Component Resolved Diagnostics for Cow's Milk Allergy in Children: a systematic review of diagnostic test accuracy

Yong Wang[1], Youfeng Ren[1], Yuxiang Zhang[1], Xuan Liang[1], and Rongfang Zhang[1]

[1]Affiliated Hospital of Gansu University of Chinese Medicine

August 23, 2023

Abstract

Background: The role of Component Resolved Diagnostics (CRD) in the diagnosis of cow's milk allergy (CMA) remains highly controversial. In this systematic review, we aimed to evaluate the accuracy of CRD in diagnosing CMA in children. **Methods:** We searched four electronic databases (EMBASE, PubMed, the Cochrane Library, and Web of Science) from January 1, 2000, to March 27, 2023, for studies that utilized milk composition and oral food challenges (OFC) as a reference standard in patients with suspected milk allergy. The quality of the included studies was assessed using QUADAS-2. Due to the heterogeneity of the studies, a meta-analysis could not be performed, and a narrative synthesis of the findings was conducted. **Results:** Our analysis included 5 prospective studies, 2 retrospective studies, and 2 case-control studies, with a total of 958 children. The sensitivity of Bos d 4 ranged from 0.50 to 0.82, and specificity from 0.78 to 0.98. Bos d 5 sensitivity 0.24-1.0, and specificity 0.58-0.98. Bos d 6 sensitivity 0.09, and specificity 0.94. Bos d 8 sensitivity 0.34-0.90, specificity 0.79-0.98. **CONCLUSION:** The specific IgE (sIgE) of the Bos d 4, Bos d 6, and Bos d 8 components of milk is highly specific but not sensitive in diagnosing cow's milk allergy in children. The use of CRD for the diagnosis of CMA in children may reduce the need for OFC.

INTRODUCTION

Cow's milk allergy (CMA) is a significant public health issue worldwide. It is defined as a reproducible adverse reaction to one or more cow's milk proteins, typically casein or serum beta-lactoglobulin, and is the most common allergen in early life[1]. Epidemiological data indicate that the prevalence of CMA in infants and young children in developed countries ranges from 0.5% to 3%, however, the prevalence of the condition in adults is extremely rare, at around 0.5%, with some regional variations[2]. Milk allergies can be classified into three types based on the immune mechanisms: Ige-mediated, non-Ige-mediated, and a combination of both. This can result in a range of symptoms, including urticaria, angioedema, gastrointestinal symptoms (such as abdominal pain, vomiting, and diarrhea, respiratory symptoms (such as dyspnea, coughing, and wheezing), and cardiovascular symptoms (such as dizziness, confusion, and hypotension). Patients with CMA often experience a severely impacted quality of life, leading to malnutrition, feeding difficulties, as well as the risk of accidental exposure resulting in fatal anaphylactic reactions[3-5].

An accurate diagnosis of milk allergy is critical to managing and preventing severe allergic reactions and preventing unnecessary dietary restrictions[6]. The diagnosis of cow's milk allergy is confirmed by allergy history, skin prick test (SPT), specific immunoglobulin E (sIgE), atopy patch test (APT), and oral food challenges (OFC), however, SPT and sIgE have low sensitivity and specificity[7], APT is rarely used in the clinic. Although the double-blind oral food challenges (DBOFC) is the gold standard for diagnosis, its limitations have become more apparent over time; this technique is difficult to perform, time-consuming, costly, and may cause severe allergic reactions[8]. In addition, OFC results do not predict the severity of subsequent reactions[9], and there is no direct correlation between the triggering thresholds experienced by patients during OFC and the severity of reactions following accidental exposure[10].

In light of the limitations of traditional methods for diagnosing milk allergy, Component Resolved Diagnostics (CRD) has emerged as a valuable tool in allergology research for measuring specific IgE antibodies over the past decade[11]. This method involves the IgE using a small amount of serum from capillaries, allowing for the identification of the main sensitizing components of milk[12]. The three most significant allergens in milk are casein (Bos d 8), b-lactoglobulin (Bos d 5), and a-lactoglobulin (Bos d 4), with sensitization to other minor proteins, such as bovine serum albumin (Bos d 6), also being reported[13], CRD can distinguish between sensitization due to co-sensitization and cross-reactivity, helping to rule out allergy[12-14]. As CRD technology improves, it can be used not only to assess the risk, severity, persistence, and prognosis of clinical reactions[15], but also to identify those patients who would benefit from it[16, 17], and provide more effective and safer allergy immunotherapy regimens for patients[18]. However, the diagnostic accuracy of the identified components has varied in different studies, so the diagnostic value and clinical application of CRD for milk allergy remain unclear.

Although our previous systematic review evaluated the diagnostic accuracy of various food allergy tests, there have been limited studies on CRD. To our knowledge, only a few studies have addressed the diagnostic test accuracy (DTA) review for CRD, with a primary focus on peanut, hazelnut, and nut allergy diagnosis[19-21]. There is only one systematic review that evaluates the diagnostic accuracy of CRD for milk allergy, but it only includes two studies[22]. With the increasing number of studies on CRD in milk allergy, there is a need for a more comprehensive review of the evidence regarding the diagnostic accuracy of CRD in milk allergy, which would help to reduce overdiagnosis and provide evidence for the necessity of OFC during the final diagnosis. Therefore, we conducted a systematic review to determine the accuracy of CRDs for the diagnosis of milk allergy.

METHODS

By the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Table S1)[23]. A comprehensive and systematic literature search was conducted. The review protocol has been registered with PROSPERO (Prospective Registry of International Systematic Reviews) under ID number: CRD42023402964.

Search strategy

Although CRD methods were originally described in the 1990s [24], their clinical implementation in food allergy diagnosis did not occur until the early 2000s [25]. Therefore, we initiated our literature search in the early 2000s. We conducted a comprehensive search of the following databases from January 1, 2000, to March 8, 2023: EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science. We used the following keywords: 'Milk Hypersensitivity', 'Milk Allergy', 'Molecular Pathology', 'Molecular Allergen Test', and 'Specific Immunoglobulin E'. Our complete search strategy is provided in the online supplement (Table S2). No language restrictions were applied.

Study selection and data collection

Two reviewers, YW and YFR, independently screened the titles and abstracts of all studies and subsequently reviewed the full texts to identify the included studies. The following data were extracted using forms specifically developed for this systematic evaluation: 1) general information such as authors, country, and year of publication, 2) study characteristics including study design, population characteristics (number of patients, age), components determined by the intervention technique, thresholds for the use of the intervention, and the gold standard, and 3) DTA measurements, such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as well as a 2x2 table of columns reflecting the true number of positives, true negatives, false positives, and false negatives. Calculated from the 2X2 column linkage table in the absence of DTA measurements and 95% confidence intervals provided by the authors[26-28]. Data extraction was done independently by YW and was confirmed through XL. Two additional reviewers, YW and YXZ, independently used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool[29] to assess the quality of the included studies. Any disagreements were resolved through consensus and discussion, with the involvement of a third reviewer, RFZ, if necessary.

Eligibility criteria

Prospective, retrospective, cross-sectional, and case-control studies were included in our study examining CRD in the diagnosis of milk allergy in children or adults. Studies needed to include sIgE measured for at least one milk allergen component (Bos d 4, 5, 6, 8) and provide sufficient data to calculate the following four relevant diagnostic indices: sensitivity, specificity, PPV, and NPV. Oral food challenge (double-blind or open) was the reference standard, and at least 50% of patients received OFC. We excluded secondary studies (e.g., reviews or systematic reviews), case reports, and animal studies. Only full-text available articles were included.

Data synthesis, analysis, and reporting

Diagnostic accuracy metrics (sensitivity, specificity, PPV, and NPV) for each study were summarized in a table by individual allergen component. We planned to perform a meta-analysis of the evidence for each allergen component using a fitted bivariate model when common thresholds were used in the included studies and a hierarchical summary receiver operating characteristic (HSROC) model when multiple thresholds were used in the included studies. However, we were unable to perform a meta-analysis due to heterogeneity in study design, testing methods, and thresholds. Grouping studies according to a topic, design, quality, and outcome, we narratively synthesized the evidence.

3 | RESULTS

3.1 | Study selection

A systematic literature search was conducted, resulting in a total of 4,600 records. After excluding 4,497 citations based on title and abstract, 103 full-text publications were selected for a secondary review. Ultimately, nine studies that were relevant to the diagnostic accuracy of sIgE to milk components for milk allergy were included [30-38]. The selection process is illustrated in Figure 1.

3.2 | Characteristics of included studies

Table 1 presents a summary of the main characteristics of the nine studies included in this analysis. A total of 958 participants were recruited across these studies, with five of them [31, 32, 34, 36, 37] conducted in Europe, two in South America [33, 35], and two in Asia[30, 38]. Of the nine studies, five were prospective [30, 31, 34, 35, 38], two were retrospective [33, 37], and two were case-control designs [32, 36]. Our literature search did not impose any age restrictions, but none of the studies on adults met the inclusion criteria. Therefore, all the included studies were conducted on children, with participants aged between 2 months and 16.7 years. At least one milk allergy component was used in the diagnostic accuracy analysis of CRD across all the included studies. Three of the studies used a blinded approach [30, 31, 37] (single- or double-blind) for OFC, and 321 (78.9%) of 407 patients with suspected CM allergy tested positive for OFC. Five studies [32, 34-36, 38] did not use blinding for OFC, and 428 patients received milk OFC, with 268 (62.6%) showing a positive reaction. In a study of CM allergy involving 123 patients [33], 26 (21%) underwent DBOFC, 51 (41%) underwent unblinded OFC, and the remaining patients did not undergo OFC. The thresholds for the fractions varied across studies and fractions. Five studies used the immunocap method to determine sIgE levels [32, 33, 35, 36, 38], one study used the microarray technique (ISAC CRD 51)[37], two studies used both ImmunoCAP and microarray technology[31, 34], one study used both ImmunoCAP and 3gAllergy technology.[30]

FIGURE 1 PRISMA Diagram for the literature search

3.3 | Quality assessment of included studies

Figure 2 summarizes the QUADAS-2 quality assessment for each study. Detailed QUADAS-2 assessment results are provided in Supplementary Information Table S3.

3.3.1 | Patient selection

Two studies [32, 36] were deemed to have a high risk of bias (ROB) due to their use of a case-control design. Additionally, seven studies[30, 31, 33-35, 37, 38] were found to have an unclear ROB, primarily because they did not indicate their sampling method and/or did not avoid inappropriate exclusions.

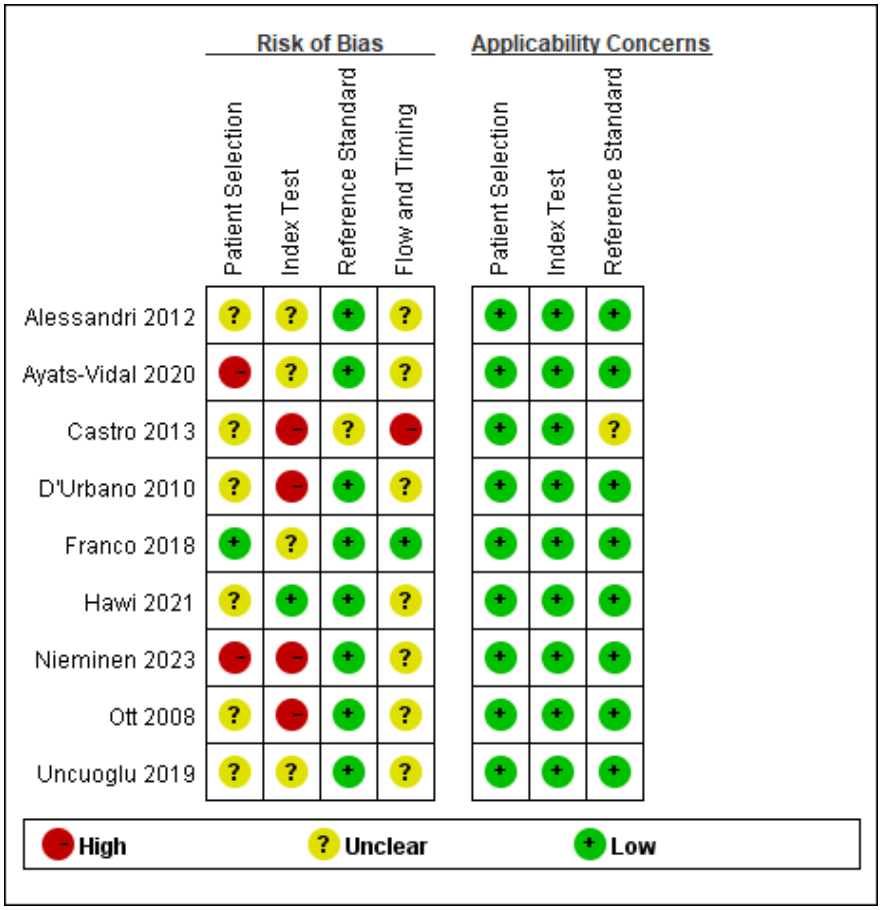

FIGURE 2 Risk of bias and applicability concerns summary

3.3.2 | Index test

Four studies[33, 34, 36, 37] had a high ROB in this area because they did not use a preset threshold for identifying positive results. Four studies[31, 32, 35, 38] had an unclear ROB in this area because they did not report whether they interpreted indicator test results without knowledge of the OFC results. Only one study had a low ROB in this area[30].

3.3.3 | Reference standard

One study[33], in which some patients did not undergo OFC, was therefore rated as having unclear ROB in this area, and its applicability to the research questions in this review was rated as uncertain.

3.3.4 | Patient flow and timing

One study[35] specified a time to compare the metrics for all patients with the interval of the reference trial based on the same reference criteria that were included in the analysis of the data for all patients and were therefore classified as having a low ROB in this area; the remaining seven studies[30-32, 34, 36-38] failed to meet at least one of the criteria and were therefore scored as having an unclear ROB. One study[33] was rated as high ROB for flow and timing due to different reference tests between participants, some patients

in the same group received DBPCFC while others were administered by OFC, and the other part did not receive OFC.

Table 1 Main characteristics of included studies

3.4 | Diagnostic accuracy of CRD

3.4.1 |

Cow's milk allergy

Table 2 presents the DTA metrics for all nine studies. The table includes the data points utilized by the studies to establish the cutoff values for all sIgE for a positive test, with some studies using multiple values. In the subsequent narrative synthesis, we provide the diagnostic accuracy outcomes for all aspects of milk allergy, reporting only the cutoff value with the greatest diagnostic potential as defined in each study.

3.4.2 |Studies that include Bos d 4

Evidence for the accuracy of the Bos d 4 diagnostic test comes from seven studies using two classes of testing equipment[31-33, 35-38]. The AUC of six studies[31-33, 36-38] showed discriminative power ranging from 0.0 to 3.3, and all studies had estimated specificities above 0.85 (0.88-0.98) regardless of the cutoff value used. Sensitivity was variable, ranging between 0.50 and 0.82. However, another study had low sensitivity and specificity[35] which were 0.56 and 0.78, respectively.

In the study by Alessandri[31], both devices were used to detect Bos d 4 accurately with essentially the same sensitivity and specificity. Using a cut-off point of 0 (kUa/L) (ISAC standard unit), the sensitivity and specificity were 0.56 and 0.88, respectively. When a cut-off value of 1.02 (kUa/L) (ImmunoCAP normalized unit) was employed, the sensitivity and specificity were 0.58 and 0.81, respectively. In Nieminen's study[36], children aged 1 ˜ 2 years had smaller AUC and higher sensitivity in this group compared to children aged 3-14 years. Their sensitivity and specificity were 0.51 and 0.94, 0.32 and 0.93, respectively.

3.4.3 |Studies that include Bos d 5

The available evidence comes from eight studies providing information on the composition of Bos d 5[30-33, 35-38]. Overall, six studies showed high specificity (0.91-0.98) at different AUCs (0-1.94) with different sensitivities (0.24-0.82). In contrast, Uncuoglu[38] showed high sensitivity (1.0) and lower specificity (0.7), while Franco[35] showed lower diagnostic efficacy with sensitivity and specificity of 0.7 and 0.58, respectively.

The research conducted by Alessandri and Hawi[30, 31] has demonstrated that the diagnostic accuracy of various detection equipment can vary significantly. In Alessandri's study[31], the sensitivity and specificity of ImmunoCAP were found to be 0.90 and 0.50, respectively. However, when the

Table 2 Summary DTA measures of CRD components tested by allergy component

ISAC test was used, the sensitivity and specificity were 0.40 and 0.94, respectively. In Hawi's study[30], the ImmunoCAP assay, when used, showed high specificity (0.90-0.93) and low sensitivity (0.40-0.47); sensitivity was (0.65-0.78) and specificity (0.66-0.80) when using 3gAllergy assay.

3.4.4 |Studies that include Bos d 6

Only one study[36] provided information on the Bos d 6 component, which showed high specificity (0.94) and low sensitivity (0.09).

3.4.5 |Studies that include Bos d 8

Nine studies[30-38] have reported on the diagnostic accuracy of Bos d 8 serum levels. The specificity and sensitivity of Bos d8 detection varied across studies (0.79 - 0.98 and 0.34 - 0.90, respectively). In Alessandri's study[31], diagnostic efficiency was affected by the use of different testing equipment. Using a cut-off point of 0 (kUa/L) (ISAC standard unit), the sensitivity and specificity were 0.54 and 0.81, respectively. However, with a cutoff value of 0.44 (kUa/L) (ImmunoCAP normalized unit), the sensitivity and specificity were 0.82

and 0.63, respectively. In Nieminen's study [36], the diagnostic sensitivity was higher in 1-2 years old children compared to 3-14 years old children, whose sensitivities and specificities were 0.34 and 0.94, 0.11 and 0.93, respectively.

4 | DISCUSSION

An analysis of CRD accuracy in CMA will certainly promote a better understanding of diagnostic efficacy and contribute to more precise and individualized diagnosis in CMA[39]. Many CRDs on food allergy have been carried out, but only a few studies have focused on milk allergy. A systematic review of the accuracy of CRD for milk allergy was conducted[22], but the results are still unclear due to the limited number of included studies and cases. Based on previous studies, more articles were included in our study. Through a systematic approach, we performed a more comprehensive analysis.

We analyzed the included studies on milk components and found that the diagnostic value of sIgE levels for Bos d 4, 5, 6, and 8 components varied greatly, with most performing poorly overall. Bos d 4 and 8 components consistently showed high specificity (0.78-0.98 and 0.79-0.98, respectively) but variable sensitivity (0.50-0.82 and 0.34-0.90, respectively), while Bos d 5 showed lower specificity (0.58-0.98) than Bos d 4 and 8. The low sensitivity indicates that a negative result for CRD cannot exclude CMA, necessitating oral food provocation. Conversely, the high specificity suggests that the oral food excitation test can be ignored, as the risk of CMA is sufficiently high in this case. Our findings confirm those of a previous DTA systematic review on CRD in milk allergy[22], indicating that sIgE levels against Bos d 4 can provide a highly accurate diagnostic indicator. In the uncuoglu study [38] of the Bos d 5 component, the test had a higher sensitivity (1.0) than specificity (0.70), while in all other studies, specificity was significantly better than sensitivity. These results can be extrapolated to other studies and components analyzed (Table 2), as the determination of individual components with the UniCAP is comparable to the diagnosis of allergy with the oral provocation test, which does not differentiate between different components of the same food. Thus, in the absence of UniCAP detection of IgE against a specific ingredient, a patient may be sensitized to another ingredient of the same food and diagnosed by OFC, resulting in a false-negative result (decreased sensitivity). Conversely, all positive reactions to any component will also be positive in the oral test, resulting in a low number of false positives (increased specificity). However, this is the first review of the diagnostic value of Bos d 6 as a component of cow's milk-related allergic reactions. It was found to have high specificity but low sensitivity. Previous studies have indicated that Bos d 6 is characterized by high heat stability and cross-reactivity with beef proteins[40], suggesting that children with high levels of Bos d 6 serum IgE may also be allergic to beef. Therefore, caution should be exercised when ingesting beef to prevent severe allergic reactions. In this review, the diagnostic accuracy of the cow's milk allergy component of the component-resolved diagnosis (CRD) was compared with that of first-line diagnostic tests, including the APT, sIgE, and SPT, as reported in previous systematic reviews. The results varied depending on the diagnostic test. The DTA results for Bos d 4, 5, and 8 for milk were similar to those of the APT, which showed a sensitivity-specificity pair of 44.2% and 86.9%[41]. However, the overall sensitivity of all components was lower than that of sIgE and SPT (87.3% and 87.9%, respectively), and the specificity was higher than that of sIgE and SPT (47.7% and 67.5%, respectively)[42].

Observations were conducted on all studies, with a particular focus on the diagnostic accuracy of the Bos d 4, Bos d 5, Bos d 6, and Bos d 8 components of milk due to the greater number of studies and the significant variability of results. Possible explanations for this variability include 1) Experimental design, which included case-control, prospective cohorts, and retrospective cohorts. Retrospective designs may pose a risk of information bias, leading to artificially maximized results. Additionally, since the oral food provocation test served as the gold standard for all studies analyzed, differences in the design of this test should be considered a source of bias in the results. Only two studies used the DBOFC test as the reference standard[31, 37], while the majority of studies used the OFC (without using double-blind or only single-blind), which carries the risk of interpretation bias and interference of subjective factors in the appearance of symptoms, potentially leading to bias in patient selection. It is also important to mention the heterogeneity due to the use of different versions of devices (ImmunoCAP, ISAC, UniCAP, and 3gAllergy). Standardization

of all CRD tests is necessary to ensure comparable results between different tests. The ImmunoCAP ISAC is considered by the World Health Organization as a complementary diagnostic tool to the component-resolved diagnosis[43]. 2) Age of the patient; our results show that there is an effect of age on diagnostic efficacy and cutoff values. In our study, children aged 1-2 years had smaller optimal cutoff values and higher diagnostic efficacy compared with children aged 3-14 years, suggesting that younger children are more sensitive to smaller cutoff values. This finding is consistent with previous studies[44-47]. However, this difference still lacks statistical power because of the limited number of studies included and the relatively small advantage. Moreover, negative results were noted in our pooled analysis. Therefore, to be applied in clinical practice, prospective studies need to be designed to evaluate the use of CRD in diagnostic tests for suspected milk allergy, and the cutoff values for optimal diagnostic efficacy at different ages need to be studied to reach a consensus.

In the scientific literature, there is a growing body of evidence demonstrating the utility of CRD in the workup of milk allergy, suggesting that the sIgE of milk allergen components can aid in the diagnosis of milk allergy. Using a systematic approach, we analyzed the evidence for the diagnostic accuracy of CRD for milk allergy within a range, filling an important research gap in this area. The strengths of our study include a comprehensive methodology, the use of a highly sensitive search strategy, no language restrictions, and the involvement of multiple countries, databases, and clinical trial registries, which allowed for a thorough literature search. Our inclusion criteria were based on clinically relevant information from carefully selected studies, as well as guidelines from reputable organizations such as the European Academy of Allergy and Clinical Immunology and the Food Allergy [48] and Anaphylaxis Guidelines Group[49]. Furthermore, the internal validity of the studies included in our review was strong, as at least 50% of the participants used 0FC as the reference standard.

Our systematic review has several limitations. First, due to the limited and relatively insufficient number of articles included in the study, a larger dataset or a more scientific approach would be needed to more accurately assess diagnostic accuracy. In addition, the included population was exclusively children and there is a lack of studies in adult populations; therefore, the role of milk CRD in adults remains to be investigated. Finally, and most importantly, there was a great deal of heterogeneity in our analyses, constituting an important obstacle to meta-analysis. This may be due to the great variation in study design: a) Differences in the level of the cutoff value chosen in different studies (e.g95% vs. 100%) may significantly change the suggested critical value. b) Methodological quality: type of equipment or test, use of OFC blinding.

5 | CONCLUSIONS

The findings of this review indicate that the measurement of sIgE levels for the Bos d 4, Bos d 6, and Bos d 8 milk components is highly specific but not very sensitive for diagnosing cow's milk allergy in children. The implementation of CRD for diagnosing CMA in children may potentially decrease the need for OFC.

Compliance with Ethical Standards

Conflict of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors do not have any conflicts of interests to declare.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

[1] GIANNETTI A, TOSCHI VESPASIANI G, RICCI G, et al. Cow's Milk Protein Allergy as a Model of Food Allergies [J]. Nutrients, 2021, 13(5).

[2] FLOM J D, SICHERER S H. Epidemiology of Cow's Milk Allergy [J]. Nutrients, 2019, 11(5).

[3] POPIELARZ M, KROGULSKA A. The importance of component-resolved diagnostics in IgE-mediated cow's milk allergy [J]. Allergologia et Immunopathologia, 2021, 49(3): 30-41.

[4] MOUSAN G, KAMAT D. Cow's Milk Protein Allergy [J]. Clin Pediatr (Phila), 2016, 55(11): 1054-63.

[5] FIOCCHI A, BROZEK J, SCHüNEMANN H, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines [J]. Pediatr Allergy Immunol, 2010, 21 Suppl 21: 1-125.

[6] LUYT D, BALL H, MAKWANA N, et al. BSACI guideline for the diagnosis and management of cow's milk allergy [J]. Clinical and Experimental Allergy, 2014, 44(5): 642-72.

[7] PETERSEN T H, MORTZ C G, BINDSLEV-JENSEN C, et al. Cow's milk allergic children—Can component-resolved diagnostics predict duration and severity? [J]. Pediatric Allergy and Immunology, 2018, 29(2): 194-9.

[8] CHAFEN J J, NEWBERRY S J, RIEDL M A, et al. Diagnosing and managing common food allergies: a systematic review [J]. Jama, 2010, 303(18): 1848-56.

[9] PETTERSSON M E, KOPPELMAN G H, FLOKSTRA-DE BLOK B M J, et al. Prediction of the severity of allergic reactions to foods [J]. Allergy: European Journal of Allergy and Clinical Immunology, 2018, 73(7): 1532-40.

[10] EIGENMANN P A, EBISAWA M, GREENHAWT M, et al. Addressing risk management difficulties in children with food allergies [J]. Pediatr Allergy Immunol, 2021, 32(4): 658-66.

[11] LUENGO O, CARDONA V. Component resolved diagnosis: when should it be used? [J]. Clin Transl Allergy, 2014, 4: 28.

[12] SAN MIGUEL-RODRíGUEZ A, ARMENTIA A, MARTíN-ARMENTIA S, et al. Component-resolved diagnosis in allergic disease: Utility and limitations [J]. Clin Chim Acta, 2019, 489: 219-24.

[13] BORRES M P, MARUYAMA N, SATO S, et al. Recent advances in component resolved diagnosis in food allergy [J]. Allergology International, 2016, 65(4): 378-87.

[14] CALAMELLI E, LIOTTI L, BEGHETTI I, et al. Component-Resolved Diagnosis in Food Allergies [J]. Medicina-Lithuania, 2019, 55(8).

[15] MATRICARDI P M, KLEINE-TEBBE J, HOFFMANN H J, et al. EAACI Molecular Allergology User's Guide [J]. Pediatr Allergy Immunol, 2016, 27 Suppl 23: 1-250.

[16] KAUPPILA T K, HINKKANEN V, SAVINKO T, et al. Long-term changes in milk component immunoglobulins reflect milk oral immunotherapy outcomes in Finnish children [J]. Allergy, 2023, 78(2): 454-63.

[17] KUITUNEN M, ENGLUND H, REMES S, et al. High IgE levels to -lactalbumin, -lactoglobulin and casein predict less successful cow's milk oral immunotherapy [J]. Allergy, 2015, 70(8): 955-62.

[18] PEVERI S, PATTINI S, COSTANTINO M T, et al. Molecular diagnostics improves diagnosis and treatment of respiratory allergy and food allergy with economic optimization and cost saving [J]. Allergol Immunopathol (Madr), 2019, 47(1): 64-72.

[19] NILSSON C, BERTHOLD M, MASCIALINO B, et al. Allergen components in diagnosing childhood hazelnut allergy: Systematic literature review and meta-analysis [J]. Pediatr Allergy Immunol, 2020, 31(2): 186-96.

[20] NILSSON C, BERTHOLD M, MASCIALINO B, et al. Accuracy of component-resolved diagnostics in peanut allergy: Systematic literature review and meta-analysis [J]. Pediatr Allergy Immunol, 2020, 31(3): 303-14.

[21] BRETTIG T, DANG T, MCWILLIAM V, et al. The Accuracy of Diagnostic Testing in Determining Tree Nut Allergy: A Systematic Review [J]. J Allergy Clin Immunol Pract, 2021, 9(5): 2028-49.e2.

[22] KIM J F, MCCLEARY N, NWARU B I, et al. Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: A systematic review [J]. Allergy, 2018, 73(8): 1609-21.

[23] PAGE M J, MCKENZIE J E, BOSSUYT P M, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews [J]. Bmj, 2021, 372: n71.

[24] VALENTA R, LIDHOLM J, NIEDERBERGER V, et al. The recombinant allergen-based concept of component-resolved diagnostics and immunotherapy (CRD and CRIT) [J]. Clin Exp Allergy, 1999, 29(7): 896-904.

[25] SICHERER S H, SAMPSON H A. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment [J]. J Allergy Clin Immunol, 2014, 133(2): 291-307; quiz 8.

[26] SMITH C J. Diagnostic tests (1) - sensitivity and specificity [J]. Phlebology, 2012, 27(5): 250-1.

[27] SMITH C J. Diagnostic tests (2) - positive and negative predictive values [J]. Phlebology, 2012, 27(6): 305-6.

[28] NEWCOMBE R G. Two-sided confidence intervals for the single proportion: comparison of seven methods [J]. Stat Med, 1998, 17(8): 857-72.

[29] WHITING P F, RUTJES A W, WESTWOOD M E, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies [J]. Ann Intern Med, 2011, 155(8): 529-36.

[30] AL HAWI Y, NAGAO M, FURUYA K, et al. Agreement Between Predictive, Allergen-Specific IgE Values Assessed by ImmunoCAP and IMMULITE 2000 3gAllergy (TM) Assay Systems for Milk and Wheat Allergies [J]. Allergy Asthma & Immunology Research, 2021, 13(1): 141-53.

[31] ALESSANDRI C, SFORZA S, PALAZZO P, et al. Tolerability of a fully maturated cheese in cow's milk allergic children: Biochemical, immunochemical, and clinical aspects [J]. PLoS ONE, 2012, 7(7).

[32] AYATS-VIDAL R, VALDESOIRO-NAVARRETE L, GARCíA-GONZáLEZ M, et al. Predictors of a positive oral food challenge to cow's milk in children sensitized to cow's milk [J]. Allergologia et Immunopathologia, 2020, 48(6): 568-75.

[33] CASTRO A P, PASTORINO A C, GUSHKEN A K F, et al. Establishing a cut-off for the serum levels of specific IgE to milk and its components for cow's milk allergy: Results from a specific population [J]. Allergologia et Immunopathologia, 2015, 43(1): 67-92.

[34] D'URBANO L E, PELLEGRINO K, ARTESANI M C, et al. Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy [J]. Clinical and Experimental Allergy, 2010, 40(10): 1561-70.

[35] FRANCO J M, PINHEIRO A P S G, VIEIRA S C F, et al. Accuracy of serum IgE concentrations and papule diameter in the diagnosis of cow's milk allergy [J]. Jornal de Pediatria, 2018, 94(3): 279-85.

[36] NIEMINEN O, PALOSUO K, KUKKONEN K, et al. Molecular allergy diagnostics in predicting oral cow's milk challenge outcome in Finnish children [J]. Allergy and Asthma Proceedings, 2023, 44(1): 71-7.

[37] OTT H, BARON J M, HEISE R, et al. Clinical usefulness of microarray-based IgE detection in children with suspected food allergy [J]. Allergy, 2008, 63(11): 1521-8.

[38] UNCUOGLU A, COGURLU M T, ESER SIMSEK I, et al. Predicting outgrowth of IgE-mediated cow's milk allergy: Diagnostic tests in children under two years of age [J]. Allergologia et Immunopathologia, 2019, 47(5): 449-56.

[39] BARTUZI Z, COCCO R R, MURARO A, et al. Contribution of Molecular Allergen Analysis in Diagnosis of Milk Allergy [J]. Current Allergy and Asthma Reports, 2017, 17(7).

[40] LINHART B, FREIDL R, ELISYUTINA O, et al. Molecular Approaches for Diagnosis, Therapy and Prevention of Cow´s Milk Allergy [J]. Nutrients, 2019, 11(7).

[41] LUO Y, ZHANG G Q, LI Z Y. The diagnostic value of APT for food allergy in children: a systematic review and meta-analysis [J]. Pediatric Allergy and Immunology, 2019, 30(4): 451-61.

[42] SOARES-WEISER K, TAKWOINGI Y, PANESAR S S, et al. The diagnosis of food allergy: a systematic review and meta-analysis [J]. Allergy, 2014, 69(1): 76-86.

[43] CANONICA G W, ANSOTEGUI I J, PAWANKAR R, et al. A WAO - ARIA - GA²LEN consensus document on molecular-based allergy diagnostics [J]. World Allergy Organ J, 2013, 6(1): 17.

[44] YAVUZ S T, BUYUKTIRYAKI B, SAHINER U M, et al. Factors that predict the clinical reactivity and tolerance in children with cow's milk allergy [J]. Ann Allergy Asthma Immunol, 2013, 110(4): 284-9.

[45] GARCíA-ARA M C, BOYANO-MARTíNEZ M T, DíAZ-PENA J M, et al. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants [J]. Clin Exp Allergy, 2004, 34(6): 866-70.

[46] KOMATA T, SöDERSTRöM L, BORRES M P, et al. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age [J]. J Allergy Clin Immunol, 2007, 119(5): 1272-4.

[47] VAN DER GUGTEN A C, DEN OTTER M, MEIJER Y, et al. Usefulness of specific IgE levels in predicting cow's milk allergy [J]. J Allergy Clin Immunol, 2008, 121(2): 531-3.

[48] SOARES-WEISER K, TAKWOINGI Y, PANESAR S S, et al. The diagnosis of food allergy: a systematic review and meta-analysis [J]. Allergy, 2014, 69(1): 76-86.

[49] MURARO A, WORM M, ALVIANI C, et al. EAACI guidelines: Anaphylaxis (2021 update) [J]. Allergy, 2022, 77(2): 357-77.