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Diagnostic Performance of the Cow's Milk-Related Symptom Score (CoMiSS) in Infants with Suspected Non-IgE-Mediated Cow's Milk Protein Allergy

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ABSTRACT

Objective: Non-IgE-mediated cow's milk protein allergy (CMPA) is difficult to diagnose in infancy because its manifestations are often nonspecific and overlap with common functional gastrointestinal disorders. The Cow's Milk-related Symptom Score (CoMiSS) was developed as an awareness tool to support recognition of symptoms potentially related to CMPA. This study aimed to evaluate the diagnostic performance of CoMiSS in infants with suspected non-IgE-mediated CMPA.

Materials and Methods: This prospective study included 51 infants aged ≤18 months with suspected non-IgE-mediated CMPA who were evaluated in a tertiary pediatric allergy clinic between November 2023 and February 2024. CoMiSS was calculated at presentation. All infants underwent a 4-week cow's milk elimination diet followed by oral food challenge (OFC) as the reference diagnostic method. In the primary analysis, a CoMiSS score of ≥12 was considered positive in accordance with previous literature. ROC analysis was also performed to assess diagnostic performance and determine the optimal cut-off value.

Results: After elimination diet and OFC, CMPA was confirmed in 37 of 51 infants (72.5%). The CoMiSS score was positive in 28 of 37 infants with CMPA and negative in 12 of 14 infants without CMPA, demonstrating a sensitivity of 75.7%, specificity of 85.7%, positive predictive value (PPV) of 93.3, and negative predictive value (NPV) of 57.1. ROC analysis demonstrated good discriminative ability, with an area under the curve (AUC) of 0.876 (95% CI: 0.767-0.986; p<0.001). The optimal cut-off value determined by the Youden index was 10.5 (practical cut-off ≥11), yielding a sensitivity of 83.8% and specificity of 85.7%. The PPV and NPV at this threshold were 93.9% and 66.7%, respectively.

Conclusion: CoMiSS showed good diagnostic performance in infants with suspected non-IgE-mediated CMPA. While the predefined cut-off of ≥12 remained clinically useful, ROC analysis suggested that a threshold of ≥11 may improve sensitivity while maintaining high specificity. CoMiSS may serve as a practical supportive tool for clinical suspicion, but it should not replace an elimination diet and oral food challenge for definitive diagnosis.

Keywords: Cow's milk protein allergy, CoMiSS, non-IgE-mediated allergy, infants, oral food challenge

INTRODUCTION

Non-IgE-mediated cow's milk protein allergy (CMPA) is an immune-mediated reaction to cow's milk proteins that commonly presents during infancy with predominantly gastrointestinal manifestations (1). Symptoms such as colic, regurgitation, vomiting, diarrhea, constipation, and excessive crying are frequently reported. However, these symptoms are also highly prevalent among otherwise healthy infants and overlap with common functional gastrointestinal disorders, making the diagnosis of non-IgE-mediated CMPA particularly challenging in early life (1,2).

Unlike IgE-mediated food allergy, there is no reliable laboratory marker for the diagnosis of non-IgE-mediated

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CMPA. The current diagnostic approach relies on clinical improvement after elimination of cow's milk protein from the diet followed by recurrence of symptoms during reintroduction through an oral food challenge (OFC) (2). Although this elimination-challenge procedure is considered the diagnostic standard, its interpretation may be difficult in routine clinical practice. Moreover, the process may require several weeks to complete, and some caregivers may be reluctant to proceed with OFC because of concerns about potential adverse reactions (2,3).

Accurate diagnosis of CMPA is essential to ensure appropriate management, relieve symptoms, prevent unnecessary dietary restrictions, and avoid potential nutritional deficiencies or impaired growth (1,2). Both overdiagnosis and underdiagnosis of CMPA may have important consequences. Misdiagnosis may lead to unnecessary elimination diets that negatively affect nutritional status and feeding behavior, whereas delayed diagnosis may prolong symptoms and reduce quality of life for affected infants and their families (4-6).

To facilitate earlier recognition of symptoms potentially associated with cow's milk intake, the Cow's Milk-related Symptom Score (CoMiSS) was developed in 2014 as a simple awareness tool (7). CoMiSS quantifies five clinical domains frequently associated with CMPA, including crying, regurgitation, stool patterns, skin manifestations, and respiratory symptoms. The score was designed to increase clinical awareness of possible CMPA rather than to serve as a definitive diagnostic test. Since its introduction, several studies have evaluated the clinical utility of CoMiSS in infants with suspected CMPA and have reported variable diagnostic performance (7-9).

Different cut-off values have been proposed for identifying infants at risk of CMPA, and the optimal threshold remains a topic of ongoing investigation. Although a score of ≥12 has been widely used in previous studies, its diagnostic accuracy may vary across different clinical settings and populations (7-10). Therefore, further studies are needed to evaluate the diagnostic performance of CoMiSS and to explore its potential role in supporting clinical suspicion of CMPA.

The aim of the present study was to prospectively evaluate the diagnostic performance of CoMiSS in infants aged 0-18 months with suspected non-IgE-mediated CMPA and to assess its ability to predict the final diagnosis confirmed by elimination diet and OFC.

MATERIALS and METHODS

Study Population

Between November 2023 and February 2024, 51 patients with suspected non-IgE-mediated CMPA who were followed in the Pediatric Allergy and Immunology Outpatient Clinic of a tertiary university hospital were included in the study. Inclusion criteria were as follows: age ≤18 months, birth weight between 2800 and 4000 g, and term birth (gestational age 37-42 weeks). Exclusion criteria included prenatal or perinatal problems (e.g., intrauterine infections or inborn errors of metabolism), congenital syndromes (e.g., Down or Silver-Russell syndromes), malabsorption disorders (e.g., celiac disease), chronic medical conditions (e.g., congenital heart disease, genetic disorders, or immunodeficiency), and evidence of IgE-mediated food allergy or positive allergy test results at the time of presentation.

CoMiSS Assessment

CoMiSS was calculated for all infants at presentation using the original scoring system (3). The assessment encompasses several parameters, including the duration of daily crying, the frequency and intensity of regurgitation episodes, the consistency of stools, the presence and severity of atopic eczema or urticaria, and the presence and severity of respiratory symptoms. The total CoMiSS score ranges from 0 to 33 points.

The severity of symptoms is measured on a scale ranging from 0 to 6, with a 1-point increase indicating an increase in symptom severity. The evaluated symptom domains include crying, regurgitation, and skin manifestations, each with a maximum score of 6 points. Respiratory symptoms are evaluated on a scale from 0 to 3, where 0 indicates the absence of symptoms, 1 indicates mild symptoms, 2 indicates moderate symptoms, and 3 indicates severe symptoms.

Stool consistency was assessed using the Bristol Stool Scale. A score of 0 was assigned to normal stools (types 3 and 4), 2 to soft stools (type 5), 4 to hard stools (types 1 and 2), and 6 to liquid stools (types 6 and 7) (3).

Following the initial assessment, CoMiSS was calculated at presentation. Subsequently, all infants underwent a 4-week cow's milk elimination diet followed by an OFC. A CoMiSS score of ≥12 was considered indicative of a positive result, in accordance with previous studies suggesting

improved specificity at this threshold (3). The association between the CoMiSS score and the final diagnosis of CMPA was evaluated.

For each patient, the following variables were recorded: age, sex, duration of symptoms, mode of delivery, feeding pattern, family history of atopy, family history of food allergy, and CoMiSS score.

Statistical Analysis

Statistical analyses were performed using the SPSS software (version 29.0; IBM Corp., Armonk, NY, USA). Non-normally distributed continuous variables were expressed as medians and interquartile ranges (IQR).

Comparisons between infants with and without confirmed CMPA were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of CoMiSS and to determine the optimal cut-off value using the Youden index. The area under the ROC curve (AUC), along with sensitivity, specificity, positive predictive value, and negative predictive value, was calculated. A p-value <0.05 was considered statistically significant.

This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine at the University (2024/166).

RESULTS

The study included 51 infants evaluated for suspected non-IgE-mediated CMPA. The median age of the patients was 6 months (IQR: 4-8 months). Of these infants, 27 (52.9%) were male and 24 (47.1%) were female. A family history of allergic disease was present in 20 patients (39.2%). Regarding the mode of delivery, 11 infants (21.6%) were born via spontaneous vaginal delivery and 40 (78.4%) via cesarean section.

Gastrointestinal symptoms were present in 45 infants (88.2%), skin symptoms in 18 (35.3%), and respiratory symptoms in 9 (17.6%). The median total CoMiSS score in the overall study population was 12 (IQR: 10-15). The baseline characteristics of the study population according to the final CMPA diagnosis are presented in Table I.

Following a 4-week cow's milk elimination diet and subsequent OFC, CMPA was confirmed in 37 of the 51 infants (72.5%) (Table II).

Using the predefined CoMiSS cut-off value of ≥12, a positive score was observed in 30 of the 51 infants (58.8%) in the overall cohort. Among infants with confirmed CMPA (n=37), 28 (75.7%) had CoMiSS scores ≥12. Among infants without CMPA (n=14), 2 (14.3%) had CoMiSS scores ≥12, indicating false-positive cases. Conversely, among infants with CMPA (n=37), 9 (24.3%) had CoMiSS scores <12 and were classified as false-negative cases (Table II).

The median total CoMiSS score was significantly higher in infants with confirmed CMPA compared with those without CMPA [13 (IQR: 12-15) vs 9.5 (IQR: 4-10); p < 0.001] (Figure 1).

ROC analysis demonstrated good discriminative ability of the CoMiSS score for predicting CMPA, with an area under the curve (AUC) of 0.876 (95% CI: 0.767-0.986;

Table I: Baseline characteristics of the study population according to CMPA diagnosis

Variable	Total (n=51)	CMPA (+) (n=37)	CMPA (–) (n=14)	p-value
Age (months), median (IQR)	6 (4-8)	6 (4-8)	6 (4-11)	0.610
Gender, male/female, n (%)	27/24 (52.9/47.1)	19/18 (51.4/48.6)	8/6 (57.1/42.9)	0.710
Family history of atopy, n (%)	20 (39.2)	15 (40.5)	5 (35.7)	0.740
Cesarean delivery, n (%)	40 (78.4)	30 (81.1)	10 (71.4)	0.470
Gastrointestinal symptoms, n (%)	45 (88.2)	34 (91.9)	11 (78.6)	0.180
Skin symptoms, n (%)	18 (35.3)	14 (37.8)	4 (28.6)	0.530
Respiratory symptoms, n (%)	9 (17.6)	7 (18.9)	2 (14.3)	0.690
Total CoMiSS score, median (IQR)	12 (10-15)	13 (12-15)	9.5 (4-10)	**<0.001**

Continuous variables are presented as median (interquartile range, IQR), and categorical variables as number (percentage). Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. **CMPA:** cow's milk protein allergy, **CoMiSS:** Cow's Milk-related Symptom Score.

p < 0.001). The optimal cut-off value determined by the Youden index was 10.5, corresponding to a practical cut-off of ≥11 points (Table III).

At this threshold, CoMiSS showed a sensitivity of 83.8% and a specificity of 85.7%, with a PPV of 93.9% and an NPV of 66.7% (Table III). The ROC curve illustrating the diagnostic performance of CoMiSS for predicting CMPA is presented in Figure 2.

DISCUSSION

This study evaluated the diagnostic performance of CoMiSS in infants with suspected non-IgE-mediated CMPA using OFC as the reference standard. The findings demonstrated that CoMiSS had good discriminative ability, with an AUC of 0.876. Using the predefined cut-off value of ≥12 points, CoMiSS showed high specificity and positive predictive value, indicating that a positive score strongly supports the likelihood of CMPA, whereas its moderate sensitivity suggests that lower scores do not reliably exclude the diagnosis. These results provide impor-

Table II: Diagnostic performance of CoMiSS (cut-off ≥12) according to CMPA status.

CMPA status	CoMiSS <12 (−)	CoMiSS ≥12 (+)	Total
CMPA (−)	12 (85.7%)	2 (14.3%)	14
CMPA (+)	9 (24.3%)	28 (75.7%)	37
Total	21 (41.2%)	30 (58.8%)	51

A CoMiSS score of ≥12 was considered positive.

CMPA: Cow's milk protein allergy, **CoMiSS:** Cow's Milk-related Symptom Score.

Table III: Diagnostic performance of CoMiSS based on ROC analysis (cut-off ≥11).

Parameter	Value
Area under the curve (AUC)	0.876 (95% CI: 0.767-0.986)
Optimal cut-off value	≥11 (Youden index = 10.5)
Sensitivity	83.8%
Specificity	85.7%
Positive predictive value (PPV)	93.9%
Negative predictive value (NPV)	66.7%

ROC analysis showed that the CoMiSS score had good discriminative ability for CMPA, with an area under the curve (AUC) of 0.876 (95% CI: 0.767-0.986; p < 0.001). The optimal cut-off value determined by the maximum Youden index was 10.5, corresponding to a practical cut-off of ≥11. At this threshold, sensitivity was 83.8%, and specificity was 85.7%. The positive predictive value was 93.9%, while the negative predictive value was 66.7%.

CMPA: Cow's milk protein allergy, **CoMiSS:** Cow's Milk-related Symptom Score.

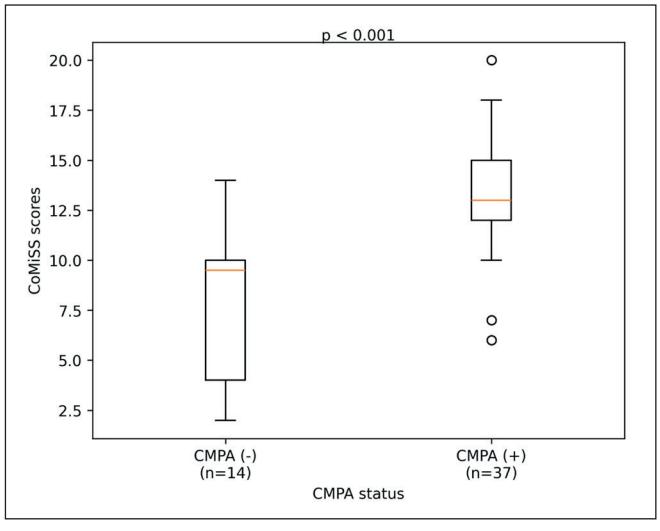

Figure 1: Distribution of CoMiSS scores according to CMPA status.
Boxplot showing the distribution of CoMiSS scores in infants with and without CMPA. The median CoMiSS score was significantly higher in the CMPA group (p < 0.001).
CMPA: *Cow's milk protein allergy;* ***CoMiSS:*** *Cow's Milk-related Symptom Score.*

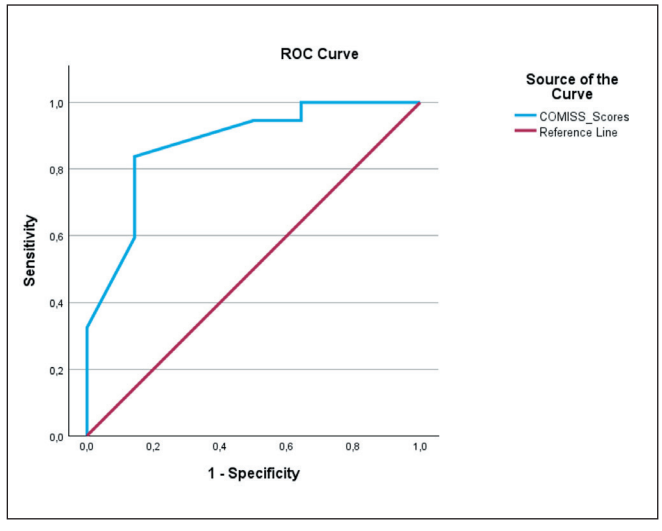

Figure 2: ROC curve of CoMiSS for predicting CMPA.
The area under the curve (AUC) was 0.876 (95% CI: 0.767-0.986, p<0.001). The optimal cut-off value was ≥11, yielding a sensitivity of 83.8% and specificity of 85.7%. The diagonal line represents the reference line.
CMPA: *Cow's milk protein allergy;* ***CoMiSS:*** *Cow's Milk-related Symptom Score.*

tant insight into how CoMiSS performs in real-life clinical settings when directly compared with OFC-confirmed outcomes.

There is currently no clear consensus in the literature regarding the predictive value and diagnostic accuracy of CoMiSS. The most frequently used cut-off for a positive CoMiSS result is ≥12 (3,11,12). In our study, among infants with confirmed CMPA (n=37), 28 (75.7%) had a positive CoMiSS score using this predefined threshold. Previous studies have suggested that lower cut-off values, such as ≥9 or ≥10, may improve sensitivity and facilitate earlier identification of symptomatic infants, although this may come at the expense of reduced specificity (7-10). In line with these findings, our results suggest that different thresholds may be appropriate depending on the clinical context.

ROC analysis in our study indicated that the optimal cut-off value based on the Youden index was 10.5, corresponding to ≥11 in clinical practice. When comparing the predefined cut-off value of ≥12 with the ROC-derived threshold of ≥11, the lower cut-off demonstrated improved sensitivity while maintaining comparable specificity. This suggests that a slightly lower threshold may enhance the screening performance of CoMiSS without substantially increasing false-positive rates. However, the higher specificity observed at the ≥12 threshold supports its continued use in clinical settings where diagnostic certainty is prioritized.

Similar findings have been reported in a recent meta-analysis including 1,238 children, which demonstrated a pooled sensitivity of 64% and specificity of 75% for CoMiSS at a cut-off value of 12, supporting the notion that CoMiSS functions primarily as an awareness and screening tool rather than a standalone diagnostic test (13).

A recent prospective study similarly identified a CoMiSS cut-off value of ≥12 with moderate sensitivity and specificity, and additionally suggested that clinical features such as mucoid or bloody stool, abdominal distention, and faltering growth may enhance diagnostic accuracy when considered alongside the score (14).

Although CoMiSS demonstrated good overall discriminative ability, a number of misclassified cases were observed. Among infants without CMPA (n=14), 2 (14.3%) had CoMiSS scores ≥12, representing false-positive cases. These patients predominantly exhibited prolonged crying and gastrointestinal symptoms such as regurgitation and altered stool consistency, which may also be observed in functional gastrointestinal disorders, infant colic, or transient feeding intolerance unrelated to CMPA.

Conversely, among infants with confirmed non-IgE-mediated CMPA (n=37), 9 (24.3%) had CoMiSS scores <12 and were classified as false-negative cases. These patients mainly presented with milder, intermittent, or less typical symptoms, particularly limited skin findings or subtle gastrointestinal complaints without significant crying time.

Consistent with the multicenter MOSAIC study, these findings highlight that while CoMiSS is a useful awareness tool, it may misclassify patients when symptoms are either non-specific but severe, or mild but clinically significant. Therefore, CoMiSS should not replace clinical judgment or OFC, but rather be used as a supportive screening instrument (15).

This study has several limitations that should be acknowledged. First, the study was conducted in a single tertiary allergy center, which may limit the generalizability of the findings to other clinical settings. Second, the relatively small sample size (n=51) may have influenced the statistical power of the analyses and the stability of the diagnostic accuracy estimates. Therefore, larger multicenter studies are warranted to validate these findings and to further clarify the role of CoMiSS in routine clinical practice.

CONCLUSION

CoMiSS appears to be a practical and useful awareness tool for assessing symptoms associated with non-IgE-mediated CMPA in infants. The present study highlights its potential role in supporting clinical suspicion and decision-making during diagnosis and follow-up. However, CoMiSS should not replace an elimination diet and OFC, and larger multicenter studies are warranted to validate these findings and to further define its role in routine clinical practice.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Author Contributions

Concept: **GK, DFKU,** Design: **GK, DFKU,** Data collection or processing: **GK, MAK,** Analysis or Interpretation: **DFKU,** Literature search: **GK, DFKU,** Writing: **DFKU, AB,** Approval: **DFKU, AB.**

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