

ORIGINAL ARTICLE

Utility of diagnostic tests in the follow-up of egg-allergic children

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Summary

Background Better knowledge of the accuracy of a skin prick test (SPT) and specific IgE (sIgE) levels to egg allergens would help to identify persistent egg-allergic children, avoiding unnecessary risky challenges. This study was designed to assess the accuracy of a SPT and sIgE levels to egg allergens in order to determine persistent egg allergy in IgE-mediated allergic children after an egg-free diet.

Methods Children below 16 years were prospectively and consecutively recruited. Inclusion criteria were: allergy to egg proteins (children with a positive clinical case of IgE-mediated egg allergy and a positive SPT to egg allergens and/or positive sIgE levels), and strict egg avoidance diet followed for at least 6 months. Clinical histories were recorded and all patients underwent SPTs, sIgE levels to egg allergens and the gold standard – a double-blind placebo-controlled egg challenge (DBPCFG). DBPCFG was interpreted without knowledge of the results of the other tests and vice-versa. A SPT and sIgE levels' ROC curves analysis was performed to compare the diagnostic performance of the different tests.

Results Finally, 157 children were included in the study. One hundred out of these 157 children (63.7%) had a positive oral challenge. Ninety-six were male (61%), and the median age was 2.5 years. One hundred and three (66.9%) had atopic dermatitis. A 7 mm egg white prick test had a positive likelihood ratio (+LR) of 6.7, and a level of 1.3 KU/L egg white-sIgE had a +LR of 5.1. A 7 mm egg white SPT had a positive predictive value of 92.3% (95% CI 85.1–99.5), and for a 9 mm egg white SPT this value was 95.6% (95% CI 87.3–100.0). For egg white-sIgE, 1.5 KU/L had a positive predictive value of 90.4% (95% CI 82.4–98.4) and for 25 KU/L it was 100.0% (95% CI 100.0–100.0). SPTs with ovotransferrin and lysozyme showed the lowest accuracy, followed by yolk and ovalbumin SPTs.

Conclusion This study is the first to evaluate both tests (SPT and sIgE levels) and all egg allergens to determine the persistence of egg allergy in IgE-mediated allergic children. Measuring the SPT and sIgE levels is useful to predict persistent allergy in these children, especially with the egg white complete extract. An oral challenge should not be performed in egg allergic paediatric patients with either an egg white prick test above 7 mm or a white egg-sIgE determination above 1.3 KU/L, because there is a 90% probability of remaining allergic.

Keywords accuracy, egg allergy, predictive value, skin prick test, specific IgE

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Introduction

The prevalence of food allergy is 1–2% in the general population [1–3] but in children this prevalence increases. Between 2.2% and 5.5% of infants have food hypersensitivity in the first year of life [4]. Egg is one of the most common food allergens in childhood. The estimated prevalence of egg allergy in children is 0.8–1.3% [4]. When an egg allergy diagnosis is established, those children are

placed on an egg protein avoidance diet. The ubiquity of egg proteins makes it difficult to follow a correct avoidance diet. Fortunately, in most cases, egg allergy is transient and most egg-allergic children become tolerant. Regular follow-up visits are scheduled every 6–12 months until tolerance is achieved. In every visit, skin prick tests (SPT) and specific IgE levels (sIgE) to egg fractions are determined. Usually, a challenge test is needed to confirm a patient's clinical reactivity to the food. A double-blind

placebo-controlled food challenge (DBPCFC) is the gold standard in food allergy diagnosis [5–10], but it is a costly and hazardous test since it must be performed in medically supervised settings and severe reactions can occur. It would be very interesting to assess SPT and sIgE levels with accuracy in order to avoid unnecessary risky oral challenges.

Previous work has shown that the accuracy of SPT and sIgE in egg allergy diagnosis is influenced by age, atopic dermatitis (AD) and type of reaction (immediate or delayed) [11–25]. There are several differences between those studies, which makes it very difficult to compare their results.

We could only find one study evaluating the accuracy of sIgE levels on the follow-up of egg-allergic children, while the rest of them evaluate the accuracy of SPT and sIgE in the first diagnosis. Other authors study the diagnostic accuracy of those tests in children with AD without any previous reaction after egg intake.

The frequency of AD and age is very different from one study to another (from 35.7% to 100% of AD, the median age being from 13 months to 17 years).

All kinds of reactions are included: some studies include just IgE-mediated immediate reactions [11, 14, 18, 20–23] but other authors also include delayed reactions (from 18% to 84% of children with delayed reactions).

All these different populations make the cut-off points proposed in the literature heterogeneous (Tables 1 and 2).

There is no published prospective study, with a double-blind placebo-controlled methodology, that evaluates the accuracy of both tests (SPT and sIgE levels) for all egg

allergens, in the follow-up of a representative population of egg-allergic children. The aim of the present study was to evaluate the accuracy of SPT with all available egg allergens (egg white, yolk, ovalbumin (OVA), ovomucoid, ovotransferrin and lysozyme) and the accuracy of sIgE levels to egg allergens too (egg white, yolk, ovalbumin and ovomucoid) when predicting persistent allergy in egg-allergic children following an avoidance diet.

Methods

From January 2002 until December 2005, all patients with an egg allergy diagnosis aged from 1 to 16 years were consecutively recruited for this cross-sectional study developed at the Allergy Department of the Ramón y Cajal Hospital (Madrid, Spain). Egg allergy diagnosis was defined as a positive clinical case of IgE-mediated food allergy and a positive SPT (≥ 3 mm) to egg fractions or positive sIgE levels to the same allergens (≥ 0.35 KU/L), and an egg challenge test, when necessary, following international guidelines [26, 27]. A positive clinical history of IgE-mediated food allergy was defined as: cutaneous symptoms (pruritus, urticaria, angioedema), digestive symptoms (vomiting, abdominal pain, diarrhoea), respiratory symptoms (rhinitis, cough, dyspnoea), or cardiovascular symptoms (tachycardia, hypotension) in the next 2 h after egg intake.

All patients included in the study had been under a strict egg avoidance diet for at least 6 months. Patients with concomitant serious disease, contraindication of adrenaline use or patients with anaphylaxis after the egg

Table 1. Published skin prick test cut-off points in egg allergic children

	Allergen	Cut-off point	Method	Sn	Sp	PPV	NPV	+LR	–LR
Noma 1998 [16]	Egg	10 mm	NR	66.3	81.1	84.6	60.5	3.51	0.42
Sporick 2000 [13]	Egg white	7 mm	100% PPV	–	100	100	–	–	–
		≥ 2 years							
	Egg white	5 mm	100% PPV	–	100	100	–	–	–
		< 2 years							
Boyano 2001 [20]	Egg white	3 mm	NR	97	71	93	86	3	0.04
	Yolk	3 mm		78	88	96	52	6.6	0.25
	OVA	3 mm		95	65	91	79	2.7	0.07
	OVM	3 mm		78	82	94	50	4.4	0.26
Monti 2002 [12]	Egg white	5 mm	100% PPV	18	100	100	37.2	–	0.82
	Yolk	5 mm	100% PPV	4.2	100	100	33.6	–	0.96
Osterballe 2004 [14]	Egg	3 mm	NR	87.5	66.7	77.8	80	2.63	0.19
Hansen 2004 [23]	Egg	3 mm	NR	100	85	77	100	6.67	0
Giusti 2005 [17]	Egg+yolk	6 months–2 years	NR	60	100	100	73.3	–	0.40
		3 years–6 years		62.5	92	71.4	88.5	7.8	0.41
		7 years–14 years		12.5	91.3	33.3	75	1.44	0.96
		All ages		46.2	93.2	75	79.7	6.8	0.58
Mehl 2006 [15]	Egg	14 mm	95% PPV	–	–	95	–	–	–
		20 mm	99% PPV	–	–	95	–	–	–

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; –LR, negative likelihood ratio; NR, no referred; OVA, ovalbumin; OVM, ovomucoid.

Table 2. Published specific IgE cut-off points in egg allergic children

	Allergen	Cut-off point	Method	Sn	Sp	PPV	NPV	+LR	−LR
Crespo 1994 [18]	Egg white	0.35 KU/L	Detection technique level	72	66	78	58	2.16	0.42
		0.70 KU/L	NR	60	80	83	54	3	0.5
		1.20 KU/L	NR	44	93	92	50	6.6	0.60
Sampson 1997 [11]	Egg	2 KU/L	90% PPV	82	84	94	62	5.23	0.21
		3.4 KU/L	Maximum sum Sn+Sp	89	73	90	71	3.29	0.15
		6 KU/L	95% PPV	72	90	95	54	7.2	0.31
Niggemann 1999 [19]	Egg	0.35 KU/L	Detection technique level	95	38	79	75	1.5	0.13
Sporik 2000 [13]	Egg white	2 KU/L	NR	38.5	88.7	84.2	48	3.41	0.69
Boyano 2001 [20]	Egg white	0.35 KU/L	Detection technique level	91	77	94	68	3.9	0.12
	Yolk	0.35 KU/L		63	93	98	37	9	0.4
	OVA	0.35 KU/L		72	83	96	36	4.3	0.33
	OVM	0.35 KU/L		73	82	96	35	4	0.33
Sampson 2001 [21]	Egg	6 KU/L	95% PPV previous retrospective study	64	90	96	39	6.08	0.4
		7 KU/L	90% Sp previous retrospective study	61	95	98	38	11.6	0.41
Monti 2002 [12]	Egg white	99 KU/L	100% PPV	16.7	100	100	36.8	–	0.36
	Yolk	17.5 KU/L	100% PPV	13.8	100	100	28.2	–	0.76
Osterballe 2003 [22]	Egg white	0.8 KU/L	Same weight Sn y Sp	75	83	88	66	4.4	0.30
		1.5 KU/L	95% PPV	60	100	100	59	–	0.4
Osterballe 2004 [14]	Egg white	1.43 KU/L	NR	62.5	66.7	71.4	57.1	1.88	0.56
	Egg white	10.9 KU/L < 1 year	95% PPV	–	–	95	–	–	–
Celik 2005 [24]		13.2 KU/L ≥ 1 year		–	–	95	–	–	–
		12.6 KU/L all		–	–	95	–	–	–
Mehl 2006 [15]	Egg	15.9 KU/L	95% PPV	–	–	95	–	–	–
		75.5 KU/L	99% PPV	–	–	99	–	–	–

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NR, no referred; OVA, ovalbumin; OVM, ovomucoid.

intake, defined as a severe reaction (grade 3) by Brown's grading system for generalized hypersensitivity reactions [28], or a moderate reaction (grade 2) with respiratory compromise, were excluded. According to these criteria, patients with hypotension, hypoxia, neurologic or respiratory compromise after egg intake were excluded.

Data on sex, age, AD, age of first egg reaction, symptoms, other food allergies, asthma, rhinitis and atopic family were collected.

Following international guidelines SPT with egg white, yolk, OVA, ovomucoid (OVM), ovotransferrin (OVT) and lysozyme commercial extracts (Bial-Aristegui Laboratories, Bilbao, Spain) were performed by a lancet in all the patients included [29]. Histamine (10 mg/mL) and physiological saline served as positive and negative controls, respectively. The largest diameter and the perpendicular one were measured, and the mean was calculated and used as the final result for this SPT. A duplicate SPT/s was performed in every allergen. The mean of the two duplicates was used for statistical analysis. A 3 mm or larger weal was regarded as positive at the time of diagnosis. SPTs were always performed by the same experienced nurses. Blood samples from every patient were taken and processed to obtain serum, which was stored at −20 °C. Total IgE and sIgE levels to egg allergens

(egg white, yolk, OVA and OVM) were simultaneously measured, by CAP System Pharmacia FEIA (Pharmacia diagnostics, Uppsala, Sweden), when the patients' recruitment process ended.

Double-blind placebo-controlled oral food challenges (DBPCFC) were performed in all cases. The allergologist and the nurse in charge of the oral challenges were trained in oral food challenges, and were blind to both SPT results and sIgE levels. All DBPCFC were performed at the Allergy Department. The oral challenge protocol lasted for 5 days (Table 3) and started the first day with increasing doses of 15 min cooked yolk, followed by increasing doses of 15 min cooked white on day 2, raw egg white on day 3 and 4 and finally a 2-min cooked whole egg the last day. Potato and carrot soup, prepared daily in the hospital's kitchen, were used as blind egg doses, following a validated receipt of the Food Allergy Committee of the Spanish Allergy and Clinical Immunology Society [30].

Those patients who completed DBPCFC without any reaction were classified as tolerant or non-allergic children. One month after the challenge, they came to the Allergy Department in order to confirm their tolerance to all egg varieties in a daily diet.

Those patients having immediate reactions during the oral challenge were classified as persistent allergic

Table 3. Egg oral challenge protocol

Day	Egg challenge dose	Time interval (h)
First day	PCB	1
	Cooked yolk 1/4	1
	Cooked yolk 3/4	1
Second day	PCB	1
	Cooked egg white 1/4	1
	Cooked egg white 3/4	1
Third day	PCB	1
	Cooked egg white 1/2	1
	Raw egg white 1/16 (2 g)	1
Fourth day	Raw egg white 1/8 (4 g)	1
	Raw egg white 1/4 (8 g)	1
	PCB	1
Fifth day	Raw egg white 1/2 (16 g)	1
	Raw egg white 1/2 (16 g)	2
	Two minutes cooked whole egg	2

PCB, placebo.

children. They were asked to follow a strict egg avoidance diet.

A positive egg oral challenge was defined as: cutaneous symptoms (pruritus, urticaria, angioedema), digestive symptoms (vomiting, abdominal pain, diarrhoea), respiratory symptoms (rhinitis, cough, dyspnoea) or cardiovascular symptoms (tachycardia, hypotension) in the 2 h following the egg dose.

Informed consent was obtained in all cases, and our research was approved by the Ramón y Cajal Hospital's Committee on Human Experimentation.

Statistics

Mean, median, first, third quartiles and standard deviation were used to describe continuous variables. Absolute and relative frequencies were used to describe categorical variables. Chi-square tests or Fisher's exact tests were used to compare persistent allergic with tolerant groups. Mann-Whitney *U* tests were used to compare SPT and sIgE levels between persistent allergic and tolerant children. The diagnostic accuracy of SPT and sIgE levels to egg allergens was evaluated with a ROC curve analysis.

Several different methods have been used in the literature to determine a cut point from a ROC curve [31]: among them, (1) the point on the ROC curve closest to the upper-left corner of the ROC plot (this point in the upper-left corner represents a perfect test with 100% sensitivity and specificity), (2) the point that reaches a predetermined desired level of sensitivity or specificity or (3) the point that maximizes the sum of sensitivity or specificity or finally (4) the point at which sensitivity equals specificity.

In the present study, cut-off points for those tests with a ROC curve area over 0.7 were calculated following three

different methodologies used in previous food allergy studies [11–25]:

- Cut-off points corresponding to the traditional 3 mm for SPT and 0.35 KU/L for sIgE levels.
- Cut-off points corresponding to a fixed 90% and 95% positive predictive value.
- Cut-off points corresponding to the maximum sum of sensitivity and specificity.

Those cut-off points with a positive likelihood ratio (+LR) over 5 (moderate clinical value of Jaeschke's classification [32]) were selected.

Sensitivity, specificity, positive and negative predictive values, and +LR and –LR were calculated for those different cut-off points.

P-values below 0.05 were considered significant. All analyses used the 10th version of the Windows SPSS program.

Results

One hundred and sixty eight egg-allergic patients were consecutively recruited (Fig. 1). Five children were excluded because of anaphylaxis after egg intake and four out of 168 were excluded because of having a symptomatic transgression with egg in the last 6 months.

One hundred and fifty nine patients were included in the DBPCFC protocol. Two patients rejected egg intake several times. These two patients were kept on an egg-free diet until following the visit, 6 months later, since the complete protocol was not achieved. One hundred and fifty seven egg-allergic patients were included in the final analyses. Ninety-six patients were males (61%). The median age was 2 years and 6 months (from 15 months to 16 years). The most frequent symptoms present at the

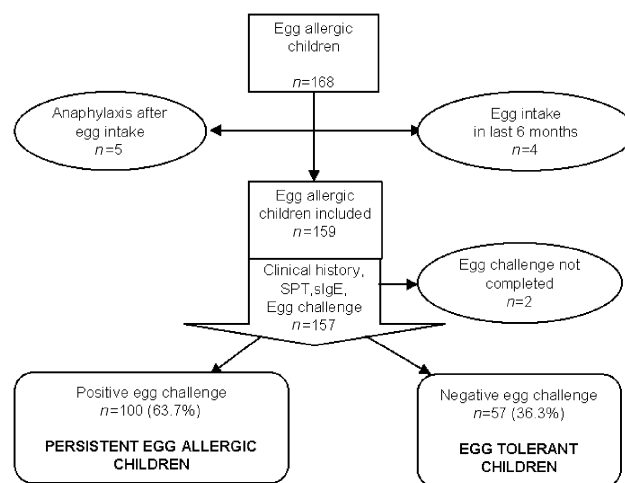


Fig. 1. Study's flow chart. SPT, skin prick test; sIgE, specific IgE antibodies to egg allergens.

Table 4. Comparison of skin prick test (SPT) and specific IgE (sIgE) results between egg persistent allergic children and tolerant groups

	Persistent allergic						Tolerant						<i>P</i> values*
	<i>n</i>	Mean	Median	SD	1st quartile	3rd quartile	<i>n</i>	Mean	Median	SD	1st quartile	3rd quartile	
Egg white SPT	100	6.54	6.50	3.59	4.50	8.50	56	3.07	3.50	2.74	0.00	5.00	<i>P</i> <0.0001
Yolk SPT	100	1.60	0.00	2.41	0.00	3.50	57	0.25	0.00	0.97	0.00	0.00	<i>P</i> <0.0001
OVA SPT	100	3.14	3.25	3.04	0.00	5.50	54	1.89	0.00	3.10	0.00	4.13	<i>P</i> =0.006
OVM SPT	100	4.62	5.50	4.48	0.00	7.00	54	1.40	0.00	2.41	0.00	3.00	<i>P</i> <0.001
OVT SPT	93	0.40	0.00	1.44	0.00	0.00	48	0.00	0.00	0.00	0.00	0.00	<i>P</i> =0.037
Lysozyme SPT	93	0.92	0.00	2.45	0.00	0.00	48	0.13	0.00	0.68	0.00	0.00	<i>P</i> =0.035
Egg white sIgE	90	5.74	1.56	11.66	0.71	5.60	53	1.30	0.40	3.38	<0.35	0.83	<i>P</i> <0.0001
Yolk sIgE	83	1.35	<0.35	3.76	<0.35	1.10	52	0.39	<0.35	0.27	<0.35	<0.35	<i>P</i> <0.0001
OVA sIgE	83	4.82	1.71	7.88	0.50	5.97	51	0.86	0.39	1.78	<0.35	0.80	<i>P</i> <0.0001
OVM sIgE	87	3.83	0.71	8.26	<0.35	2.91	51	0.82	<0.35	2.79	<0.35	<0.35	<i>P</i> <0.0001

*Mann-Whitney test.

OVA, ovalbumin; OVM, ovomucoid; OVT, ovotransferrin; SD, standard deviation.

diagnosis stage were cutaneous (102 patients, 86%), followed by digestive symptoms (44 patients, 29.3%) and finally, respiratory symptoms (22 patients, 14.6%).

One hundred and three children were diagnosed with AD (66.9%) according to Hanifin and Rajka [33]. Thirty one patients had allergic rhinitis or asthma (19.7%), and 35 children (22.9%) had non-allergic asthma. 63.6% of the patients included had other food allergies (confirmed by positive SPT, positive sIgE levels and, when necessary, an oral challenge test) [26, 27]. Seventy-two patients were allergic to milk and egg (46.5%).

In 57 patients out of 157 (36.3%), egg tolerance was confirmed by a negative oral challenge (tolerant group). Tolerance was confirmed during their visit at the clinic 1 month later. Hundred patients out of 157 (63.7%) had positive egg challenge tests (persistent allergic group). Eighty-three patients had cutaneous symptoms during the oral egg challenge, 31 children had digestive symptoms and 17 patients had respiratory symptoms. SPT and sIgE levels to all the egg allergens tested were statistically higher in the persistent allergic group (Table 4). The median time reaction was 15 min (ranging from 5 to 180 min). Ninety-eight percent of the children with positive challenges reacted in the next hour after taking the egg dose. Only two children reacted after 1 h (one of them 120 min after the egg intake and the other one after 180 min). The percentage of positive challenge tests with cooked egg vs. raw egg was not significantly different (Table 5).

SPT and sIgE levels were not different between children with and without AD and between children younger than 2 and 2-year-old and older children.

No differences were found as to age, sex, AD, atopic parents, asthma and other food allergies between the persistent allergic and the tolerant groups.

The accuracy of the SPT and sIgE levels was evaluated by the ROC curve analysis. ROC curves for every egg

Table 5. Positive egg challenges distribution

<i>Positive challenge test</i>		<i>n</i>
Cooked yolk		8/100
Cooked egg white		40/100
Raw egg white		46/100
Whole egg*		6/100
<i>Symptoms</i>		
Cutaneous		57/100
Digestives		14/100
Cutaneous+digestives		13/100
Cutaneous+respiratories		9/100
Respiratories		5/100
Cutaneous+digestives+respiratories		3/100
Mean (minimum–maximum)		SD
Time to reaction	15 (5–180)	34

*Whole egg: 2 min cooked whole egg.

SD, standard deviation.

allergen are shown in Fig. 2, and the corresponding areas under the curves are shown in Table 6.

OVT and lysozyme SPT had areas under 0.6 (not statistically different from the reference line). Yolk and OVA SPT curve areas were between 0.6 and 0.7. Egg white and OVM SPT and sIgE to all egg allergens tested reached areas over 0.7, indicating that they were useful tests [34] to predict the outcome of the challenge in the egg-allergic population. ROC analysis of the SPT/histamine ratio and the sIgE/total IgE ratio showed no significant differences compared with SPT wheal and sIgE curves.

Sensitivity, specificity, positive and negative predictive values, and positive and negative LR were calculated for different cut-off points. These are shown in Table 7, egg white extract showing the highest diagnostic accuracy.

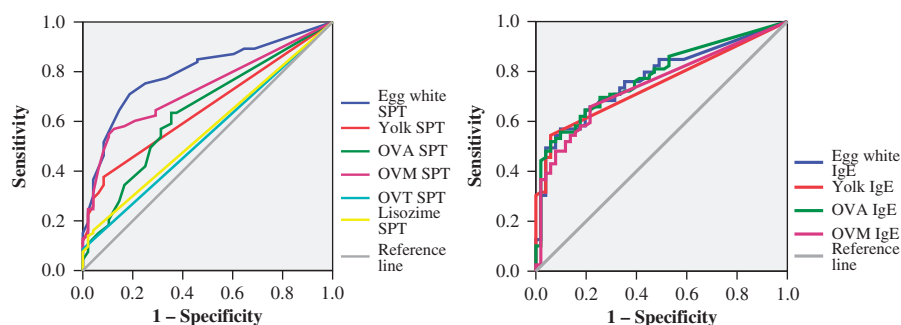


Fig. 2. Areas under ROC curves of skin prick test and specific IgE to egg allergens. SPT, skin prick test; sIgE, specific IgE; OVA, ovalbumin; OVM, ovomucoid; OVT, ovotransferrin.

Table 6. Areas under ROC curves of skin prick test (SPT) and specific IgE (sIgE) to egg allergens

Test	Area	95% Confidence interval	
Egg white SPT	0.79	0.71	0.86
OVA SPT	0.78	0.71	0.86
Egg white sIgE	0.77	0.69	0.85
OVM sIgE	0.74	0.66	0.83
Yolk sIgE	0.74	0.66	0.82
OVM SPT	0.71	0.63	0.79
Yolk SPT	0.64	0.56	0.73
OVA SPT	0.63	0.53	0.72
Lysozyme SPT	0.56	0.46	0.66
OVT SPT	0.54	0.44	0.64

OVA, ovalbumin; OVM, ovomucoid; OVT, ovotransferrin.

In the egg white SPT, the 7 mm cut-off point obtained a +LR of 6.7, which is a moderate clinical value [32]. Having a 7 mm egg white SPT was almost seven times more frequent for an egg-allergic child in the persistent allergic group than in the tolerant group. For sIgE levels, the 1.3 KU/L cut-off point obtained a +LR of 5.1, which means that having an egg white sIgE level of 1.3 KU/L was five times more frequent for an egg-allergic child in the persistent allergic group than in the tolerant group (Table 7).

Both cut-off points (a 7 mm egg white SPT and 1.3 KU/L egg white sIgE) have a +LR over 5, which is a moderate clinical value of Jaeschke's classification [32].

Figure 3 shows how many children in the present study met the selected cut-off points. The proportion of children in the study population with SPT ≥ 7 mm was 35.6% or sIgE ≥ 1.3 was 17.8%.

Age analysis

The analysis described above was performed in the following two groups of age: children under 2 years and 2-year-old and older children. ROC curves were not significantly different between these two groups. Cut-off

points were calculated following the same methodology in both groups and they were not clinically different.

Atopic dermatitis analysis

The same statistical analysis described above was performed in the following two groups: children with AD and children without AD. ROC curves were not significantly different between these two groups. Cut-off points were calculated following the same methodology in both groups and they were not clinically different.

Discussion

The aim of the present study was to evaluate the accuracy of SPT and sIgE levels to egg allergens when predicting the persistence of allergy in children. As it was already mentioned, few papers have been published on this topic. Compared with the previous studies, the present study makes two main contributions: first, all egg allergens were evaluated while in other accuracy evaluation studies authors usually focus only on egg white and yolk. Second, a representative sample of egg-allergic children under follow-up was included (in age, AD, other food allergies, other allergic diseases and all sIgE levels).

In our study, egg white extract was the most accurate diagnostic allergen as a whole. This result agrees with the conclusion of the only study published evaluating the validity of different egg allergen fractions to diagnose egg allergy during the first visit [20]. OVT and lysozyme SPT were not useful to predict a positive egg challenge. Yolk and OVA SPT have shown important limitations when used in the follow-up of those egg-allergic children. However, a 7 mm egg white SPT and a 1.3 KU/L egg white sIgE had a +LR very useful for clinical practice. For example, for an egg-allergic child diagnosed 3 years ago, the pretest probability of still being allergic, according to previously published studies, would be 68% [35]. Considering 7 mm white egg SPT as the cut-off point, if this patient had a white egg SPT result of 7 mm or higher, the

Table 7. Sensitivity, specificity, predictive values and likelihood ratios of different skin prick test (SPT) and specific IgE cut-off points

Cut-off point		Method	Sn	Sp	PPV	NPV	+LR	−LR
Egg white SPT	3 mm	Classic	86.0 (79.2–92.8)	42.9 (29.9–55.8)	72.9 (64.9–80.9)	63.2 (47.8–78.5)	1.51 (1.18–1.91)	0.33 (0.18–0.58)
	5 mm	Sn+Sp maximum sum	74.0 (65.4–82.6)	69.6 (57.6–81.7)	81.3 (73.3–89.3)	60.0 (48.1–71.9)	2.44 (1.61–3.69)	0.37 (0.26–0.54)
	7 mm	PPV > 90%	48.0 (38.2–57.8)	92.9 (86.1–99.6)	92.3 (85.1–99.5)	50.0 (40.4–59.6)	6.72 (2.56–17.6)	0.56 (0.46–0.69)
	9 mm	PPV > 95%	22.0 (13.9–30.1)	98.2 (94.7–100.0)	95.6 (87.3–100.0)	41.3 (33.0–49.7)	12.32 (1.71–89.0)	0.79 (0.71–0.89)
OVM SPT	3 mm	Classic	59.0 (49.4–68.6)	74.1 (62.4–85.8)	80.8 (71.8–89.9)	49.4 (38.5–60.3)	2.28 (1.41–3.68)	0.55 (0.42–0.73)
	5 mm	Sn+Sp maximum sum	52.0 (42.2–61.8)	87.0 (78.1–96.0)	88.1 (79.9–96.4)	49.5 (39.4–59.5)	4.01 (1.996–8.21)	0.55 (0.44–0.69)
	6 mm	PPV > 90%	46.0 (36.2–55.8)	92.6 (85.6–99.6)	92.0 (84.5–99.5)	48.1 (38.5–57.7)	6.21 (2.36–16.33)	0.58 (0.48–0.71)
	8 mm	PPV > 95%	23.0 (14.7–31.2)	98.1 (94.5–100.0)	95.8 (87.8–100.0)	40.8 (32.3–49.2)	12.42 (1.72–89.47)	0.78 (0.70–0.88)
Egg white IgE	0.35 KU/L	Classic	86.7 (79.6–93.7)	39.6 (26.4–52.8)	70.9 (62.4–79.4)	63.6 (47.2–80.0)	1.44 (1.14–1.81)	0.34 (0.18–0.63)
	1 KU/L	Sn+Sp maximum sum	57.8 (47.6–68.0)	88.7 (80.1–97.2)	89.7 (81.8–97.5)	55.3 (44.7–65.9)	5.10 (2.35–11.07)	0.48 (0.37–0.62)
	1.5 KU/L	PPV > 90%	52.2 (41.9–62.5)	90.6 (82.7–98.4)	90.4 (82.4–98.4)	52.7 (42.5–63.0)	5.54 (2.35–13.05)	0.53 (0.42–0.67)
	25 KU/L	PPV > 95%	4.4 (0.2–8.7)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	38.1 (30.0–46.2)	–	0.96 (0.91–1.00)
Yolk IgE	0.35 KU/L	Classic, Sn+Sp maximum sum, PPV > 90%*	55.4 (44.7–66.1)	92.3 (85.1–99.5)	92.0 (84.5–99.5)	56.5 (45.9–67.0)	7.20 (2.76–18.84)	0.48 (0.38–0.62)
	1 KU/L	PPV > 95%	26.5 (17.0–36.0)	98.1 (94.3–100.0)	95.6 (87.3–100.0)	45.5 (36.3–54.8)	13.78 (1.91–99.21)	0.75 (0.65–0.86)
OVA IgE	0.35 KU/L	Classic	86.7 (79.4–94.0)	47.1 (33.4–60.8)	72.7 (63.9–81.5)	68.6 (53.2–83.9)	1.64 (1.25–2.15)	0.28 (0.15–0.52)
	1.3 KU/L	Sn+Sp maximum sum, PPV > 90%*	55.4 (44.7–66.1)	90.2 (82.0–98.4)	90.2 (82.0–98.4)	55.4 (44.7–66.1)	5.65 (2.41–13.29)	0.49 (0.38–0.64)
	2 KU/L	PPV > 95%	49.4 (38.6–60.1)	96.1 (90.7–100.0)	95.3 (89.0–100.0)	53.8 (43.6–64.1)	12.60 (3.18–49.86)	0.53 (0.42–0.66)
OVM IgE	0.35 KU/L	Classic	65.5 (55.5–75.5)	78.4 (67.1–89.7)	83.8 (75.1–92.6)	57.1 (45.5–68.7)	3.04 (1.76–5.24)	0.44 (0.32–0.61)
	1 KU/L	Sn+Sp maximum sum, PPV > 90%*	41.4 (31.0–51.7)	94.1 (87.7–100.0)	92.3 (83.9–100.0)	48.5 (38.6–58.3)	7.03 (2.28–21.69)	0.62 (0.52–0.75)
	2 KU/L	PPV > 95%	28.7 (19.2–38.2)	98.0 (94.2–100.0)	96.1 (88.8–100.0)	44.6 (35.4–53.8)	14.66 (2.05–104.95)	0.73 (0.63–0.84)

*The cut-off point calculated by all methods referred is the same.

OVA, ovalbumin; OVM, ovomucoid; OVT, ovotransferrin; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

probability of remaining allergic should be approximately 90%; therefore, an oral challenge test would not be necessary.

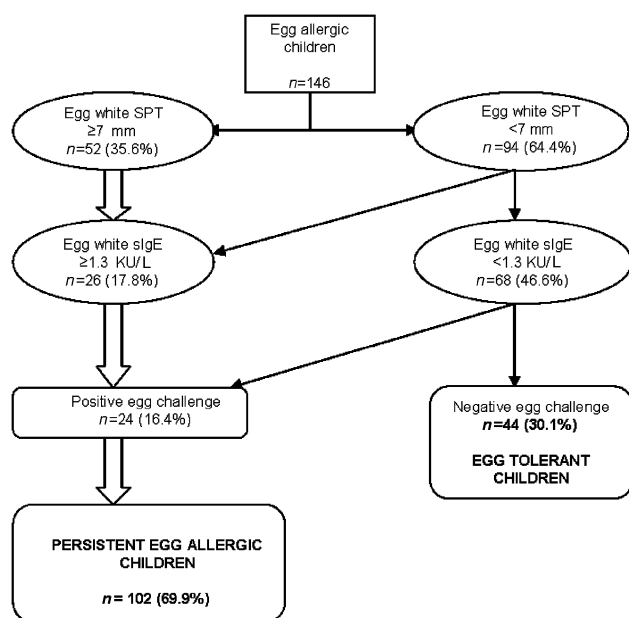
Only one article has been published studying the SPT accuracy in the follow-up of egg-allergic children [25]. The aim of the study was to determine whether SPT can differentiate children with low egg white sIgE levels (with egg white sIgE under 2.5 KU/L) who passed an oral egg

challenge from those who failed. A retrospective analysis concerning serum egg white sIgE levels, SPT results and oral egg challenge outcomes of children with egg allergy was performed. Seventy-four oral egg challenges were included in the final analysis. Egg white median weal was significantly different between children who failed their oral egg challenge (median weal of 5 mm) and those who passed (median weal of 3 mm). Our study obtained the

Table 8. Accuracy of egg white specific IgE determination in predicting oral challenge's result in allergic children

	Crespo [18]	Present study	Crespo [18]	Crespo [18]	Present study	Present study	Present study
Egg white IgE cut-off point	0.35 KU/L	0.35 KU/L	0.70 KU/L	1.20 KU/L	1.3 KU/L	1.5 KU/L	25 KU/L
Method	Classic	Classic	NR	NR	Sn+Sp maximum sum	PPV > 90%	PPV > 95%
Sn (%)	72	86.7	60	44	57.8	52.2	4.4
Sp (%)	66	39.6	80	93	88.7	90.6	100.0
PPV (%)	78	70.9	83	92	89.7	90.4	100.0
NPV (%)	58	63.6	54	50	55.3	52.7	38.1
+LR	2.16	1.44	3	6.6	5.10	5.54	–
–LR	0.42	0.34	0.5	0.60	0.48	0.53	0.96

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; –LR, negative likelihood ratio; NR, non-referred.

**Fig. 3.** How many children in the present study satisfied the selected cut-off points.

same results (egg white median of 6.5 mm in the persistent allergic group, egg white median of 3.5 mm in the tolerant group), suggesting the usefulness of egg white SPT to predict a positive challenge. This was confirmed by later analysis. A different data analysis was performed, and only egg-allergic patients with egg white sIgE under 2.5 KU/L were included; it is therefore difficult to perform further comparisons between both studies.

For sIgE accuracy, Boyano et al. used the Kaplan–Meier method to determine the relationship between the cumulative probability of egg tolerance and the egg white sIgE level. In children younger than 2 years of age, sIgE levels were an important prognostic marker for those children who only experienced cutaneous symptoms [36]. An age analysis was performed in the present study, but no differences were found in the accuracy of SPT or sIgE

levels between these two groups (< 2 years and ≥ 2 years old).

There is another published study focusing on sIgE accuracy in the follow-up of egg-allergic children [18]. Proposed egg white cut-off points were 0.70 and 1.20 KU/L. The methodology used by the author to calculate those cut-off points was not specified in the paper, but after comparing 0.35 KU/L cut-off point predictive values and LR ratios obtained in that study and ours, we conclude that they are quite similar (Table 8).

AD is well known as a risk factor in the development of egg allergy [37, 38]. Patients with AD were found to have a higher proportion of egg allergy, according to several authors. We could not find any differences in the accuracy of both tests (SPT and sIgE levels) carried out between children with and without AD, perhaps because AD is a risk factor of having egg allergy, but it has not been described as a prognostic factor associated with persistent allergy to egg. Longitudinal studies are needed to clarify the role of AD as a prognostic factor in egg allergy.

We further considered some significant methodological aspects.

Firstly, only egg-allergic children following an egg avoidance diet for at least 6 months were included in the study, in order to be sure that all the patients included were not in the diagnosis phase. As egg allergy is a transient disease in most patients; it makes sense to think that SPT and sIgE accuracy may change during this entire process, which goes from allergy to tolerance, and that optimal cut-off points would be different at different time-points of their allergy.

Secondly, we were also very careful to include only egg-allergic patients with immediate reactions (within 2 h after the egg intake), typically IgE-mediated reactions. These IgE reactions were the ones that SPT and sIgE levels are able to diagnose. Usually, studies published include, on the one hand, immediate reactions and delayed reactions, and on the other, IgE-mediated reactions and reactions mediated through other mechanisms [12, 13,

15–17, 19, 24, 25]. Probably, the SPT and sIgE accuracy in these two different situations would not be the same.

Thirdly, all egg oral challenges performed in the present study were double-blind placebo controlled. As the double blind placebo methodology is more expensive in terms of human resources and is time consuming, many published studies performed open challenges [12–14, 16–18, 20, 22], both challenges (open and blind) being included [11, 15, 24] or, following criteria previously fixed by other authors, challenges were not performed in some patients (i.e. the challenge test was not performed if the child reported any allergic reaction clearly related to egg ingestion within 3 months before the date of the follow-up visit) [16, 20, 21]. The present study made an effort in order to ensure the quality of the data.

One exclusion criteria that the authors were concerned about was anaphylaxis. However, only five children were excluded because of this criterion, and their clinical characteristics and SPT and sIgE levels were not significantly different from the ones of the patients included in the study (data not shown). In order to check the impact of excluding those anaphylactic children a sensitivity analysis was performed. Including those patients, even if they were persistent allergic (sensitivity 86.7%, specificity 42.9) or tolerant (sensitivity 86%, specificity 39.3), did not change the accuracy of the 3 mm egg white cut-off point in a significant way. Including them would not change significantly the results of the study.

Another limitation of our study was the difficulty of choosing optimal cut-off points. It is actually a limitation in all diagnostic accuracy studies. Depending on how cut-off points are calculated, they will be completely different. This may explain the different cut-off points suggested in previously published studies and the difficulties that may be encountered when trying to compare those cut-off points. In previous egg allergy reports, authors assume a pre-fixed positive predictive value to calculate cut-off points. But predictive values depend on prevalence, and so they cannot be applied to a population with a different frequency of the disease. This is not a problem for LRs [39]: they do not depend on prevalence, and so they can be useful for populations with a different disease frequency and they can be applied individually to each patient. In our opinion, LRs are useful tools in order to take this complicated cut-off point decision.

Finally, it must be taken into consideration that the results of the present study are only applicable to a similar population and the same techniques and extracts used in this study.

In conclusion, the present study is the first to demonstrate that SPT and sIgE levels are useful to predict persistent allergy in IgE-mediated egg-allergic children, especially complete egg white extract. Oral challenges should not be performed in egg-allergic paediatric patients with either egg white SPT above 7 mm, or a white

egg-sIgE level above 1.3 KU/L, because there is a 90% probability of remaining allergic.

It would be necessary to combine criteria and to select a universal methodology in order to calculate a test cut-off point taking into consideration the risks and benefits of over-treating and under-treating patients and the prevalence of the disease in the clinical situation for which the diagnostic test is applicable.

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