

## Characteristics of cow's milk allergy and sensitization in Chinese patients

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Globally, the prevalence of food allergy in children is estimated to be approximately 4% to 10%.<sup>[1]</sup> Food allergy usually begins early in the allergic march, and cow's milk allergy (CMA) is one of the most common food allergens in infants and children. In Europe, the overall incidence of challenge-proven CMA is 0.54%, and in the United States, the overall prevalence is 0.4% and pediatric prevalence is 1.9%.<sup>[2-4]</sup> In China, the prevalence of oral food challenge (OFC)-confirmed CMA is 0.83% to 3.5% in various cities.<sup>[5]</sup> Double-blind placebo-controlled food challenge is not applied widely in clinical practice because of its complex process and the risk of anaphylaxis for patients that receive the test. Allergen-specific IgE (sIgE) is usually used as a critical assessment method for food allergy.

In China, studies of CMA on the basis of medical history, serum cow's milk sIgE, component sIgEs, and long-term follow-up of remission of CMA are limited. In this study, patients with allergic diseases were enrolled and serum cow's milk sIgE and cow's milk component sIgEs were analyzed.

Patients referred to the Tertiary Allergic Clinical Center of Peking Union Medical College Hospital in 2011, who were aged 0 to 70 years old, met the diagnosis of allergic disease, which included allergic rhinitis (AR), allergic asthma, food allergy, atopic dermatitis (AD), drug allergy and anaphylaxis, made by experienced allergists, and successfully answered and completed the follow-up questionnaire [Supplementary material, <http://links.lww.com/CM9/B56>] in 2021 were enrolled in this study. Information on demographics, diagnosis, sIgE, and milk component sIgEs was collected.

CMA was defined as a convincing reaction (defined by symptoms within 2 h of isolated ingestion, which included at least urticaria and/or angioedema, difficulty breathing, wheezing, throat tightness, and/or vomiting, shock) or a flare of AD associated with cow's milk ingestion and sensitization to milk (milk sIgE level  $\geq 0.35$  kUA/L).<sup>[1,6]</sup> CMA resolution was defined by the successful home introduction of uncooked milk products (milk, yogurt, or ice cream).<sup>[6]</sup>

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (CTN10SP049.01, S-K1674). All patients or guardians of patients had signed informed consent.

All patients had detectable serum sIgEs, which included cow's milk (f2), f76 nBos d 4 $\alpha$ -lactalbumin, f77 nBos d 5 $\beta$ -mactoglobulin, f78 nBos d 8Casein, and e204 nBos d 6bovine serum albumin (BSA), Cow, at their first visit in 2011. sIgE levels were detected by enzyme-linked immunosorbent assays (ImmunoCAP system).

Patients with cow's milk sIgE values  $\geq 0.1$  kUA/L were considered to have suspected milk sensitization and were enrolled for follow-up.<sup>[7]</sup> We considered this cutoff to enroll as many patients as possible to reduce missed diagnoses.

Continuous and categorical variables were compared by the independent samples *t*-test and Pearson's  $\chi^2$  test or Fisher's exact probability test, respectively. Potential factors associated with milk allergy were further evaluated

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with multivariable logistic regression models. All statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

Among the 709 patients with allergic diseases, which included AR, asthma, food allergy, AD, drug allergy, and anaphylaxis, 50 patients (7.1%) had cow's milk sIgE of  $>0.35$  kUA/L and 158 patients (22.3%) had cow's milk sIgE of  $\geq 0.1$  kUA/L. Allergists followed up these 158 patients 10 years later in 2021 and 109 patients completed the follow-up questionnaire. Among the 109 patients, the median age was 14.0 (Q<sub>1</sub>–Q<sub>3</sub>: 8.5–29.0) years and 64 were male (58.7%). Five patients had CMA (4.6%) among the 109 milk-sensitized patients, four patients had a history of an acute reaction to milk (including one patient with anaphylaxis), and one patient had a diagnosis of CMA on the basis of AD criteria [Supplementary Figure 1, <http://links.lww.com/CM9/B56>]. Detailed description of cases with CMA is shown in Supplementary Table 1, <http://links.lww.com/CM9/B56>. The first time that symptoms had occurred after ingestion of milk was 6 to 10 months of age. A total of 96 milk-sensitized patients (88.1%) had combined AR, 62 patients (56.9%) had asthma, 21 patients (19.3%) had AD, 12 patients (11.0%) had a drug allergy, and 33 patients (30.3%) had another food allergy. Compared with milk-sensitized patients without symptoms, patients with CMA were younger (median ages of 3.0 [Q<sub>1</sub>–Q<sub>3</sub>: 2.5–8.0] and 16.0 [Q<sub>1</sub>–Q<sub>3</sub>: 9.0–29.8] years,  $P = 0.003$ ) and more were combined with AD (80.0% *vs.* 16.3%,  $P = 0.005$ ) [Supplementary Table 2, <http://links.lww.com/CM9/B56>].

Cow's milk (f2) sIgE and milk component sIgEs, which included f76 nBos d 4 $\alpha$ -lactalbumin, f77 nBos d 5 $\beta$ -lactoglobulin, and f78 nBos d 8Casein, e204 nBos d 6BSA, Cow, were compared in milk-sensitized patients with or without symptoms. The f2 sIgE level in patients with CMA was significantly higher than that in milk-sensitized patients without symptoms (median 1.04 [Q<sub>1</sub>–Q<sub>3</sub>: 0.70–5.88] and 0.20 [Q<sub>1</sub>–Q<sub>3</sub>: 0.13–0.45] kUA/L,  $P = 0.002$ ). The f77 nBos d 5 $\beta$ -lactoglobulin level was also significantly higher in patients with CMA than in milk-sensitized patients without symptoms (median 0.48 [Q<sub>1</sub>–Q<sub>3</sub>: 0.25–1.99] and 0.09 [Q<sub>1</sub>–Q<sub>3</sub>: 0.05–0.20] kUA/L,  $P = 0.014$ ). Other components were comparable in the two groups. Specific information is shown in Supplementary Table 3, <http://links.lww.com/CM9/B56>.

We further compared the positive rates of cow's milk and component sIgEs. When sIgE  $\geq 0.1$  kUA/L was considered positive, the positive rate of cow's milk and components was comparable in the two groups [Supplementary Table 4, <http://links.lww.com/CM9/B56>]. When sIgE  $\geq 0.35$  kUA/L was considered positive, the positive rate of f2 sIgE was the highest (100.0%), followed by f77 nBos d 5 $\beta$ -lactoglobulin (80.0%) with e204 nBos d 6BSA, Cow as the lowest (40.0%) in CMA patients. The positive rate of f2 sIgE was significantly higher in the CMA group than in the milk-sensitized group (100.0% *vs.* 29.8%,  $P = 0.001$ ). The positive rates of f77 nBos d 5 $\beta$ -lactoglobulin (80.0% *vs.* 11.5%,  $P < 0.001$ ) and e204 nBos d 6BSA, Cow (40.0% *vs.* 8.7%,  $P = 0.024$ ) were also significantly different in the two groups [Figure 1A].

Factors that were different between the two groups, which included age, combination with AD, f2 sIgE, f77 nBos d 5 $\beta$ -lactoglobulin sIgE, and e204 nBos d 6BSA, Cow sIgE, were applied to logistic regression analysis. We found that the combination with AD was a potential risk factor of CMA (odds ratio = 46.146, 95% confidence interval: 1.939–1098,  $P = 0.018$ ) [Figure 1B].

The patients had completed a follow-up questionnaire 10 years later. All five patients (100%) with milk allergy had a natural resolution. The mean age of resolution was  $7.0 \pm 3.5$  years. At 4 years of age, one patient had resolution (20%), at 6 years of age, four patients had resolution (80%), and at 13 years of age, all five patients had resolution (100%). They drink milk in daily life at present and do not have any symptoms [Figure 1C].

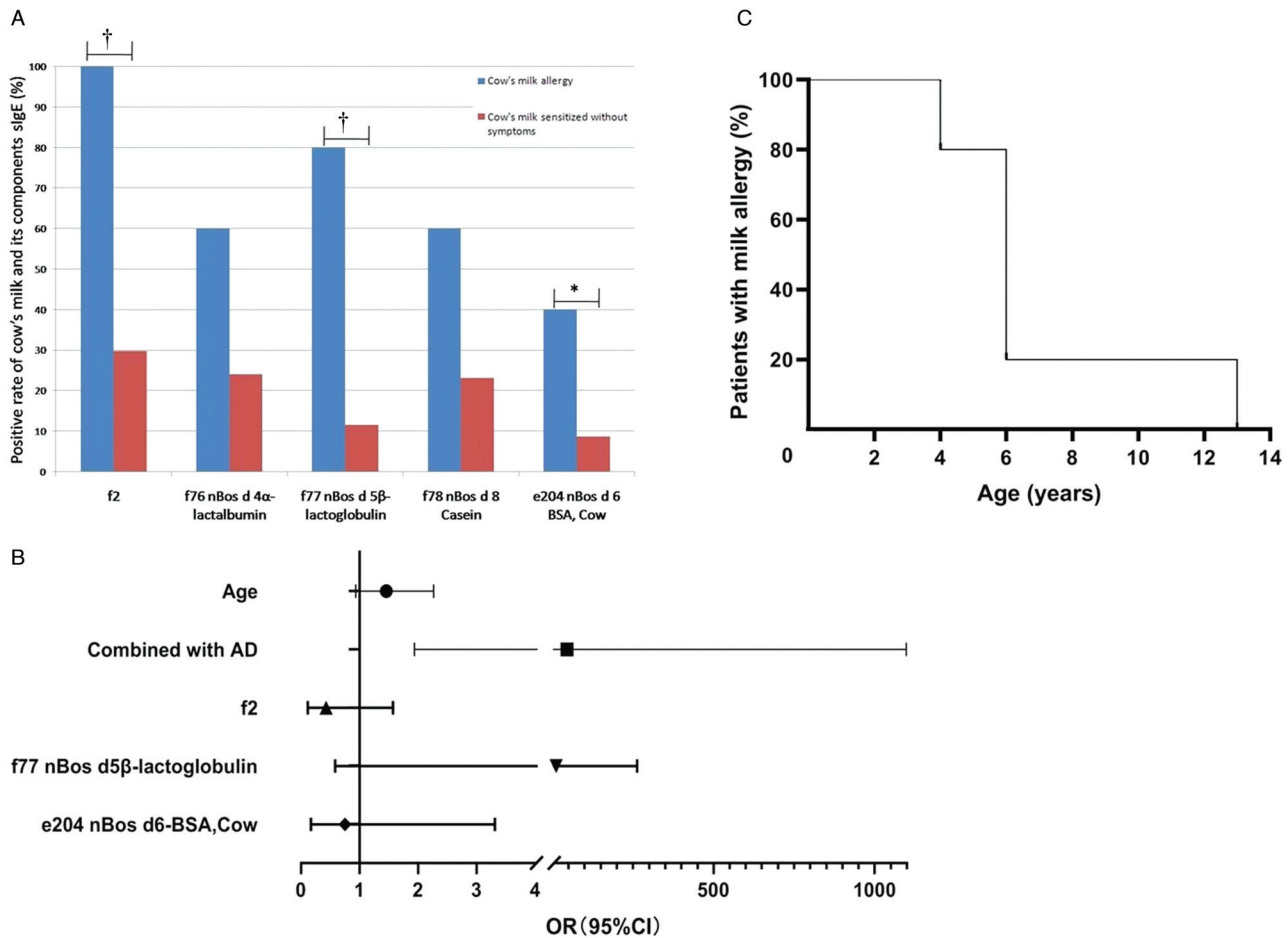
In this study, patients with CMA were younger than those with milk sensitization and had a higher proportion of combination with AD. Logistic regression also showed that combination with AD was a potential risk factor of CMA. Previous studies have also concluded that young children have a high prevalence of food allergy. For example, the HealthNuts study on the basis of a population in Australia found that the prevalence of OFC-confirmed food allergy was 11% in children at 1-year-old, while the prevalence was 3.8% when these children were followed up at 4 years old.<sup>[8]</sup> A Greek study of newborns and their follow-ups suggested that AD was an independent factor for food allergy.<sup>[9]</sup>

Among patients with CMA, the positive rate of  $\beta$ -lactoglobulin was the highest compared with other components in our study, followed by  $\alpha$ -lactalbumin, casein, and BSA. Another study of children with CMA showed that the positive rates of  $\beta$ -lactoglobulin and casein were the highest, followed by  $\alpha$ -lactalbumin.<sup>[10]</sup> Therefore,  $\beta$ -lactoglobulin might be a more sensitive indicator of CMA.

After 10 years of follow-up, all five patients with CMA had a natural resolution and most patients (80%) had a resolution at approximately 6 years of age. An observational study of the natural history of milk allergy reviewed data of children in Korea and the results showed that half of the children had a natural resolution of CMA at a median age of 8.7 years.<sup>[6]</sup>

This study also had some limitations. This was a single-center study. The sample size of CMA in this study was relatively small. Therefore, the results of this study might have limitations and biases and not representative for patients in other areas.

In conclusion, among patients who visited the Tertiary Allergic Clinical Center of Peking Union Medical College Hospital with milk sensitization, 4.6% of patients had milk allergy. Patients with milk allergy were young and more likely to also have AD. Milk and  $\beta$ -lactoglobulin sIgE levels were higher in the CMA group than in the milk-sensitized group. When the cutoff value of sIgE was 0.35 kUA/L, milk,  $\beta$ -lactoglobulin, and e204 nBos d 6BSA, Cow sIgEs had a preferred diagnostic value. After a long-term follow-up of 10 years, children with milk allergy had a natural resolution rate of 80% at 6 years of age.



**Figure 1:** (A) Positive rate of cow's milk sIgE and its component sIgEs in patients with CMA and cow's milk-sensitized patients without symptoms (sIgE≥0.35 kU/L); (B) Risk factors of CMA in cow's milk-sensitized patients. (C) Natural resolution rate of CMA. \*P<0.05, †P<0.01. AD: Atopic dermatitis; BSA: Bovine serum albumin; CI: Confidence interval; CMA: Cow's milk allergy; OR: Odds ratio; sIgE: Allergen-specific IgE.

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**Conflicts of interest**

None.

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