ORIGINAL ARTICLE

EXPLORING THE PREVALENCE OF COW MILK AND SOY ALLERGIES AMONG BREASTFEEDING MOTHERS BY EXAMINING T-IgE AND SPECIFIC IgE LEVELS

Tengku NorbayaTengku Azhar[1], Radiah Abd Ghani[2], Siti Noorfahana Mohd Idris[1], Nur Azalina Suzianti Feisal[3] and Mohd Hamzah Bin Mohd Nasir[2]

[1]Centre Foundation Studies, Universiti Teknologi MARA, Cawangan Selangor, Kampus Dengkil, 43800 Dengkil, Selangor, Malaysia.
[2]Department of Biomedical Science, International Islamic University Malaysia, Kampus Kuantan, 25200 Kuantan, Pahang, Malaysia
[3]Department of Diagnostic and Allied Health Science, Faculty of Health & Life Sciences, Management and Science University, University Drive, Off Persiaran Olahraga, 40100 Shah Alam, Selangor, Malaysia

***Corresponding Author: Tengku Norbaya Tengku Azhar**
Email: tengku2888@uitm.edu.my

ABSTRACT

Cow and soy milk are recognized as common allergens that can trigger allergic reactions among infants, including those breastfed. It is most likely that the cow and soymilk allergens can be transmitted to infant through breast milk. Investigation on the maternal allergy status is essential to scrutinize the determining source of breastmilk transmitting allergens among the lactating mothers. This cross-sectional study is aimed to assess the prevalence of cow and soymilk allergies among lactating mothers by examining immunoglobulin E (IgE) levels. 36 lactating mothers were selected through convenience sampling in Dengkil, Selangor, and Kuantan, Pahang, Malaysia. Laboratory tests conducted using the ImmunoCAP 100 with CAP RAST (Radio-allegro-sorbent Test) system revealed Total IgE (T-IgE) levels ranging from 82 to 233 kU/L, with a mean SD of 142.27 ± 41.49. Specific IgE (s-IgE) levels for cow milk ranged from 0.10 ± 0.48 kU/L with a mean ± SD of 0.251 ± 0.09 kU/L, and s-IgE levels for soy ranged from 0.02 ± 0.04. The study found that 19.4% of respondents were clinically diagnosed with cow milk allergy and none were diagnosed with soy allergy. The Pearson correlation demonstrated a strong positive correlation ($r = 0.691$, $p < 0.001$), between T-IgE and cow milk IgE. No significant was observed between T-IgE and soy IgE as $r = 0.159$, $p > 0.05$. An independent T-test revealed a significant difference in T-IgE levels between positively diagnosed mothers with cow milk allergy ($p = 0.022$). This study suggests that relying solely on T-IgE levels may not be sufficient to determine allergy prevalence. By combining with s-IgE it can offer a more accurate diagnosis as a foundation for effective allergy management.

Keywords: Total Immunoglobulin E (T-IgE); Specific IgE (s-IgE);exclusive breastfeeding); infants

INTRODUCTION

Milk is a well-rounded diet in the form of liquid, providing sufficient and readily absorbable nutrients for humans1. Presently, there is a controversy surrounding the balance between the advantages and drawbacks of dairy fat in long term. The increasing prevalence of allergic conditions, particularly food allergies, is a cause for concern in Malaysia. Recently, various allergies or sensitivities have been identified among infants, children, and adults, inclusive of allergies towards cow's milk protein, known as CMPAs2. CMPA is the most prevalent food allergy during infancy and childhood, and it can persist into adulthood3. A food allergy is described as an adverse health reaction that consistently arises from a specific immune response upon exposure to a particular food4. Food allergies can be classified into two types: immunoglobulin E (IgE)-mediated (atopic) and non-IgE mediated (resulting in gastrointestinal symptoms)5. The occurrence of food allergies is influenced by an intricate interplay of genetic predisposition, dietary choice, and environmental factors, leading to a variety of symptoms. Based on genetic and epidemiological research, genetic predisposition can account for up to 80% of the heritability of allergies and plays a major influence in maternal immunological condition6,7,8.

CMPA can be triggered through various immunological pathways9. The IgE-mediated type, which is activated by IgE, accounts for approximately 60% of cases. Symptoms of this allergy manifest within two hours of exposure to allergenic proteins. The non-IgE-mediated reaction, on the other hand, may lead to symptoms between three hours and one week after consuming allergenic proteins, with a predominant involvement of gastrointestinal symptoms. CMPA stands as one of the prevalent food allergies during early childhood, impacting 2% to 3% of children under the age of 310 and manifests to resolve naturally during childhood before the age of 6 months11. Consecutively, maternal food allergies become a potential risk factor for infants allergy12,13as human milk could be a medium for transmission of allergen14. Thus, exclusively breastfed infants are not exempt from the risk of developing cow milk allergy (CMA). In

addition, partially and non-breastfeeding infants also at substantial risk of CMPA involves an immune reaction to cow's milk proteins found in infant formula. Infants affected by CMPA cannot tolerate cow's milk and require amino acid-based formula (AAF) or extensively hydrolysed casein formula (EHCF)15.

Although it is recommended to continue breastfeeding while the mothers eliminate cow's milk protein (CMP) from their diet, a recent publication challenges this practice14.The atopic condition of parents, particularly the mothers, plays a pivotal role in influencing diverse allergic manifestations in both the respondents and their infants. Thus, the atopy status of parents especially mothers is a crucial determinant of various allergic manifestations in both respondents and their infants16. In contrast to other allergies like peanut and shellfish allergies, there has been a consistent rise in the occurrence of instances of both CMA and SMA among Malaysian infants17.Earlier research indicates that sensitization to cow's milk is more prevalent than soy, with rates ranging from 14 to 23.8% and 7.7 to 10%, respectively.6,18,19.

The occurrence of food allergies fluctuates depending on the diagnostic method. For instance, the documented prevalence of CMA was 2.3% through self-report, but this can rise to 4.7% when tested with Skin Prick Testing (SPT) and clinical testing with specific IgE (s-IgE)20. Elevated levels of s-IgE and total IgE (T-IgE) are more indicative of clinical reactivity in allergic reaction21,22. Nevertheless, relying solely on clinical history without additional in vivo (skin testing) or in vitro (food-specific serum IgEs) examinations can diminish the precision of diagnosis as it becomes less specific and sensitive22. The focus of this paper is on Ig-E-mediated cow's milk and soy allergy, which is a type I hypersensitivity reaction. This study aims to investigate the diagnostic utility of T-IgE and s-IgE in detecting CMA and SMA.

METHODS

A cross-sectional study was conducted on consecutive individual pregnant woman considering the inclusion factors such as full-term singleton infants, within the age range of 18 to 39 years old and were exclusively breastfeeding their children below six months of age. Respective mothers also underwent a simple survey to self-perceive their allergy status and their infants. The respondents were selected using a convenience and snowball sampling technique.The sample size was determined using the two-mean formula, after considering the 80% response rate and 90% eligibility rate, the total sample size obtained from two mean samples which indicate six respondents per groups. Informed consent was obtained from the respondents and the study was approved by the ethics committee of the IIUM Research Ethics Committee (IREC-2019/011) and the Kulliyyah of Allied Health Science (KAHS42/18). The study was performed at Dengkil, Selangor, and Kuantan, Pahang, Malaysia with 36 samples recruitment.

Sample Collection and Analysis

All subjects were interviewed by investigators for sociodemographic and anthropometric measurements, followed by a serum collection. A questionnaire was used to determine the allergy symptoms. The allergy symptoms of the respondents were assessed using a validated pre-tested questionnaire. It consists of three sections; sociodemographic, anthropometry measurements, and symptoms with dual languages, which are Malay and English.

Blood samples were collected in a Vacuette Greiner serum separator tube using a 21-gauge needle and a 5 ml syringe (Terumo) by qualified nurses from a government health clinic. After collection, the samples were allowed to clot for 15 minutes. Then, the samples were centrifuged using the refrigerated centrifuge at a rate of 1,000 to 2,000 rpm x g for 10 mins at 4oC. Following centrifugation, 2 ml liquid supernatant (serum) was immediately transferred into a clean polypropylene tube using a Pasteur pipette. The samples were maintained at 2-8oC in an ice box to prevent contamination and haemolysis process. If the plasma was not analysed immediately, the plasma was stored at -20°C before being transported to another clinical laboratory to avoid freeze-thaw cycles. All procedures followed WHO best Infection prevention and control practices for phlebotomy in 201023.

Laboratory tests for T-IgE and s-IgE were conducted using the ImmunoCAP 100 with CAP RAST (Radio-allegro-sorbent Test) system. ImmunoCAP provides precise and reproducible quantification of specific IgE antibodies which has been confirmed in multiple studies and quality scheme by quantitatively measuring range from 0.1-100 kUA/l. and limit of quantitation as low as 0.1 kUA/l.

It is a system that fully integrated diagnostic system for the quantitative measurement of well accepted markers of allergic disease like IgE. During pre-analytical process, the reagent, purified water as rinse solution, immunoCAP software and 40ul sample were loaded to the instrument. Software Prompts the Operator to Load ImmunoCAP Tests and start the walk-away process. Temperature was set to 37°C of the processing chamber and run for 25 minutes hands-on time per run for 40 samples. Assays calibrated against WHO reference preparations provide results in quantitative mass-units. Two linked instruments controlled via PC running ImmunoCAP Data Manager (IDM) software were used to quantify the IgE in the sample.

Statistical Analysis
All data were entered into the SPSS (Statistical Package for the Social Sciences, version 17, Chicago, IL, USA) program for analysis, and data were analyzed using descriptive and inferential statistics. Descriptive data depicted the levels of T-IgE and specific IgE to cow milk and soy within the sample. Furthermore, an analysis was conducted to examine whether there is a correlation between T-IgE levels and specific IgE to cow milk and soy. Pearson correlation was employed for this analysis, with a significance level set at $p<0.005$. Additionally, a simple t-test was utilized to assess the difference in T-IgE levels based on the prevalence of cow milk allergy.

RESULTS

Demographic Characteristics
The age distribution is enumerated in Table 1, where the mean age was 30.33 years, with 97.2% of cases identified as Malay. All respondents experienced childbirth through natural vaginal delivery. Anthropometric data showed the mean weight and height of the respondents were 59.47 ± 9.74 kg and 1.56 ± 0.056 m, respectively. Meanwhile, infants had an average birth weight of 3.05 ± 0.39 kg (ranging from 2.2 to 3.9 kg) and 5.70 ± 1.75 kg (ranging from 3.58 to 8.8 kg).

Prevalence of Allergies in Respondents
As shown in Table 2, the table illustrates the levels of Total Immunoglobulin E (T-IgE) and specific Immunoglobulin E (s-IgE) for cow milk and soy in the maternal blood serum. The T-IgE levels varied from 82 to 233 kU/L, with a mean of 142.27 ± 41.49. The range for cow milk-IgE (CM-IgE) was 0.10 to 0.48 kU/L, with a mean of 0.251 ± 0.09. Additionally, Soy-IgE (S-IgE) ranged from 0.22 kU/L, with a mean of 0.127 ± 0.04. The positive diagnosis was determined using a cut-off point equal to or above 0.35 kU/L. Out of the respondents, only 19.4% received a positive diagnosis of cow milk allergy, with none being diagnosed with soy allergy.

The criterion for positive determination of allergy using the CAP RAST system was fulfilled when s-IgE levels equaled or exceeded 0.35 kU/L. Out of the tested respondents, 7 (19.4%) received a positive diagnosis for Cow's Milk Allergy (CMA) based on their cow milk IgE (CM-IgE) levels. Conversely, none of the respondents tested positive for soy allergy. In the range of CM-IgE levels, the 25th percentile of respondents had values of 0.173 kU/L or lower, while the 75th percentile had values of 0.328 kU/L or higher. As for S-IgE, the levels varied from 0.02 kU/L to 0.22 kU/L, with an average of 0.127 ± 0.04. The 25th percentile of respondents exhibited levels of 0.08 kU/L or below, while the 75th percentile had levels of 0.14 kU/L or above. Association between T-IgE and specific-IgE Table 3 examined the association between T-IgE levels with CM-IgE and soy-IgE. A significant correlation was found between T-IgE and CM-IgE, with $r = 0.691$, $p < 0.00$. However, there was no significant correlation between T-IgE and s-IgE, with $r = 0.159$, $p > 0.05$. Furthermore, no significant correlation was observed between CM-IgE and soy-IgE, with $r = 0.007$, $p > 0.05$.

Association between CMA prevalence with T-IgE
The independent t-test (Table 4, compares respondents positively and negatively diagnosed with CMA based on T-IgE concentration in maternal serum, and found a significant difference. Respondents with a positive diagnosis ($\bar{x}$ = 174.00, SD = 40.52) had a higher mean T-IgE compared to those with a negative diagnosis ($\bar{x}$ = 134.62, SD = 38.57) conditions ($t(34) = -2$, $p = 0.022$). This indicates that the mean T-IgE was elevated among mothers with a positive diagnosis of CMA compared to those without.

DISCUSSION

According to the MyHealth portal of the Malaysian Ministry of Health (MOH)17, the normal range for infant birth weight is summarized to be between 2.5 and 3.5 kg based on demographic and anthropometric factors. This range is indicative of the infants being in a healthy and well-cared-for condition. Furthermore, it is noteworthy that all respondents in the study exclusively breastfed their infants for a lactation period of up to 180 days.

Previous studies have suggested that both T-IgE and s-IgE levels can be employed to predict the allergy prevalence and pinpoint the allergen responsible for eliciting symptoms18,19,20,21.The study indicated that the average T-IgE value among the respondents was 142.27 ± 41.49 kU/L, a level notably higher than the mean T-IgE value reported in a study conducted in India (75 kU/L)21.Concerns have been raised among researchers worldwide due to the variability in the cut-off value of T-IgE. For example, in a study conducted in Sri Lanka10, a cut-off value of 200 kU/L was utilized, whereas another study in Malaysia defined a T-IgE value exceeding 100 kU/L as high for individuals with allergies14 .

Moreover, T-IgE values at the 25th percentile was under 104.25 kU/L, while those at the 75th percentile was 179 kU/L and higher. In Tehran, a study reported that the T-IgE score at the 90th percentile for 147 females was 238.4 kU/L, indicating a comparatively higher value than the previous study22.T-IgE concentrations can be influenced by factors such as heredity, environmental allergen exposures, ethnicity, and aging10,23. Hence, the subjectivity of the T-IgE reference poses a challenge when considering its use in clinical allergy diagnosis without taking into account other clinical history and tests.

Consistent findings from prior studies indicate that CMA is more prevalent in infants and relatively rare among adults12,24. In a Singaporean study involving 222 adult participants, it was discovered that the prevalence of cow milk allergy was 6%, and the prevalence of soybean allergy was 5%24. These findings are aligned with previous research, indicating that the prevalence of CMA is relatively higher compared to soy allergy. Moreover, it has been noted that individuals under the age of six months with milk allergy frequently exhibit adverse reactions to soy24.

IgE is a class of antibodies which are strongly linked to allergic reactions. This study did not identify and significant correlation between T-IgE and Soy-IgE with a correlation coefficient (r) of 0.159 and a p-value exceeding 0.05 for the sample size of 36. Furthermore, there was no notable correlation detected between CM-IgE and Soy-IgE, as indicated by a correlation coefficient (r) of -0.007 and a p-value exceeding 0.05 for the sample size of 36. Proteins obtained from cow's milk, such as whey α-Lactalbumin (α-La), alternatively labeled as Bos d 4, ß-Lactoglobulin (ß-Lg), also known as Bos d 5, and the casein (CN) fraction, also identified as Bos d 8, serve as examples.25 The proteins ß-conglycinin (Gly m 5) and glycinin (Gly m 6) originate from soybeans26, Kunitz trypsin inhibitor (KTI) and Gly m Bd 30K, which is a thiol protease inhibitor, are two soy proteins recognized as potential allergens that can induce allergic responses in certain individuals18.

Despite the diverse sources of protein derivation, cross-reactivity is infrequent due to the distinct allergenic properties inherent in each. Nevertheless, individuals with CMA often display co-sensitization to soy, as highlighted by numerous studies25,26. Cross-reactivity may happen when the protein allergen from various sources possesses similar molecular characteristics. This implies that identical IgE antibodies can attach to multiple allergens having shared epitopes, leading to the occurrence of allergic reactions27. Glycinin, a prominent protein constituent found in soybeans, is part of the protein family referred to as globulins. In certain instances, individuals with allergies or sensitivities to both soy and milk proteins may encounter cross-reactivity between the A5-B3 glycinin molecule present in soy and casein. This implies that the body might erroneously recognize the two proteins as resembling each other, thereby eliciting an allergic or sensitive reaction to both27.

In the context of soy and milk, research indicates that certain soy proteins can possess comparable epitopes, or regions of the protein that induce an immune response, to those present in cow's milk protein, such as casein. Gly m Bd 30K, also known as P34, is an example of a soy protein found to share epitopes with cow's milk casein, suggesting that individuals with soy allergy may also experience an allergic reaction when consuming cow's milk due to cross-reactivity between these two allergens28. It's important to note that cross-reactivity and co-sensitization are distinct concepts in the context of the immune response. Co-sensitization occurs when a person is sensitized to multiple allergens, but these allergens do not necessarily share similar molecular features27.

Conversely, atopic factors represent a blend of genetic, immunologic, and environmental elements that can predispose an individual to the development of allergic disorders such as asthma, allergic rhinitis, and atopic dermatitis. Research conducted in Malaysia confirmed the correlation between elevated T-IgE concentrations and allergic conditions. Specifically, the study revealed that 68% of respondents with skin symptoms, 76% with asthma, 75% with food allergies, and 100% with anaphylaxis had T-IgE levels surpassing the cutoff value of 100 kU/L, indicating heightened T-IgE levels21. In contrast, the research carried out in India observed a substantial elevation in T-IgE levels among individuals with allergies, specifically those with asthma and allergic rhinitis, in comparison to healthy women. To be specific, the study indicated T-IgE levels of 586 kU/L for asthma and 324 kU/L for allergic rhinitis, while healthy women exhibited only 75 kU/L29.Similarly, a previous Korean study found that the atopic group exhibited higher T-IgE levels compared to the non-atopic group, recording levels of 158.00 kU/L against 52.75 kU/L22.

It is typical for individuals with atopic conditions, such as atopic dermatitis, to manifest elevated T-IgE levels compared to those without such conditions. This is attributed to the role T-IgE plays in the immune response to allergens, triggering symptoms in individuals with atopic conditions. In summary, T-IgE and s-IgE levels serve as diagnostic and management indicators for allergies, but assessing the severity of an allergy should also consider other factors such as symptoms and medical history21.

Table 1: Demographic and Anthropometric Data for Mothers and Infants

Characteristic		n	Mean ±SD	Percentage or range
Age (years)		36	30.33±5.14	19-40
Races				
	Malay	35		97.2
	Chinese	1		2.8
Infant Birth Weight (kg)		36	3.05±0.39	2.2-3.9
Infant Latest Weight (kg)		36	5.70±1.75	3.58-8.8
Infant's Age (day)		36	114.17±50.10	30-180
	30	4		11.1
	60	6		16.7
	90	5		13.9
	120	5		13.9
	150	10		27.8
	180	6		16.7

Table 2: Descriptive Statistics of Total IgE, Cow Milk IgE and Soy IgE Concentrations in Maternal Serum

Items		Total IgE (kUL)	CM-IgE (kUL)	Soy-IgE (kUL)
n		36	36	36
Mean±SD		142.27±41.49	0.251±0.09	0.127±0.04
Range (kUL)		82-233	0.10-0.48	0.02-0.22
Percentiles	25	104.25	0.1725	0.08
	50	138.5	0.255	0.11
	75	179	0.3275	0.14
Allergy Status (n)(%)	Yes		7 (19.4)	0(0)
	No		29 (81.6)	36 (100)

Table 3: Pearson's correlation among T-IgE, CM-IgE, and S-IgE concentration in maternal serum

Variables	Cow Milk IgE		Soy IgE	
	r-coefficient	p-value	r-coefficient	p-value
Total IgE (kU/L)	0.691**	<0.001	0.159	0.355

Table 4: Independent T-test analysis for T-IgE concentration in maternal serum with CMA

Variables		N	Mean ± SD	Total IgE t	df	p-value
Cow Milk Allergy						
	Positive	7	174.00 ± 40.52	-2	34	0.022*
	Negative	29	134.62 ± 38.57			

CONCLUSION

The utility of T-IgE levels as a diagnostic tool for allergy diagnosis has garnered considerable interest. While T-IgE levels alone may not be sufficient to confirm an individual's sensitization status, they align with the specificity demonstrated by s-IgE clinical tests, offering a more accurate allergy diagnosis. However, this study has certain limitations, such as the adequacy of the sample size. Consequently, the presented T-IgE values may not be conclusive for determining a cut-off and representing the chosen population. Nonetheless, as a preliminary study, it does provide essential insights into the potential of T-IgE, in conjunction with s-IgE, as a predictive value, warranting further research which can be varied depending on factors such as population, age, time since the last ingestion of suspected food, or the presence of other

associated disorders.

ACKNOWLEDGEMENTS

The author would like to express sincere gratitude to Universiti Teknologi Mara (UiTM), particularly UiTM Kampus Dengkil for their invaluable support and facilitation of this project through 600-UiTMSEL (PI. 5/4) (009/2020)) grant. The author also like to extend a special thank-you to Global Allergy Centre, Malaysia for corporation for this project accomplishment.

Declarations Ethics
All participants were required to sign the written consent for participation, and ethical approval was acquired from the IIUM Research Ethics Committee (IREC-2019/011) and the Kulliyah of Allied Health Science (KAHS42/18).

REFFERENCES

1. Gorska-Warsewicz H, Rejman K, Laskowki W, Czeczotko M. Milk and dair products and their nutritional contribution to the average polish diet. Nutrients 2019; 11(8): 1771.

2. Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R. Cow's milk-induced gastrointestinal disorders: from infancy to adulthood. World J Clin Pediatr 2022; 11(6): 437-454.

3. Sichere SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food allergy from infancy through adulthood. J Allergy Clin Immunol Pract 2021; 8(6): 1854-1864.

4. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. Gastroenterology 2015; 148(6): 1120-1131.

5. Frank NM, Lynch KF, Uusitalo U, Yang J, Lonnrot M, Virtanen SM, Hyoty H, Norris JM. The relationship between breastfeeding and reported respiratory and gastrointestinal infection rates in young children. BMC Pediatr 2019; 19:339.

6. Zepeda-Ortega B, Goh A, Xepapadaki P, Sprikkelman A., Nicolaou N, Hernandez REH, Latif AHA, Yat MT, Diab M, Hussaini BA, Setiabudiawan B, Kudia U, Van Neerven RJJ, Muhardi L, Warner JO. Strategies and future opportunities for the prevention, diagnosis, and management of cow milk allergy. Front Immunol 2021; 12:608372.

7. Lee MK, Binns C. Breastfeeding and the risk of infant illness in Asia: A Review. Int J Environ Res Pub Health 2020; 17(1):186.

8. Abdulla F, Hossain MM, Karimuzzaman M, Ali M, Rahman A. Likelihood of infectious diseases due to lack of exclusive breastfeeding among infants in Bangladesh. PLoS One. 2022 Feb 16;17(2):e0263890.

9. Yang Y, Li X, Yang Y, Shoaie S, Zhang C, Ji B, Wei Y. Advances in the relationships between cow's milk protein allergy and gut microbiota in infants. Front. Microbiol 2021; 12: 716667.

10. Cronin C, Ramesh Y, Pieri CD, Velasco R, Trujillo J. 'Early introduction' of cow's milk for children with IgE-Mediated cow's milk protein allergy: a review of current and emerging approaches for CMPA management. Nutrients 2023; 15(6): 1397.

11. Lozinsky AC, Meyer R, Anagnostou K, Dziubak R, Reeve K, Godwin H, Fox AT, Shah N. Cow's milk protein allergy from diagnosis to management: a very different journey for general practitioners and parents. Children 2015; 2(3): 317-329.

12. Monjaraz EMT, Mayans JAR, Busta,amte RC, Morales EG, Rosales AM, Barrios EM, Mondragon FZ, Leon JC, Mendez MC, Lopez-Ugalde ML. Perinatal factors associated with the development of cow's milk protein allergy. Rev Gastroenterol Mex 2015; 80(1): 27-31.

13. Martin-Masot R, Diaz-Martin JJ, Santamaria-Orleans A, Navas-Lopez VM. Spanish pediatricians' positions regarding prevention, diagnosis, nutritional management, and challenges in cow milk protein allergy. Nutrients 2023; 15(16): 3586.

14. Munblit D, Perkin MR, Palmer DJ, Allen KJ, Boyle RJ. Assessment of evidence about common infant symptoms and cow's milk allergy. JAMA Ped 2020; 1:174(6):599-608.

15. McWilliam V, Netting MJ, Volders E, Palmer DJ. World allergy organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines update – X – breastfeeding baby with cow's milk allergy. World Allergy Organization J 2023; 16(11): 100830.

16. Batac ALR, Merrill KA, Golding MA, Bhamra M, Harbotthle Z, Kopsch I, Wilking E, Jonsson M, Ekstrom S, Abrams EM, Halbrich MA, Simons E, Roos LE, Keddy-Grant JA, Gerstner TV, St-Vincent JA,

Protudjer JLP. Infantile atopic dermatitis and maternal-infant bonding: a mixed methods study. Allergy, Asthma and Clinical Immunology 2023; 19(100).

17. Giannetti A, Vespasiani GT, Ricci G, Miniaci A, di Palmo E, Pession A. Cow's milk protein allergy as a model of food allergies. Nutrients 2021; 13(5):1525.

18. Colas L, Magnan A, Brouard S. Immunoglobulin E response in health and disease beyond allergic disorders. Allergy 2022; 77(6):1700-1718.

19. Vandenplas Y, Bajerova K, Dupont C, Eigenmann P, Kuitunen M, Meyer R, Ribes-Koninckx C, Salvatore S, Shamir R, Szajewska H. The cow's milk related symptom score: the 2022 update. Nutrients 2022; 14(13):2682.

20. Domenici R, Vierucci F. Exclusive breastfeeding and vitamin D supplementation: A positive synergistic effect on prevention of childhood infections? Int J Environ Res Public Health 2022; 19(5):2973.

21. Axod NA, Md Sani M, Zamry AA, Ahmad S, Mohd Ashari NS, Tan HTT, Wong KK, Mohamud R. Total IgE levels and their relevance in the diagnosis of allergy among Malaysian population in the North-East region of Peninsular Malaysia. J Biomed Clin Sci 2019; 4(2):1-74.

22. Sichere SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention and management. J Allergy Clin Immunology 2018; 141(1):41-58.

23. World Health Organization (WHO). WHO Guidelines on Drawing Blood: Best Practices in Phlebotomy; 2010. 125 p.

24. Dahdah L, Roelofs M, Knipping K, de Vries E, Rijnierse A, Garssen J, Brand PLP, Fiocchi A. Hypoallergenicity assessment of an extensively hydrolyzed whey-protein formula in cow's milk allergic infants. Pediatric Allergy and Immunology 2022; 33(6):e13814.

25. Cong Y, Li Y, Li L. Immunoglobulin E and immunoglobulin G cross-reactive allergens and epitopes between cow milk αS1-casein and soybean protein. J Dairy Sci 2020; 103(11): 9815-9824.

26. Radosavljevic J, Apostolovic D, Mihailovic J, Atanaskovic-Markovic M, Burazer L, van Hage M, Velickovic TC. Digestomics of cow's milk: short digestion-resistant peptides of casein form functional complexes by aggregation. Foods MDPI 2020; 9(11):1576.

27. Setiabudiawan B, Sitaresmi MN, Sapartini G, Sumadiono, Citraresmi E, Sekartini R, Putra AM, Jo J. Growth patterns of Indonesian infants with cow's milk allergy and fed with soy-based infant formula. Pediatr Gastroenterol Hepato Nutr 2021; 24(3):316-324.

28. Pang KA, Pang KP, Pang EB, Cherilynn TYN, Chan YH, Siow JK. Food allergy and allergic rhinitis in 435 asian patients - A descriptive review. Med J Malaysia 2017; 72(4):215–220.

29. Wong MM, Keith PK. Presence of positive skin prick test to inhalant allergens and markers of T2 inflammation in subjects with chronic spontaneous urticaria (CSU): a systematic literature review. Allerg Asthma Clin Immunol 2020; 16(72).