Nomogram for predicting food allergy in infants with feeding problems and malnutrition

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Abstract

BACKGROUND: It is difficult to diagnose food allergy in infants in General Outpatient Department of Pediatrics as oral food challenge (OFC) cannot be performed routinely.

OBJECTIVE: To construct a nomogram to screen for a high probability of food allergy in infants with feeding problems and malnutrition.

METHODS: From August 2018 to December 2021, 289 infants with feeding problems and malnutrition from 7 hospitals in Shanghai, China were recruited. Food allergy was defined as positive response of skin prick test or OFC with gastrointestinal, dermatologic, or respiratory symptoms. Demographic characteristics, the cow’s milk-related symptom scores (CoMiSS) and blood eosinophils (EOS) were obtained for evaluating their correlation with food allergy. Variables identified by multivariate logistic regression were included to develop the nomogram model with the bootstrapped-concordance index as an assess index.

RESULTS: Altogether, 249 of 289 infants with feeding problems and malnutrition had food allergy (86.2%). After analyzing, feeding pattern (Odds ratio (OR) = 5.284; 95% confidence interval (CI): 2.133-13.086), family history of allergy (OR=1.793; 95%CI: 0.713-4.508), CoMiSS score (OR=1.450; 95%CI: 1.187-1.771) and EOS percentage (OR=1.332; 95%CI: 1.111-1.598) were included to develop the model, which had a good performance with an area under the curve of 0.868 (95% CI: 0.792-0.944) and a bootstrapped-concordance index of 0.868. Among them, EOS percentage was the strongest factor producing a highly probability in the model.

CONCLUSION: Nomogram model can be a useful tool to screen infants with high probability of food allergy among infants with feeding problems and malnutrition for further food allergy diagnosis.

Introduction

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1], including immunoglobulin E (IgE) mediated reactions, non-IgE mediated responses and mixed IgE and non-IgE mediated reactions [2]. Feeding problems in infants and young children are frequent [3–6]. Among a variety of medical conditions associated with feeding problems, up to 88% of infants with feeding problems were reported to sensitize to multiple food allergens [7, 8]. Importantly, the first 2 years of life is not only a crucial period of growth and development, but also the peak period of children developing food allergy [2]. The feeding problems during this period without timely and effective interventions can lead to important unconstructive nutritional, developmental and psychological sequelae [9]. However, only a few studies currently focus on food allergy in infants with feeding problems, which needs to be given more attention by pediatrician.
So far, oral food challenge (OFC) remains the gold standard for food allergy diagnosis due to its most accuracy [10]. However, the procedure can be costly, time- and resources-consuming, and in some cases carry risks, which restrict its use only in hospitals where healthcare professional has trained, and a medical facility is equipped [10, 11]. Although there are other tests, such as skin prick test (SPT), IgE test, intradermal test and atopy patch test, aiding in food allergy diagnosis, while these tests only are used for identifying food allergens and diagnosing food allergy involving IgE, and some of the tests even do not have high specificity and sensitivity [11]. Therefore, screening infant with a high suspect of food allergy for further diagnoses is a way to save resources and improve efficacy of food allergy diagnosis.

Nomogram is a pictorial representation of a complex mathematical formula and a widely used prediction tool, which uses biologic and clinical variables to graphically depict a statistical prognostic model that generates a probability of a clinical event, such as cancer recurrence or death, for a given individual [12]. In recent years, blood eosinophiles [13–15], the cow's milk-related symptom scores (CoMiSS) [15–18], and feeding patterns [19] have been widely found to be associated with allergic disorders. Taking the advantages of nomogram, our study recruited infants with feeding problems and malnutrition to diagnosis of food allergy based on OFC or SPT in combination with symptoms and aimed to obtain variables related to food allergy, e.g., blood eosinophiles, CoMiSS, and feeding patterns, etc. to develop a nomogram to predict the probability of food allergy in individual infant with feeding problems and malnutrition.

**Methods**

**Population**

From November 2018 to January 2021, infants visited one of the 7 hospitals in Shanghai, China, including Shanghai Children’s Medical Center, Yangjing Community Hospital, Jinyang Community Hospital, Lianyang Community Hospital, Maternal and Child Health Hospital, Shanghai East Hospital and Puxing Community Hospital, all had an assessment for feeding problems and malnutrition. Among them, 345 infants were diagnosed with feeding problems and malnutrition. Exclusion of infants with birth defects, a history of neonatal hypoxic ischemic encephalopathy, or having metabolic or organic disease (Chronic diarrhea, malabsorption syndrome caused by enzyme deficiency, recurrent respiratory tract infection, chronic urinary tract infection, congenital malformation of digestive tract and serious congenital heart disease), and infants refused to participate, 289 infants (6.27 ± 3.10 months) were included in the study (Fig. 1).

All participants underwent physical examinations. General information included gender, age, gestational age, birth weight, delivery mode, symptoms, feeding patterns (exclusive breastfeeding: the duration of exclusive breastfeeding was at least 4 months; non-exclusive breastfeeding: the duration of exclusive breastfeeding was shorter than 4 months [20, 21]), family history of allergy (parents or siblings with a history of any allergic diseases, i.e., food allergy, atopic dermatitis, allergic retinitis, asthma [22]) were
collected from parents or guardians. Besides, 100 µl of fingertip blood for detection of eosinophils was collected using disposable trace blood straws.

This study was approved by the medical ethics committee at Shanghai Children's Medical Center (No. SCMCIRB-K2018010), and written informed consents were obtained from all parents or guardians.

**Assessment of feeding problems and malnutrition**

Infants younger than 6 months of age, feeding problems is diagnosed with difficulty in remaining quiet during feeding, resistance of feeding by crying or slow weight or height gain in the last three months [23]. For infants older than 6 months, the diagnosis is based on the Montreal Children Hospital Feeding Scale, which consists of 14 items covering the following feeding domains: oral motor, oral sensory, appetite, and maternal feeding behavior (appendix 1). Feeding problems is defined as the standardized score > 50 [24].

Based on 2015 Shanghai Child Health Physical Growth Assessment Criteria, malnutrition is defined when the weight measured by age is below the tenth percentile of the same sex (≤ P10) [25].

**Determination of CoMiSS**

The CoMiSS is a questionnaire filled out by parents or guardians to help recognize the symptoms of cow’s milk protein allergy (CMPA) in infants, including crying, reflux, stool changes, dermatologic and respiratory symptoms [26]. Its score ranges from 0 to 33, the maximum score of each symptom is 6 except the respiratory symptoms where the maximum score is 3 [27].

Currently, the cut-off value of CoMiSS score is varied in different studies [18, 26, 28]. Zeng et al. assessed the optimal cutoff value of CoMiSS score to identify Chinese infants with milk allergy, hence we applied the same ≥ 6 as the criterion [17].

**Food allergy diagnosis**

Infants presenting with any of the symptoms or signs (Table 1) [29], food allergy should be suspected and further diagnosis including food avoidance for 4 weeks, OFC or SPT test are performed. Food allergy is confirmed based on a documented dietary exposure to cow’s milk, egg, or wheat plus one of the following criteria: 1) gastrointestinal, respiratory or dermatologic symptoms, a positive response of SPT and significant symptoms improvement or resolution after 4 weeks of food avoidance; 2) gastrointestinal, respiratory or dermatologic symptoms with a negative SPT or no tested by SPT, but significant symptom improvement or resolution after 4 weeks of food avoidance and a positive OFC with suspected foods [30].
Table 1
Symptoms and signs related to food allergy [29]

<table>
<thead>
<tr>
<th>Organs</th>
<th>Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Dysphagia, abdominal pain, vomiting, regurgitation, refusal to feed, early satiety,</td>
</tr>
<tr>
<td></td>
<td>diarrhea ± intestinal protein or blood loss, constipation ± perianal rash, failure to</td>
</tr>
<tr>
<td></td>
<td>thrive, occult blood loss, iron-deficiency anemia</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Runny nose, chronic coughing, wheezing / stridor, breathing difficulties</td>
</tr>
<tr>
<td>Skin</td>
<td>Urticaria, atopic eczema, angioedema</td>
</tr>
<tr>
<td>Others</td>
<td>Anaphylaxis, shock like symptoms with severe metabolic acidosis</td>
</tr>
</tbody>
</table>

SPT was performed based on the skin prick test-European standards [31] at Shanghai Children's Medical Center where has medications, facilities and experienced doctors and nurses. The procedure is as follows: 1) positive control (1 mg/mL histamine), negative control (saline), and fresh foods (cow's milk, egg white, egg yolk, and wheat flour) were prepared; 2) a single-head metal lancet was applied to pricking the positive control, negative control, or fresh food, and then pricking the skin; 3) after 20 minutes of observation and exclusion of tests with a wheal diameter below 3 mm elicited by histamine, a wheal diameter response of at least 3 mm above the negative control is considered positive [31, 32].

Oral food challenge was conducted at the same hospital mentioned in Skin prick testing. Challenge dose of foods and procedure were displayed in Table 2 [33]. After the last intake, symptoms occurring the first 2 h were recorded in hospital; symptoms occurring beyond 2 h were documented at home. Notably, OFC test in infants who have not been given complementary foods was as follows: for infants who may be allergic to food from human milk, mothers avoided food containing allergens which exposed to before, when infants’ symptoms were improvement after food elimination in maternal diet, re-introduction of corresponding food is needed for confirmation [34]; for infants who may react to milk protein from formula, corresponding formula was selected for OFC test [17].

Table 2
Challenge doses in oral food challenge test [33]

<table>
<thead>
<tr>
<th>Target foods</th>
<th>Challenge foods</th>
<th>Initial dose</th>
<th>Total dose</th>
<th>Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiled egg</td>
<td>Egg yolk</td>
<td>1 g</td>
<td>15 g (1 egg yolk)</td>
<td>1-2-4-8 g</td>
</tr>
<tr>
<td></td>
<td>Egg white</td>
<td>1 g</td>
<td>16–32 g (1 egg)</td>
<td>1-2-4-8-16 g</td>
</tr>
<tr>
<td>Milk</td>
<td>Raw milk</td>
<td>1–5 mL</td>
<td>100–200 mL</td>
<td>1-5-10-25-50-100 mL</td>
</tr>
<tr>
<td>Wheat</td>
<td>Noodles (boiled)</td>
<td>1 g</td>
<td>50–100 g</td>
<td>1-2-5-15-25-50 g</td>
</tr>
</tbody>
</table>

Statistical analysis

Continuous and categorical variables were presented as mean ± SD and numbers and percentages, respectively. Comparison of the variances between two groups, T-test was used for continuous data and
Chi-square test for categorical data; one-way ANOVA was used to continuous data comparison between multiple groups. All p values were two-sided. P < 0.05 indicates the statistical significance.

Univariate logistic regression analysis was performed to identify risk factors causing food allergy, multivariable logistic regression analysis to identify independent risk factors. A stepwise method was used to identify the useful combination of factors that could most precisely predict food allergy. A nomogram was established based on the multivariable logistic regression model. The performance of the nomogram was evaluated using a concordance index and bootstrap samples calibration plots. All analyses were performed using Empower (R) (www.empowerstats.com, X&Y solutions, Inc. Boston MA) and R 4.0.5 (http://www.R-project.org) [35].

Results

Food allergy in infants

Altogether, 289 infants with feeding problems and malnutrition were included in this study, and 269 of them underwent food allergy diagnosis due to food allergy suspicious (Fig. 2). Eventually, food allergy was confirmed in 249 infants (86.16%), including 126 diagnosed by SPT (50.60%), and 123 by OFC (49.39%).

Among 249 infants with food allergy, infants allergic to milk protein was in dominant (91.16%, 227/249), followed by infants reacted to egg white (54.33%, 157/249), egg yolk (52.25%, 151/249), and wheat (40.83%, 118/249). Besides, infants having 4 allergens and 1 allergen accounted for the highest frequency of 42.17% (105/249) and 32.93% (82/249), respectively; infants having 2 and 3 allergens were less common with the occurrence of 10.04% (25/249) and 14.86% (37/249), respectively.

Participant characterization

Based on the results of food allergy diagnosis, 289 infants with feeding problems and malnutrition were categorized into non-food allergy and food allergy group (Table 2). Comparison between the two groups, infants with food allergy were significantly inclined to weight < P3 (72.3%), non-exclusive breastfeeding (69.1%), more common family history (59.0%), and higher EOS value and CoMiSS (p < 0.001).

Peripheral blood EOS is a good indicator in allergic disease diagnosis [13–15], we further investigated the relationship of EOS% with food allergy by subdividing EOS% into more groups (< 3%, 3–5%, 5–8%, and < 8%). The results showed that the percentages of high EOS% were significantly higher in food allergy group (Table 3).
Table 3
General characteristics of participants

<table>
<thead>
<tr>
<th>Factors</th>
<th>N</th>
<th>Food allergy (-) (n = 40)</th>
<th>Food allergy (+) (n = 249)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N %/M ± SD</td>
<td>n</td>
<td>N %/M ± SD</td>
</tr>
<tr>
<td>Age (month)</td>
<td>289</td>
<td>40 5.85 ± 2.86</td>
<td>249 6.34 ± 3.13</td>
<td>0.352</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>116</td>
<td>14 35.00</td>
<td>99 39.76</td>
<td>0.567</td>
</tr>
<tr>
<td>≥ 6</td>
<td>173</td>
<td>26 65.00</td>
<td>150 60.24</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151</td>
<td>17 42.50</td>
<td>134 53.82</td>
<td>0.184</td>
</tr>
<tr>
<td>Female</td>
<td>138</td>
<td>23 57.50</td>
<td>115 46.18</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;P3</td>
<td>202</td>
<td>22 55.00</td>
<td>180 72.29</td>
<td>0.027</td>
</tr>
<tr>
<td>P3-P10</td>
<td>87</td>
<td>18 45.00</td>
<td>69 27.71</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;P3</td>
<td>104</td>
<td>13 32.50</td>
<td>91 36.55</td>
<td>0.97</td>
</tr>
<tr>
<td>P3-P10</td>
<td>75</td>
<td>11 27.50</td>
<td>64 25.70</td>
<td></td>
</tr>
<tr>
<td>P10-P20</td>
<td>40</td>
<td>6 15.00</td>
<td>34 13.65</td>
<td></td>
</tr>
<tr>
<td>&gt;P20</td>
<td>70</td>
<td>10 25.00</td>
<td>60 24.10</td>
<td></td>
</tr>
<tr>
<td>Gestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>52</td>
<td>10 25.00</td>
<td>42 16.87</td>
<td>0.214</td>
</tr>
<tr>
<td>Term</td>
<td>237</td>
<td>30 75.00</td>
<td>207 83.13</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>144</td>
<td>21 52.50</td>
<td>123 49.40</td>
<td>0.716</td>
</tr>
<tr>
<td>Cesarean</td>
<td>145</td>
<td>19 47.50</td>
<td>126 50.60</td>
<td></td>
</tr>
<tr>
<td>Feeding patterns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>107</td>
<td>30 75.00</td>
<td>77 30.92</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-exclusive breastfeeding</td>
<td>182</td>
<td>10 25.00</td>
<td>172 69.08</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>-</td>
<td>131 29 72.50</td>
<td>102 40.96</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Eleven infants were missing EOS value

Continuous variables are indicated as means ± SDs, and categorical variables as numbers and percentages

EOS = eosinophils; CoMiSS = Cow's milk-related symptom scores

Negative→“-”, Positive→“+”
<table>
<thead>
<tr>
<th>Factors</th>
<th>N</th>
<th>Food allergy (-) (n = 40)</th>
<th>Food allergy (+) (n = 249)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>N %/M ± SD</td>
<td>n</td>
<td>N %/M ± SD</td>
</tr>
<tr>
<td>+</td>
<td>158</td>
<td>11</td>
<td>27.50</td>
<td>147</td>
</tr>
<tr>
<td>EOS*</td>
<td>278</td>
<td>32</td>
<td>3.80 ± 3.38</td>
<td>246</td>
</tr>
<tr>
<td>&lt; 3%</td>
<td>57</td>
<td>17</td>
<td>53.13</td>
<td>40</td>
</tr>
<tr>
<td>3%-5%</td>
<td>66</td>
<td>8</td>
<td>25.00</td>
<td>58</td>
</tr>
<tr>
<td>5%-8%</td>
<td>80</td>
<td>5</td>
<td>15.63</td>
<td>75</td>
</tr>
<tr>
<td>≥ 8%</td>
<td>75</td>
<td>2</td>
<td>6.25</td>
<td>73</td>
</tr>
<tr>
<td>Eos count (×10⁹)</td>
<td>278</td>
<td>32</td>
<td>0.33 ± 0.30</td>
<td>246</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>152</td>
<td>27</td>
<td>84.40</td>
<td>125</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>126</td>
<td>5</td>
<td>15.60</td>
<td>121</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Dermatologic</td>
<td>-</td>
<td>41</td>
<td>67.50</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>248</td>
<td>13</td>
<td>32.50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>-</td>
<td>103</td>
<td>32</td>
<td>80.00</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>186</td>
<td>8</td>
<td>20.00</td>
</tr>
<tr>
<td>Respiratory</td>
<td>-</td>
<td>194</td>
<td>38</td>
<td>95.00</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>95</td>
<td>2</td>
<td>5.00</td>
</tr>
<tr>
<td>CoMiSS score</td>
<td>289</td>
<td>40</td>
<td>2.85 ± 2.58</td>
<td>249</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>164</td>
<td>37</td>
<td>92.50</td>
<td>127</td>
</tr>
<tr>
<td>≥ 6</td>
<td>125</td>
<td>3</td>
<td>7.50</td>
<td>122</td>
</tr>
</tbody>
</table>

* Eleven infants were missing EOS value

Continuous variables are indicated as means ± SDs, and categorical variables as numbers and percentages

EOS = eosinophils; CoMiSS = Cow's milk-related symptom scores

Negative→“-”, Positive→“+”

Factors for construction of a nomogram
As expected, using multivariate logistic regression model, CoMiSS score (Odds ratio (OR) = 1.45; 95% confidence interval (CI:1.19–1.77), feeding pattern (OR = 5.28; 95%CI:2.13–13.09), and EOS% (OR = 1.33; 95%CI:1.11–1.60) showed significant correlation with food allergy (p < 0.001) (Table 4). Although family history was not found to have an association with food allergy, it reached a significant difference in univariate analysis (Table 3) and was a well-recognized critical genetic risk factor for food allergy [22, 36]. Ultimately, family history along with CoMiSS score, feeding pattern, EOS% were included for the development of a nomogram.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correlation between factors and food allergy using logistical regression analysis (n = 289)</strong></td>
</tr>
<tr>
<td><strong>Factors</strong></td>
</tr>
<tr>
<td>CoMiSS score</td>
</tr>
<tr>
<td>Feeding patterns, exclusive breastfeeding (vs non-exclusive breastfeeding)</td>
</tr>
<tr>
<td>Family history (+)</td>
</tr>
<tr>
<td>EOS %</td>
</tr>
<tr>
<td>EOS = eosinophils</td>
</tr>
<tr>
<td>Positive→“+”</td>
</tr>
</tbody>
</table>

**Development of a nomogram**

The nomogram was constructed from a logistic regression model by above four predictors (Fig. 3). The area under curve and bootstrapped concordance index both were 0.868 (Fig. 4A and 4B), implying the good performance. Based on the maximum points assigned to each variable (Fig. 3), EOS% was the strongest factor contributing to the probability, followed by CoMiSS score, feeding pattern and family history. The highest probability to diagnose with food allergy was up to 0.999.

**Discussion**

To our knowledge, this is the first study to investigate the occurrence of food allergy in infants with feeding problems and malnutrition. To prompt the efficacy of food allergy diagnosis, we constructed a food allergy prediction tool with a good performance.

In our study, food allergy was confirmed in 86.2% of infants with feeding problems and malnutrition. Shanghai as one of the most economically developed cities in China has the abundance of food resources, malnutrition in infants basically is resulted from feeding problems. While diseases, such as food allergy, are the main factors contributing to feeding problems. Notably, non-IgE mediated food allergy is the main type of food allergy in infants [11, 37], whereas symptoms caused by this class of
food allergy are non-specific, including vomiting, regurgitation, nausea, diarrhea, food refusal with weight loss, blood loss, or urticaria and eczema. The atypical symptoms not only increase the challenge of diagnosis and influence the nutrients absorption, but also result in an irreversible impairment of growth and behavioral development [37]. Nowadays, the prevalence of food allergy is rising in infants and children around the world [38, 39], suggesting the feeding problems and malnutrition will be more severe and prevalent. So far, food allergy in infants with feeding problems and malnutrition has not been given much attention. Evidently, implementation of an early screening of food allergy in these infants will be of great significance.

The most common allergens triggering food allergy in infants was not the same in different countries. In our study, cow's milk was the predominant allergen (> 90%), followed by egg (> 60%) and wheat (47.4%). The participants in our study were infants with feeding problems and malnutrition, which limits the generalization of our findings. In Japan, the same three categories of allergen as in our study were reported in infants < 1 year of age, but the frequency were 24.3% (cow's milk), 57.6% (egg), and 12.7% (wheat) [36]. In a Korean study, the three top-ranking food allergens in infants within 1 year of age with immediate type food allergy were egg (53.2%), cow's milk (32.2%), and peanut/nuts (12.9%) [40]. In Europe, milk and dairy products were the most often blamed foods in infancy (65.2%), and eggs and fruits accounted for 17.4% each [41]. While in a study from the United States, the most common food allergens in children within two years of age were milk (31.5%), peanut/tree nut (27.9%), and egg (15.8%) [42]. Overall, probably due to the eating habits or food culture difference between each country, the most common allergens in infants varied [43], but milk and egg seem to be the top allergens in infants around the world.

In other studies, the greater the number of allergens had by patients with food allergy, the fewer the number of corresponding patients [40, 44]. In the Korean study mentioned above, infants with food allergy having one food allergen were most common (80.6%), infants having two, three, and five were 12.9%, 4.8%, and 1.6%, respectively [40]. So far, related data in infants in western countries have not been found. Nevertheless, in a study from the United States, children aged 3 to 18 years allergic to one allergen was the most frequent (60%), followed by children to two (28%), three (8%) and four (4%) [44]. In our study, infants allergic to four allergens was in dominant (42.2%), whereas allergic to one allergen ranked in the second place (32.9%). Since our participants had feeding problems and malnutrition, our figures were not representative of that in general infants.

Our study confirmed that EOS, CoMiSS score, feeding patterns, and family history of allergy are reliable markers associated with food allergy, especially EOS which was the strongest factor producing a highly probability in the model. EOS as a biomarker correlated to atopic dermatitis and asthma has been studied [14, 45, 46]. However, the relationship between food allergy and eosinophils has not been investigated. Our study confirmed that EOS could be a good biomarker correlated to food allergy. CoMiSS can recognize manifestations related to CMPA [26]. In our study, more than 90% of infants with CMPA. In addition, CoMiSS has been used in infants with egg allergy with a good performance [47]. Combined the results of our study, the use of CoMiSS score might not limit to infants with CMPA. Regarding feeding
patterns, non-exclusive breastfeeding has been found to increase the risk of allergic diseases including food allergy [19, 48]. In our study, we also confirmed that infants with non-exclusive breastfeeding have significantly higher risk for food allergy. Koplin et al. [22] and Sasaki et al. [49] found that the risk of food allergy in infants and adolescents were increased as the number of family member with allergic history growing. Consistent with previous studies, in our study family history of allergy was also a risk factor for food allergy. Based on the above, the four biologic or clinic variables are good indicators applied to the construction of a nomogram for food allergy prediction.

We developed a food allergy prediction model with a good performance. In fact, nomogram has been constructed in prediction of allergic disease. Li et al. [50] developed a nomogram with relative humidity, fungi, self-reported allergic rhinitis symptoms, and exposure to smoking for the prediction of incidence of allergic rhinitis. Santos et al. [51] constructed nomograms using skin prick, specific IgE and basophil activation tests to predict the severe reactions and low threshold dose during peanut challenges. By contrast, we developed the first model to predict the probability of food allergy in individual infants with advantages as follows: all the factors used for the construction of the model were objective and easily obtained; our model easier to be operated and executed; the probability of food allergy diagnosis predicted by the model can be up to 0.999. In general, our nomogram will have a potential broad application prospect.

There are some limitations in our study. Firstly, oral food challenge as the gold standard for food allergy diagnosis was not performed in all of our participants. Although we have screen out infants with suspected food allergy based on symptoms first and performed the SPT test after infants’ response to 4 weeks of food avoidance, the over-diagnosed food allergy cannot be completely excluded. Secondly, the pathophysiology of IgE-mediated and non-IgE-mediated food allergy is different, implying that the predictive ability of the model for the two classes food allergy may be not the same. Therefore, the performance difference of the model to predict the probability of the two classes of food allergy in infants should be assessed further. Lastly, the characteristic of non-exclusive breastfeeding, having family history of allergy, and higher eosinophile value and CoMiSS score also present in general infants, the potential application of this model and its clinical use needs to be determined and validated in general infants with a large sample size.

In conclusion, our study for the first time confirmed that food allergy is common in infants with feeding problems and malnutrition. The nomogram we developed could be a useful tool to predict the probability of food allergy in infants with feeding problems and malnutrition but needs further validation with a large sample size.

Abbreviations

CI - confidence interval

CoMiSS - cow's milk-related symptom scores
Declarations

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Conflicts of interest/Competing interests
There are no conflicts of interest.

Authors' contributions
Xiaodan Yu conceptualized and designed the study, supervised data collection, and critically reviewed and revised the manuscript. Fan Yang supervised data collection, performed analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Chunyan Zhou performed analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Xirui Wang collected data, performed analyses, and critically reviewed and revised the manuscript. Bin Wang and Yabin Hu performed analyses and reviewed and revised the manuscript. Yue Zhang, Chen Chen, Juan Li and Luanluan Li collected data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics approval
This study was approved by the medical ethics committee at Shanghai Children's Medical Center (No. SCMCIRB-K2018010).

**Consent to participate**

Written informed consent was obtained from the parents or guardians.

**Consent for publication**

Not applicable

**References**


**Figures**
Figure 1

Flow chart of the participants included in the study. After application of the exclusion criteria, 326 of 345 infants were eligible for inclusion, but 37 infants were refused participation. In total, 289 infants with written informed consent by their parents or guardians involved in.
Flow chart for food allergy diagnosed in infants. A total of 289 infants with feeding problems and malnutrition were included in this study, and 249 infants were diagnosed with food allergy.
Figure 3

A nomogram for prediction of food allergy. Mark the values at each axis, draw a vertical line to the “Points” axis, and add up the points for all variables. Based on the sum, draw a vertical line from “Total Points” to “Risk” to calculate the probability of food allergy.

EOS= eosinophils; CoMiSS= Cow’s milk-related symptom scores.
**Figure 4**

The performance of the nomogram. **4A.** The receiver operating characteristic curve with the area under the curve of 0.868 (95% confidence interval: 0.792-0.944). **4B.** The calibration curves.

**Supplementary Files**

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