

Receiver Operating Characteristic analysis: A useful method for a comparison of the clinical relevance of two in vitro IgE tests

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Background: The objectives of this study were to demonstrate the usefulness of Receiver Operating Characteristic (ROC) analysis in the definition of a positive threshold in the comparison of two in vitro tests for detecting IgE antibodies and to determine the clinical relevance of specific IgE tests according to the sensitivity and specificity determined by ROC analysis.

Methods: Specific IgE levels were compared with the use of both MATRIX (Abbott Laboratories, Chicago, Ill.) and PHADEZYM (Pharmacia, Uppsala, Sweden) tests in 109 patients: 86 allergic patients and 23 control subjects. All allergic patients had a clinical history of allergy to mite, cat, grass pollen, or birch pollen and positive skin prick test results to the suspected allergen. Using various levels of specific IgE, we determined the points of the ROC curves with the best ratio of true positives to false positives for four aeroallergens (i.e., mite, cat, grass pollen, and birch pollen).

Results: Except for mite allergen there was no correspondence between the positive threshold values determined by ROC analysis with MATRIX and PHADEZYM tests. In terms of class, when ROC analysis was used, the threshold was class III with the MATRIX test and class II with PHADEZYM test for cat, grass pollen, and birch pollen and class III for mite. According to the threshold value, sensitivity and specificity for MATRIX and PHADEZYM tests were similar except for cat, for which the PHADEZYM test had a lower sensitivity (0.71) than the MATRIX test (0.90). With mite allergen the predictive value of only one positive MATRIX test result was 0.96. The specificities of MATRIX and PHADEZYM tests were 100% in both nonatopic and atopic control groups.

Conclusions: We conclude that ROC analysis is a reliable method for comparing IgE in vitro tests and that it emphasizes the lack of correspondence between arbitrary units given for each in vitro test. ROC analysis appears to be a good method for helping to standardize IgE in vitro tests. (*J ALLERGY CLIN IMMUNOL* 1993;92:255-63.)

Key words: ROC analysis, in vitro IgE tests, clinical relevance, comparison

Diagnosis of allergy for the most part is based on the clinical history. However, other tests are performed to confirm or negate clinical suspicions. In vitro tests for IgE constitute a technically valid method for detecting allergen-specific IgE

Abbreviation used

ROC: Receiver operating characteristic

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antibody in sera. By the early 1980s, the market for in vitro testing had grown sufficiently to induce many companies to develop new in vitro tests. Recently, in vitro multiple allergen tests have been marketed as a screening method for the diagnosis of allergic diseases.¹⁻³ The major drawback of all these tests is the lack of correspondence between arbitrary class scores and units of IgE antibody. Therefore the positive threshold for an in vitro IgE test is usually chosen arbitrarily, which makes it impossible to com-

pare the sensitivities and specificities of different tests. Using the receiver operating characteristics (ROC) curve, we statistically defined the positive threshold for two different tests: a multitest MATRIX (Abbot Laboratories, Chicago, Ill.) and the reference test, PHADEZYM (Pharmacia, Uppsala, Sweden). After the threshold values were determined, the sensitivity and specificity of the tests were compared.

METHODS

Subjects

One hundred nine patients were selected and divided into three groups: group A was composed of 86 patients (50 men and 36 women) aged 27.8 ± 10.9 years, with a clinical history of allergy to one or several aeroallergens (i.e., *Dermatophagoides pteronyssinus*, cat, grass pollen, birch pollen) and a positive skin test result to the suspected allergen; group B consisted of 20 nonatopic patients (12 men and 8 women) aged 35.2 ± 8 years, with no clinical history of allergy and no positive skin test results to 10 aeroallergen extracts (i.e., *D. pteronyssinus*, *D. farinae*, *Alternaria* species, *Aspergillus* species, dog, cat, grass pollen, birch, mugwort, and plantain pollen); group C comprised 3 patients (3 women) aged 43.6 ± 13 years, with elevated total IgE levels from 660 to 880 KU/L (normal values <150 KU/L) without clinical or skin test evidence of sensitivity to the 10 aeroallergens tested. These patients were selected to assess the occurrence of nonspecific IgE binding to the four aeroallergens in patients with high levels of total IgE.

All patients in group A had asthma and/or rhinitis (25 had rhinitis alone; 31 had asthma and rhinitis; 30 had asthma alone). Allergies to cat, grass pollen, and birch pollen were suspected when exposure provoked allergic symptoms. The criteria used to define clinical allergy to mites were: (1) perennial asthma or rhinitis, and (2) improvement at high altitudes (i.e., >1500 M), and/or (3) clinical symptoms provoked by dust, and/or (4) exacerbation of symptoms in specific places, and/or (5) more than $10 \mu\text{g/gm}$ of *Der p* 1 in domestic dust or Acarex test result greater than or equal to 3+.

Patients with perennial asthma or rhinitis to another aeroallergen were excluded. All clinical evaluations were performed by the same physician.

Skin tests

Prick tests were performed with Prick-Lancette (Dome-Hollister-Stier Laboratories, Puteaux, France) on the volar surface of the forearm with 10 aeroallergen extracts. *D. pteronyssinus*, *D. farinae*, *Alternaria* species, *Aspergillus* species, cat, and dog were obtained from Dome-Hollister-Stier. Grass, mugwort, plantain, and birch pollen extracts were provided by Stallergènes Laboratories (Paris, France). A negative control test was performed with saline solution, and a positive control test was done with histamine 1 mg/ml . The result of a prick test was considered to be positive when

the mean diameter ($D + d/2$) of the wheal induced by the allergen was 75% of the mean diameter of the wheal obtained with the histamine control.

Specific IgE determination

MATRIX is an enzyme immunoassay for panel testing, which has been previously described.⁴ The system includes disposable test cards, a reagent, and an analyzer. Each test card contains 14 aeroallergens (i.e., *D. pteronyssinus*, *D. farinae*, *Aspergillus fumigatus*, *Alternaria alternata*, *Penicillium* species, cat, dog, timothy and Bermuda grasses, *Parietaria* species, olive, birch, plantain, and mugwort pollen, which are coated onto individual areas, with ultrasonically welded borders on the nitrocellulose. Positive and negative control areas or "spots" are included on each card. The analyzer can process up to 10 test cards at a time. Manufacturer-determined calibration curves for each analysis are provided in bar-code form with each test kit.

In the initial step, $500 \mu\text{l}$ of serum sample are incubated with the test card for 16 hours. Then an anti-human IgE antibody labeled with alkaline phosphatase is incubated for 90 minutes. Finally, the substrate (i.e., alkaline phosphatase-responsive chromogen with azide) is added for the last 90 minutes.

An optical reader measures diffuse reflectance, monitors source intensity, and features wavelength compensation. Units converted into classes are derived from calibration curves determined for each allergen and expressed in MATRIX units (i.e., SIgE). Results are based on the following classification system: 0 = less than 0.25, I = 0.25 to 0.49, II = 0.50 to 2.49, III = 2.5 to 12.49, and IV = greater than 12.5.

PHADEZYM RAST has been described previously.⁵ The allergen covalently coupled to a paper disk is allowed to react with the specific IgE in the patient sample for 3 hours. After washing, a disk-allergen-IgE complex remains. Anti-IgE conjugated with the enzyme B-galactosidase reacts with the bound IgE. After washing, substrate is added, and the absorbance is measured at 420 nm. The standard curve is based on a standardized human serum pool with a high content of specific IgE to the reference allergen (i.e., birch pollen). Results are based on the following classification system and expressed in Phadebas RAST (Pharmacia) units (PRU/ml): 0 = less than 0.35, I = 0.35 to 0.7, II = 0.7 to 3.5, III = 3.5 to 17.5, and IV = greater than 17.5.

ROC curve and predictive values

The sensitivity (i.e., true positives/true positives + false negatives) corresponds to the ratio of patients that have the disease and a true positive test result to all patients with the disease and with either a true positive or a false negative test result. The specificity (i.e., true negatives/true negatives + false positives) corresponds to the ratio of patients that do not have the disease and have a true negative test result, to all patients without the disease and with either a true negative or a false positive test result. False positive ratio corresponds to

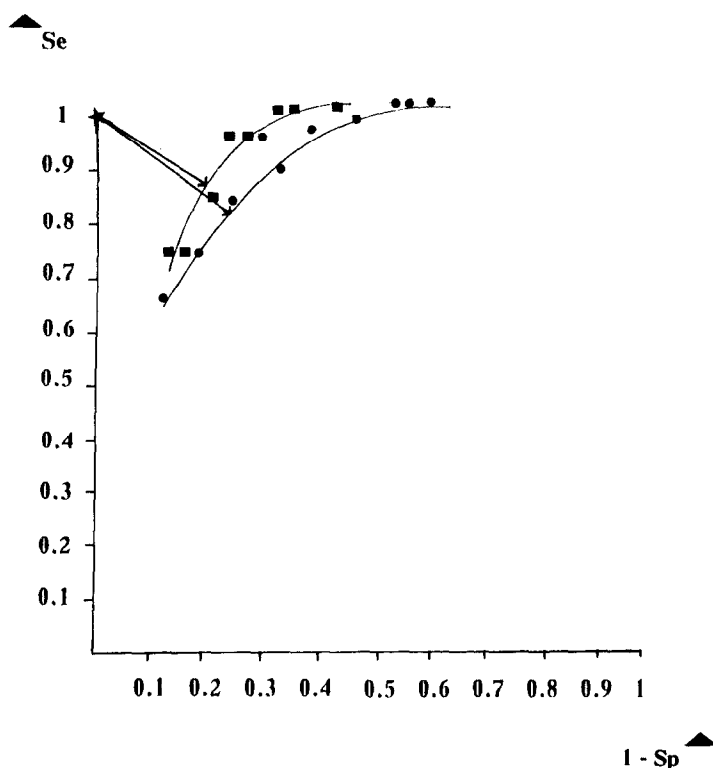


FIG. 1. ROC curve obtained with M (circles) and P (squares) with mite allergen. *Se*, Sensitivity = true positive fraction; *1-Sp*, 1-specificity = false positive fraction. In each figure, the star indicates the ideal point, which represents the best IgE level on an ROC curve that provides both a sensitivity and a specificity equal to 1 (which corresponds to 1-specificity equal to zero). In practice, the point on an ROC curve that is the closest to the ideal point (*) is the threshold value that provides the best compromise between the sensitivity (true positive fraction) and 1-specificity (false positive fraction). These points are represented on each ROC curve by an arrow. For example, with mite allergen the shortest distance between the ideal point and the ROC curve obtained with the MATRIX test is 17 mm and with the PHADEZYM test is 22 mm. When the threshold value determined by inspection of the graph lies between two points, the closest point on the curve is considered to be the threshold value.

1-specificity. With the ROC curve, by plotting the false positive fraction (i.e., 1-specificity) against the true positive fraction (i.e., sensitivity) and varying the threshold of specific IgE levels, we defined the positive threshold that offers the best compromise between the highest false positive fraction and the highest true positive fraction.^{6, 7} The optimal threshold for specific IgE was determined by measuring distances from the ideal point on the ROC curve by inspection of the graphs (Figs. 1 to 4). An ideal point, obtained with an ideal test, is the value of specific IgE giving a sensitivity equal to 1 and a specificity equal to 1, which corresponds to 1 (1-specificity) equal to zero. For each allergen, we ranked the 109 specific IgE values from > 2.5 to > 17.5 SIgE for the MATRIX test and from > 0.75 to > 17.5 PRU/ml for PHADEZYM test. Then the threshold values used to plot the ROC curve were determined by dividing the range into equal groups of 7 to 11 of the specific IgE values. Among the group of specific IgE values, the value chosen was the lowest of that group. With the use of the positive threshold defined by ROC

analysis, sensitivity and specificity were calculated. To estimate the a posteriori probability that a patient does have the disease, given a positive or a negative result, Baye's theorem was used.⁸ The predictive value of a positive MATRIX or PHADEZYM result to a given aeroallergen was calculated with prevalences of allergy to the four aeroallergens studied, in a group of 3962 outpatients who were followed up in our department between 1968 and 1984.⁸ The predictive value of a positive test was:

$$\frac{\text{Sensitivity} \times \text{Prevalence}}{(\text{Sensitivity} \times \text{Prevalence}) + (1 - \text{Specificity})(1 - \text{Prevalence})}$$

Chi square tests were performed to assess independence between allergic and nonallergic patients.

RESULTS

Positive threshold of specific IgE

ROC curves were constructed by plotting true positive versus false positive results obtained for 8

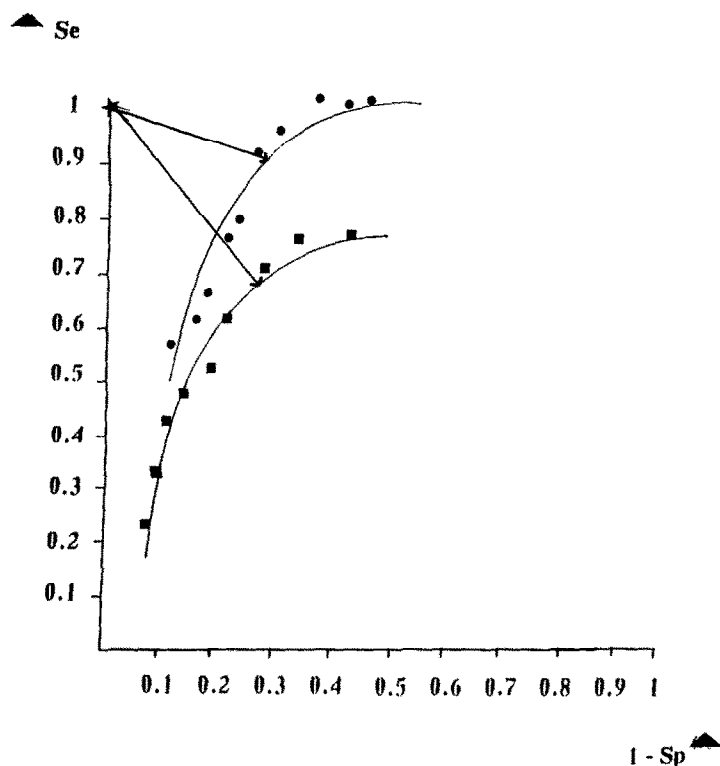


FIG. 2. ROC curve obtained with M (circles) and P (squares) with cat allergen. *Se*, Sensitivity = true positive fraction; *1-Sp*, 1-specificity = false positive fraction.

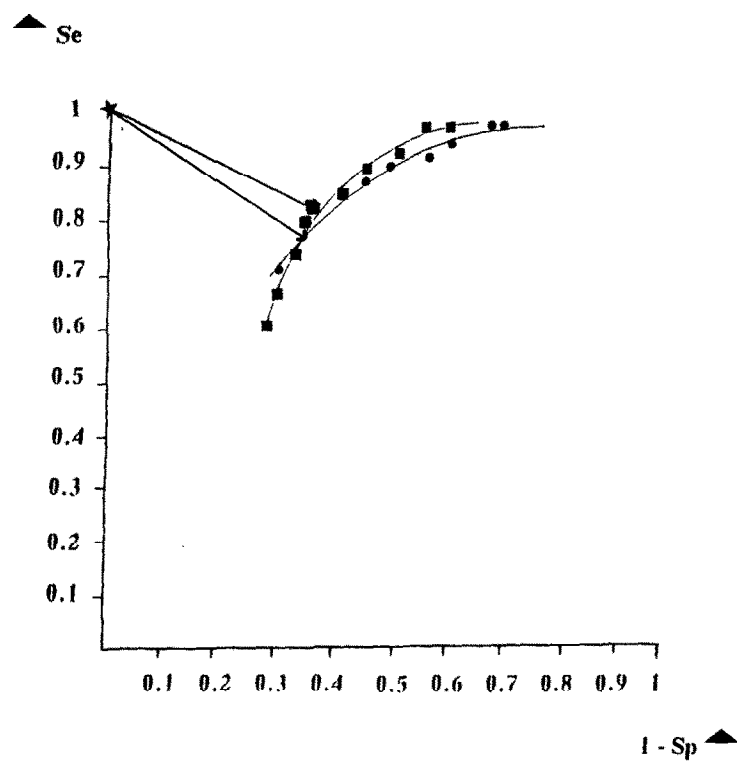


FIG. 3. ROC curve obtained with M (circles) and P (squares) with grass pollen. *Se*, Sensitivity = true positive fraction; *1-Sp*, 1-specificity = false positive fraction.

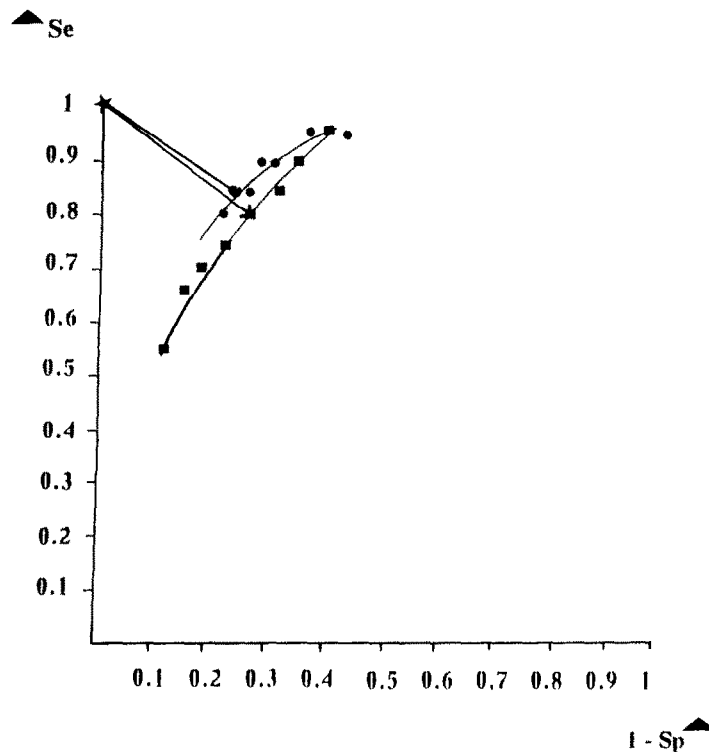


FIG. 4. ROC curve obtained with M (circles) and P (squares) with birch pollen. *Se*, Sensitivity = true positive fraction; *1-Sp*, 1-specificity = false positive fraction.

TABLE I. Sensitivity (i.e., true positive ratio), specificity, and 1-specificity (i.e., false positive ratio) obtained for eight and nine specific IgE values to mite with the MATRIX or PHADEZYM test

MATRIX test				PHADEZYM test			
Threshold*	Se	Sp	1-Sp	Threshold†	Se	Sp	1-Sp
≥ 0.25	1	0.41	0.59	≥ 0.35	1	0.6	0.4
≥ 0.4	1	0.46	0.54	≥ 0.5	1	0.6	0.4
≥ 0.5	1	0.49	0.51	≥ 0.7	1	0.65	0.35
≥ 0.8	0.96	0.55	0.45	≥ 2	0.92	0.69	0.31
≥ 1	0.96	0.59	0.41	≥ 2.5	0.92	0.73	0.27
≥ 2.5	0.88	0.69	0.31	≥ 3.5	0.84	0.77	0.23
≥ 3.5	0.84	0.74	0.26	≥ 10	0.73	0.77	0.23
≥ 5	0.76	0.80	0.20	≥ 17	0.73	0.83	0.17
≥ 12.5	0.65	0.84	0.16				

Se, Sensitivity; *Sp*, specificity; *1-Sp*, 1-specificity.

*In MATRIX units.

†In Phadebas RAST units per milliliter.

to 10 specific IgE values. True positive and false positive fractions obtained with mite are shown on Table I. The absolute value of the positive cutoff for specific IgE was determined with the ROC curve for each allergen and each test. All specific IgE levels equal to or greater than the threshold value were considered to be positive. To express

the results in terms of class of specific IgE, we arbitrarily considered that the class that contained the cutoff value was the threshold class. All specific IgE classes equal to or greater than this threshold class were considered to be positive. The positive cutoff with mite allergen was 3.5 PRU/ml for the PHADEZYM and 3.5 SIgE for

TABLE II. Sensitivity and specificity of skin prick test and MATRIX and PHADEZYM tests with group A patients

	Mite (<i>n</i> = 26)			Cat (<i>n</i> = 21)			Grass pollen (<i>n</i> = 43)			Birch pollen (<i>n</i> = 21)		
	SPT	M*	P†	SPT	M*	P†	SPT	M*	P†	SPT	M*	P†
Positive threshold*												
Absolute value	—	3.5	3.5	—	3.0	0.75	—	7.5	2.25	—	7.7	2.7
Class value	—	III	III	—	III	II	—	III	II	—	III	II
Sensitivity	1	0.84	0.84	1	0.90	0.71	1	0.79	0.81	1	0.85	0.80
Specificity	0.32	0.74	.77	0.63	0.75	0.78	0.36	0.66	0.64	0.67	0.73	0.73

Sensitivity and specificity were determined at the positive threshold level of specific IgE. Eighty-six patients were selected from group A, which was composed of 111 sensitizations (i.e., 36 polysensitized and 75 monosensitized patients).

SPT, Skin prick test; M, MATRIX test; P, PHADEZYM test.

*Values expressed in MATRIX units.

†Values expressed in Phadebas RAST units per milliliter.

MATRIX tests, which corresponded to class III (Fig. 1). For cat allergen (Fig. 2), the threshold was 0.75 PRU/ml with the PHADEZYM test and 3 SIgE with the MATRIX test. With grass pollen, the cutoff was 7.5 SIgE with the MATRIX test and 2.25 PRU/ml with the PHADEZYM test (Fig. 3). With birch pollen, the cutoff value was 7.7 SIgE with the MATRIX test and 2.7 PRU/ml with the PHADEZYM test (Fig. 4).

Sensitivity and specificity results

In terms of specific IgE levels, there was a statistical independence between allergic and nonallergic patients for the four aeroallergens when chi square tests were used (data not shown).

Table II shows the sensitivities and specificities obtained with skin prick tests and MATRIX and PHADEZYM tests in group A patients. Sensitivities of skin prick tests with the four aeroallergens were all equal to 1, because it was the selection criterion. Specificity obtained with skin prick test to grass pollen was low (0.36) compared with the specificity obtained with the MATRIX or PHADEZYM test (0.66 and 0.64, respectively). Sensitivities and specificities obtained with the MATRIX test were very similar to those with the PHADEZYM test, except for cat allergen, for which the MATRIX test appeared to be more sensitive.

Sensitivity and specificity were also determined in group A patients who had only one positive MATRIX or PHADEZYM test result (Table III). When both MATRIX and PHADEZYM tests were used, sensitivity was dramatically reduced, except in the case of mite-allergic patients. On the other hand, use of both tests provided a very high specificity.

Predictive values

Table IV shows the predictive values of only positive MATRIX or PHADEZYM test results to the four aeroallergens when the positive threshold determined with the ROC curve was used. According to the skin test results obtained from 3962 patients, 47% were considered to be allergic to mites, 39% to grass pollen, 8% to tree pollen, and 32% to cat allergen.

No patients from control groups B and C elicited any measurable levels of specific IgE to the four aeroallergens.

DISCUSSION

Diagnosis of allergy is based for the most part on the clinical history. In vitro IgE tests are technically valid methods for detecting allergen-specific IgE antibody. They are often used to confirm or negate clinical suspicions. The aims of this study were to demonstrate the usefulness of the ROC analysis in the definition of a positive threshold in the comparison of two in vitro tests for detection of IgE antibodies and also, according to the sensitivity and specificity determined with the ROC analysis, the clinical relevance of specific IgE tests. In a comparative study of the capacity of in vitro IgE tests for detecting specific IgE, a precise clinical description of the patients selected is of great importance. We tried to define as accurately as possible the clinical diagnosis of the patients who were selected on the basis of both an evocative clinical history of sensitization to one or several aeroallergens and a positive skin test result to the suspected aeroallergen. Although it was simple to obtain a clear clinical history of allergy to cat allergen, grass pollen, and birch pollen, it was more difficult to make a

TABLE III. Sensitivity and specificity of only one positive MATRIX or PHADEZYM test result to the suspected allergen with group A patients

	Mite 18, (26)		Cat 5, (21)		Grass pollen 9, (43)		Birch pollen 5, (21)	
	M	P	M	P	M	P	M	P
Positive threshold								
Absolute value	3.5	3.5	3.0	0.75	7.5	2.25	7.7	2.7
Class of value	III	III	III	II	III	II	III	II
Sensitivity	0.76	0.73	0.42	0.29	0.3	0.23	0.23	0.24
Specificity	0.95	0.96	0.97	0.98	0.95	0.97	0.98	0.96

Allergic patients (i.e., number in brackets) were considered to have one positive MATRIX or PHADEZYM test result (see numbers without brackets) when specific IgE levels to the suspected allergen were superior or equal to the threshold value and specific IgE levels to the three other aeroallergens were below the threshold value. When MATRIX or PHADEZYM values with the suspected allergen were below or superior to the threshold value and one of the three other aeroallergens was superior to the threshold value, patients were considered to be allergic with a negative test result (false negative).

M, MATRIX; P, PHADEZYM test.

TABLE IV. Predictive value of only one positive MATRIX or PHADEZYM test result to the four aeroallergens with the positive threshold determined with ROC curve

	MATRIX test	PHADEZYM test
Mite allergen (0.47)*	0.96	0.94
Grass pollen (0.39)*	0.78	0.82
Birch pollen (0.08)*	0.48	0.34
Cat allergen (0.32)*	0.87	0.87

*Prevalence of positive skin test results among 3962 outpatients who came to our department because of suspected allergy from 1968 to 1984.

diagnosis of mite allergy. This prompted us to define criteria for identifying a clinical history of mite sensitization. The absence of another perennial allergy was the major inclusion criterion. This could explain the high ratio of mite-monosensitized patients (i.e., 96%) compared with 60% for grass pollen-allergic patients. The four aeroallergens were chosen because of their high frequencies in allergies.⁹⁻¹¹ MATRIX and PHADEZYM tests were not applied to other less frequent aeroallergens because of the small number of patients sensitized to them available. Our study may be performed with other aeroallergens of the MATRIX panel in order to determine whether the results obtained with them would be as reliable as those obtained with mite, cat, grass, pollen, and birch pollen.

ROC curve analysis was initially described in radiology,¹²⁻¹⁴ in pulmonology,¹⁵ and in allergy by Ollier et al.⁶ Souille et al.¹⁶ performed a comparative study of bronchial challenge tests, skin tests, and specific IgE antibodies with ROC analysis. More recently, Williams et al.¹⁷ performed a comparative study of three in vitro IgE tests (i.e., Pharmacia CAP System, Phadebas RAST, and

modified RAST) with ROC analysis. An ROC curve demonstrates the variation of sensitivity and specificity of a test as a function of threshold values and helps to determine a positive threshold value. The threshold chosen is open to discussion: if the cutoff value is "low," sensitivity is increased and specificity decreased; consequently, there will be an increased number of false diagnoses of clinical allergy. Hoffman¹⁸ demonstrated that increasing the sensitivity of a test induced serious difficulties in clinical interpretation. Because IgE immune responses occur more frequently than symptomatic disease, there is an appreciable risk of overdiagnosis if the sensitivity of a test is artificially increased. The positive threshold was defined as the value that offers the highest sensitivity and the highest specificity. In terms of morbidity and cost-effectiveness, we considered that a false-positive diagnosis of allergy is as undesirable as a false-negative diagnosis. A statistical determination of a positive threshold with an IgE test emphasizes (Tables I and Table II) the lack of correspondence between arbitrary units and class ranges used with each test. Therefore it is impossible to compare two in vitro IgE tests that use

classes with the same "number" as threshold criteria. This point was underlined by Bernstein¹⁹ and recently in a statement by the American Academy of Allergy.²⁰ At the determined threshold, MATRIX and PHADEZYM tests had comparable sensitivities and specificities for mite, grass pollen, and birch pollen. The MATRIX test appeared to be more reliable than the PHADEZYM test for measuring specific IgE antibody to cat. Using the RAST method, Souille et al.¹⁶ found a similar sensitivity (0.78) and specificity (0.70) with mite at the same cutoff (class III). The specificities of MATRIX and PHADEZYM tests in group B and C patients were 100%. With Phadebas RAST, Williams et al.¹⁷ found higher sensitivity and specificity with timothy grass and cat than the values that we found with grass pollen and cat with the PHADEZYM test. In this study the authors did not determine the positive threshold with the ROC curve but used the threshold given by the manufacturer (i.e., <0.35 PRU/ml; class 0).

Both in vitro tests for IgE antibody and skin tests are plagued by the same interpretational difficulties. However, skin tests are usually performed by specialists and are integrated into a pertinent and thoughtful clinical evaluation. Recently, multiple-allergen in vitro tests of specific IgE have been presented to nonspecialist practitioners as screening methods for allergy. In European countries, and in France in particular, only 12% of the initial diagnoses of allergies in patients older than 18 years are made by a specialist.²¹

Consequently, it seemed necessary to calculate the predictive values of a single positive MATRIX test result in order to assess the clinical relevance of the test. Prevalences were determined with 3962 outpatients who came to our clinic because of a suspected allergy from 1968 to 1984.⁹ This group of patients presented two advantages. First, the subjects came from the same geographic area as the patients we studied, and the importance of local factors on the type of sensitization is well known.²² Second, most patients came to our clinic because of a suspected allergy, which corresponds to the situation in which nonspecialist practitioners find themselves when they consider prescribing a multiple-allergen in vitro test. Our results showed that multiple-allergen in vitro tests may be useful tools for nonspecialist practitioners in the diagnosis of allergy, keeping in mind that only

class II with the PHADEZYM test or class III with the MATRIX test or greater class results should be considered positive.

However, judicious use of in vitro data requires consideration of clinical factors that must be integrated into a final decision by a knowledgeable physician who has seen and evaluated the patient.²³ It has been demonstrated that there are fewer asthma relapses resulting in emergency room visits and a greater improvement in asthma symptoms when patients with asthma are followed up by a specialist.^{23, 24}

Comparative studies of in vitro IgE tests with a sera of well-defined groups of patients and a statistical determination such as the ROC curve of positive thresholds should contribute to the standardization, and consequently, to the greater reliability of in vitro IgE tests. The development of new in vitro IgE tests should encourage allergists to define the role of each test in the diagnosis of allergy, keeping in mind the interests of the patient and the cost-effectiveness of each method.

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