the result of SPT in individuals with chronic nasal symptoms (ROC curve areas is 0.95 for our logistic model). The logistic regression model had all of the metric values >80%, at ideal thresholds. The logistic model is simple and easy to interpret. Logistic regression yields a regression equation with coefficients for each significantly associated covariate. This is the first study that considering the clinical features of patients with nasal chronic symptoms predicted the result of SPT. Using our model, the primary care doctors could have a simple tool that might help in the selection of patients who will benefit from the performance of allergy testing. We do not want to take the doctor's place but we would like to provide a tool that can help to make a decision. Our model correctly classified 96% of patients who will have a positive SPT, and 94% of those who will have a negative SPT. The use of our model would rationalize the access of patients with chronic nasal symptoms, to allergy clinics in the public health system. This consideration would reduce the direct cost of the patients and the indirect cost of the public health system.

Prior study examined patients with AR and nonallergic rhinitis; however, these included a smaller number of variables than our analysis and may have excluded important input variables.^{18–21} To our knowledge, this is the first study for prediction of the results of SPT as positive or negative on the basis of clinical history. We believe this approach produces the model that could be the most useful for primary care doctors, without interfering with the role of the doctor who, in our opinion, can not be replaced by a computer. We are currently investigating whether our logistic model can be translated into software.

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