analesdepediatría

www.analesdepediatria.org

ORIGINAL ARTICLE

When can the Cow's Milk-related Symptom Score (CoMiSS) be a useful tool for Spanish pediatricians?☆

Rafael Martín-Masot[a], **Juan J. Díaz-Martín**[b,*], **Alicia Santamaria-Orleans**[c], **Víctor Manuel Navas-López**[a]

[a] *Unidad De Gastroenterología y Nutrición Pediátrica, Hospital Regional Universitario de Málaga, Málaga, Spain*
[b] *Unidad De Gastroenterología y Nutrición Pediátrica, Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Spain*
[c] *Área de Comunicación Científica, Laboratorios Ordesa, S.L., Barcelona, Spain*

Received 22 February 2025; accepted 21 July 2025
Available online 14 November 2025

KEYWORDS
CoMiSS;
Cow's milk allergy;
Survey study;
IgE-mediated;
Non-IgE-mediated;
Extensively hydrolyzed formula (EHF)

Abstract
Introduction: The Cow's Milk-related Symptom Score (CoMiSS) is a practical tool to assess for cow's milk protein allergy (CMPA) in infants based on clinical manifestations, although the diagnosis of CMPA should be confirmed subsequently by a specialist in pediatrics and/or pediatric gastroenterology and nutrition. The aim of this study was to compare CoMiSS results in infants diagnosed with IgE-mediated and non-IgE-mediated CMPA.
Material and methods: Multicenter, cross-sectional survey study with participation of pediatricians throughout Spain. Pediatricians were directed to apply the CoMiSS to infants at the time of diagnosis of CMPA and 7 days after initiating nutritional management with an extensively hydrolyzed formula (EHF). We interpreted a CoMiSS score of 12 or greater as positive.
Results: A total of 294 pediatricians (mean age, 51 years) participated in the study. The analysis included CoMiSS results for 1176 infants with CMPA (mean [SD] age, 6.4 [4.9] months), of who 66.8% (n = 745) had non-IgE-mediated CMPA. We found a greater decrease in the mean score in the IgE-mediated group compared to the non-IgE-mediated group (mean [SD], −9.06 [5.74] vs −6.00 [4.05]; $P < .0001$). When it came to individual symptoms, there were significantly greater reductions in the mean scores for crying and regurgitation in the non-IgE-mediated group, and, conversely, significantly greater reductions in the scores for atopic eczema in the head and arms, urticaria and respiratory symptoms in the IgE-mediated group. There was also a greater decrease in the total CoMiSS score in infants with very severe CMPA compared to infants with severe, moderate and mild CMPA.

DOI of original article: https://doi.org/10.1016/j.anpedi.2025.504056
☆ Previous meetings: this study was presented at the 56th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; May 15–18, 2024; Milan, Italy; and at the 70th Congress of the Asociación Española de Pediatría; June 6–8, 2024; Cordoba, Spain.
* Corresponding author.
E-mail address: diazmjuan@uniovi.es (J.J. Díaz-Martín).

Conclusion: This survey showed that only one third of infants diagnosed with CMPA had a positive CoMiSS result of 12 points or greater at the time of diagnosis, which suggests an inadequate use of the CoMiSS. We recommend the implementation of strategies to increase knowledge of the utility of the CoMiSS for the assessment of CMPA.

PALABRAS CLAVE
CoMiSS;
Alergia a la proteína de leche de vaca;
Encuesta;
IgE mediada;
No IgE mediada;
Fórmula extensamente hidrolizada

Sistema de puntuación CoMiSS de síntomas asociados a la leche de vaca: ¿Cuándo puede ser útil para los pediatras españoles?

Resumen
Introducción: CoMiSS es una herramienta práctica para evaluar la alergia a la proteína de la leche de vaca (APLV) en los lactantes teniendo en cuenta su sintomatología a pesar de que el diagnóstico de APLV debe ser confirmado posteriormente por un especialista en pediatría y/o gastroenterología y nutrición pediátricas. El presente estudio tiene como objetivo comparar los resultados de la herramienta Cow's Milk-related Symptom Score (CoMiSS) en lactantes diagnosticados de alergia a las proteínas de la leche de vaca (APLV) IgE y no IgE mediada.
Material y métodos: Estudio multicéntrico, transversal, tipo encuesta realizado entre pediatras de toda España. Se les pidió que obtuvieran la puntuación CoMiSS en lactantes en el momento del diagnóstico de APLV y 7 días después de iniciar el manejo nutricional con una fórmula extensamente hidrolizada (FHE). Se consideró positiva una puntuación CoMiSS $\geq$ 12.
Resultados: Participaron en el estudio 294 pediatras (edad media 51 años). Se registró la puntuación CoMiSS en 1176 lactantes con APLV (edad media $\pm$ DE 6,4 $\pm$ 4,9 meses), el 66,8% (n = 745) no-IgE mediada. La puntuación CoMiSS media total mostró una mayor disminución en el grupo con alergia IgE mediada que en el grupo no-IgE mediada ($-9{,}06 \pm 5{,}74$ frente a $-6{,}00 \pm 4{,}05$; $p < 0{,}0001$). Las puntuaciones medias de los síntomas individuales, llanto y regurgitación mostraron reducciones significativamente mayores en el grupo APLV no-IgE mediada, mientras que el eccema atópico en la cabeza y los brazos, la urticaria y los síntomas respiratorios mostraron reducciones significativamente mayores en el grupo IgE mediada. La puntuación CoMiSS total mostró una mayor disminución en el grupo con APLV muy grave en comparación con las graves, moderadas y leves.
Conclusión: Esta encuesta muestra que en los lactantes diagnosticados con APLV, solo un tercio tenía una puntuación CoMiSS positiva $\geq$ 12 puntos en el momento del diagnóstico, lo que respalda un uso inadecuado de la herramienta CoMiSS. Se recomiendan acciones para aumentar el conocimiento del valor de CoMiSS para la evaluación de la APLV.

Introduction

Cow's milk protein allergy (CMPA) affects from 2% to 6% of children[1] and is the most prevalent food allergy diagnosed in infants in the first year of life.[2] According to data from the EuroPrevall study conducted in a birth cohort of children from nine European countries, the overall incidence of challenge-proven CMPA in children aged less than 2 years is 0.54%.[3] Nevertheless, most children develop tolerance to cow's milk over time, with the prevalence of CMPA decreasing to less than 1% by the age of six.[4] The adverse event that occurs following the ingestion of cow's milk involves an immune response that can be IgE-mediated (type I hypersensitivity immune response) or non-IgE-mediated. In the Spanish population, there is a reported incidence of Ig-E-mediated CMPA of 0.36% in the first year of life.[5]

Broad clinical manifestations involving the gastrointestinal tract, the skin and the respiratory system make diagnosis of CMPA a challenge for clinicians. Misdiagnosing CMPA in everyday practice is easy due to the nonspecificity of its presenting symptoms and the high frequency of diagnosis based on clinical experience as opposed to confirmed by testing, for instance, through allergen elimination and challenge procedures, skin prick tests or detection of CMP-specific IgE antibodies.[6] Misdiagnosis can lead to unnecessary dietary restrictions, potentially impairing growth and development when hypoallergenic formulas are not used, increasing stress in families and placing an additional burden on the health care system. Delayed diagnosis and underdiagnosis also have a detrimental impact on the child's health in the form of persistent symptoms, growth impairment and risk of micronutrient deficiencies. Moreover, overdiagnosis of CMPA may have significant cost implications due to the overuse of

a variety of therapeutic infant formulas available for this condition.[7]

In September 2014, a group of experts in the management of children with gastrointestinal problems and/or atopic diseases participated in a workshop held in Brussels (Belgium) and reached consensus on the proposal of a symptoms-based score for the assessment of CMPA, the Cow's Milk-related Symptom Score (CoMiSS™).[8] The CoMiSS is a rapid, short and easy-to-use instrument that assesses the presence and intensity of crying and regurgitation, stool consistency and cutaneous and respiratory manifestations. It is a useful screening tool for CMPA, helps to establish its diagnosis, especially in cases of non-IgE-mediated allergy, and can be used for monitoring symptom improvement.[8] A score of 12 points or greater, used as an inclusion criterion in the original trial (proposed arbitrary cutoff of 12 points), is accepted for identifying infants at risk of CMPA.[9] Numerous studies have evaluated the usefulness of the CoMiSS under different circumstances, mostly in infants presenting symptoms possibly related to cow's milk allergy as well as before and after cow's milk elimination, in IgE-mediated and non-IgE-mediated CMPA, as a stand-alone diagnostic tool, in healthy infants and in infants with conditions other than CMPA.[10–16] Additionally, some review articles provide an in-depth summary of the results of these clinical studies.[17–19] In a meta-analysis of 14 studies and 1238 children, a cutoff value of 12 points or greater was found to offer a pooled sensitivity of 64%, with a specificity of 75% and an area under ROC curve of 0.786, providing evidence of the advantages of the CoMiSS for CMPA screening and monitoring the response to a cow's milk-free diet.[20]

To our knowledge, however, no study has been conducted in Spain to assess the clinical utility of the CoMiSS. Therefore, the main objective of the study was to determine whether the CoMiSS could be helpful to Spanish pediatricians in the evaluation of infants (defined as age < 2 years) with CMPA by comparing CoMiSS results in patients with a diagnosis of IgE-mediated versus non-IgE-mediated CMPA and with different estimated levels of severity.

Methods

Design and participants

We conducted a multicenter cross-sectional and observational study through a survey of Spanish pediatricians with the objective of collecting real-world data on the application of the CoMiSS in infants with a diagnosis of CMPA.

Pediatricians working at the primary care level in the public health care system or in private institutions throughout Spain were eligible, provided that their routine daily workload included the outpatient management of at least 10 infants. We recruited participants using the information available in the database of clinical pediatricians hosted by Laboratorios Ordesa LLC. Around 50% of all primary care pediatricians currently active in Spain are registered in this database. We sent individual invitations to participate in the study, highlighting that it was both voluntary and anonymous. A digital data collection logbook was provided to the pediatricians who provided written informed consent to participation. The fieldwork lasted 6 months and was conducted between January and September 2023.

Study procedures and data collection

Participants were asked to complete the CoMiSS questionnaire using retrospective data for the previous 6 months in order to obtain the score for infants at the time of diagnosis of CMPA based on customary pediatric clinical practice, the findings of the history-taking and physical examination, in addition to 7 days after initiation of restrictive nutritional management with extensively hydrolyzed formula (EHF). Patients who needed to be fed elemental formula were excluded from the study. The data for the study were collected in the context of routine real-world clinical practice, and pediatricians were provided with the instrument without being notified that it was the CoMiSS and did not receive any specific training before using it. The CoMiSS is a simple assessment tool based on rating the following five symptoms: daily duration of crying; number and volume of episodes of regurgitation, consistency of stools, presence and severity of atopic eczema or urticaria and presence and severity of respiratory symptoms. Crying, regurgitation, and skin manifestations are rated according to severity on a scale from 0 to 6, with 6 points standing for the greatest possible severity. Stool consistency was scored based on the Bristol stool scale (BSS)[21] as 0 points for normal stools (types 3 and 4), 2 for soft stools (type 5), 4 for hard stools (types 1 and 2) or liquid stools (type 6) and 6 for watery stools (type 7). Cutaneous symptoms, which included the presence of atopic dermatitis (involving head/neck/trunk and arms/hands/legs/feet) or urticaria, were also scored on a scale from 0 to 6. Respiratory symptoms were scored on a scale from 0 to 3 points: 0 for no symptoms, 1 for mild, 2 for moderate and 3 for severe respiratory symptoms. The total score in the CoMiSS ranges from 0 to 33, with scores of 12 points or greater indicating the presence of CMPA.

In addition to the CoMiSS, the study questionnaire included items to collect demographic data for the infant, the diagnosis of IgE-mediated or non-IgE-mediated CMPA established by each pediatrician based on their experience and customary clinical practice, the age at diagnosis and the severity of symptoms. The severity of symptoms was rated on a 4-point Likert scale (mild, moderate, severe and very severe). The time elapsed to symptom improvement after the introduction of EHF was also documented. The first section of the study questionnaire was used to collect data on the demographic characteristics of the pediatricians, the type of practice, the work setting and the number of patients aged up to 2 years that the pediatrician managed per month.

Statistical analysis

We summarized categorical data as absolute frequencies and percentages, and continuous data as mean and standard deviation (SD) or, if the data did not follow a normal distribution, median and interquartile range (IQR). We compared differences in the distribution of variables in the IgE-mediated group versus the non-IgE-mediated group as well as changes in the individual items of the CoMiSS

between day 0 (before introducing changes in the type of formula) and day 7 (after switching to an EHF) using the Kruskal-Wallis test, the Mann-Whitney *U* test and analysis of variance (ANOVA) as applicable. We defined statistical significance as a *P* value of less than 0.05. The data were analyzed with Statistical Analysis Systems, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Participating pediatricians

A total of 294 pediatricians (51.4% female) with a mean (SD) age of 51 (11.2) years participated in the study. Most of them (82.6%) worked in urban settings, 51.7% in a public health care facility, 22.4% in a private clinic, and 23.1% in both public and private institutions. In addition, 55.4% worked in primary care centers, 18.7% in outpatient hospital clinics and 25.8% in private clinics. The median (IQR) number of infants of age managed per month was 150 (100–200).

Characteristics of the infants

The sample included 1176 infants aged less than 2 years diagnosed with CMPA by their pediatricians. The median (IQR) age was 5 (3–9) months and 55.7% were male. The median (IQR) age at diagnosis of CMPA was 2 (1–4) months. Non-IgE-mediated CMPA was documented in 66.8% (n = 745) of infants and IgE-mediated CMPA in 33.2% (n = 371). In the group with non-IgE-mediated CMPA, a cow's milk challenge was performed only in 56.4% of cases. The severity of cow's milk allergy was considered mild in 22.9% of infants (n = 262), moderate in 58% (n = 664), severe in 17.3% (n = 198) and very severe in 1.8% (n = 21). An EHF was prescribed in all cases.

Differences in CoMiSS values before and after the introduction of an extensive hydrolyzed formula

A total CoMiSS score of 12 points or greater was documented in 33.1% of infants on day 0 and in 1.7% on day 7. The proportion with a score of less than 12 points increased from 66.9% on day 0 to 98.3% on day 7. The median (IQR) total score of the CoMiSS decreased from 10 (7–13) points to 3 (1–5) points after introduction of the EHF.

Table 1 shows the changes in the individual items of the CoMiSS between days 0 and 7. The mean score of all symptoms decreased from day 0 to day 7, a difference that was statistically significant for all except stool consistency. The reduction was particularly relevant in crying and regurgitation, with a marked increase in the percentage of infants that cried one hour or less a day (from 16.7% to 57.1%) and the percentage that had 0–2 episodes of regurgitation a day (from 23.7% to 63.8%). The percentage of children with normal stools increased from 24.6% to 58.2%. Moderate and severe atopic eczema involving both the head/neck/trunk and the arms/hands/legs/feet decreased, from 24.1% to 2.9% and from 15.9% to 2.3%, respectively. Also, 97.9% of infants were free from urticaria and 91.4% from respiratory symptoms on day 7.

Changes in the CoMiSS based on diagnosis of IgE-mediated versus non-IgE-mediated CMPA

In the IgE-mediated group, the mean (SD) CoMiSS score on day 0 was 12 (5.2) points, decreasing to 3.4 (3.4) on day 7 ($P <$ .001). The corresponding values in the non-IgE-mediated group were 8.9 (4.1) and 3.1 (2.8), respectively ($P <$ .001). We also found a significant difference in the percentage of infants with a score of 12 or higher between the IgE-mediated and non-IgE mediated groups (52.9 % vs 24.27%; $P <$ .05) (Fig. 1).

The comparison of the mean scores in the CoMiSS showed statistically significant differences between the IgE-mediated and non-IgE-mediated groups in the changes in CMPA-related symptoms between days 7 and 0 (Table 2). There was a greater decrease in the mean total score of the CoMiSS in the IgE-mediated group compared to the non-IgE-mediated group (mean [SD], −9.06 [5.74] vs −6.00 [4.05]; $P <$ .0001). However, when it came to the mean scores for individual symptoms, we found significantly higher reductions in crying and regurgitation in the non-IgE-mediated group, and, on the other hand, significantly higher reductions in atopic eczema in the head and arms, urticaria and respiratory symptoms in the IgE-mediated group.

Differences in the CoMiSS according to the severity of CMPA symptoms

When we analyzed CoMiSS scores based on the severity of CMPA symptoms, we found statistically significant differences among the groups of infants with mild, moderate, severe, and very severe symptoms. As can be seen in Table 3, there was a greater decrease in the mean total score of the CoMiSS in the group with very severe CMPA (mean, −9.20; SD, 4.92) compared to all the other severity categories. When we analyzed decreases in individual CMPA-related symptoms, we found statistically significant differences between scores on days 7 and 0 in all symptoms except stool consistency. In general, there were greater score reductions in the severe symptom groups compared to the remaining groups (Table 3).

Fig. 2 shows the mean changes in CoMiSS scores in the overall sample and in the subsets of infants categorized according to the mechanism of CMPA and the severity of symptoms.

Time elapsed to improvement in symptoms

The mean (SD) time elapsed to observation of symptom improvement was 7.1 (5.7) days. The perceived improvement was rated as ''very high'' in 533 cases (46.5%), ''high'' in 497 (43.4%), ''moderate'' in 106 (9.3%) and ''low'' in 9 (0.8%).

The median time elapsed to improvement of symptoms was not associated to having a negative (< 12) versus a positive (≥ 12) CoMiSS score on day 0 (median [IQR], 6 [3–8] vs 5 [3–7] days; P = .301) or to the severity of CMPA symptoms (median [IQR]: mild 7 [4–9] days, moderate 6 [3–7] days, severe 5 [3–10] days, very severe 7 [1.5–14] days;

Table 1 Differences in CoMiSS items before and after initiation of the exclusion diet in the sample.

Variables	Day 0 n (%)	Day 7 n (%)
Total score, mean (SD)	9.95 (4.81)	3.16 (2.98)
	P < .0001	
Crying		
≤1 h/day	181 (16.7)	617 (57.1)
1 to 1.5 h/day	143 (13.2)	299 (27.6)
1.5 to 2 h/day	148 (13.6)	102 (9.4)
2 to 3 h/day	201 (15.8)	32 (3.0)
3 to 4 h/day	188 (17.3)	22 (2.0)
4 to 5 h/day	121 (11.1)	3 (0.3)
≥5 h/day	103 (9.5)	6 (0.6)
Missing	91 (7.7)	95 (8.1)
Score, mean (SD)	2.78 (1.90)	0.68 (1.02)
	P = .004	
Regurgitation		
0 to 2 episodes/day	258 (23.7)	697 (63.8)
≥3 to ≤5 of small volume	248 (22.8)	290 (26.5)
>5 episodes of > 1 coffee spoon	136 (12.5)	66 (6.0)
>5 episodes of ± half of the feed in < half of the feedings	155 (14.2)	21 (1.9)
Continuous regurgitations of small volume >30 min after each feeding	139 (17.8)	16 (1.5)
Regurgitation of half to complete volume of a feeding in at least half of the feedings	102 (9.4)	1 (0.1)
Regurgitation of the ''complete feeding'' after each feeding	50 (4.6)	2 (0.2)
Missing	88 (7.5)	83 (7.1)
Score, mean (SD)	2.16 (1.84)	0.52 (0.86)
	P = .0298	
Stool (Bristol scale)		
Type 1 and 2 (hard stools)	116 (6.6)	140 (12.8)
Type 3 and 4 (normal stools)	269 (24.6)	635 (58.2)
Type 5 (soft stools)	260 (23.7)	275 (25.2)
Type 6 (liquid stools, if unrelated to infection)	291 (26.6)	33 (3.0)
Type 7 (watery stools)	159 (14.5)	8 (0.7)
Missing	81 (6.9)	85 (7.2)
Score, mean (SD)	2.29 (1.67)	1.19 (1.57)
	P = .1974	
Skin symptoms		
Atopic eczema		
Head, neck, and trunk		
Absent	549 (50.0)	737 (68.4)
Mild	285 (26.0)	309 (28.7)
Moderate	237 (21.6)	30 (2.8)
Severe	27 (2.5)	1 (0.1)
Missing	78 (6.7)	99 (8.4)
Score, mean (SD)	0.77 (0.87)	0.35 (0.54)
	P < .0001	
Arms, hands, legs, and feet		
Absent	656 (61.5)	819 (78.7)
Mild	241 (22.6)	198 (19.0)
Moderate	151 (14.1)	21 (2.0)
Severe	19 (1.8)	3 (0.3)
Missing	109 (9.3)	135 (11.5)
Score, mean (SD)	0.56 (0.80)	0.24 (0.49)
	P < .0001	
Urticaria		
No	865 (77.4)	1056 (97.9)
Yes	253 (22.6)	23 (2.1)
Missing	58 (4.9)	97 (8.2)
Score, mean (SD)	1.36 (2.51)	0.13 (0.87)

Table 1 (*Continued*)

Variables	Day 0 n (%)	Day 7 n (%)
	P < .0001	
Respiratory symptoms		
No respiratory symptoms	821 (73.8)	993 (91.4)
Slight symptoms	198 (17.8)	86 (7.9)
Mild symptoms	87 (7.8)	6 (0.6)
Severe symptoms	7 (0.6)	1 (0.1)
Missing	63 (5.4)	90 (7.6)
Score, mean (SD)	0.35 (0.65)	0.09 (0.32)
	P < .0001	

Abbreviations: CoMiSS: Cow's Milk-Related Symptom Score; h: hour; SD: standard deviation.

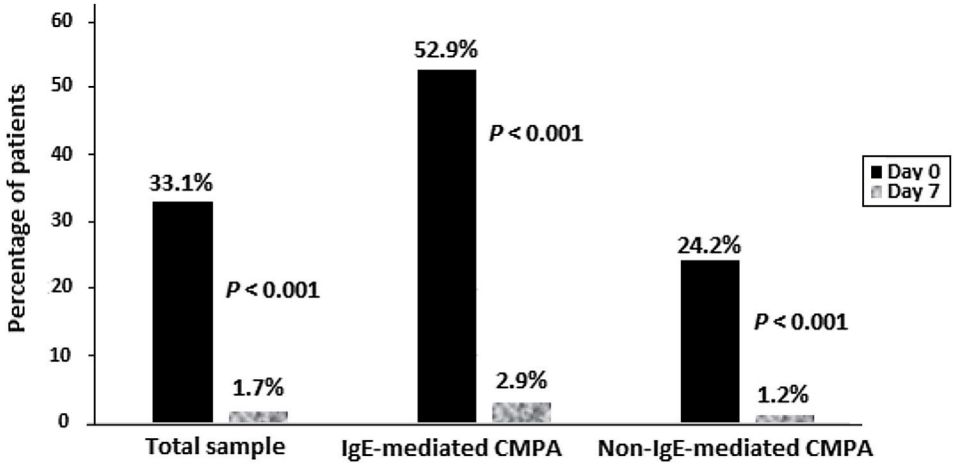

Figure 1 Percentage of infants with a CoMiSS score ≥12 on day 0 and day 7 in the total sample and in the of IgE-mediated and non-IgE-mediated cow's milk protein allergy (CMPA) groups.

Table 2 Changes in mean CoMiSS scores according to CMPA diagnosis.

Variables	Differences between day 7 and day 0		
	Ig-E-mediated mean (SD)	Non-IgE-mediated mean (SD)	*P* value*
CoMiSS total score	−9.06 (5.74)	−6.00 (4.05)	<.0001
Crying	−1.86 (1.88)	−2.22 (1.70)	.0003
Regurgitation	−1.57 (1.77)	−1.67 (1.59)	.029
Stools	−1.07 (2.07)	−1.24 (2.07)	.197
Atopic eczema, head	−0.71 (0.71)	−0.30 (0.53)	<.001
Atopic eczema, arms	−0.59 (0.71)	−0.20 (0.48)	<.0001
Urticaria	−3.28 (3.20)	−0.29 (1.36)	<.0001
Respiratory symptoms	−0.45 (0.68)	−0.17 (0.44)	<.0001

Abbreviations: CoMiSS, Cow's Milk-Related Symptom Score; CMPA, cow's milk protein allergy; SD, standard deviation.
* Mann-Whitney *U* test.

P = .345), although the time elapsed to improvement was longer in the group with very severe symptoms. However, the time elapsed to improvement of symptoms was significantly longer in the group with non-IgE-mediated CMPA compared to the group with IgE-mediated CMPA (Fig. 3).

Discussion

One of the main findings of the study was the low proportion of patients with a positive CoMiSS score of 12 or greater, of only 33.1%, despite the fact that CMPA had already been

Table 3 Changes in mean CoMiSS scores according to severity of CMPA symptoms.

Variables	Differences between day 7 and day 0				
	Mild mean (SD)	Moderate mean (SD)	Severe mean (SD)	Very severe mean (SD)	*P* value*
CoMiSS total score	−4.94 (3.70)	−7.33 (4.81)	−8.68 (5.52)	−9.20 (4.92)	<.0001
Crying	−1.69 (1.66)	−2.20 (1.74)	−2.27 (1.89)	−2.47 (2.42)	.00016
Regurgitation	−1.37 (1.54)	−1.68 (1.75)	−1.78 (1.70)	−2.22 (2.16)	.0157
Stools	−1.11 (1.91)	−1.26 (2.10)	−1.12 (2.18)	−1.00 (2.14)	.671
Atopic eczema, head	−0.27 (0.51)	−0.39 (0.59)	−0.65 (0.72)	−0.83 (0.92)	<.0001
Atopic eczema, arms	−0.17 (0.48)	−0.31 (0.56)	−0.50 (0.66)	−0.78 (1.00)	<.0001
Urticaria	−0.57 (1.84)	−1.23 (2.50)	−2.22 (2.97)	−1.50 (4.30)	<.0001
Respiratory symptoms	−0.10 (0.35)	−0.23 (0.49)	−0.48 (0.72)	−1.15 (1.09)	<.001

Abbreviations: CoMiSS, Cow's Milk-Related Symptom Score; CMPA, cow's milk protein allergy; SD, standard deviation.
* Kruskal-Wallis test.

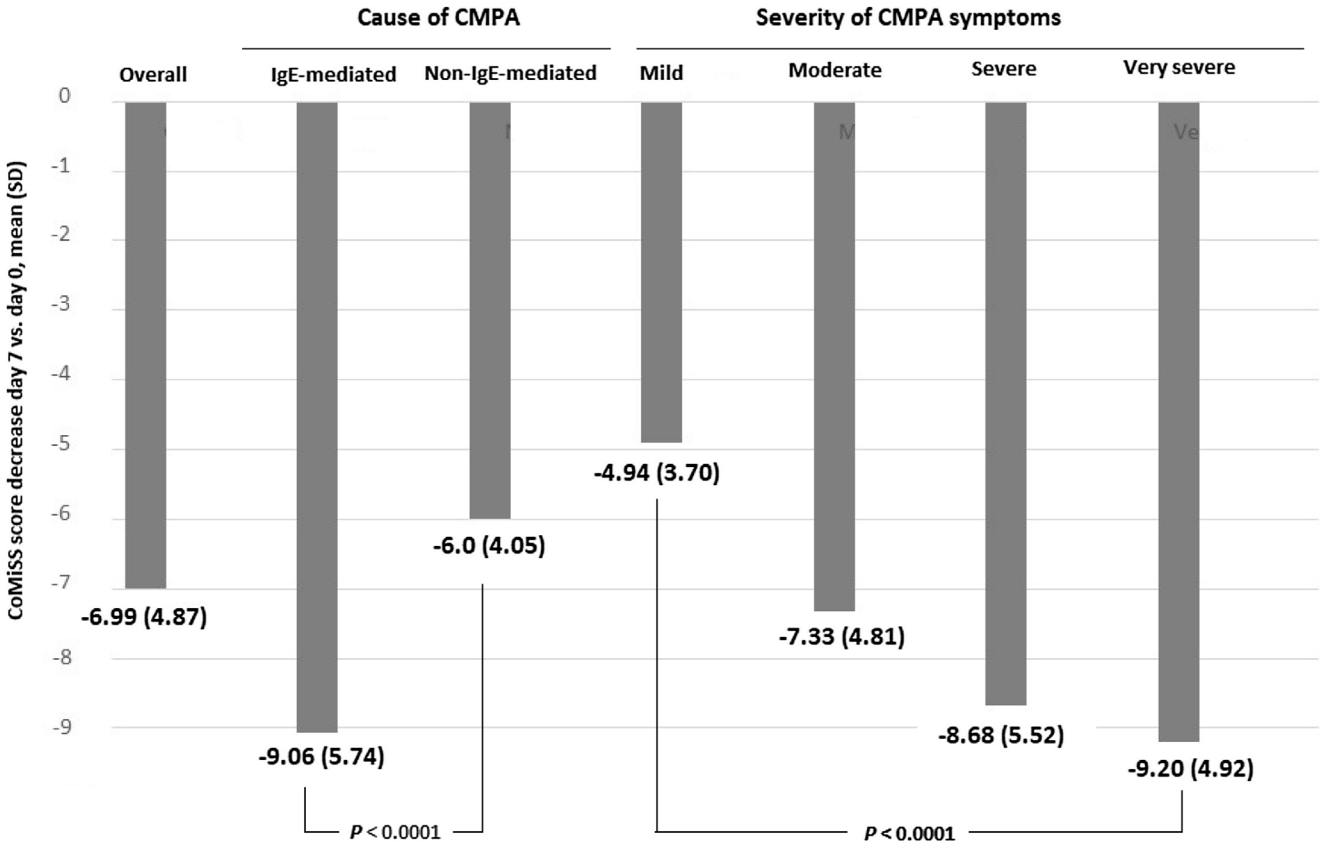

Figure 2 Changes in the mean scores of the CoMiSS between days 0 and 7 in the total sample, in the IgE-mediated and non-IgE-mediated cow's milk protein allergy (CMPA) groups and according to symptom severity.

diagnosed in all patients. This observation suggests the possibility of an inadequate use of the tool in non-IgE-mediated cases. However, some researchers have warned of the fact that international guidelines[22] developed to help doctors diagnose non-IgE-mediated CMPA in infants may be leading to overdiagnosis of the condition.[22] In a secondary analysis of the Enquiring About Tolerance (EAT) randomized controlled trial in 1303 infants, the prevalence of symptoms outlined in the international Milk Allergy in Primary Care (iMAP) guideline[23] was 38% for mild to moderate symptoms at 3 months and 74% between 3 and 12 months.[24] One of the main concerns in regard to the overdiagnosis of non-IgE-mediated CMPA is the contribution to excessive dietary restrictions during the first year life, a key period for growth and immune development. Guidelines, however, have the potential to help clinicians if they are followed carefully and oral challenges are actually performed. In our study, challenge testing was performed in only 56% of non-IgE-CMPA cases, so it is likely that some of the patients included in the study were actually not allergic to cow's milk.[25]

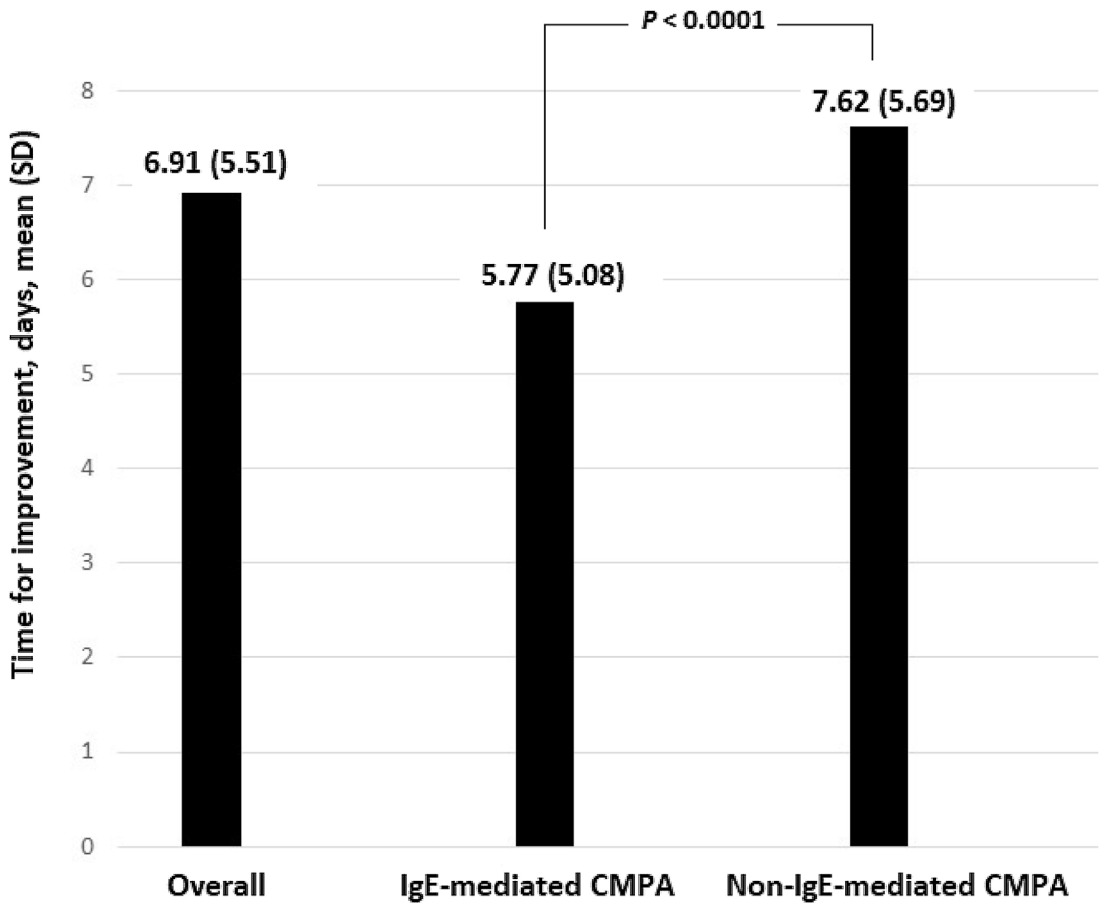

Figure 3 Mean time elapsed to observed improvement of symptoms in the total sample and in the IgE-mediated and non-IgE-mediated cow's milk protein allergy (CMPA) groups.

There has been debate regarding the most appropriate CoMiSS cut-off value for recognition of cow's milk allergy symptoms in infants. The group of experts that participated in the development of the original tool have proposed lowering the initial cutoff of 12 to 10 points, in addition to the inclusion of angioedema and substituting the Brussels Infant and Toddlers Stool Scale (BITSS) for the Bristol scale for the assessment of stool changes.[26] Further studies are needed to determine whether changes to the CoMiSS cut-off value and other small modifications improve the sensitivity and specificity of the scale. However, other authors continue to recommend a score of 12 points as the best cutoff for identifying infants who may benefit from a cow's milk-free diet.[27] There is agreement that CMPA is unlikely if the score in the CoMiSS is 6 points or less.[8,26,27] In our study, we interpreted the standard CoMiSS range of 12 points or greater as positive.

The temporal trends in the CoMiSS were different in the IgE-mediated versus the non-IgE-mediated CMPA group, with higher values at diagnosis and a greater reduction at day 7 from initiation of EHF in IgE-mediated cases compared to non-IgE-mediated cases. In the analysis of individual symptoms in the CoMiSS, we found significantly greater reductions in crying and regurgitation in the non-IgE-mediated CMPA group, while there were significantly greater decreases in atopic eczema, urticaria and respiratory symptoms in the IgE-mediated group. These findings are consistent with the fact that cutaneous and respiratory symptoms are common manifestations in infants with IgE-mediated CMPA compared to the broad and nonspecific gastrointestinal symptoms that could be suggestive of a non-IgE-mediated cow's milk allergy. In clinical practice, differentiating IgE-mediated and non-IgE-mediated CMPA based on the presenting symptoms and the physical examination can be challenging. At any rate, the differences in the CoMiSS observed between the IgE-mediated and non-IgE-mediated groups in our study should be interpreted taking into account that the diagnoses were reported by pediatricians and that we did not investigate the tests or procedures used for assessing and classifying CMPA.

Another relevant finding was the significantly longer time elapsed to symptom improvement after introduction of the elimination diet with EHF in infants with a diagnosis of non-IgE-mediated CMPA compared to IgE-mediated CMPA. According to the algorithm of the consensus statement for non-IgE-mediated CMPA of the Asociación Española de Pediatría (Spanish Association of Pediatrics), improvement with the elimination diet can be expected after a variable period of time depending on the clinical presentation, ranging from 1 to 5 days in acute forms, 1 to 2 weeks in cases presenting with eczema and gastrointestinal bleeding and 2 to 4 weeks in cases presenting with constipation, diarrhea and growth faltering.[28]

The analysis of the distribution of CoMiSS values according to the severity of symptoms (categorized as mild, moderate, severe and very severe) found statistically significant differences, with greater reductions in individual symptom scores, particularly crying, regurgitation, urticaria and respiratory complaints, in the most severe cases. Other studies have found a decrease in CoMiSS values in infants with suspected CMPA after a dietary intervention[12] as well as more pronounced decreases in infants with a positive challenge compared to those with a negative challenge,[10] but the association between the severity of symptoms and the magnitude of the reduction in CoMiSS scores after the introduction of EHF had not been evaluated before.

The results of our study should be interpreted taking into account some of its limitations. Selection bias may have affected the representativeness of the sample and the external validity of the findings. The study sample was not randomized nor proportionally stratified to the number of specialists in pediatrics registered in each of the 17 autonomous communities of Spain. However, the 294 participants provided valuable information on a very large group of infants aged less than 2 years with a diagnosis of CMPA to whom the CoMiSS tool was applied before and 7 days after introduction of an extensively hydrolyzed formula. In this regard, our study's sample of 1176 infants is the largest reported so far. The classification of CMPA was reported by the participating pediatricians, but the questionnaire did not include specific items regarding the diagnostic approach implemented to establish an IgE-mediated vs non-IgE-mediated etiology. On the other hand, given that oral challenges for CMPA were not performed in every case, it is possible that the occurrence of CMPA was overestimated, which could explain the small percentage of children with positive CoMiSS scores. In addition, the 7-day interval between the two CoMiSS assessments was short, and we do not know whether the results could be affected by extending this period further.

Conclusion

This survey reveals that only one-third of infants with suspected CMPA based on clinical features had a positive CoMiSS score ($\geq$ 12 points). In cases of IgE-mediated CMPA, the mean scores were significantly higher at diagnosis compared to non-IgE-mediated cases, and there were also greater reductions in the scores one week after the introduction of an EHF. The diagnosis of CMPA should be carefully reconsidered in patients with negative CoMiSS scores, particularly in those with suspected non-IgE-mediated allergy, in adherence to the recommendations published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). Greater familiarity and expertise with the CoMiSS as a reference tool could enhance its reliability and utility in clinical practice for assessment of CMPA.

Funding

The research was funded by Laboratorios Ordesa LLC.

Declaration of competing interest

Alicia Santamaria-Orleans is an employee of Laboratorios Ordesa LLC, which contributed to the funding of the study. Notwithstanding, Laboratorios Ordesa LLC played no role in analyzing or interpreting the data. The remaining authors declare no conflicts of interest.

Acknowledgments

We thank all the pediatricians who participated in this study, K Access Health Projects for their support in the statistical analysis of the data, and Marta Pulido, MD, for revising the manuscript and editorial assistance.

References

1. Høst A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol. 2002;89 6 Suppl 1:33–7, http://dx.doi.org/10.1016/s1081-1206(10)62120-5.
2. Díaz Martín JJ, Blesa Baviera L, Campoy Folgoso C, Espín Jaime B, Leis Trabazo MR, Mesa Del Castillo M, et al. Consensus document on the primary prevention of cow's milk protein allergy in infants aged less than 7 days. An Pediatr (Engl Ed). 2022;97:59.e1–7, http://dx.doi.org/10.1016/j.anpede.2022.05.004.
3. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children — EuroPrevall birth cohort. Allergy. 2015;70:963–72, http://dx.doi.org/10.1111/all.12630.
4. Høst A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunol. 2002;13 Suppl 15:23–8, http://dx.doi.org/10.1034/j.1399-3038.13.s.15.7.x.
5. Sanz Ortega J, Martorell Aragonés A, Michavila Gómez A, Nieto García A, Grupo de Trabajo para el Estudio de la Alergia Alimentaria. Incidence of IgE-mediated allergy to cow's milk proteins in the first year of life. [Article in Spanish]. An Esp Pediatr. 2001;54:536–9.
6. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr. 2012;55:221–9, http://dx.doi.org/10.1097/MPG.0b013e31825c9482.
7. Suratannon N, Prapansilp P, Srinarongsook A, Tanpowpong P, Chatchatee P, Pongpirul K. Cost-effectiveness of therapeutic infant formulas for cow's milk protein allergy management. Front Nutr. 2023;10:1099462, http://dx.doi.org/10.3389/fnut.2023.1099462.
8. Vandenplas Y, Dupont C, Eigenmann P, Host A, Kuitunen M, Ribes-Koninckx C, et al. A workshop report on the development of the Cow's Milk-related Symptom Score awareness tool for young children. Acta Paediatr. 2015;104:334–9, http://dx.doi.org/10.1111/apa.12902.
9. Vandenplas Y, Steenhout P, Planoudis Y, Grathwohl D, Althera Study Group. Treating cow's milk protein allergy: a double-blind randomized trial comparing two extensively hydrolysed formulas with probiotics. Acta Paediatr. 2013;102:990–8, http://dx.doi.org/10.1111/apa.12349.
10. Vandenplas Y, Zhao ZY, Mukherjee R, Dupont C, Eigenmann P, Kuitunen M, et al. Assessment of the Cow's Milk-related Symptom Score (CoMiSS) as a diagnostic tool

for cow's milk protein allergy: a prospective, multicentre study in China (MOSAIC study). BMJ Open. 2022;12:e056641, http://dx.doi.org/10.1136/bmjopen-2021-056641.
11. Selbuz SK, Altuntaş C, Kansu A, Kırsaçlıoğlu CT, Kuloğlu Z, İlarslan NEÇ, et al. Assessment of cows milk-related symptom scoring awareness tool in young Turkish children. J Paediatr Child Health. 2020;56:1799–805, http://dx.doi.org/10.1111/jpc.14921.
12. Vandenplas Y, Belohlavkova S, Enninger A, Frühauf P, Makwana N, Järvi A. How Are infants suspected to have cow's milk allergy managed? A real world study report. Nutrients. 2021;13:3027, http://dx.doi.org/10.3390/nu13093027.
13. Kozłowska-Jalowska A, Horvath A, Vandenplas Y, Szajewska H. Retrospective and prospective determination of the Cow's Milk-Related Symptom Score (CoMiSS™) values in symptomatic infants. Pediatr Gastroenterol Hepatol Nutr. 2021;24:384–91, http://dx.doi.org/10.5223/pghn.2021.24.4.384.
14. Lemale J, Decline JL, Dive-Pouletty C, Touboul C, Pichon N, Dupont C. Managing cow's milk protein allergy with an extensively hydrolyzed formula: Results from a prospective, non-interventional study in France (EVA Study). Nutrients. 2022;14:1203, http://dx.doi.org/10.3390/nu14061203.
15. Vandenplas Y, Gerlier L, Caekelbergh K, Nan-Study-Group, Possner M. An observational real-life study with a new infant formula in infants with functional gastro-intestinal disorders. Nutrients. 2021;13:3336, http://dx.doi.org/10.3390/nu13103336.
16. Bajerova K, Hrabcova K, Vandenplas Y. The evolution of Cow's Milk-related Symptom Score (CoMiSS™) in presumed healthy infants. Eur J Pediatr. 2024;183:4329–35, http://dx.doi.org/10.1007/s00431-024-05693-2.
17. Bajerova K, Salvatore S, Dupont C, Eigenmann P, Kuitunen M, Meyer R, et al. The Cow's Milk-Related Symptom Score (CoMiSS™): A useful awareness tool. Nutrients. 2022;14:2059, http://dx.doi.org/10.3390/nu14102059.
18. Thompson G, Zhelev Z, Peters J, Khalid S, Briscoe S, Shaw L, et al. Symptom scores in the diagnosis of pediatric cow's milk protein allergy: A systematic review. Pediatr Allergy Immunol. 2021;32:1497–507, http://dx.doi.org/10.1111/pai.13537.
19. Calvani M, Anania C, Cuomo B, D'Auria E, Decimo F, Indirli GC, et al. Non-IgE- or mixed IgE/non-IgE-mediated gastrointestinal food allergies in the first years of life: Old and new tools for diagnosis. Nutrients. 2021;13:226, http://dx.doi.org/10.3390/nu13010226.
20. Saad K, Elgenidy A, Atef M, Abdelsattar MK, Al-Ashwah M, Hammad EM, et al. Cow's Milk-related Symptom Score for cow's milk allergy assessment: A meta-analysis for test accuracy. Pediatr Res. 2023;93:772–9, http://dx.doi.org/10.1038/s41390-022-02334-y.
21. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920–4, http://dx.doi.org/10.3109/00365529709011203.
22. Mahase E. Guidance on cow's milk allergy may be fuelling overdiagnosis in infants, study finds. BMJ. 2021;375:n3037, http://dx.doi.org/10.1136/bmj.n3037.
23. Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Wegrzyn A, et al. An update to the Milk Allergy in Primary Care guideline. Clin Transl Allergy. 2019;9:40, http://dx.doi.org/10.1186/s13601-019-0281-8.
24. Vincent R, MacNeill SJ, Marrs T, Craven J, Logan K, Flohr C, et al. Frequency of guideline-defined cow's milk allergy symptoms in infants: Secondary analysis of EAT trial data. Clin Exp Allergy. 2022;52:82–93, http://dx.doi.org/10.1111/cea.14060.
25. Martin VM, Marget M, Yuan Q, Shreffler WG. In response to Frequency of guideline-defined cow's milk allergy symptoms in infants: Secondary analysis of EAT trial data by Vincent et al. Clin Exp Allergy. 2022;52:581–2, http://dx.doi.org/10.1111/cea.14090.
26. Vandenplas Y, Bajerova K, Dupont C, Eigenmann P, Kuitunen M, Meyer R, et al. The Cow's Milk Related Symptom Score: The 2022 update. Nutrients. 2022;14:2682, http://dx.doi.org/10.3390/nu14132682.
27. El-Shafie AM, Omar ZA, El Zefzaf HMS, Basma EM, Al Sabbagh NM, Bahbah WA. Evaluation of Cow's Milk Related Symptom Score [CoMiSS] accuracy in cow's milk allergy diagnosis. Pediatr Res. 2023;94:987–95, http://dx.doi.org/10.1038/s41390-023-02539-9.
28. Espín Jaime B, Díaz Martín JJ, Blesa Baviera LC, Claver Monzón Á, Hernández Hernández A, García Burriel JI, et al. Non-IgE-mediated cow's milk allergy: Consensus document of the Spanish Society of Paediatric Gastroenterology, Hepatology, and Nutrition (SEGHNP), the Spanish Association of Paediatric Primary Care (AEPAP), the Spanish Society of Extra-hospital Paediatrics and Primary Health Care (SEPEAP), and the Spanish Society of Paediatric ClinicaL Immunology, Allergy, and Asthma (SEICAP)]. An Pediatr (Engl Ed). 2019;90:193.e1–11, http://dx.doi.org/10.1016/j.anpedi.2018.11.007.