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Assessing the Potential Diagnostic Value of Indonesian Local Allergen Skin Prick Testing (SPT) for Cow's Milk Allergy among Atopic Dermatitis Patients

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ABSTRACT

Background: Atopic dermatitis (AD) is a multifactorial chronic, frequently recurrent, inflammatory skin condition. The development of IgE-mediated food allergies and food sensitivity are both associated with atopic dermatitis. Cow's milk allergy (CMA) caused the most common hypersensitivity reaction during childhood; however, the prevalence in adults is around 0.5%. Patients with AD use the Skin Prick Test (SPT) to evaluate the specific sensitization process. **Purpose:** This study aimed to assess cow's milk allergy among adult AD patients using local allergen extract SPT, standard SPT, and specific IgE (sIgE), as well as evaluating the conformity and relevance of the test results. **Methods:** Using consecutive sampling technique, the study was conducted twice on 45 adult AD patients with a one-week interval between administrations. **Result:** Local cow's milk SPT showed 4 positive results, and standard SPT showed 5. No sIgE test was positive. Local SPT was negative for 86.67% of individuals without a history of suspected cow's milk allergies. Standard SPT results were positive for 2.22% of individuals with a history of suspected cow's milk allergies and negative for 86.67% of those without. The relevance between local and standard SPT was shown to be substantial ($\kappa = 0.384$, $p = 0.000$). **Conclusion:** The result of the local cow's milk SPT and the patient's history had good conformity, and the relevance with standard SPT was significant in diagnosing cow's milk allergy among AD patients.

Keywords: Skin prick test, Cow's milk, Atopic dermatitis, Diagnostic, Human and health.

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BACKGROUND

Atopic dermatitis (AD) is a multifactorial, chronic, inflammatory skin condition that often recurs. It involves interactions between the environment (allergen exposure), the host (deficient skin barrier function), and the agent (microbial or viral).[1,2] Atopic dermatitis is the most prevalent chronic skin disease in children, affecting between 4% and 7% of adults and 17% to 24% of children.[2] Atopic dermatitis has a complicated pathophysiology that involves both genetic predisposition and environmental factors. Family history of atopic dermatitis and genetic mutations, such as the filaggrin gene, are the main risk factors for atopic dermatitis. Asthma, allergic rhinitis, and food allergies are all regarded as following atopic dermatitis as the first stage in the "atopic march," which is a succession of allergic disorders. Because of this, sensitivity to environmental and food allergens is typically present in patients with moderate-to-severe atopic dermatitis, and up to one-third of these patients have an IgE-mediated food allergy.[3]

Atopic dermatitis is classified into two subtypes depending on the presence of IgE specific to environmental allergens. The subtype is divided into the extrinsic subtype with an IgE-high and a normal IgE level in the intrinsic subtype. The former is

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primarily composed of the major subtype, which exhibits protein and food allergies, whereas patients with normal IgE levels notably experienced metal allergies.[4] The development of IgE-mediated food allergies and food sensitivity are both associated with atopic dermatitis.[3] Furthermore, there is evidence that in some children, food sensitization occurs before the onset of AD, while in other infants, AD occurs before food sensitization. The atopic march is known to be exacerbated by food sensitization alone. It is evident that eating certain foods might aggravate certain skin conditions. An epidemiologic study showed food allergens differed among countries. In Japan and Italy, cow's milk sensitization is more frequently developed than in other countries. Asian-born infants have a lower risk of peanut sensitization compared to those born in Western countries; therefore, the number of cases of hypersensitivity to shellfish and fish was more common. Differences in food allergy prevalence between countries can be partially influenced by regional dietary practices.[4] Animal and vegetable sources of protein may expose people to allergens, which frequently cause AD.[1] A cow's milk allergy (CMA) is a repeated allergic reaction to one or more milk proteins, usually whey-lactoglobulin or caseins. Allergies to cow's milk typically appear in early childhood, usually before a child turns one year old. Since most children outgrow their cow's milk allergy during childhood, this allergy frequently has a favorable natural history.[2] Cow's milk allergy is one of the most common and early causes of newborn food allergies, affecting 1.4% to 3.8% of young children.[5] Children diagnosed with CMA exhibited a significantly higher rates of developing asthma and rhinoconjunctivitis at 15 years of age. Furthermore, by age of 26, individuals with CMA in early childhood demonstrated significantly increased prevalence of current asthma and atopic dermatitis.[6] There are fewer reports on the prevalence of CMA in adults. According to what is known about the natural history of CMA, prevalence in adults should be lower and is typically estimated at around 0.5%. However, greater estimates have been recorded, with some misclassification likely resulting from self-reporting errors.[5] The intricate relationship between AD and CMA is largely attributed to the hyperactivity of T-helper 2 (Th2 cell) mediated mechanisms and their impact on the epidermal barrier. Type I hypersensitivity, or IgE-mediated, leads to the activation of Th2 cells. Influenced by various interleukins such as IL-4, IL-5, and IL-13 in the local microenvironment, Th2 cells play a critical role in type 1 hypersensitivity reactions by promoting IgE antibody production. Individuals with CMA showed increased spontaneous IL-4 production, which has been linked to compromised epidermal barrier function and dry skin observed in AD patients. This impaired skin barrier increases susceptibility to environmental factors, leading to the worsening allergy reaction.[1,7]

A thorough clinical history, skin prick testing (SPT), and/or sIgE testing, as well as an elimination diet experiment, are necessary for the diagnosis because parents are frequently unaware of the numerous allergy symptoms.[5,8] A skin prick test is advisable for type I hypersensitivity reactions (rapid type), which includes AD. This test could determine a person's susceptibility to different allergies.[1] Specific food allergies, such as CMA, have a significant detrimental influence on an individual's and their family's quality of life, including an emotional, psychological, and financial burden. Therefore, more research is needed to understand the causes, effects, prevention, and treatment of these allergies.[5] This study aimed to assess cow's milk allergy among adult AD patients using local SPT, standard SPT, and specific IgE (sIgE) as well as evaluate the conformity and relevance of the test results.

METHODS

The sample in this study were adult AD patients who came to the Dermatologic Allergy-Immunology Division outpatient clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in November 2020. The study was conducted for 2 months and used the consecutive sampling technique. The participants were atopic dermatitis patients aged 18-64 years with a history of AD who were in good health, willing to participate in the study, and willing to sign an informed consent. Patients who were pregnant, suffered from other chronic diseases (kidney failure, CVA, malignancy, and diabetes mellitus), took antihistamines, oral and topical steroids, antidepressants, beta-blockers, and ACE-inhibitors within 2 weeks before the study, and experienced exacerbations/acute attacks of AD were excluded.

Patients were interviewed beforehand regarding the data on their medical history needed for this study. SPT was conducted at the first and second meetings (one week after the first meeting). The SPT was performed on the volar side of the patient's forearms, and the area for the SPT was marked using a marker. The patient's skin that has been dripped with drops of the allergen to be tested was pricked using a microlancette. 15–20 minutes after treatment, the induration diameter was calculated. A translucent tape was affixed to the pen-marked margins of the induration. Then the translucent tape was attached to millimeter-sized paper, and the diameter of the lesion was measured. SPT results were considered positive if they had an induration > 3mm.

Microsoft Excel (Microsoft Corp., USA) was used to collect and analyze the data, and IBM SPSS Statistics for Windows Ver. 26 (IBM Corp., USA) was used to determine the relevance between variables. Cohen's Kappa relevance was used to analyze the relevance , and a p-value of less than 0.05 was considered statistically significant. This research has been reviewed and approve by the Ethics Committee at Dr. Soetomo General Academic Hospital Surabaya (No.1493/KEPK/IX/2019).

RESULT

The mean age of the 45 adult AD patients in this study was 27.2 ± 8.01 years. Eleven men and 34 women participated in this study. Forty-three individuals stated that they had a history of allergic reactions, while the remaining participant had no history of allergies. Two of the participants in the study reported that they had previously suffered from an allergy to cow's milk.

Table 1. Results of cow's milk SPT and sIgE

	Local SPT		Standard SPT		sIgE	
History of suspected cow's milk allergy	Yes	No	Yes	No	Yes	No
Yes (2)	0	2	1	1	0	2
No (43)	4	39	4	39	0	43

SPT: Skin Prick Test

The local cow's milk SPT showed 4 positive results, and the standard SPT showed 5 positive results. The sIgE test showed no positive result. According to the patient's history of suspected cow's milk allergy, 86.67% of patients who had no history of suspected cow's milk allergy got a negative result on the local SPT (Table 1). On the standard SPT, however, 86.67% of patients without a history of suspected cow's milk allergy acquired a negative result and 2.22% of patients with a history of suspected cow's milk allergy acquired a positive result.

Table 2. Clinical relevance of cow's milk local SPT

Clinical Relevance of Cow's Milk Local SPT		History of suspected Cow's Milk allergy	Result of Cow's Milk Local SPT	Total	Percentage
Yes	39 (86.67 %)	Yes	Positive	0	0%
		No	Negative	39	100%
No	6 (13.33 %)	Yes	Negative	2	33.33%
		No	Positive	4	66.67%

SPT: Skin Prick Test

Table 2 shows the clinical relevance of cow's milk SPT at 86.67%. None of the subjects had ever been suspected of having a cow's milk allergy, and the SPT test using the local allergen from cow's milk produced a positive result. Furthermore, 39 participants who had no history of suspected cow's milk allergies got a negative result. Meanwhile, there were 2 participants who had a history of suspected cow's milk allergies but got a negative result from SPT using cow's milk local allergen, and 4 participants who had no history of suspected cow's milk allergies got a positive result.

Table 3 displays the degree of relevance between the patient's history of cow's milk allergy, the local SPT, and the standard SPT. There was a statistically significant degree of relevance between the local SPT and the standard SPT, with a fair relevance. Nevertheless, there was no correlation found between the history of cow's milk allergy and either the local or standard SPT measurements.

Table 3. Relevance between a history of suspected cow's milk allergy and test results

	k	p
History of cow's milk allergy and local SPT	-.063	.651
History of cow's milk allergy and standard SPT	.237	.073
Local and standard cow's milk SPT	.384	.000*

* Statistically significant

k = Cohen's kappa coefficient

SPT: Skin Prick Test

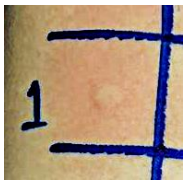

Figure 1. Patients with a positive skin prick tes result.

DISCUSSION

There is an increasing incidence of food allergies, especially in children. Regular skin prick tests (SPT) with the appropriate food allergens are the usual procedure for monitoring children with allergies. The commonly used extract for SPT is Food-Food (FF). Nevertheless, the reliability of FF is uncertain and varies among different types of foods. For peanuts, eggs, tree nuts, and fruits, the SPT using FF has shown more dependable outcomes, with sensitivity and specificity levels at least comparable to commercial extract (CE).[9] In this study, the SPT was performed on the volar side of the patient's forearms, and the area for the SPT was marked using a marker. The patient's skin that has been dripped with drops of the allergen to be tested was pricked using a microlancette. SPT with

precise weight management was applied to the volar forearms and backs. During the SPT technique, the weight of the lancet is a crucial aspect. Increased lancet weights cause noticeably bigger wheal reactions, which may have diagnostic implications. In order to increase the procedure's sensitivity and specificity, more study on the ideal lancet weight in accordance to SPT recommendations is necessary.[10]

Particularly in allergic disorders like AD, SPT is one of numerous diagnostic instruments used to validate the sensitization process to an allergen by identifying specific IgE antibodies. This method's simplicity, safety, accuracy, and affordability make it a dependable diagnostic tool for allergic disorders. SPT is crucial for quickly determining whether patients are sensitized to specific allergens, helping prevent the worsening of the disease. Test accuracy is crucial, much like with other diagnostic instruments, and it is evaluated using validity metrics including sensitivity (Sn), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV), likelihood ratios (LR), and disease prevalence. Positive Sp rules in the illness (SpPIN), whereas negative Sn rules out the disease (SnNOUT). The chance that a patient actually does not have the disease is represented by NPV, whereas the probability that a patient actually has the condition is represented by PPV. The ability of the exam is often evaluated using LR, where a higher LR+ and a lower LR-signify a better test.[11]

The optimal sensitivity and specificity are achieved with a cutoff of ≤ 3 mm for negative results in the CMA diagnostic test. Previous research suggested higher cutoff points, offering increased specificity but leading to a higher incidence of reactions during oral food challenges (OFC) with minimal benefits. As a result, the previous study recommended adopting the safer cutoff. It is important to emphasize that these cutoff values, which were obtained from the study's findings, apply only to people who believe they may be allergic to cow's milk and who show symptoms promptly after consuming dairy products. These could also be essential for follow-up evaluations to evaluate the safety of children who have already received a diagnosis of CMA. However, for children experiencing mild and uncertain symptoms, further research is necessary to evaluate the reliability of these cutoff values.[12, 13]

In our study, the patients' history of suspected cow's milk allergy determined that 86.67% of those without a history of suspected cow's milk allergy received negative results on their local SPT tests. On the standard SPT, however, 2.22% of patients with a history of suspected cow's milk allergy received a positive result, whereas 86.67% of patients without a history of suspected cow's milk allergy received a negative result. The sIgE test showed no positive result. This is a result of the use of total serum IgE in this study rather than specific serum IgE. Serum-specific IgE is better for diagnosing allergies to cow's milk than total serum IgE. A negative IgE test alone does not rule out the diagnosis of cow's milk allergy.[14,15] A prior study indicated that locally manufactured allergen extracts ranged in sensitivity (Sn) from 15.38% to 84.61%, with the house dust mite extract exhibiting the highest sensitivity. The range of specificity (Sp) observed was 81.48% to 93.75%, with the highest specificity observed in the shrimp extract. House dust mite extracts that were imported and generated locally both had favorable sensitivity (92.9% and 85.7%, respectively) when compared to IgE findings. Furthermore, for locally manufactured egg white and cow's milk extracts, the specificity (86.4% and 84.4%, respectively) was considered satisfactory.[16] There were 2 participants who had a history of suspected cow's milk allergies but got a negative result from SPT using cow's milk local allergen, and 4 participants who had no history of suspected cow's milk allergies got a positive result. Consistent with previous research findings, the study notes that a positive SPT result does not always indicate the presence of a true hypersensitivity reaction. However, a positive SPT can be considered an indicator of an IgE-mediated allergic response, even in the absence of a clear clinical history of allergy.[17]

According to several investigations, the sensitivity (Sn) and specificity (Sp) of SPT for cow's milk have varied. These studies include those conducted in Thailand (Sn 22%, Sp 85%), the Czech Republic (Sn 33.3%, Sp 97.9%), and Sweden (Sn 41%, Sp 99%).[18–20] In Anggraeni et al.'s study, 45 AD patients at Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, had their SPT results from a new, locally produced cow's milk extract compared to imported allergen extracts with specific IgE. The new extract had Sn and Sp values of 27.27% and 88.23%, respectively, whereas the imported extract did not. The Sp for cow's milk was greater than other allergen extracts (84.4%) when compared to specific IgE. Although several criteria could not be examined since there was no positive specific IgE in this group, the negative predictive value (NPV) was the greatest (78.9%; 100%). It is pointed out that in order to acquire more reliable evaluation results, more selective inclusion criteria are essential, especially with regard to the patient's history of specific food allergies.[12] Specificity was defined as the percentage of patients who reported a negative test result and no history of a specific disease, whereas sensitivity was defined as the percentage of patients who reported a positive test result and a history of a specific disease.

The possibility of curing CMA is a frequently asked question by parents of individuals with allergies. Analyzing the SPT results with casein from the initial allergic assessment can provide insights into the potential resolution of CMA over time. A patient's likelihood of outgrowing CMA is correlated with a greater initial SPT with casein. In particular, there is very little possibility of gaining tolerance in following

three years if the first casein SPT measures ≥ 14 mm. To ascertain whether a casein SPT of ≥ 14 mm represents a negative prognostic factor for the overall recovery rate, an additional study is required. According to prior studies, the first SPT with formula milk (FM) did not predict the possibility of later acquiring tolerance. Nevertheless, to create a comprehensive risk assessment, more investigation is necessary.[13]

Age has a notable impact on wheal size, particularly with FM. As such, we suggest applying fixed cutoffs for all age groups when using them for clinical purposes. Patients who failed the OFC showed a higher prevalence of specific clinical indicators. In spite of this, multivariate analyses were unable to find credible clinical score models that could compute all the variables needed to identify the patients who had the best chance of undergoing OFC without developing a reaction. This could be explained by the findings of the SPT for casein and milk extract having a significant impact and overshadowing other factors. Most statistical analyses were performed on information gathered from patients who had OFC in order to reduce bias.[22]

In order to determine positive and negative predictive values for intentional challenges, this group of patients with sIgE-mediated cow's milk protein allergy (CMPA) offers a valuable opportunity that will help clinicians decide whether they should proceed with a food challenge or not. After considering the test outcomes and talking with parents, the allergist made the subjective decision to take on the task. In a prospective birth cohort, numerous factors associated with the outcome of food challenges have been identified. Atopic dermatitis and urticaria were found to be the predictive symptoms of the inability to complete the food challenge (p-values < 0.05 and 0.001, respectively). The SPT has a fairly high specificity range of 51%, but a relatively low sensitivity range of 61% to 83%. A skin prick test showing a wheal diameter ≤ 3 mm has a high 98% negative predictive value, whereas one showing a wheal diameter ≥ 15mm has a 95% positive predictive value. However, despite its utility, the predictability of the SPT alone is insufficient to replace the need for a food challenge. The correlation between the results of reintroduction testing and cow's milk-specific IgE (CM sIgE) concentration in serum has also been highlighted in studies. Evaluating the sIgE levels for casein, β-lactoglobulin, and α-lactalbumin did not show any statistically significant variations across the child groups that succeeded or failed in their food challenges. It is not recommended to use the two tests in conjunction for diagnosis, even though both SPT and sIgE determination are useful diagnostic tools in pediatric clinical practice. Recent studies have revealed that 23% of children who were given cow's milk and were orally challenged had conflicting results between sIgE and SPT, indicating neither consistently negative nor consistently positive outcomes.[23-25]

The result indicates that there was conformity between the local cow's milk skin prick test (SPT) outcomes and the patient's history. Furthermore, the analysis revealed a statistically significant level of relevance between the local cow's milk SPT and the standard SPT. This finding indicates that both types of SPT tests can be considered reliable in diagnosing cow's milk allergy (CMA) among patients with atopic dermatitis. These imply that the local cow's milk SPT can be a reliable diagnostic tool to identify CMA in atopic dermatitis patients.

REFERENCES

1. Pessôa, R., Clissa, P. B., Sanabani, S. S. The Interaction between the Host Genome, Epigenome, and the Gut–Skin Axis Microbiome in Atopic Dermatitis. Int. J. Mol. Sci. 2023;24(18):14322.
2. Bylund S, Kobyletzki LB, Svalstedt M, Svensson, A. Prevalence and Incidence of Atopic Dermatitis: A Systematic Review. Acta Derm Venereol. 2020; 100(12):adv00160.
3. Graham F, Eigenmann PA. Atopic dermatitis and its relation to food allergy. Curr Opin Allergy Clin Immunol. 2020;20(3):305-310.
4. Tokura Y, Hayano S. Subtypes of atopic dermatitis: From phenotype to endotype. Allergol Int. 2022;71(1):14-24.
5. Zepeda-Ortega B, Goh A, Xepapadaki P, Sprikkelman A, Nicolaou N, Hernandez REH, et al. Strategies and Future Opportunities for the Prevention, Diagnosis, and Management of Cow Milk Allergy. Front Immunol. 2021;12:608372.
6. Hansen MM, Nissen SP, Halken S, Høst A. The natural course of cow's milk allergy and the development of atopic diseases into adulthood. Pediatr Allergy Immunol. 2021;32(4):727-733.
7. Weimer DS, Demory Beckler M. Underlying Immune Mechanisms Involved in Cow's Milk-Induced Hypersensitivity Reactions Manifesting as Atopic Dermatitis. Cureus. 2022;14(8):e27604.
8. Robison RG, Singh AM. Controversies in allergy: food testing and dietary avoidance in atopic dermatitis. J Allergy Clin Immunol Pract. 2020;7(1):35–9.
9. Uncuoglu A, Eser Simsek I, Cogurlu MT, Baydemir C, Aydogan M. Utility of fresh egg skin prick test and egg yolk specific immunoglobulin E for outgrowth. Ann Allergy Asthma Immunol. 2020;125(4):418–24.
10. Popov TA, Passalacqua G, González-Díaz SN, Plavec D, Braido F, García-Abujeta JL, et al. Medical devices in allergy practice. World Allergy Organ J. 2020;13(10):100466.
11. Kang SY, Yang MS, Park SY, Kim JH, Won HK, Kwon OY, et al. The role of allergen-specific IgE in predicting allergic symptoms on dog and cat

exposure among Korean pet exhibition participants. World Allergy Organ J. 2020;13(12):100488.
12. Díaz MC, Lavrut AJ, Slullitel P, Souza MV. Usefulness of analytic tests for the diagnosis of cow's milk protein allergy. Arch Argent Pediatr 2022;120(1):21- 29.
13. Lachover-Roth I, Giorno N, Hornik-Lurie T, Cohen-Engler A, Rosman Y, Meir-Shafrir K, et al. Cow's milk allergy skin tests: fresh milk, commercial extracts, or both? Allergy Asthma Clin Immunol. 2023;19(1):6.
14. Toca MC, Morais MB, Vázquez-Frias R, Becker-Cuevas DJ, Boggio-Marzet CG, Delgado-Carbajal L, et al. Consensus on the diagnosis and treatment of cow's milk protein allergy of the Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Rev Gastroenterol Mex (Engl Ed). 2022;87(2):235-250.
15. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020;13(2):100080.
16. Anggraeni S, Ayu Umborowati M, Endaryanto A, et al. The Accuracy of Indonesian New Local Skin Prick Test (SPT) Allergen Extracts as Diagnostic Tool of IgE-mediated Atopic Dermatitis. Vol. 15, Indian Journal of Forensic Medicine & Toxicology. Indian J Forensic Med Toxicol. 2021;15(3):4278–4285.
17. Saad K, Elgenidy A, Atef M, Abdelsattar MK, Al-Ashwah M, Hammad EM, et al. Cow's Milk-related Symptom Score for cow's milk allergy assessment: a meta-analysis for test accuracy. Pediatric res. 2023;93(4):772–9.
18. Anggraeni S, Umborowati MA, Damayanti, Endaryanto A, Prakoeswa CRS. Correlation between Skin Prick Test and Specific IgE of Local Mites Allergen in Atopic Dermatitis Patients: an Indonesian Study. CMUJ Nat Sci. 2022;21(4):e2022053.
19. Sripramong C, Visitsunthorn K, Srisuwatchari W, Pacharn P, Jirapongsananuruk O, Visitsunthorn N. Food sensitization and food allergy in allergic Thai patients from a tertiary care center in Thailand. Asian Pac J Allergy Immunol. 2022;40(2):147-154.
20. Gupta N, Anand M. Allergy skin testing. Pediatr Pulmonol. 2023;2(5):112–118.
21. Monaghan TF, Rahman SN, Agudelo CW, Wein AJ, Lazar JM, Everaert K, et al. Foundational Statistical Principles in Medical Research: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value. Medicina. 2021;57(5):503.
22. Lopes JP, Sicherer S. Food allergy: epidemiology, pathogenesis, diagnosis, prevention, and treatment. Curr Opin Immunol. 2020;66:57–64.
23. Jensen SA, Fiocchi A, Baars T, Jordakieva G, Nowak-Wegrzyn A, Pali-Scholl I, et al. Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - III - Cow's milk allergens and mechanisms triggering immune activation. World Allergy Organ J. 2022;15(9):100668.
24. Günaydin NC, Akarcan SE, Gülen F, Bal CM, Tanaç R, Atasever M, et al. Cut-Off Values of Specific IgE and Skin Prick Test to Predict Oral Food Challenge Positivity in Children with Cow's Milk Allergy. Turk Arch Pediatr. 2022;57(6):603-610.
25. Vandenplas Y, Meyer R, Nowak-Wegrzyn A, Salvatore S, Venter C, Vieira MC. The Remaining Challenge to Diagnose and Manage Cow's Milk Allergy: An Opinion Paper to Daily Clinical Practice. Nutrients. 2023;15(22):4762–2.