

Incidence of cow's milk protein allergy during the first six months of age

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Abstract

Cow's milk protein allergy (CMPA) is one of the most common food allergies in infants and young children. Prospective studies estimating the occurrence of confirmed CMPA during early infancy are limited. We aimed to analyze the incidence of clinically confirmed CMPA during the first six months of life in a prospective birth cohort in Trabzon, Turkey. Newborns delivered at our hospital who met the study's inclusion criteria were prospectively followed for six months. Following monthly telephone-based symptom screening, infants whose parents were reported to have symptoms suggestive of CMPA were invited to the hospital. Elimination and oral food challenge were performed on infants with CoMiSS above the study-derived cut-off threshold. In an exploratory-case control analysis, threshold 10 was selected as optimal cut-off for CoMiSS due to higher AUROC (0.934) and specificity (84.21%). 418 newborns were included in the study, and 27 infants had symptoms suggesting CMPA and of whom 14 had CoMiSS ≥ 10 . 12 infants had diagnosed CMPA after elimination and oral food challenge (2.9%, 95% CI: 1.2–4.3). All confirmed cases had a phenotype consistent with non-IgE-mediated disease. A family history of allergic disease was more frequent among infants with CMPA than among those without CMPA (58.3% vs. 15.5%; Fisher's exact $p < 0.05$, unadjusted OR 7.62, 95% CI: 2.35–24.77).

Conclusions: Confirmed CMPA in early infancy showed a cumulative incidence of 2.9%, predominantly presenting as non-IgE-mediated disease. Further larger-scale studies are warranted to validate these findings.

What is Known

CMPA may cause non-specific gastrointestinal, cutaneous, respiratory, and behavioral symptoms during infancy.

- CoMiSS is an awareness tool; suspected CMPA requires confirmation through diagnostic elimination followed by cow's milk reintroduction or challenge

What is New:

- Clinically confirmed CMPA occurred in 2.9% of infants prospectively followed during the first six months of life.
- All confirmed cases had a non-IgE-mediated phenotype; an exploratory association was observed with family history of allergic disease.

Introduction

Cow's milk protein allergy (CMPA) is one of the most common food allergies in infants and young children. It is an important clinical concern because of its heterogeneous presentation, risk of both overdiagnosis and underdiagnosis, and potential effects on infant nutrition and family quality of life [1, 2].

It is classified into IgE-mediated and non-IgE-mediated types, with mixed forms also reported [1]. The diagnosis of non-IgE-mediated CMPA is particularly challenging because no validated diagnostic biomarker is available. Affected infants may present with non-specific symptoms, including vomiting, regurgitation, diarrhea, constipation, abdominal distension, feeding difficulties, or excessive crying. These manifestations overlap with common disorders of gut–brain interaction and may lead to both overdiagnosis and underdiagnosis. For suspected non-IgE-mediated CMPA, diagnostic confirmation generally requires a 2–4-week cow’s milk elimination diet followed by planned reintroduction or oral food challenge. This approach helps avoid both unnecessary dietary restrictions and failure to identify infants who require treatment. IgE-mediated CMPA is typically more easily recognized due to symptoms that occur early after ingestion of cow’s milk. The diagnosis can be supported by elevated cow’s milk specific IgE levels or a positive skin prick test [2].

Early and accurate diagnosis is crucial to avoid unnecessary treatment and minimize negative impacts on the child’s development, quality of life, and future health. Prospective studies estimating the occurrence of confirmed CMPA during early infancy are limited. This period is of particular importance as infants are exclusively breastfed and/or formula fed, prior to the introduction of complementary foods. Furthermore, functional gastrointestinal disorders are highly prevalent in early infancy which may cause confusion or pose significant challenges in establishing accurate diagnosis [3]. We therefore aimed to estimate the cumulative incidence of clinically confirmed CMPA during the first six months of life in a prospective birth cohort in Trabzon, Turkey, and to explore the performance of a locally derived CoMiSS referral threshold.

Materials and Methods

Study population

Newborns delivered at the Department of Obstetrics and Gynecology, Karadeniz Technical University Faculty of Medicine, over a six-month period were considered for inclusion. The inclusion criteria were as follows: (i) gestational age > 35 weeks, (ii) birth weight > 2500 g, (iii) singleton pregnancy, (iv) absence of a serious comorbid condition (infants who underwent gastrointestinal or neurosurgical procedures, had congenital heart disease requiring treatment, renal failure requiring treatment, metabolic disease, septic shock, or multiple congenital anomalies) or infants who died before enrollment or before initiation of follow-up were not eligible. Infants who met the inclusion criteria were enrolled. Parents were required to provide written consent and a valid telephone number for follow-up. Infants who did not complete the six-month follow-up were recorded as lost to follow-up.

The required sample size was calculated based on a previously reported CMPA prevalence of 4% among 2256 children younger than one year in Turkey [4]. With a margin of error of 3% and a design effect of 1, the minimum required sample size was determined to be 164 infants. Accounting for an anticipated drop-out rate of approximately 15%, the final required sample size was determined to be 193 infants.

Gestational age, sex, birth weight, mode of delivery, birth order, and family history of allergic disease [defined as a known history of allergic in at least one first- (father, mother, and/or sibling)] were recorded for all included newborns. Families received an information leaflet about CMPA, and the mother and/or father were provided with verbal information about the condition. Families were also given a telephone number to contact the study team if the infant developed symptoms potentially associated with CMPA.

Regardless of whether symptoms were present, all families were contacted monthly until their infants reached six months of age. During each telephone interview, the same investigator assessed general symptoms potentially compatible with CMPA, including irritability and crying, as well as gastrointestinal symptoms, including vomiting, regurgitation, stool pattern, and bloody stools with or without mucus. Respiratory symptoms and skin manifestations were also assessed.

Infants with symptoms suggestive of CMPA were invited to the hospital for a detailed clinical evaluation and were assessed using the Turkish version of the CoMiSS [5]. Infants whose CoMiSS was above the prespecified threshold underwent a 2-4-week elimination diet followed by a cow's milk challenge. In breastfed infants, a maternal CMP-free diet was prescribed, in line with guidelines. In formula-fed infants with mild to moderate symptoms, an extensively hydrolyzed formula was provided. Amino acid-based formula was prescribed in severe cases (defined as the presence of anaphylaxis, growth faltering, severe enteropathy, profuse bloody stools with anemia/hypoalbuminemia, multiorgan involvement) or those infants unresponsive to extensively hydrolyzed formula for 2–4 weeks. After the 2-4-week exclusion diet, the patient was re-evaluated. If the symptoms improved, an open label oral food challenge was conducted by reintroducing cow's milk protein into mother's or infant's diet depending on feeding modality. Reintroduction was initiated under medical supervision using prespecified incremental doses. Infants were observed for immediate reactions and, if no immediate reaction occurred, cow's milk protein was continued at home for up to 2–4 weeks to assess delayed symptoms. If the baseline symptoms recurred or clearly worsened and no alternative explanation was identified during the subsequent 2–4 weeks, CMPA was confirmed [2]. The diagnosis was reviewed jointly by a pediatric gastroenterologist and pediatric allergist. The infants remained on CMP-free diet until 9–12 months of age. Otherwise, the diagnosis of CMPA was ruled out. Oral tolerance was assessed at 9 months, 12 months and 16 months of age. Milk-specific immunoglobulin E and skin prick testing were performed in infants diagnosed with CMPA.

The primary outcome was the six-month cumulative incidence of CMPA confirmed by symptom resolution during elimination and recurrence following diagnostic cow's milk reintroduction. Secondary outcomes were exploratory CoMiSS threshold, clinical characteristics of confirmed cases, family-history association and age at tolerance of infants with CMPA.

Exploratory case–control analysis of a locally applicable CoMiSS threshold

As a separate case-control analysis, a preliminary study was conducted to determine the optimal CoMiSS threshold in our study population. CoMiSS was administered prior to the initiation of the elimination diet in all infants presenting with suspected CMPA at the Pediatric Gastroenterology and Pediatric Allergy and Immunology outpatient clinics of our hospital. Following elimination and oral food challenge procedures, infants in whom CMPA was ruled out were excluded, leaving 38 infants with a confirmed diagnosis of CMPA. The control group (n = 38) consisted of children who presented to our healthy baby clinic for other reasons (such as vaccination or routine control), had no known underlying chronic disease or CMPA and were comparable to the CMPA group in terms of age and sex. CoMiSS was calculated through face-to-face interviews with the parents of participants in both groups by the same physician, and only the baseline CoMiSS values of the 38 confirmed CMPA patients were included in the analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the threshold that best differentiated patients with CMPA from healthy controls.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., USA). Continuous variables were evaluated for normal distribution using the Shapiro-Wilk test alongside visual inspection of histograms and Q-Q plots. Normally distributed continuous variables are presented as means and standard deviations, whereas non-normally distributed continuous variables are presented as median and interquartile range. Categorical variables are presented as numbers and percentages. For independent group comparisons, normally distributed continuous variables were analyzed using Student's t-test, and non-normally distributed continuous variables using the Mann-Whitney U test, and categorical variables using the Pearson's chi-square test or Fisher's exact test, as appropriate. For repeated measurements of CoMiSS within the same cohort, changes over time were evaluated using the Friedman test, followed by post-hoc pairwise comparisons using Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons.

The 95% confidence intervals (CI) for cumulative incidence were calculated using the exact binomial method. Unadjusted odds ratios (ORs) with 95% CIs were calculated to quantify associations between binary clinical characteristics and CMPA. Analyses of factors associated with CMPA were exploratory; no multivariable model was fitted because of the small number of confirmed cases. Receiver operating characteristic (ROC) curve analysis was conducted, the optimal CoMiSS threshold was selected by maximizing Youden's J statistic. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and area under the ROC curve (AUROC) were calculated with 95% CI. A two-sided p -value < 0.05 was considered statistically significant. There were no missing data for the variables included in the primary analysis.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Scientific Research Ethics Committee of Karadeniz Technical University Faculty of Medicine (approval

no. 2018/381). The study objectives and procedures were explained in detail to the parents who agreed to participate. Written informed consent was obtained from all participating parents or legal guardians.

Results

During the six-month study period, 627 deliveries and 644 live births occurred at our hospital. After applying the eligibility criteria, 418 newborns were included in the study. The demographic characteristics of the 418 included newborns are presented in Table 1.

Table 1
Baseline characteristics of the prospective birth cohort

Parameters	Study cohort (n = 418)
Male sex, n (%)	213 (51)
Gestational age, mean ± SD weeks	38.1 ± 1.3
Birth weight, mean ± SD g	3220 ± 320
Cesarean delivery, n (%)	340 (81.3)
At least one sibling, n (%)	303 (72.5)
Family history of allergic disease, n (%)	70 (16.7)

The demographic characteristics of the patients with CMPA and the healthy controls included in the preliminary study are shown in Table 2. A family history of allergic disease was more common in the CMPA group than in the control group (42.1% vs. 15.8%, $p < 0.05$). The mean CoMiSS was also higher among patients with CMPA than among controls (13.52 ± 2.64 vs. 6.71 ± 2.80 , $p < 0.05$).

Table 2
Characteristics of confirmed CMPA cases, and healthy controls included in the exploratory CoMiSS threshold analysis

Parameters	CMPA group (n = 38)	Control group (n = 38)
Male sex, n (%)	26 (68.4)	22 (57.9)
Age, mean $\pm$ SD, months	4.65 $\pm$ 2.12	4.86 $\pm$ 1.18
Birth weight, mean $\pm$ SD, g	3187 $\pm$ 579	3180 $\pm$ 416
Cesarean delivery, n (%)	31 (81.5)	24 (63.1)
Exclusive breastfeeding, n (%)	10 (26.3)	12 (31.6)
Presence of siblings, n (%)	25 (65.8)	23 (60.5)
Family history of allergic disease, n (%)	16 (42.1) ^a	6 (15.8) ^b
CoMiSS, mean $\pm$ SD (median)	13.52 $\pm$ 2.64 (13.5) ^c	6.71 $\pm$ 2.80 (7) ^d
Data are presented as mean $\pm$ SD, median, or n (%), as appropriate. Between-group comparisons were performed using Student's t-test, the Mann–Whitney U test, Pearson's chi-square test, or Fisher's exact test, as appropriate. CMPA, cow's milk protein allergy; CoMiSS, Cow's Milk-related Symptom Score; SD, standard deviation. p^{a-b} , p^{c-d} <0.05.		

The thresholds of 9 and 10 both maximized Youden's J statistics. Although threshold 9 provided higher sensitivity (97.37% vs. 89.47%), threshold 10 was selected as optimal cut-off because it demonstrated a higher AUROC (0.918 vs. 0.934) and superior specificity (76.32% vs. 84.21%) providing a better overall diagnostic balance. At this threshold, sensitivity was 89.47% (95% CI: 75.2–97.06), specificity was 84.21% (95% CI: 68.75–93.98), LR + = 5.67 (95% CI: 2.68–11.97), LR- = 0.13 (95% CI: 0.05–0.32). The area under the receiver operating characteristic curve was 0.934 (95% CI, 0.853–0.978; $p < 0.001$) (Table 3 and Fig. 1).

Table 3
Diagnostic performance of CoMiSS thresholds in the preliminary study

CoMiSS threshold	Sensitivity (%)	Specificity (%)	Youden index (J)	LR+	LR-	AUROC (95% CI)
≥ 8	100	68.42	0.684	3.17	0.00	0.840 (0.740–0.931)
≥ 9	97.37	76.32	0.737	4.11	0.03	0.918 (0.852–0.984)
≥ 10	89.47	84.21	0.737	5.67	0.13	0.934 (0.853–0.978)
≥ 11	71.05	84.21	0.553	4.50	0.34	0.728 (0.614–0.842)
1 ≥ 2	60.53	94.74	0.553	11.51	0.42	0.804 (0.705–0.903)
AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LR+, positive likelihood ratio; LR–, negative likelihood ratio.						

During follow-up, 27 infants developed symptoms potentially associated with CMPA and were invited to the hospital for further evaluation. Of these, 14 had a CoMiSS ≥ 10. One infant (CoMiSS = 12) had bloody stools and irritability; however, an anal fissure was identified on physical examination. Because the symptoms were resolved after medical treatment of the fissure, CMPA was not considered the primary diagnosis. The remaining 13 symptomatic infants had a CoMiSS < 10, with a median (range, IQR) score of 6 (3–8, 2). Main symptoms were crying (n = 8), regurgitation (n = 7), slight respiratory symptoms (n = 6) and constipation (n = 5).

An elimination diet was initiated in the remaining 13 infants. Symptoms did not improve after elimination in one infant (CoMiSS = 13 before elimination and 11 after elimination). In the other 12 infants, symptoms improved during the elimination period and recurred after the cow's milk challenge. Their median (range, IQR) CoMiSS decreased from 13 (12–15, 2.25) before elimination to 6 (3–8, 2.25) after elimination and increased to 12 (11–14, 2) after the challenge. The differences between the pre-elimination and post-elimination scores and between the post-elimination and post-challenge scores were statistically significant after Bonferroni correction (both adjusted $p < 0.01$).

A total of 12 infants were diagnosed with CMPA. The six-month cumulative incidence of clinically confirmed CMPA was 2.9% (95% CI: 1.2–4.3) (Fig. 2). None of the 15 symptomatic infants (13 with CoMiSS < 10, 1 with anal fissure and 1 with unresponsive to elimination) who were not diagnosed with CMPA developed further symptoms suggestive of CMPA during follow-up to six months of age. No additional infant in this group was diagnosed with CMPA or developed persistent or progressive symptoms prompting diagnostic elimination during follow-up.

Among the 12 infants diagnosed with CMPA, 58.3% were male, and the mean age at symptom onset was 2.2 ± 1.2 months. Skin manifestations were present in 11 infants (91.6%), marked irritability and crying in 10 (83.3%), and regurgitation in 10 (83.3%). Constipation was observed in 4 (33.3%), diarrhea in 6 (50%) and respiratory symptoms were in 3 (25%) patients. Five infants (41.6%) had bloody stools with or without mucus in addition to other symptoms. Half of the affected infants were exclusively breastfed. None of the infants exhibited severe clinical manifestations that required amino acid-based formula. All 12 infants had negative milk-specific IgE and skin prick test results, and none had a history of immediate symptoms following cow's milk exposure; their clinical phenotype was therefore considered non-IgE-mediated. During follow-up, tolerance to cow's milk developed between 9 and 12 months of age in 50.0% of the infants, between 12 and 16 months in 41.7%, and after 16 months in 8.3%.

A family history of allergic disease was more frequent among infants with CMPA than among those without CMPA (58.3% vs 15.5%; Fisher's exact $p < 0.05$); the corresponding unadjusted OR was 7.62 (95% CI 2.35–24.77). Mode of delivery, gestational age, birth weight, feeding pattern, presence and number of siblings, and sex were not significantly associated with the development of CMPA ($p > 0.05$ for all).

Discussion

This prospective study found a six-month cumulative incidence of clinically confirmed CMPA of 2.9%. An exploratory case–control analysis identified a CoMiSS threshold of ≥ 10 as having the highest Youden index, and family history of allergic disease was the only examined characteristic significantly associated with CMPA.

CoMiSS was developed as an awareness tool to help general pediatricians recognize infants with mild or moderate manifestations potentially related to CMPA. Although concerns were initially raised that its use might contribute to overdiagnosis, subsequent guidelines and meta-analyses have consistently emphasized that a definitive diagnosis should be confirmed by symptom improvement during cow's milk elimination and symptom recurrence after reintroduction or challenge. Because CoMiSS is rapid, non-invasive, and easy to administer, it is now primarily used to identify infants who may require further assessment with an elimination diet and subsequent cow's milk challenge [6]. In the prospective MOSAIC study conducted in China, a CoMiSS threshold of ≥ 12 had low sensitivity for CMPA (20.3%) but relatively high specificity (87.9%) and positive predictive value (91.7%). However, the area under the receiver operating characteristic curve was 0.67, which was below the prespecified target of ≥ 0.75 . The investigators therefore concluded that CoMiSS was more appropriate as an awareness or screening tool than as a diagnostic test [7]. Although the optimal threshold may vary across populations, the 2022 consensus recommended lowering the proposed threshold from ≥ 12 to ≥ 10 and stated that CMPA is unlikely in infants with a score ≤ 6 [8]. Severe manifestations, such as anaphylaxis or severe food protein-induced allergic proctocolitis, are not adequately represented in CoMiSS because infants with these presentations should be assessed and managed in specialized centers. A previous study from Turkey identified an optimal threshold of > 12 during the first year of life [4]. Methodological differences between studies, including differences in age groups, feeding patterns, socioeconomic characteristics,

and eligibility criteria, led us to conduct a preliminary analysis to determine a locally applicable threshold. In the prospective cohort, most infants who met the ≥ 10 referral threshold and underwent diagnostic elimination and reintroduction were subsequently diagnosed with CMPA. However, because infants below the threshold did not undergo the same reference procedure, the cohort was not designed to provide an unbiased estimate of diagnostic accuracy.

The cumulative frequency of CMPA during the first six months of life was 2.9% in our cohort. Previous prevalence studies have reported widely varying estimates, largely attributed to differences in study design, age groups, diagnostic criteria, and population characteristics. In challenge-based European cohorts like the EuroPrevall study, CMPA frequency was as low as 0.54% (range 0-1.3%), whereas studies from China and South America reported higher rates ranging from 2.7% to 5.2% [9, 10, 11]. Cruchet et al. [12] reported a CMPA frequency of 4.9% among infants from birth to 12 months. Similarly to our study, the investigators contacted families regularly and invited symptomatic infants for hospital assessment, elimination, and challenge, with all confirmed cases exhibiting a non-IgE-mediated phenotype. Studies from the Chile and Poland likewise found non-IgE-mediated CMPA to be more common than IgE-mediated disease [11, 13]. Several symptom-based infant cohorts have reported a predominance of non-IgE-mediated presentations, although the observed phenotype distribution varies according to case-ascertainment and diagnostic methods. One possible explanation is that CoMiSS and similar symptom-based tools are primarily designed to identify mild or moderate presentations. Symptoms such as gastroesophageal reflux, colic, constipation, and feeding intolerance may reflect disorders of gut–brain interaction but may also occur in unrecognized non-IgE-mediated CMPA. Symptom-based awareness tools may help identify infants who warrant a structured elimination and challenge procedure. Nevertheless, these symptoms are non-specific, and CoMiSS should not be used as a stand-alone diagnostic test.

An exploratory association was observed between family history of allergic disease and CMPA in our cohort. Family history is biologically plausible as a marker of inherited atopic susceptibility. However, the small number of cases prevented adjustment for potential confounders, and this finding should be regarded as exploratory.

A major strength of this study was its prospective design. Each included newborn was followed through monthly telephone interviews, during which symptoms potentially associated with CMPA were systematically assessed. Infants with suggestive symptoms were invited for clinical evaluation, assessed using CoMiSS, and, when indicated, underwent cow's milk elimination and challenge. This approach enabled estimation of the frequency of CMPA confirmed through diagnostic elimination and reintroduction rather than reliance solely on parental reports, diagnostic codes, or sensitization tests.

This study also has several limitations. First, screening was symptom-based, and IgE testing was not systematically performed in the entire cohort, which may have led to unrecognized cases. Second, clinical evaluations were not blinded, introducing potential reporting or assessment bias during telephone follow-ups and open-label challenges. Third, threshold derivation and evaluation were

conducted within the same single cohort, and infants under the threshold did not undergo the reference procedure (verification bias). Finally, the study was conducted at a single center and excluded infants with a gestational age ≤ 35 weeks, a birth weight ≤ 2500 g, serious comorbidities, or incomplete telephone follow-up. The findings may therefore not be generalizable to all newborn populations. Furthermore, the CoMiSS threshold was derived from a relatively small case–control sample of previously diagnosed patients with CMPA and healthy controls, rather than symptomatic non-CMPA infants, and was not externally validated. This design may have overestimated its discriminatory performance. Finally, while the overall sample size was adequate for determining overall CMPA prevalence, the low number of confirmed CMPA cases limited the statistical power to identify associated risk factors

Conclusion

In this prospectively followed birth cohort, the six-month cumulative incidence of CMPA confirmed by elimination and reintroduction was 2.9%, and all confirmed cases had a phenotype consistent with non-IgE-mediated disease. Family history of allergic disease showed an exploratory association with CMPA. CoMiSS may help identify symptomatic infants requiring structured assessment, but it should not be used as a stand-alone diagnostic test. Larger multicenter studies applying the same reference procedure, irrespective of CoMiSS, are required

Declarations

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Author Contribution

All authors reviewed manuscript, and equally contributed to the manuscript while writing and preparing figures

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Figures

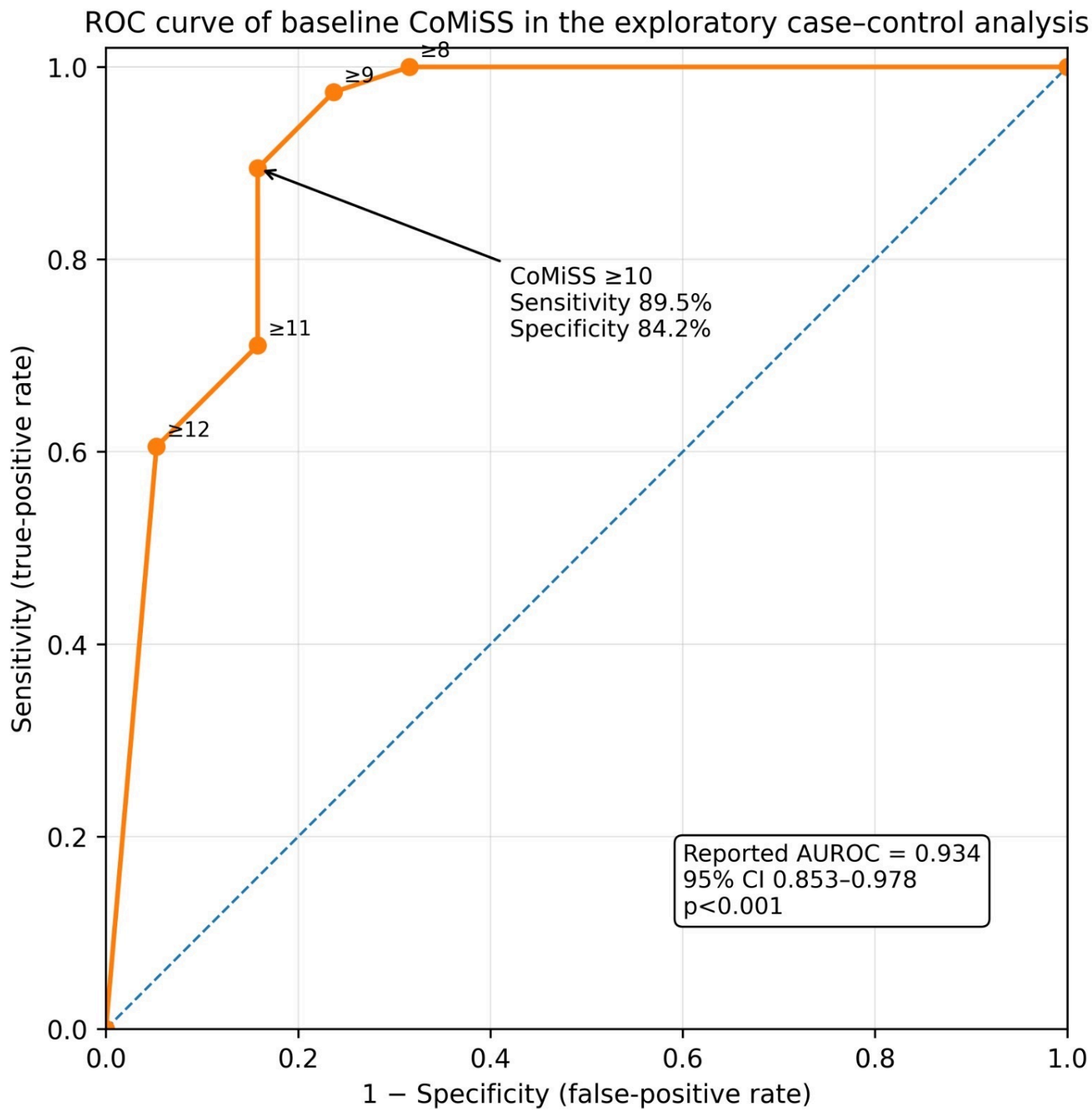


Figure 1

Receiver operating characteristic curve of baseline CoMiSS for differentiating infants with elimination–reintroduction-confirmed cow’s milk protein allergy from healthy controls in the exploratory case–control analysis. The AUROC was 0.934 (95% CI:0.853-0.978, $p < 0.001$). The referral threshold of ≥ 10 corresponded to a sensitivity of 89.5% and specificity of 84.2%.

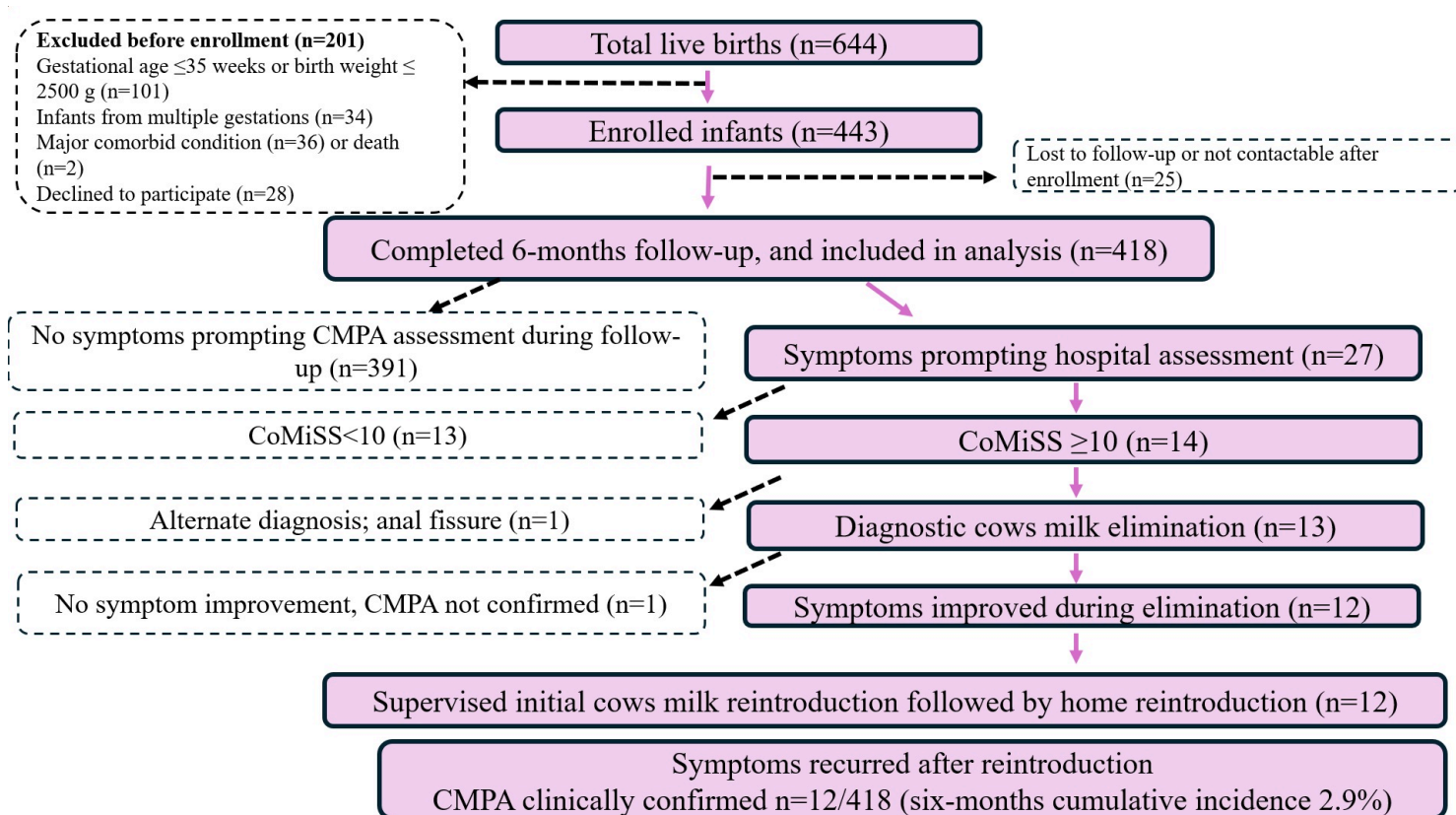


Figure 2

Flowchart of the study; enrollment, evaluation and diagnostic confirmation of CMPA

Supplementary Files

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