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## Total IgE levels and their Relevance in the Diagnosis of Allergy Among Malaysian Population in the North-East Region of Peninsular Malaysia

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**Abstract**—Total immunoglobulin E (IgE) has been an indicator for early diagnosis of allergic diseases due the important role of IgE in the sensitization towards allergens. Although total IgE is a common diagnostic test that screens for possible allergic diseases, reports are still lacking on the profile of total IgE levels of allergic patients from the north-east region of Peninsular Malaysia. Hence, this study aimed to investigate the association of total IgE levels with clinico-demographic parameters and whether increasing total IgE levels were associated with certain allergic manifestations in this study cohort. A local cohort of allergic patients (n=71) diagnosed in between 2009 and 2016 in Hospital Universiti Sains Malaysia (HUSM) were evaluated for the relevance of total IgE levels in allergy diagnosis. Our study did not demonstrate significant association between total IgE with age ( $p=0.75$ ) or gender ( $p=0.65$ ). However, we showed that elevated total IgE levels were associated with disease severity. Our data suggests that increasing total IgE levels beyond the conventional cutoff used to define abnormal IgE levels were more commonly associated with patients presenting allergic asthma and skin allergy manifestations. Total IgE level is a useful indicator for diagnosis of allergic diseases. Although total IgE level might not be sufficient to confirm the sensitization status of an individual, it may reflect the severity of the allergic disease suffered and it has a high correlation with positive sIgE values.

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### 1 INTRODUCTION

Allergic diseases such as asthma, allergic rhinitis (AR), eczema and food allergy are very common with more than 20% of the populations in developed countries affected [1]. Allergic reactions are usually mild to moderate, affecting the quality of life of patients and their families, but the severe allergic reaction known as anaphylaxis is life-threatening. The reactions and symptoms of allergies are dependent on the allergen and the site of the body affected. Organs of the body commonly involved in allergic reactions are the nose, eyes, skin, respiratory system (lungs), and gastrointestinal system [2].

Apart from clinical symptoms, the diagnosis of allergic diseases is aided by various tests including the skin prick test (SPT), food challenge, total immunoglobulin E (IgE) and allergen-specific IgE (sIgE) assays. IgE is the immunoglobulin isotype that activates allergic sensitization to various allergens. Total IgE test has been one of the important indicators used to diagnose allergic diseases for many years [3]. Elevated levels of total IgE were reported in asthma, allergic rhinitis, eczema and even in the

event of anaphylaxis [4][5][6][7]. Moreover, total IgE levels are crucial in monitoring disease activity and response of patients towards therapy especially for allergic bronchopulmonary aspergillosis (ABPA) [8]. Although total IgE were also elevated in helminth and parasites infection, it is the cross link of IgE- FcεRI complex on sensitized mast cells with allergens that leads to the release of mediators of allergy including histamine, leukotrienes, prostaglandin and proteases [9]. Another key feature of IgE in allergy is that the responses are extremely rapid, unlike in the case of slowly replicating parasites. Furthermore, a genome-wide association study (GWAS) identifies a high affinity receptor for IgE gene (FCER1A), which was associated with allergic sensitization [10]. Numerous studies have been conducted proving the significant relationship between high total IgE levels and allergic diseases [11]. However total IgE levels vary among people with different ethnicity, geographic area, age, and gender [12][13]. Therefore, studies have been conducted to identify the normal range of total IgE level in different population in order to set the ideal cutoff

value for the diagnosis of allergy accordingly [3][13][14][15][16][17][18].

Although total IgE is a common diagnostic test that screens for possible allergic diseases, reports are lacking on the profile of total IgE levels in allergic patients from the north-east region of Peninsular Malaysia. In this retrospective study, we set out to investigate the association of total IgE levels with clinico-demographic parameters of a local cohort of allergic patients (n=71) diagnosed in between 2009 and 2016 in Hospital Universiti Sains Malaysia (HUSM). We also assessed the correlation between total IgE and sIgE levels, and whether increasing total IgE cutoff levels for allergy diagnosis is associated with various allergic manifestations in this group of allergic patients.

## 2 MATERIALS AND METHODS

### 2.1 Patients and Data Collection

This retrospective study was performed on the total IgE results of allergic patients tested in Immunology Laboratory of HUSM. The medical records of allergic patients tested in the laboratory from 2009 to 2016 were reviewed and 71 patients were included in this study. This study was approved by the Human Research Ethic Committee (HREC), USM, (USM/JEPeM/16080265).

The information collected from the Medical Records Unit in HUSM for all patients were as follows: (1) Demographic data (age and gender); (2) Medical diagnosis and allergic manifestations; and (3) Immunological laboratory test results of total and sIgE levels. The final number of samples obtained was based on the maximum number of samples with available laboratory records. The allergic diseases were classified according to the patients' symptoms and/or diagnosis done by the physicians based on clinical history. The allergic manifestations were as follows: anaphylaxis, respiratory (asthma), allergic rhinitis (AR), gastrointestinal, food, skin (dermatitis, urticaria, angioderma, skin or body rashes), or 'others' if the symptoms were not clear or overlapped with more than one allergic symptom.

### 2.2 Immunoassays

The serum concentration of total IgE (kU/l) was determined by ImmunoCAP® Total IgE (Phadia

Laboratory System, Thermo Fisher Scientific, Uppsala, Sweden) for all the 71 patients, and sIgE (kUA/l) as determined by ImmunoCAP® Specific IgE (Phadia Laboratory System) was tested only if requested by physician.

The reference values for total IgE cutoff levels for children aged below 10 years old were according to the manufacturer's standard expected test values [19] since the level of total IgE increases during childhood [20] until the age of 10 and the level is then maintained beyond 10 years old, in which the cutoff level of 100kU/l was used [3][21]. Patients with values above the cutoff levels were considered having high total IgE levels.

### 2.3 Statistical Analysis

The association between age and total IgE was compared between patients according to different age groups as follows: children (<13 years old) and adults (≥13 years old). The association between clinico-demographic parameters with IgE results were assessed by chi-square or Fisher's exact test (IBM® SPSS® Statistics version 22) and a two-tailed  $p < 0.05$  was considered to be statistically significant.

## 3 RESULTS

### 3.1 Association of Total IgE Levels with Clinico-demographic Parameters

Majority of our cohort of allergic patients demonstrated high total IgE levels (n=55/71; 77%; Table I). In terms of total IgE levels' association with demographic parameters, there was no significant relationship between total IgE levels with age ( $p=0.75$ ) and gender ( $p=0.65$ ). Allergic diseases were more common in adults (n=38/71; 53.5%) and male (n=39/71; 54.9%) compared to children (n=33/71; 46.5%) and females (n=32/71; 49.1%), respectively.

In terms of proportion of patients with high total IgE levels according to allergic manifestations, all patients (n=5/5; 100%) with anaphylaxis demonstrated high total IgE levels (Fig 1), followed by respiratory asthma (n=13/17; 76%), AR (n=3/4; 75%), gastrointestinal manifestations (n=6/8; 75%), food allergies (n=5/7; 71%) and skin manifestations (n=13/19; 68%). The allergy symptoms shown by the patients classified with gastrointestinal manifestation were including chronic diarrhoea, abdominal pain and gastroenteritis. Most of the

allergic patients categorised as 'others', which were diagnosed as allergic but with no specific diagnosis or had more than one allergic manifestation, also demonstrated high total IgE levels (n=10/11; 91%).

### 3.2 Association of Extreme Total IgE Cutoff Levels with Allergic Manifestations

We observed that majority of the patients (n=42; 59%) in our cohort showed very high total IgE levels that were more than two-fold of the usual cutoff for definition of having high total IgE. In order to examine whether extreme total IgE levels were associated with certain allergic manifestations, we interrogated if these manifestations consist of extreme total IgE levels in 100% increment of the cutoff total IgE levels conventionally used to determine high levels, *i.e.* we defined new cutoff levels for having high total IgE with 100% increment denoted as "H2", 200% as "H3", 300% as "H4" and 400% as "H5" of the conventional high total IgE cutoff levels. For example, for patients aged  $\geq 10$  years old where the conventional high total IgE cut-off level is 100 kU/l, H2, H3, H4 and H5 are equivalent to 200 kU/l, 300 kU/l, 400 kU/l and 500 kU/l, respectively.

For the H2-H5 cutoff levels for patients below 10 years of age, standard curves of 100% increment from the standard curve of total IgE (kU/l) (mean + SD) against age (year) according to manufacturer's standard expected test values (Phadia) were plotted (Fig 2). Therefore, for each new category of definition of high total IgE, only patients with values higher than the new cutoff level were considered having high total IgE while those below the cutoff level were considered to be in normal range.

As anticipated, the number of patients diagnosed with allergic disease with high total IgE decreased when the cutoff values were increased (Table II). However, the numbers of patients having total IgE levels above the H2 cutoff were relatively high in all allergic manifestations, with more than 50% of the patients remained high, except for AR, with only 25% patients having high levels according to H2 cutoff (n=1/4). None of the patients with anaphylaxis or AR were observed as having high total IgE when the cutoff increased up to 400% of the conventional value used to determine high total IgE levels. However, the number of patients presenting with asthma and skin allergy with total IgE level levels above H5

cutoff were relatively high with 41% (n=7/17) in asthma and 37% (n=7/19) in skin allergy. A smaller proportion of patients with food (n=2/7; 29%) and gastrointestinal allergy (n=2/8; 25%) had total IgE levels higher than H5 cutoff.

### 3.3 Specific IgE Profile of Patients with High Total IgE Level

The majority of patients (n=13/14, 92.9%) with high total IgE were positive for specific IgE test (Table III). These patients had positive specific IgE values for *Blomia tropicalis* (n=5), milk (n=7), egg white (n=3), soya (n=1), peanut (n=1), wheat (n=1), shrimp (n=3), crab (n=3) or tuna (n=1). For specific IgE test on *Dermatophagoides farinae* or *D. pteronyssinus*, 83% (n=5/6) and 80% (n=4/5) of the patients tested were positive, respectively. Most of the patients with high total IgE had multiple sensitization to allergens especially allergens in the same group *e.g.* house dust mites (HDM) (*D. farinae*, *D. pteronyssinus* and *B. tropicalis*) and seafood (shrimp and crab). One atopic patient who showed very high total IgE level (5000 kU/l) was positive to all allergens tested except *D. pteronyssinus* and *B. tropicalis*. Besides, one of the anaphylaxis patients also shown positive specific IgE for HDM allergens (*D. farinae*, *D. pteronyssinus* and *B. tropicalis*).

## 4 DISCUSSION

In our retrospective study, the cohort of patients did not demonstrate significant relationship between the total IgE levels with age or gender, which was similar with previous findings [22]. Allergic diseases in our cohort of patients were more common in males (54.9%) than females (45.1%), and this observation was in agreement with previous studies that reported higher number of male patients with various allergic diseases including inhalant allergy and allergic rhinitis [17][23][24][25][26]. These results possibly indicate gender-related genetic factors that may increase the susceptibility of males to develop allergic diseases [20]. The prevalence of allergy is higher in boys than girls at younger age, and more common in women than men in adulthood [27]. This can be explained by hormonal changes among the gender group throughout the life. Estrogen exerts stimulating effects on allergic reactions, enhancing IgE-dependant mast cells activation and degranulation [28]. Hence, the high level of estrogen could predispose individuals to clinical symptoms of sensitization [29]. In theory,

total IgE level increases during early ages [20]. In our study, we compared between two age groups i.e. children and adults. The insignificant relationship between age and high total IgE levels amongst our allergic patients indicate that people with allergic manifestations tend to have high total IgE levels despite the age group.

Elevated total IgE levels in allergic diseases is well documented [30] as IgE plays an important role in mediating allergic sensitization to various allergens [3]. The range of total IgE levels above 100 kU/l is recommended for allergy diagnosis in adult as it has been widely applied in most healthcare institutions. However, different countries adopt different reference values for total IgE since total IgE level is affected by several factors including ethnicity and geographical area. A lower total IgE cutoff level (above 81 kU/l) was used as recommended by East Kent Hospital University [31] and a much higher cutoff was used in studied population; for example, 195 kU/l by Al-Mughales in Saudi Arabia [18]. The differences of IgE levels in different race-ethnicity studied in the United States population is attributed to the genetic variation among the ethnic groups [32]. Furthermore, genome-wide association study (GWAS) has successfully identified a novel genome-wide significant association of a polymorphism in the zinc finger protein 365 gene (*ZNF365*) with total IgE level which vary in the mapping peaks (6p21.32-p22.1, 13p22-31, 14q23.2, and 22q13.1) among the Latinos [32].

Higher total IgE levels are usually observed in patients with severe allergic manifestation as well as atopic diseases such as dermatitis, asthma and allergic rhinitis [8], and high total IgE levels were present in all patients with anaphylaxis in our cohort of allergic patients. Interestingly, a sizeable proportion (>35%) of patients with asthma manifestations or skin allergy showed extreme levels of total IgE with 500% more than the conventional cutoff used to define abnormal IgE levels. Increased levels of total IgE have been associated with increased in several inflammatory cells such as basophils, mast cells, and eosinophils [8]. These effector cells play crucial roles in allergic diseases especially in asthma. The eosinophils are responsible in allergic asthma for inducing eosinophilic airway inflammation which results in chronic cough and worsens the symptoms [33]. Although mast cells and basophils are primary

cells involved in IgE synthesis in allergic reaction, eosinophils can contribute to the disease severity in asthma by upregulating other cytokines as well as IgE production [34].

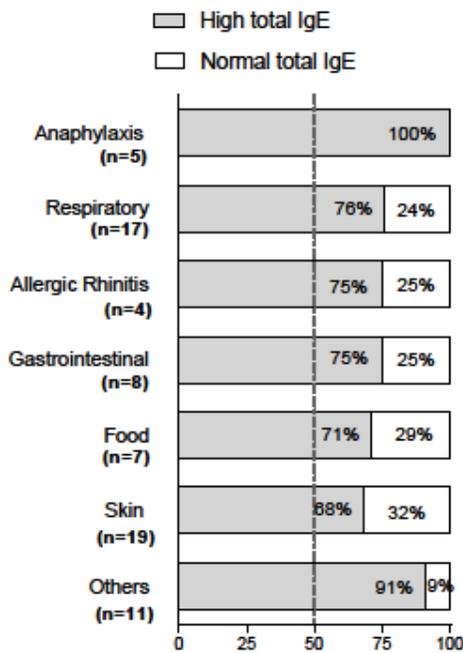
Although our study consists of relatively low number of patients (n=71), a high correlation of high total IgE values with positive specific IgE results was observed. We found many patients reacted to most of the tested specific allergens within the same group, especially HDM (*D. farinae*, *D. pteronyssinus*, and *B. tropicalis*) and seafood (shrimp and crab). The cross-reactivity between species is a common phenomenon due to high homology of the allergens [35]. Studies have found numerous allergenic proteins in different species or groups of allergens that caused sensitization as well as cross-reactivity, for example tropomyosin, a well-known allergen in shellfish allergy which also can be found in arthropods arthropods such as HDM [35][36]. Although the allergens of shellfood and HDM shared high molecular homology among the groups, the monoclonal antibodies produced against the allergens are species-specific, thus emphasizing on the measurement of specific IgE as a more accurate diagnosis tool in allergy [37].

## 5 CONCLUSION

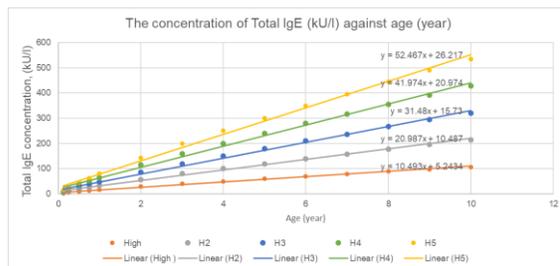
In conclusion, our study cohort which demonstrated high level of total IgE, indicating it as a useful tool for diagnosis of allergic diseases in our region. In this study we used total IgE cutoff level recommended by the ImmunoCap standard reference and experimented with different higher cutoff values. We found that higher cutoff levels would eliminate allergic patients by misdiagnosis, but at a H2 cutoff levels which is 100% increment than the standard cutoff value, more than half of the patients remained as having high total IgE level in each allergic manifestation, except for allergic rhinitis. Although total IgE level might not be sufficient to confirm the sensitization status of an individual as the specificity of the allergen is required, it may reflect on the severity of the allergic disease suffered. Since it has a high correlation with the positive sIgE values, this makes it a valuable tool in places lacking the resources to test multiple sIgE levels.

**Table 1:** The relationship between demographic data (age and gender) and total IgE level  
 \*\* The definition of normal and high total IgE level cutoff follows ImmunoCap standard reference for age <10 y/o while for age >10 year old, >100 kU/l is considered as high.

		n (%)	Total IgE level (n=71)		P-value
			Normal, n (%)	High, n (%)	
<b>Age (year)</b>	Age <13 (46.5)	33	8 (11)	25 (35)	0.75
	Age ≥13 (53.5)	38	8 (11)	30 (42)	
<b>Gender</b>	Female (45.1)	32	8 (11)	24 (34)	0.65
	Male (54.9)	39	8 (11)	31 (44)	



**Figure 1:** High total IgE and allergic manifestation



**Figure 2:** Standard curve tIgE for the different age

**Table 2:** Numbers of patients presenting allergic manifestations with total IgE levels 200% to 500% (H2-H5) of the conventional high total IgE cutoff (H) used to determined abnormal total IgE levels (kU/l)

Allergic manifestation	n (%)	H, n (%)	H2, n (%)	H3, n (%)	H4, n (%)	H5, n (%)
Anaphylaxis	5 (7)	5 (100)	3 (60)	2 (40)	0	0
Respiratory	17 (23.9)	13 (76)	9 (53)	9 (53)	8 (47)	7 (41)
Allergic rhinitis	4 (5.6)	3 (75)	1 (25)	0	0	0
Skin allergy	19 (27)	13 (68)	10 (53)	10 (53)	7 (37)	7 (37)
Food allergy	7 (90)	5 (71)	4 (57)	3 (43)	3 (43)	2 (29)
gastrointestinal	8 (11)	6 (75)	5 (63)	4 (50)	2 (25)	2 (25)
Others	11 (15)	10 (91)	10 (91)	9 (81)	7 (64)	4 (36)

\*sIgE test > 0.35 kU/l considered as positive

**Table 3:** Number of patients presenting positive allergen specific test respective to their total IgE levels

Allergen	Positive for sIgE, n (%)		sIgE (mean±SD)
	Patient with high total IgE	Patient with normal total IgE	
<b>House Dust Mites (HDM)</b>			
<i>D. farinae</i>	5 (83)	1 (17)	55.16
<i>D. pteronyssinus</i>	4 (80)	1 (20)	74.38
<i>B. tropicalis</i>	5 (100)	0	64.87
<b>Food</b>			
Milk	7 (100)	0	77.53
Egg white	3 (100)	0	91.26
Soya	1 (100)	0	100
Peanut	1 (100)	0	18.8
Wheat	1 (100)	0	100
<b>Seafood</b>			
Shrimp	3 (100)	0	1.10
Crab	3 (100)	0	1.33
Tuna	1 (100)	0	7.27

\*sIgE test > 0.35 kU/l considered as positive

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