

Comparison of Specific Immunoglobulin E with the Skin Prick Test in the Diagnosis of House Dust Mites and Cockroach Sensitization in Patients with Asthma and/or Allergic Rhinitis

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ABSTRAK

Latar belakang: pemeriksaan IgE spesifik serum baru diperkenalkan di Indonesia, tetapi belum ada data uji diagnostik mengenai kinerjanya dalam mendeteksi alergen hirupan yang sering pada pasien alergi pernapasan. Tujuan penelitian ini adalah untuk mendapatkan akurasi diagnostik pemeriksaan IgE spesifik serum dalam mendiagnosis sensitisasi alergen hirupan tertentu pada pasien alergi pernapasan. **Metode:** penelitian ini adalah studi potong lintang pada pasien alergi pernapasan dan merupakan bagian dari studi epidemiologi mengenai sensitisasi IgE spesifik di Divisi Alergi-Immunologi, RS Cipto Mangunkusumo, Jakarta, pada bulan November sampai Desember 2016. Pengukuran sensitisasi IgE spesifik dilakukan dengan metode imunoblot (Euroline®, Euroimmun AG, Germany). Alergen yang diuji adalah tungau debu rumah [*Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), *Blomia tropicalis* (*Blo t*)], dan kecoa [*Blattella germanica* (*Bla g*)]. Hasilnya dibandingkan dengan baku emas uji tusuk kulit. Uji diagnostik yang dilakukan meliputi sensitivitas, spesifisitas, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positif dan negatif (*LR+* and *LR-*). **Hasil:** sebanyak 101 pasien dilibatkan dalam studi, 77 (76,2%) di antaranya adalah perempuan. Rerata usia pasien adalah 38,8 tahun. Berdasarkan uji tusuk kulit, sensitisasi tertinggi yang didapatkan adalah terhadap *Blo t* (76,2%), disusul oleh *Der p* (70,3%), *Der f* (69,3%), dan *Bla g* (41,6%). Sensitisasi IgE-spesifik tertinggi ditunjukkan oleh *Der f* (52,9%), diikuti oleh *Der p* (38,2%), *Blo t* (33,3%) dan *Bla g* (10,8%). Alergen *Der p* memiliki 50,7% sensitivitas, 90% spesifisitas, 92,3% PPV, 43,5% NPV, 5,1 *LR+* dan 0,1 *LR-*. *Der f* memperlihatkan 71,4% sensitivitas, 87,1% spesifisitas, 82,6% PPV, 57,4% NPV, 5,5 *LR+* dan 0,3 *LR-*. Alergen *Blo t* menunjukkan 41,6% sensitivitas, 91,7% spesifisitas, 94,1% PPV, 32,8% NPV, 5,0 *LR+*, dan 0,6 *LR-*. Alergen *Bla g* menghasilkan 23,8% sensitivitas, 98,3% spesifisitas, 90,9% PPV, 64,4% NPV, 14,5 *LR+* dan 0,8 *LR-*. **Kesimpulan:** pemeriksaan IgE spesifik serum terhadap alergen inhalan pada pasien alergi pernapasan memperlihatkan sensitivitas rendah sampai sedang, tetapi spesifisitas dan PPV yang tinggi. Pemeriksaan dapat digunakan mendiagnosis sensitisasi alergen pada populasi dengan prevalensi TDR dan kecoa yang tinggi.

Kata kunci: alergi, alergen inhalan, IgE spesifik, uji diagnostik, uji tusuk kulit.

ABSTRACT

Background: nowadays, specific IgE measurement has been conducted in Indonesia, however there is still lack of data regarding diagnostic test to detect inhalant allergen in patients with respiratory allergies. This study aimed to determine the accuracy of specific IgE test in diagnosing specific sensitization of inhalant allergen in patients with respiratory allergies. **Methods:** this was a cross sectional study in patients with respiratory allergies and part of

epidemiology study regarding to specific IgE sensitization in Allergy-Immunology Division, Cipto Mangunkusumo Hospital, Jakarta within November-December 2016. Measurement of specific IgE sensitization using Immunoblot method (Euroline®, Euroimmun AG, Germany). The tested allergen is house dust mites [*Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), *Blomia tropicalis* (*Blo t*)] and cockroach [*Blatella germanica* (*Bla g*)]. The result is compared with gold standard, skin prick test. The diagnostic result includes sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-). **Results:** a total of 101 patients were enrolled; 77 (76.2%) were women. Patients mean age was 38.8 years old. Based on SPT, sensitization was highest for *Blo t* (76.2%), followed by *Der p* (70.3%), *Der f* (69.3%), and *Bla g* (41.6%). Specific IgE-sensitization was highest for *Der f* (52.9%), followed by *Der p* (38.2%), *Blo t* (33.3%) and *Bla g* (10.8%). *Der p* allergen had 50.7% sensitivity, 90% specificity, 92.3% PPV, 43.5% NPV, 5.1 LR+ and 0.1LR-. *Der f* showed 71.4% sensitivity, 87.1% specificity, 82.6% PPV, 57.4% NPV, 5.5 LR+ and 0.3 LR-. *Blo t* allergen had 41.6% sensitivity, 91.7% specificity, 94.1% PPV, 32.8% NPV, 5.0 LR+, and 0.6 LR-. *Bla g* allergen had 23.8% sensitivity, 98.3% specificity, 90.9% PPV, 64.4% NPV, 14.5 LR+ and 0.8 LR-. **Conclusion:** serum specific IgE testing to common inhalant allergen in patients with respiratory allergy showed only low-to-moderate sensitivity, but high specificity and PPV. This new assay can be used to diagnose allergen sensitization in the population with high prevalence of TDR and cockroach.

Keywords: allergy, diagnostic test, inhalant allergen, specific IgE, skin prick test.

INTRODUCTION

The prevalence of allergy including allergic asthma, allergic rhinitis, food allergies, atopic eczema, skin allergies, or anaphylaxis tends to increase and affects 30–40% of population worldwide.¹ In 2025, it is predicted that 400 million of individuals will suffer from allergic asthma and 500 million from allergic rhinitis.^{2,3} It may occur not only in developed countries, but also in developing countries.⁴ The development of allergy is characterized by atopic march, topical eczema and food allergies during childhood, followed by respiratory allergy such as allergic asthma and allergic rhinitis in adulthood.^{5,6}

Allergen exposure, air pollution, climate changes, lifestyle changes, diet, psychological stress are factors influencing increased sensitization of allergen, prevalence of allergy, and different profile of allergen sensitization in each countries.⁷⁻⁹ In tropical countries, house dust mites exposure is an important factor causing the development of respiratory allergy. Besides *Dermatophagoides pteronyssinus* and *Blomia tropicalis* is the main cause of allergen in tropical region like Indonesia.¹⁰

The formation of IgE-specific antibody against allergen is the essential part of diagnosing allergen sensitization. Measurement of IgE-

specific antibody can be conducted in vivo with skin prick test or in vitro with IgE-specific serum measurement.¹¹

World Allergy Organization (WAO) mentions that skin prick test is the gold standard in detecting IgE.⁸ Skin prick test is a safe diagnostic approach, yet some adverse reactions are reported. In conducting skin prick test, trained personnel is needed and patients with history of antihistamine or corticosteroid treatment, patient with dermatographism are contraindicated.¹²⁻¹⁵ Specific serum IgE measurement aim at detecting IgE in serum. The price of specific serum IgE measurement is higher than skin prick test. However, it is not influenced by antihistamine drugs, skin disease, or skin adverse reactions.

This is the first study determining specific serum IgE diagnostic test in patients with asthma and/or rhinitis allergy using the most frequent etiology respiratory allergen such as *Blomia tropicalis*, in Indonesia. The objective of this study is to determine the accuracy of specific serum IgE measurement compared to skin prick test as the gold standard in examining allergen sensitization of individual to several allergens such as *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, and *Blatella germanica*.

METHODS

This was a cross sectional study conducted in outpatient clinic and procedure room of Allergy Immunology Division, Cipto Mangunkusumo Hospital, Jakarta including patients with asthma or allergic rhinitis. The method of sample recruitment was through consecutive sampling. This study had been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia on September 19th, 2018, with reference number: 796/UN2.F1/ETIK/2016.

There were 101 patients who attended clinic and procedure room of Allergy Immunology Division within November–December 2016. The inclusion criteria was patients with diagnosis of asthma and/or allergic rhinitis, aged 19–59 years, who signed informed consent, agreed to have skin prick test, and was free from antihistamine and corticosteroid within 7 days. The exclusion criteria was pregnant or breastfeeding women, patients with reduced skin reactivity condition such as chronic renal failure, malignancy, diabetes neuropathy, paralysis, and neurogenic disorders.

The subjects underwent skin prick test using several allergens, including Stallergenes (Europe) such as house dust mites (*Dermatophagoides pterossinus*, *Dermatophagoides farinae*, *Blomia tropicalis*), and German cockroach (*Blatella germanica*). During skin prick test, the diameter of skin undulation and skin erythema was measured using ruler. The result of measurement was recorded in millimeter. If the skin undulation was circle in shape, it was measured only once. However, if the shape was irregular then the measurement was based on the mean of median [(the longest length + the shortest length)/2]. If the skin undulation > 3 mm, it means that there was specific IgE of allergen.

In the same time, all included subjects were examined the specific IgE serum using commercial kit (Euroline Test®, Euroimmune, Germany) which consisted of 54 allergens. However, there was only house dust mites *Dermatophagoides pterossinus*/*Der p*, *Dermatophagoides farinae*/*Der f*, *Blomia tropicalis*/*Blo t* and cockroach (*Blatella germanica*/*Bla g*) which were analysed in this study. It was stated positive of specific IgE serum if IgE specific concentration was > 0.35 kU/l.

RESULTS

There were 101 respiratory allergic patients fulfilled the inclusion criteria; 77 (76.2%) subjects were female. The mean of age was 38.8 years. In general, patients suffer from asthma and allergic rhinitis (**Table 1**).

Table 1. Characteristic of subjects (n=101)

Characteristics	n (%)
Gender	
- Female	77 (76.2)
- Male	24 (23.8)
Age group	
- < 20 years	4 (4.0)
- 20 – 29 years	27 (26.7)
- 30 – 39 years	20 (19.8)
- 40 – 49 years	25 (24.8)
- 50 – 59 years	25 (24.8)
Diagnosis	
Asthma	21 (20.8)
Asthma and allergic rhinitis	62 (61.4)
Allergic rhinitis	18 (17.8)
Category of asthma	
Intermittent	28 (27.7)
Persistent	55 (66.3)
Family history of allergy	
- Yes	66 (65.3)
- No	35 (34.7)

Skin prick test was conducted with 3 inhalant allergens of house dust mites and 1 cockroach allergen. It is shown that most of the subjects were sensitive to *Blomia tropicalis* with the mean of skin undulation diameter was 6 mm (**Table 2**). Moreover, most of sensitization of serum specific IgE testing was sensitization to *Der f* (52.9%), followed by *Der p* (38.2%), *Blo t* (33.3%), and German cockroach (*Bla g*) (10.8%) (**Table 3**).

In this study the diagnostic test of IgE-specific measurement showed sensitivity of 23.8-71.4 %, specificity of 87.1-98.3%, PPV of 92.3-94.1%, and NPV of 32.8-64.4% (**Table 4**).

DISCUSSION

This was the first study conducted in Indonesia related to serum specific IgE testing using three house dust mites allergen and one

Table 2. Result of skin prick test (n=101)

Allergen	Diameter of skin undulation	n (%)
	Mean (SD), mm	
Der p		
Positive	6.4 (2.7)	71 (70.3)
Negative	0.9 (1.0)	30 (29.7)
Der f		
Positive	6.4 (3.1)	70 (69.3)
Negative	0.9 (1.1)	31 (30.7)
Blo t		
Positive	6.1 (2.8)	77 (76.2)
Negative	0.9 (1.1)	24 (23.8)
Bla g		
Positive	4.6 (1.9)	42 (41.6)
Negative	0.6 (1.0)	59 (58.4)

Table 3. Result of serum specific IgE testing (n=101)

Allergen	n (%)
Der p	
Positive (Class 1-6)	39 (38.6)
Negative (Class 0)	62 (61.4)
Der f	
Positive (Class 1-6)	54 (53.5)
Negative (Class 0)	47 (46.5)
Blo t	
Positive (Class 1-6)	34 (33.7)
Negative (Class 0)	67 (66.3)
Bla g	
Positive (Class 1-6)	11 (10.9)
Negative (Class 0)	90 (89.1)

Table 4. Result of diagnostic test: Serum specific IgE testing compared to skin prick test

Allergen	Sen	Spec	PPV	NPV	LR+	LR-
Der p	50.7%	90.0%	92.3%	43.5%	5.1	0.6
Der f	71.4%	87.1%	92.6%	57.4%	5.5	0.3
Blo t	41.6%	91.7%	94.1%	32.8%	5.0	0.6
Bla g	23.8%	98.3%	90.9%	64.4%	14.5	0.8

German cockroach allergen in patient with asthma and rhinitis allergic. In this study, most of the subjects were female (76.2%), with mean of age of 38.8 years. This study supports previous studies reporting the most of patients suffering from allergy is female. Study in Malaysia reported that there was 61.1% female patients and aged 32.6 years (range 18 - 66 year).¹⁶ Similar subjects' characteristic was also reported

in Texas, there were 61.6% female patients aged 37.1 years (range 18 - 65 years).¹³ The role of estrogen is being suspected in allergic event. Mast cell is known for expressing α -estrogen receptor, estrogen could trigger mast cell degranulation and increase IgE immune reaction.

This study showed that asthma and allergic rhinitis mostly occurred in those aged 20-29 years (26.7%) and least in < 20 years of age (4%). In normal individual, IgE increases since birth (0-1 KU/l) until adulthood and then starts to slowly decrease. The peak of IgE concentration is during 20 - 30 years of age.¹⁸

Most subjects in this study (63.8%) presented with history of asthma and allergic rhinitis, which was similar to the study in India; 13 (65%) among 20 allergic patients suffered from asthma bronchial and allergic rhinitis.¹⁹ In 50% of respiratory allergic cases, rhinitis and asthma could be found in one individual.¹⁷

Skin prick test shows that Blo t is the most commonly found house dust mites allergen (76.2%), followed by Der p (70.3%), and Der f (69.3%). Previous study in Jakarta showed similar result; Der p had the highest prevalence (77.5%) followed by Der f (69.6%) and Blo t (72%).²⁰⁻²² In comparison to skin prick test study in China (CARRAD study), it showed that the most common house dust mites was Der p (59%), Der f (57.6%) and Blo t (40.7%).²³

This study showed that sensitization against the German cockroach (*Blattella germanica*) was found in 41.6% patients. It was different from previous study conducted in Jakarta (44.9%).^{20,21} Another skin prick test study in China showed that German cockroach sensitization was 18.7%.²⁴ House dust mites and cockroach are well breed on air temperature of 23-25°C and humidity of 80-90%. Meanwhile in Indonesia, air temperature is 23-30°C and humidity is >68%. This condition might cause house dust mites and cockroach to be easily found in Indonesia.

Serum specific IgE testing shows that Der f was the most found allergen (52.9%) in this study, in contrast with United States study which used immunoassay (ImmunoCAP) method (37.2%). However, subjects with positive Der p in this study is similar with the previous study

(38.2% vs 38.4%).¹³ Recently, immunoassay method with ImmunoCAP is the gold standard to detect serum specific IgE testing (in vitro) compared to inhalant allergen (aeroallergen) though there are inconsistent results in various allergen extracts.²³

Another study in China reported that the prevalence of IgE-specific for dust mites was found in Guanzhou, was 61.1% Der p, 60.2% Der f and 41% Blo t. The study used Immunoassay ADVIA Centaur® (Bayer Healthcare LLC, USA) which was the reverse sandwich immunoassay with direct chemo-luminescent technology.²⁴

In this study, serum specific IgE testing was used to detect sensitization of Der p allergen in patients with asthma and/or allergic rhinitis showed low sensitivity (50.7%), while it was better for detecting Der f (71.4%). It means that serum specific IgE testing might be use to detect asthma and/or allergic rhinitis patients who are truly sensitized by Der p allergen (50.7%) and Der f allergen (71.4%). Furthermore, the specificity for detecting Der p and Der f is good, 90% and 87.1%, respectively. It means that the ability of the test to correctly identify those without the Der p allergen was 90%, while Der f allergen was 87.1%. It shows that serum specific IgE testing measurement could not be used as a screening tool for Der p and Der f allergens in the population.

In this study, the PPV of serum specific IgE testing was excellent (92.3% for Der p allergen and 92.6% for Der f allergen, however the NPV was low (43.5% and 57.4% for Der p and Der f allergen, respectively). This shows that positive serum specific IgE testing represents true allergy to Der p and Der f, yet it might be false negative to Der p and Der f. Application of the result depends on the prevalence of asthma and/or allergic rhinitis. So, it could not be applied in population with lower prevalence of asthma and/or allergic rhinitis.

The similar result was reported in Calabria et al. study¹³, the sensitivity and specificity of serum specific IgE testing for Der p and Der f allergen were 69.4% and 75.7%; 90.7% and 91.6%, respectively. Moreover, the PPV for Der p and Der f allergen was 87.1% and 87.5%. Although

this study used different method, similar result is found due to same allergen extract (i.e. Der p1 and Der p 2 as well as Der f 1 and Der f 2 as the main allergen for *D. pteronyssinus* and *D. farina*). The different result was in its NPV, 83.4% for Der p and 76% for Der f allergens.

Bogomolov²⁵ study compared serum specific IgE testing to gold standard skin prick test to determine the sensitivity of Der p and Der f allergen in patients with asthma and/or allergic rhinitis in Ukraine. They used skin prick test from original Ukrainian manufacture Vinnitsa allergens on 45 patients. They reported high sensitivity and specificity of serum specific IgE testing for Der p and Der f allergens [(85%, 93.3%) and (87.5%, 89.6%)].

Another study by Asha'ari et al.¹⁶, which was conducted within 1 year in Malaysia and included 90 allergic patients with age group 18 – 66 years showed that the sensitivity of serum specific IgE testing for house dust mites were 86%, yet had low specificity of 45.5%. This study used serum specific IgE testing with chemo-luminescent technology.

The different result from previous study^{16,25} might be due to other factors including the number of patients, origin of allergen, and methods of serum specific IgE testing. In Bogomolov study²⁵, they recruited 45 patients with allergen from original Ukrainian manufacture Vinnitsa allergens, while this study included 101 patients with allergen from Stallergenes (Europe). Moreover, Asha'ari study¹⁶ recruited patients with asthma and/or allergic rhinitis, and other allergic conditions. Also it did not mention the house dust mites allergen. They also used different serum specific IgE testing, chemo-luminescent; while this study used immunoblotting method.

Our study showed that the probability of positive serum specific IgE testing was 5.1 times in patients with asthma and/or allergic rhinitis who are allergic to Der p compared to non-allergic. In addition, the probability was 5.5 times for Der f allergen. The probability of negative serum specific IgE testing in respiratory allergic patients who were Der p allergic compared to those who were not allergic was 0.6 times, while 0.3 times in Der f allergen.

Sensitivity of serum specific IgE testing Blo t was 41.6% which means that the probability of patients with asthma and/or allergic rhinitis who were truly allergic to Blo t showed positive serum specific IgE testing was 41.6%. Moreover, specificity of serum specific IgE testing Blo t was 91.7%, meaning that the ability of this study to correctly identify those without the disease was 91.7%. So far, there was not any other publication showing result of serum specific IgE testing *Blomia troidalis* compared to gold standard skin prick test in patients with asthma and/or allergic rhinitis.

PPV of 94.1% and NPV of 32.8% means that the proportion of positive results in statistics and diagnostic tests were truly positive for Blo t allergen was 94.1%; while the proportion of negative results was 32.8%. High PPV might be found due to patients who are truly allergic Blo t. The serum specific IgE testing could be used in diagnosing sensitization of Blo t allergen in patients with asthma and/or allergic rhinitis. The prevalence in population is important in determining PPV and NPV. In population with low prevalence of asthma and/or allergic rhinitis cases, this result should be re-analyzed.

This study shows LR+ 5.0 and LR- 0.6, which means that the probability of individual without the condition having a positive test of Blo t allergic was 5 times.

The probability of patients with asthma and/or allergic rhinitis having positive Blo t allergic reaction compared to those without asthma and/or allergic rhinitis but with positive Blo t allergic reaction was 5 times; while there was only 0.6 times of probability of patients with asthma and/or allergic rhinitis with negative Blo t allergic reaction compared to those without asthma and/or allergic rhinitis with negative Blo t allergic reaction.

The examination of serum specific IgE testing to detect allergy to Bla g in patients with asthma and/or allergic rhinitis showed low sensitivity (23.8%), yet high specificity (98.3%). It means that serum specific IgE testing examination could not be used as screening test for Bla g allergy in population. The PPV and NPV for this test was 90.9% and 64.4%, respectively. This result means the probability that subjects with a

positive screening Bla g allergy test truly have the disease was 90.9%, while the probability that subjects with a negative result in screening for Bla g allergy test truly have the disease was 64.4%.

Calabria et al¹³ showed similar result with this study, with low sensitivity of serum specific IgE testing (34.5%) and high specificity (88.2%).²¹ This result might be due to similar allergen extracts, Bla g 1 and Bla g 2, the main allergen of German cockroach. However, Kumar et al.¹⁹ in India stated that sensitivity of Bla g was high (92.8%), with specificity of 66.6%, PPV of 86%, and NPV of 80%. It was caused by different allergen that Kumar et al used American cockroach allergen (*Periplaneta americana spp*).

In this study, the positive likelihood ratio (14.5) and negative likelihood ratio (-0.8) means that the likelihood of positive serum specific IgE testing was 14.5 times found in patients with asthma and or allergic rhinitis due to Bla g compared to non-Bla g allergy. In addition, the likelihood of negative serum specific IgE testing was 0.8 times presents in patients with allergy to Bla g compared to non-allergy.

CONCLUSION

Serum specific IgE testing test can replace skin prick test in determining allergen sensitization in high population with respiratory allergy (asthma and/or allergic rhinitis), individuals with dermatographism, individuals with generalized skin disorder and patients who need continued antihistamine treatment or treatment which affects diagnostic test.

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