Cost-effective allergy screening: a retrospective observational study

María Dolores Martín-Martínez, Gema García-de la Rosa

Department of Clinical Analysis Laboratory, University Hospital Nuestra Señora de Candelaria, Carretera General del Rosario, Santa Cruz de Tenerife, Spain

Summary

Background. Allergies represent a substantial health concern affecting individuals across all age groups. Diagnostic screenings, such as phadiatop and phadiatop infant, are employed to identify specific IgE antibodies associated with allergic reactions. This study delves into the relationship between total IgE levels and screening test outcomes, with the objective of establishing a total IgE threshold capable of predicting the likelihood of negative results in these screenings. **Methods**. This retrospective observational study included adults and children under 15 years old who underwent total IgE tests in addition to phadiatop and phadiatop infant screenings from January 2018 to December 2022. Exclusion criteria were applied to patients with insufficient serum samples or those whose IgE determinations or screening tests had been invalidated according to standard laboratory protocols. **Results**. Data analysis uncovered a robust correlation between total IgE levels and screening test outcomes. Additionally, thresholds of 20 UI/mL and 28 UI/mL were pinpointed for total IgE levels, below which the likelihood of obtaining a positive result in phadiatop or phadiatop infant, respectively, significantly decreased. **Conclusions**. These findings present cost-effective strategies for healthcare practitioners by recommending the initial use of total IgE testing. Subsequently, reflex testing with phadiatop or phadiatop infant, depending on the IgE value, could be considered.

Key words:
Allergy screening; accuracy; cost-effective.

Impact statement:
Establishing IgE thresholds improves allergy screening accuracy and resource efficiency.

INTRODUCTION

Allergies, stemming from heightened immune sensitivity to environmental allergens, encompass a broad array of conditions including food allergy (FA), allergic rhinitis (AR), asthma, atopic dermatitis (AD), conjunctivitis, and chronic rhinosinusitis with or without nasal polyposis (CRSwNP) (1). While often local, these conditions can also trigger systemic responses, potentially leading to severe outcomes like anaphylactic shock.

In medical research, allergies present a complex challenge, affecting individuals across diverse demographics. Currently, FA impacts 1–10% of the global population, while AR and asthma collectively affect approximately 500 million and 300 million individuals worldwide, respectively, with these numbers increasing. Globally, AD has an 8% prevalence, with a lifetime occurrence reaching 20%. Notably, the World Health Organization (WHO) recognizes allergic diseases as one of the top three disorders requiring prevention and management in the 21st century (2).

Elevated levels of IgE are a characteristic feature of allergic diseases (3). Allergic sensitization, indicated by the presence of allergen-specific IgE antibodies in the skin or blood, is a crucial diagnostic

marker for allergic diseases. However, relying solely on this marker is insufficient for a definitive diagnosis without a direct correlation to a detailed clinical history of allergic symptoms linked to allergen exposure (4).

Skin tests, particularly the skin prick test (SPT), are the most commonly used method for allergy diagnosis. This involves pricking the skin, usually on the inner forearm, with a lancet containing a drop of allergen extract (5). The objective is to identify allergen-specific IgE antibodies bound to mast cells by triggering mast cell degranulation in response to the specific allergen tested (6). While skin testing is minimally invasive and allows for the evaluation of multiple allergens within a short timeframe, it may cause discomfort, anxiety, and stress, especially in pediatric patients (7). Moreover, interpretation of results requires expertise (6).

Serum IgE detection in vitro serves as a valuable adjunctive diagnostic tool, offering streamlined processes, reduced costs, and minimized errors, enhancing the reliability of assessments. Results from serum IgE testing closely correlate with those from skin testing, and the procedure involves minimal patient risk through blood sampling. It is preferred under various circumstances, including when a patient's medical condition is unstable, there's a high risk of anaphylaxis, medications interfere with skin tests, the patient is young and likely to find the procedure distressing, or when skin conditions limit testing sites.

Diagnosing IgE-mediated allergic diseases via in vitro methods involves various laboratory techniques. While the total IgE assay provides general insights, serum-specific IgE assays targeting allergen sources or molecules are the primary approach. These assays can be conducted using singleplex or multiplex methodologies (8).

This manuscript aims to comprehensively investigate the correlation between serum-specific IgE screening assay outcomes and total IgE levels. Subsequently, it seeks to establish a specific IgE threshold below which it reliably indicates a negative outcome in allergy screening tests. By attaining this dual objective, this research fosters the development of more efficient and cost-effective strategies for allergy diagnosis and management.

MATERIALS AND METHODS

Study Population

We conducted a retrospective observational study approved by the ethical committee (CHUNSC_2023_90). Our study involved both adult and pediatric patients who underwent total IgE testing and allergy screening between January 1, 2018, and December 31, 2022. Adults typically underwent the Phadiatop test, while pediatric patients under 15 years old commonly underwent the Phadiatop Infant test. Exclusion criteria included patients with insufficient serum samples or invalidated IgE, Phadiatop, or Phadiatop Infant determinations according to the laboratory's standard procedure.

Patient information, including registration number, gender, and age, was extracted from the DragoAE Hospital Information System (HIS). IgE levels and screening results (positive or negative) were obtained from the OpenLab Laboratory Computer System (LCS).

IgE values were measured using the Cobas® 8000 modular analyzer (Roche Diagnostics S.L.U., Switzerland), while Phadiatop or Phadiatop Infant assays were conducted using the Phadia™ 250

immunoassay analyzer (Thermo Scientific®, Sweden). These tests aim to confirm or exclude the presence of specific IgE antibodies associated with the clinical condition. A negative result indicates a low likelihood of allergy.

Phadiatop is a qualitative in vitro initial screening method that detects IgE-mediated sensitization to common aeroallergens (e.g., dust mites, pollens, pet dander, fungi). It covers over 90% of sensitizations in children over 5 years old. Phadiatop Infant includes aeroallergens and a selection of food allergens (milk, egg, peanut, soy, and codfish), representing over 98% of antigens responsible for allergic sensitization in children under 4 years old.

Variables Analyzed

Hypersensitivity is defined as a total IgE serum level exceeding 100 IU/mL for adults and 90 IU/mL for children, or when the Phadiatop or Phadiatop Infant level exceeds 0.35 KU/L, indicating positivity.

Statistical Analysis

The IgE values were analyzed using ROC curves to establish an IgE threshold with high sensitivity and specificity for the prediction of negative screening results. We assessed sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values for the designated screening test cut-off of 0.35 kUI/L.

Statistical analysis was conducted using the SPSS statistical package (version 25.0), with a significance level set at 0.05.

RESULTS

Study patient characteristics

A total of 54199 samples were collected. Out of these, 33746 samples were finally included in the phadiatop cohort and 12702 samples in the phaditop infant cohort after excluding 3747 and 4004 samples, respectively, due to insufficient serum samples for the study or invalidated determinations according to the laboratory's standard procedure (figure 1).

Table I presents demographic and laboratory data for both cohorts. Regarding the phadiatop cohort, the median IgE values were lower (59.40 IU/mL) in comparison to those observed in the phaditop infant cohort (79.24 IU/mL, $p<0,0001$).

Main results

The area under the curve (AUC) was calculated to be 0.826 in the phadiatop cohort and 0.844 in the phadiatop infant cohort, respectively, indicating a strong discriminatory ability of our IgE-based screening test. Figure 2 illustrates the ROC curves, depicting the trade-off between sensitivity and specificity at various threshold values.

Through the Youden index, we identified the optimal threshold value for IgE to be 63,05 UI/mL in the phadiatop cohort and 78,53 UI/mL in the phadiatop infant cohort. This demonstrated a sensitivity of 0.78 and 0.79, respectively, along with specificities of 0.72 and 0.74, respectively.

Our primary goal was to enhance sensitivity and reduce the risk of false negatives in the screening test. To achieve this, we deliberately selected a sensitivity threshold at 95.19 and a corresponding specificity level at 39.54 in the phadiatop cohort (IgE = 20 UI/mL), and a sensitivity threshold at 95.18 and a corresponding specificity level at 49.65 in the phadiatop infant cohort (IgE = 28 UI/mL). The calculated values for sensitivity, specificity, positive and negative likelihood ratios, as well as positive and negative predictive values, are presented in Table II.

DISCUSSION

This study highlights the discriminatory capacity of the total IgE test, with AUC values of 0.826 and 0.844 in the phadiatop and phadiatop infant cohorts respectively, confirming its robust diagnostic efficacy. While Chang et al. (9) demonstrated the superior sensitivity and specificity of the phadiatop test over total IgE levels in detecting positive aeroallergies, our ROC curve analysis enabled us to identify optimal threshold values for IgE levels. These thresholds aim to enhance sensitivity and minimize false negatives in the screening process, establishing an IgE cutoff point below which phadiatop or phadiatop infant testing is unnecessary, thus reducing unnecessary testing.

By establishing specific IgE threshold values indicative of negative screening outcomes, clinicians can confidently exclude allergies in patients, thereby avoiding unnecessary diagnostic procedures and reducing healthcare costs. The Phadiatop and Phadiatop Infant screening tests are priced at around 10 euros each, while the IgE test costs approximately 1.50 euros. Given these costs, it is evident that utilizing IgE levels as a primary allergy screening tool would be more efficient and cost-effective for individuals when allergy is suspected. Depending on the IgE value, if it exceeds a certain threshold (20 UI/mL y 28 UI/mL), reflex testing with the phadiatop or phadiatop Infant, respectively, should be considered. However, in cases of high suspicion of allergy, serum specific IgE screening assay should be considered, regardless of IgE levels.

While our study offers valuable insights and represents the largest sample size to date, it is important to recognize its limitations, such as its retrospective design and the lack of clinical data correlation. Although serum-specific IgE and total IgE levels could indicate hypersensitivity, definitive confirmation of an allergy requires clinical correlation. Future research should incorporate extensive clinical data to validate the proposed IgE threshold and enhance understanding of its predictive value.

In conclusion, our study contributes valuable insights into the correlation between serum specific IgE levels and allergy screening outcomes. By establishing specific IgE threshold values, we provide clinicians with a practical tool to enhance diagnostic accuracy and efficiency in managing allergies.

Fundings

None.

Contributions

MM: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review & editing. GR: formal analysis, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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Fig. 1. Flowchart of enrollment

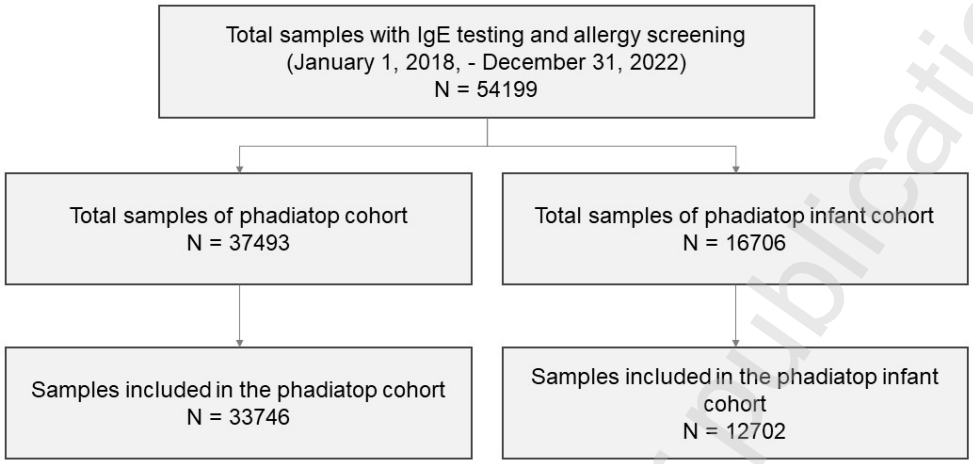

Figure 2. ROC curve analysis A. Phadiatop cohort. B. Phadiatop infant cohort

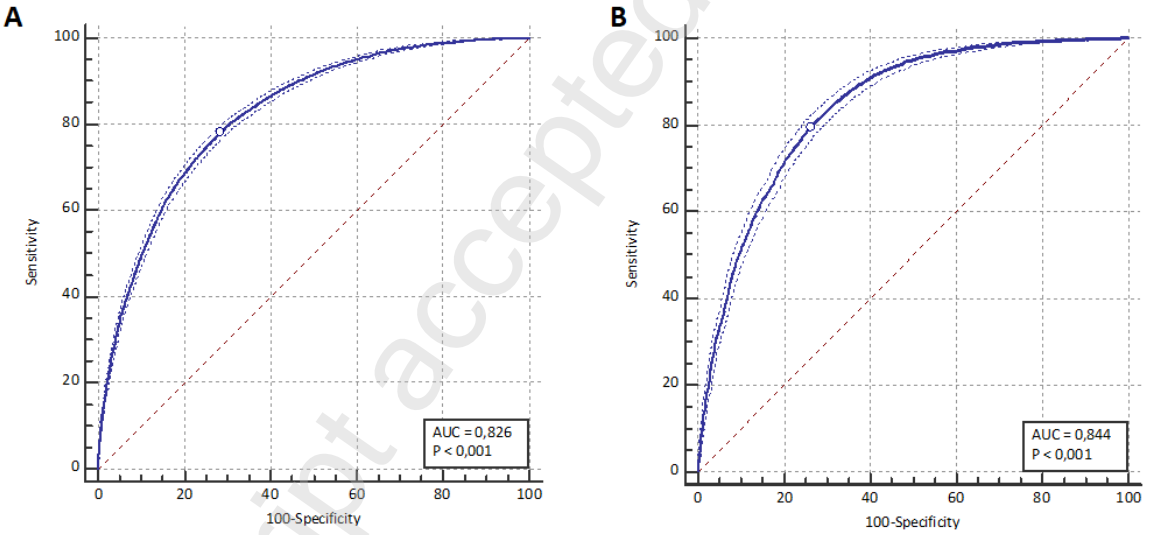

Table I. Comparison of demographic and laboratory data of adult and pediatric cohort			
	Phadiatop cohort (n=33746)	**Phaditop Infant cohort (n=12702)**	**p**
Demographic data			
Age (years), median (IQR)*	37,00 (18,00-53,00)	8,00 (4,00-12,00)	<0,0001*
Sex (n male), (% male)	13493 (40%)	6314 (49,70%)	0,711†
Laboratory data			
Total IgE (IU/mL), median (IQR)*	59,40 (19,70-182,00)	79,24 (22,30-242,00)	<0,0001*
Screening (n positives), (% positives)	13774 (40,8%)	5750 (45,3%)	0,721†

*Mann–Whitney test; †Chi-squared test

Table II. Sensitivity and specificity analysis of phadiatop and phadiatop infant cohorts									
	IgE value (UI/mL)	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**+LR**	**95% CI**	**-LR**	**95% CI**
Phadiatop cohort	63,05	77,99	77,3 - 78,7	71,75	71,1 - 72,4	2,76	2,7 - 2,8	0,31	0,3 - 0,3
	20	95.19	94,8 - 95,5	39.54	38,9 - 40,2	1.57	1,6 - 1,6	0.12	0,1 - 0,1
Phadiatop infant cohort	78,53	79,48	78,4 - 80,5	74,02	73,0 - 75,0	3,06	2,9 - 3,2	0,28	0,3 - 0,3
	28	95.18	94,6 - 95,7	49.65	48,5 - 50,8	1.89	1,8 - 1,9	0.097	0,09 - 0,1