Validity of Cow's Milk-related Symptom Score among Children suspected to have Cow's Milk protein Allergy

By

Eman Mohammed Fahmy, Mohamed Abd El Aal Mohamed Bakhit, Hend Abd El Raheem Saber Mohammed

Pediatrics Department, Faculty of Medicine, Sohag University, Sohag, Egypt

Correspondance :

Dr. Eman Mohammed Fahmy, Pediatrics Department, Faculty of Medicine, Sohag University, Naser City, 82524, Sohag, Egypt

Tel: +2 01017590751

Email: ahmodiemad@yahoo.com

Abstract

Background: Cow's milk allergy is a predictable immune response to certain proteins found in cow's milk. This reaction consistently causes a range of symptoms, such as gastrointestinal, respiratory, and skin issues, after consuming the problematic food. This condition affects approximately 2-5% of infants.

Objectives: The aim of the current study was to evaluate the validity of CoMiSS in children suspected to have Cow's Milk Protein Allergy (CMPA).

Methods: A prospective observational study was conducted among 100 targeted patients presenting with one or more of the following CMPA symptoms: cutaneous (atopic dermatitis and urticaria), respiratory (cough and dyspnea, rhinitis), and gastrointestinal (digestive regurgitation, vomiting, rectal bleeding, constipation and diarrhea) at Pediatrics department, Sohag university hospitals, Egypt from 1st of December 2022 to 31st August, 2023 ,CoMiSS, 2016 and elimination diet and food challenge test were applied to all cases.

Results: comparison between Confirmed CMA (positive challenge test) and non-CMA (negative challenge test) regarding CoMiSS at first visit. There was statistically significant difference between confirmed CMA and non-CMA according to cut off point of CoMiSS either < 12 or ≥ 12 (P-value < 0.001). 9 cases had CoMiSS < 12 and confirmed CMA by food challenge elimination test. On the other hand, 2 of cases had CoMiSS ≥ 12 and confirmed No CMA by food challenge test. 64 cases had CoMiSS ≥ 12 and confirmed CMA by diet elimination and food challenge test and assessment of ROC curve showed that the accuracy of CoMiSS in diagnosis of CMA, it was 89 %. The percentage of Sensitivity was (87.7 %), Specificity (92.6 %), Positive predictive value % (96.9 %) when the score is ≥ 12, Negative predictive value % (73.5 %).

Conclusion: The accuracy of CoMiSS in diagnosis of CMA was 89 % with sensitivity (87.7 %), specificity (92.6 %), positive predictive value % (96.9 %) when the score is ≥ 12 & negative predictive value % (73.5 %) so, CoMiSS is an easy-to-use and practical awareness tool for evaluating CM-related symptoms but cannot be considered a stand alone diagnostic tool for CMA.

Keywords: Cow's milk allergy, Cow milk related symptoms score (CoMiSS), Cow's milk protein allergy.

Introduction

Cow's milk protein allergy (CMPA) is an immune response to the protein found in cow's milk. It is categorized into IgE-mediated, non-IgE-mediated, and mixed kinds based on the specific immunological mechanisms involved (Cronin et al., 2023)
It is the predominant food allergy in children under the age of 3, and its occurrence is increasing in both developed and developing nations, with an estimated prevalence ranging from 2% to 5% (Elghoudi and Narchi, 2022). In 2015, the EuroPrevall birth cohort study of 12,000 infants found an overall prevalence of CMA in Europe of 0.54% (Schoemaker et al., 2015). CMPA is an immunological response to certain proteins found in cow's milk. It affects around 2-5% of infants and can manifest as cutaneous, gastrointestinal, and/or respiratory symptoms (Al-Beltagi et al., 2022). Non-IgE-mediated CMPA leads to gastrointestinal symptoms through inflammation and impaired movement, including persistent diarrhea, presence of mucus and blood in the stool, poor weight gain, regurgitation, feeding refusal, colic, vomiting, and constipation. The diagnosis of CMPA is often difficult due to the presence of non-specific symptoms such as regurgitation, bowel habit issues, and colic, which are also commonly seen in functional gastrointestinal diseases in newborns. This similarity in symptoms poses a clinical challenge in accurately diagnosing CMPA (Al-Beltagi et al., 2022).

Non-IgE-mediated CMPA lacks a definitive diagnostic test, hence the diagnosis relies on observing the patient's recovery following the removal of cow's milk from their diet, and the subsequent recurrence of symptoms with reintroduction of cow's milk. Pediatricians and family physicians may face challenges in distinguishing between CMPA and functional gastrointestinal diseases in newborns who exhibit similar symptoms (Dupont, 2014). The Cow's Milk-associated Symptom Score (CoMiSS) takes into account overall symptoms as well as symptoms connected to the skin, digestive system, and respiratory system. It was created as a means to raise awareness about symptoms associated to cow's milk. CoMiSS is a clinical scoring system designed to assist primary health-care providers in identifying newborns who may have CMPA. Therefore, it can be regarded as a diagnostic tool (Dupont, 2014). Infants with a symptom-based score (SBS) of ≥12 have been suggested to be at risk of CMPA (Selbuz et al., 2020). The current study aimed to evaluate the validity of CoMiSS in children suspected to have CMPA.

Methods

This cross-sectional study that was conducted at Pediatrics department, Sohag university hospitals, Egypt from 1st of December 2022 to 31st August, 2023 among children presenting with one or more of suspected CMPA symptoms

Ethical considerations

- An approval was obtained from the ethics research committee of Sohag Faculty of Medicine (Soh-Med-23-01-01).
- Permissions were obtained from the university hospitals' president.
- An informed written consent after explaining the aim of the study was obtained from parents or care givers of children preservation their privacy as the questions were anonymous
- . All data and results are kept confidential.
- Caregivers of the participants have the right to refuse or withdraw from the study at any time.
- The authors declare that they have no conflict of interests regarding the study or the publication.
- The study and the publication are self-funded.

The sample size was calculated according to the following equation:

$N=z^2 p (1- p) / d^2$ (Pourhoseingholi et al., 2013)

as N= the desired sample size, Z= the statistic corresponding to level of confidence (1.96), P= Expected prevalence or proportion (0.034) (Maksoud et al., 2019).

We increased the enrolled cases to overcome non-response and loss of interest to follow up

So, the study included 100 children after fulfilling the eligibility criteria during the period of the study

,

inclusion criteria:

children from birth up to five years, both males and females were included and all children who suspected to have CMPA who have the following symptoms (Chronic unexplained failure to thrive, regurgitation, chronic abdominal distension, skin manifestation such as urticarial and eczema, respiratory symptoms such as chronic cough, recurrent wheezy chest and chronic rhinorrhea and other GIT manifestations such as vomiting, recurrent diarrhea, excessive colic, abdominal pain, malabsorption, constipation, esophageal reflux and steatorrhea)

exclusion criteria:

Functional GIT disorders such irritable bowel syndrome, GERD according to Rome IV criteria in children, organic gastrointestinal diseases like coeliac disease, cystic fibrosis and chronic gastrointestinal infections as parasitic infections.

Study procedure:

Data was collected from children through personal interviews with their parents or care givers and included five sections.:

Section I included
demographic (age, gender, residence, family history of allergic disease and type of feeding).

Section II included
General and systemic examination of the studied cases .

.
Section III included
assessment of Cow's Milk-related Symptom Score (CoMiSS) 2016, it rates five symptoms: Crying, regurgitation, stool pattern, skin, and respiratory symptoms with a total score ranging from 0 to 33 points and an arbitrary cut-off value ≥ 12 to pick up children at risk of CMA. The score was applied at first visit and after assessment of elimination diet and food challenge test at second visit.
Some items like crying, regurgitation and skin manifestation were scored on a scale of 0 to 6, according to the severity with each increase of 1 point meaning more severe symptoms up to 6 points for the worst symptom. Crying (from less than an hour to over five hours daily), regurgitation (0 to 2 episodes, 3-5 episodes, >5 episodes with >1 coffee spoon, and >5 episodes with ± half of the meal), and skin manifestations (nonexistent, mild, moderate, or severe). Stool consistency is graded on the Bristol stool scale (BSS) as 0 for regular 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). The respiratory symptoms were scored on a scale of 0 to 3, with 0 indicating no symptoms, 1 indicating mild, 2 indicating moderate, and 3 indicating severe symptoms (Vandenplas et al., 2022).

Section IV jncluded
laboratory investigations e.g. CBC, occult blood in stool, specific IgE level for cow milk protein allergy

Section V included
Elimination diet and food challenge test that was applied on all children suspected to have cow milk protein allergy, and comprised the oral administration of the suspected allergen in a controlled and standardized setting.
Interpretation of test as following:
•Positive: when clear objective signs of allergic reaction appear or multiple subjective symptoms in several organ systems occur.
•Negative results indicate no symptoms (Cronin et al., 2023)

Statistical analysis

Statistical package of social science (SPSS) version 25.0 was used for data entry and analysis. **Quantitative variables** were expressed as means and standard deviation for normally distributed data and as median and range (minimum – maximum) for not normally distributed data. The normality of data distribution was tested using Kolmogrov-Sminrov test. **Qualitative variables** were described as frequencies (percentages). Receiver operator characteristic curve (ROC curve) was evaluated and sensitivity, specificity, PPV, NPV and accuracy was calculated.

Results

The study was conducted among 100 cases suspected clinically to have Cow Milk Protein Allergy (CMPA). Cow's Milk-related Symptom Score (CoMiSS) was applied on all cases with ≥ 12 cutoff point and revealed that 66 cases obtained CoMiSS ≥ 12 and 34 cases < 12. For confirmation of diagnosis food challenge test was done to all cases and revealed that 73 cases (73%) show positive result and 27 cases (27%) were negative

Table (1): Comparison between confirmed CMPA (Positive challenge test) and non-confirmed CMPA (Negative challenge test) regarding socio-demographic characteristics.

Variable			Confirmed CMPA (n = 73)	Non confirmed CMPA (n = 27)	P-value
Age (Months)		**Mean ± S. D**	6.9 ± 3.3	9.3 ± 5.2	0.08
		Median	6	6	
		Range (Min-Max)	(2-20)	(3 – 20)	
Gender	**Male**	**No.**	32	15	0.2
		%	43.8	55.6	
	Female	**No.**	41	12	
		%	56.2	44.4	
Residence	**Urban**	**No.**	10	15	<0.001
		%	40	60	
	Semi urban	**No.**	44	8	
		%	84.6	15.4	
	Rural	**No.**	19	4	
		%	82.6	17.4	
Family history of	**+ ve**	**No.**	53	4	<0.001
		%	93	7	

allergic disease	**- ve**	**No.**	20	23	
		%	46.5	53.5	
Type of feeding	**Breast fed**	**No.**	10	3	0.13
		%	76.9	23.1	
	Formula	**No.**	40	9	
		%	81.6	18.4	
	Mixed	**No.**	16	12	
		%	57.1	42.9	
	Fresh cow milk	**No.**	7	3	
		%	70	30	

Table (1) shows that the mean age of the studied cases was (7.61 ± 4) months with a range of (2-20) months. More than half of the studied cases (53%) were females and (47%) were males. Also, there was statistically insignificant difference between positive food challenge test cases and negative food challenge test cases as regards age, gender and type of feeding. Furthermore, there is statistically significant relation between confirmed CMPA and non-confirmed CMPA according to residence and family history of CMPA. 40% of urban cases showed positive food challenge test positive in comparison to 84.6% and 82.6% of semi-urban and rural cases. As regards family history, 93% of cases with +ve family history showed positive food challenge test in comparison to 46.5% of cases with –ve family history.

Table (2) Comparison between confirmed CMPA (Positive challenge test) and non-confirmed CMPA (Negative challenge test) according to complete blood picture (CBC)

Variable		**Confirmed CMPA (n = 73)**	**Non confirmed CMPA (n = 27)**	**P-value**
HB (gm/dl)	**Mean ± S. D**	9.5 ± 0.98	8.9 ± 0.85	0.01
	Median	9.5	9	
	Range (Min-Max)	(7.5 – 11.5)	(7.5- 10.5)	
MCV (%)	**Mean ± S. D**	72.9 ± 5.7	70 ± 4.2	0.01
	Median	72	70	
	Range (Min-Max)	(62-90)	(62-76)	
HCT (Fl)	**Mean ± S. D**	29.8 ± 2.16	29.5 ± 2	0.54
	Median	30	29	
	Range (Min-Max)	(25-34)	(26-33)	
Eosinophilic count	**Mean ± S. D**	422.6 ± 90.6	180.3 ± 113.3	< 0.001
	Median	420	150	
	Range (Min-Max)	(120-620)	(40-500)	

Table (2) illustrates that there was statistically significant difference between positive food challenge test cases and negative challenge test cases according the hemoglobin level, mean

corpuscular volume and eosinophilic count. Regarding to hemoglobin level, the mean of hemoglobin level was higher among positive challenge test cases than negative challenge test cases (9.5 ± 0.98 and 8.9 ± 0.85) gm/dl. Moreover, the mean of mean corpuscular volume was higher among positive food challenge test cases than negative food challenge test cases (72.9 ± 5.7 and 70 ± 4.2). As regards eosinophilic count, the mean of eosinophilic count was higher among positive food challenge cases than negative food challenge test cases (422.6 ± 90.6 and 180.3 ± 113.3). However, there was statistically insignificant difference between positive and negative food challenge test cases according to hematocrit test.

Table (3): **Comparison between confirmed CMPA (Positive challenge test) and non-confirmed CMPA (Negative challenge test) regarding presence of occult blood in stool abd IgE level.**

Variable	Confirmed CMPA (n = 73)		Non confirmed CMPA (n = 27)		P-value
	No.	%	No.	%	
Occult blood in stool					
+ve occult blood	26	35.6	4	14.8	0.04
-ve occult blood	47	64.4	23	85.2	
IgE level					
Mean ± S. D	1.4 ± 1.3		0.36 ± 0.3		< 0.001
Median	1.1		0.2		
Range (Min-Max)	(0.1 – 6)		(0.1 – 2.1)		
Interpretation of IgE level					
Normal	27	37	26	96.3	<0.001
High	46	63	1	3.7	

Table (3) describes that there was statistically significant difference between positive food challenge test and negative challenge test cases according to presence of occult blood in stool. 35.6% of positive challenge test positive cases had +ve occult blood in stool in comparison to only 14.8% of negative challenge test cases that showed positive occult blood in stool. On the other hand, 85.2% of negative challenge test cases had - ve occult blood in stool in comparison to 64.4% of positive challenge test cases. Also, regarding specific IgE level for cow milk protein allergy, it was found that there was highly statistically significant difference between positive challenge test cases and negative challenge test cases according to level of IgE for milk protein allergy. The mean of level of IgE for milk protein allergy was higher among positive challenge test cases than that among negative challenge cases (1.4 ± 1.3 and 0.36 ± 0.3). Interpretation of level of specific IgE for milk protein allergy indicated that 63 % of positive challenge test cases had high level of IgE for protein milk allergy in comparison to only 3.7 % of negative food challenge test. On the other hand, most of negative challenge test cases (96.3%) had normal level of IgE in comparison to 37% of positive food challenge test cases.

Table (4): Comparison between confirmed CMPA and non-confirmed CMPA according to Cow's Milk-related Symptom Score (CoMiSS)

Variable		Confirmed CMPA (n = 73)	Non confirmed CMPA (n = 27)	P-value
CoMiSS at first visit	**Mean ± S. D**	15.04 ± 2.9	9.9 ± 1.7	< 0.001
	Median	15	10	
	Range (Min-Max)	(9 - 22)	(6 – 14)	
CoMiSS at second visit	**Mean ± S. D**	6.4 ± 1.8	11± 2.3	< 0.001
	Median	6	11	
	Range (Min-Max)	(4 – 11)	(7 – 15)	

Table (4) describes that there was highly statistically significant difference between positive food challenge test cases and negative challenge test cases according to either CoMiSS at first visit or CoMiSS at second visit. As regards CoMiSS at first visit, the mean of the score at first visit was higher among positive food challenge test cases than negative food challenge test cases (15.04 ± 2.9 and 9.9 ± 1.7) respectively. On the other hand, the mean of CoMiSS at second visit (2:4 week after first visit) was lower among positive food challenge test cases than negative food challenge test cases (6.4 ± 1.8 and 11± 2.3) respectively.

Table (5): Comparison between Confirmed CMA (positive challenge test) and No CMA (negative challenge test) regarding CoMiSS at first visit

Variable	CoMiSS (≥ 12) No. (%)	CoMiSS (< 12) No. (%)	Total	P-value
Food challenge test (+ve)	64 (64%)	9 (9%)	73 (73%)	< 0.001
Food challenge test (-ve)	2 (2%)	25 (25%)	27 (27%)	
Total	66 (66%)	34 (34%)	100 (100%)	

Table (5) that there was statistically significant difference between confirmed CMA and No CMA according to cut off point of CoMiSS either < 12 or ≥ 12 (P-value < 0.001). 9 cases had CoMiSS <

12 and confirmed CMA by food challenge test. On the other hand, 2 of cases had CoMiSS ≥ 12 and confirmed No CMA by food challenge test. 64 cases had CoMiSS ≥ 12 and confirmed CMA by food challenge test.

Table (6) Accuracy of CoMiSS in diagnosis of CMA

Total CoMiSS	Sensitivity%	Specificity%	Positive predictive value %	Negative predictive value %	Accuracy%
cut off value 12	87.7 %	92.6 %	96.9 %	73.5 %	89 %

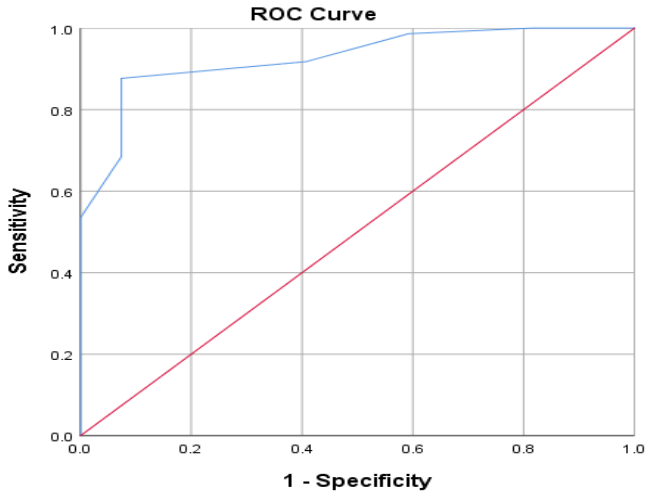

Figure (1): ROC curve for CoMiSS in diagnosis of CMPA

Table (6) shows the accuracy of CoMiSS in diagnosis of CMA, it was 89 %. The percentage of Sensitivity was (87.7 %), Specificity (92.6 %), Positive predictive value % (96.9 %) when the score is ≥ 12, Negative predictive value % (73.5 %), as shown in figure (1).

Discussion

When the immune system reacts abnormally to proteins found in cow milk or cow products, it is known as cow's milk allergy (CMA). According to EuroPrevall, the incidence of CMA is as low as 0.54%,

although the declared prevalence is less than 5.0%. IgE-mediated, non-IgE-mediated, and mixed CMA responses are based on immunology (El-Shafie et al., 2023). According to Samir et al. who indicated milk allergy was 38.4% among children aged from 1.5 years to 5 years comparing to other allergies (Samir et al., 2020).

The majority of responses that are not IgE-mediated impact the gastrointestinal system, while the skin is the most common site for IgE-mediated responses. Anaphylaxis and cardiovascular collapse may occur in infants with IgE-mediated food hypersensitivity, which manifests as atopic dermatitis, urticaria, diarrhea, vomiting, difficulty breathing, swelling of the larynx, and/or low blood pressure. Diarrhea, vomiting, and, in extended cases, stunted development and blood in the stool are symptoms that are not mediated by IgE. Babies with functional gastrointestinal issues often exhibit certain CMA symptoms, such as constipation, diarrhea, regurgitation, and (El-Shafie et al., 2023).

As with other food allergies, the majority of individuals have at least two symptoms that impact at least two organ systems. Approximately 50:70% of individuals have cutaneous symptoms; 50:60% have gastrointestinal symptoms; and 20:30% have respiratory symptoms (Turnbull et al., 2015)

It was found in the study that was conducted by El-Desoky et al. in in Ismailia, Egypt, there is a lack of knowledge about CMPA for doctors when it comes to diagnosis and management For parents: As people learn more about CMPA from the media than from doctors, there is an inflated concern about expected symptoms and indicators, and there is a lack of knowledge about what foods include milk that must be avoided during elimination (El-Desoky et al., 2023). These findings were urgent motives to the investigators to study CMPA and methods for diagnosis among children in Sohag governorate.

In this study 100 patients included (suspected CMPA), after application of CoMiSS, 2016 on them we found that 66% confirmed (≥ 12) while 34% were non-confirmed (< 12). Then next step was done with food challenge test, the results showed that out of 66 of cases with CoMiSS ≥ 12, 64 showed positive food challenge test and 2 cases with negative results. On the other hand, out of 34 cases with CoMiSS < 12, 9 cases showed positive food challenge test and 25 cases with negative results.

In this work there was statistically insignificant difference between the studied cases according to age. Our findings are in line with Zeng et al. and Eslamian et al. who reported that there was statistically insignificant difference between the studied cases according to age (Zeng et al., 2019, Eslamian et al., 2018).

In this work, it was found that among confirmed CMPA cases, 43.8% of them were males and 56.2% were females. Our work results were in line with Warren et al. who indicated that the prevalence of CMA was higher among females than males (63.7% and 36.3%) respectively (Warren et al., 2022). However, our findings weren't in line with Al Rushood et al. who indicated that the prevalence of CMA among males was higher than females (63.3% and 36.7%) respectively (Al Rushood et al., 2023).

In this work, regarding type of feeding, the majority of cases were formula fed (49%), followed by mixed fed (formula and breast fed) (28%) then (13%) breast fed and less common cow milk fed (10%). Our findings weren't in line with Raziani et al. who reported that two-thirds of cases were cow

milk fed (60%), followed by mixed fed (cow milk and breast milk) (39%) then breast fed (21%) (Raziani et al., 2022).

Our study results were in line with Saad et al. who described that (48%) of cases were formula feed, followed by mixed fed (formula and breast milk) (29.3%) then breast fed (22.7%) (Saad et al., 2020).

In this work, it revealed that 93% of confirmed CMA cases had positive family history of allergic disease

Which was in line with the findings of several studies that revealed that 91.1%, 71.7%, 60.5% and 82% of the studied cases reported positive family history (Al Rushood et al., 2023, Korol and Kaczmarski, 2001, Saad et al., 2020, El-Asheer et al., 2022)

According to comparison to HB, MCV, HCT and eosinphilic count, the current study showed that the mean value of hemoglobin level showed significant increase among positive challenge test cases than negative challenge test cases (9.5 ± 0.98 and 8.9 ± 0.85) gm/dl. Also, the mean of eosinophilic count showed significant increase among positive food challenge cases than negative food challenge test cases (422.6 ± 90.6 and 180.3 ± 113.3). This is in line with a study that was conducted by El Desouky et al. who reported that confirmed CMA cases had significant higher eosinophilic count in comparison to no CMA cases (463.89 ± 37.6 and 317.42 ± 1.95) (El Desouky et al., 2021).

Our results aren't similar to the results of a study that was carried out by El-Sebay et al. who revealed that there was significant decrease of HB level among CMPA cases than controls (11.72 ± 1.28 and 13.10 ± 1.18) (El-Sebay et al., 2016).

Regarding relation between confirmed CMPA cases and no CMPA cases with CoMiSS at first visit, the current study showed that the mean of the score at first visit was significantly higher among positive food challenge test cases than negative food challenge test cases (15.04 ± 2.9 and 9.9 ± 1.7).

Our findings are in line with El-Shafie at al. who revealed that the mean of the score at first visit was statistically significant higher among positive food challenge test cases than negative food challenge test cases (15.76 ± 5.29 and 12.44 ± 5.01) (El-Shafie et al., 2023).

In this work, it was revealed that there was highly statistically significant difference between CoMiSS at first and second visit among the positive challenge test case. Also, there was highly statistically significant difference between CoMiSS at first and second visit among the positive challenge test case. Confirmed CMA cases by food challenge test showed improvement at CoMiSS of second visit in comparison to that of first visit (6.4 ± 1.8 and 15.04 ± 2.9). However, non-confirmed CMPA cases showed no improvement at CoMiSS of second visit in comparison to that of first visit (11± 2.3 and 9.9 ± 1.7).

This is in agreement with a study that was done by El-Shafie et al. who reported that confirmed CMA cases by food challenge test showed improvement at CoMiSS of second visit in comparison to that of first visit (2.07 ± 2.24 and 16.39 ± 5.13). However, non-confirmed CMA cases showed slight improvement at CoMiSS of second visit in comparison to that of first visit (7.19 ± 5.55 and 12.44 ± 5.01) (El-Shafie et al., 2023).

As regards relation between Confirmed CMA (positive challenge test) and non-confirmed CMA (negative challenge test) regarding CoMiSS at first visit. Our study showed that there was statistically significant difference between confirmed CMA and non-confirmed CMA according to cut off point of CoMiSS

either < 12 or ≥ 12. 9% cases had CoMiSS < 12 and confirmed CMA by food challenge test. On the other hand, 2% of cases had CoMiSS ≥ 12 and detected non-confirmed CMA by food challenge test. 64% cases had CoMiSS ≥ 12 and detected confirmed CMA by food challenge test.

In this work, our findings are in line with Prasad et al. who revealed that 78.6% of confirmed CMA cases had CoMiSS > 12 while 61.5 % of non-confirmed CMA cases had CoMiSS > 12 (Prasad et al., 2018). Also, this is in line with El Desouky et al. who reported that there was statistically significant difference between Confirmed CMA (positive challenge test) and non-confirmed CMA (negative challenge test) regarding total score and 77 cases (64.2%) had CoMiSS < 12 and 43 cases (35.8%) had CoMiSS ≥ 12. Also, Food challenge test was applied to all cases which revealed that 44 cases showed positive result and 76 cases showed negative result (El Desouky et al., 2021).

Regarding accuracy of CoMiSS in diagnosis of CMA, our study showed that accuracy was 89 % at ≥ 12 cut off point. The percentage of Sensitivity was (87.7 %), Specificity (92.6 %), Positive predictive value % (96.9 %) when the score is ≥ 12, Negative predictive value % (73.5 %).

Our findings weren't in line with Vandenplas et al. who revealed that CoMiSS of ≥12 had a low sensitivity (20.3%), but high specificity (87.9%) and high positive predictive value (91.7%) for CMPA (Vandenplas et al., 2022).

Our study findings are inconsistent with El-Shafie et al. who reported that the ROC curve identified the score of ≥12 as the best cut-off point (area under the curve 0.716) with a sensitivity of 76.19%, specificity of 62.50%, PPV of 91.43, NPV of 33.33, and overall accuracy of 74.00% (El-Shafie et al., 2023).

Our study findings are nearly equal to El Desouky et al. who reported that accuracy of CoMiSS in diagnosis of CMA was 90.8%. the percentage of Sensitivity (86.4%), Specificity (93.4%), Positive predictive value % (88.3%) when the score is ≥12, Negative predictive value % (92.2%) (El Desouky et al., 2021).

In this work CMPA diagnosis is challenging as there is no specific clinical presentation suggestive of CMPA diagnosis. In addition, symptoms and signs of CMPA may overlap with functional GI disorders (colic, regurgitation, and constipation).

Strengths of the study: Estimation of specific IgE level among all cases and diet elimination and food challenge test divided the study population into confirmed CMA group and no CMA for efficient comparison.

Constrains and limitations of the study: The sample size was relatively small and the single-center design, the study only included patients from a single hospital, which may not fully represent the broader population, using of CoMiSS, 2016 instead of using CoMiSS, 2023 as enrollment of cases began before updating CoMiSS.

Conclusion: CoMiSS, 2016 was applied to all cases and diagnosis was confirmed by diet eliminatioan and food challenge test with ≥ 12 cutoff point and revealed that 66 cases obtained CoMiSS ≥ 12 and 34 cases < 12. For confirmation of diagnosis elimination diet and food challenge test was done to all cases and revealed that 73 cases (73%) showed positive result and 27 cases (27%) showed negative result. Among positive food challenge test cases, 64 of them had CoMiSS ≥ 12. Moreover, among negative food challenge test cases, 2% of them had CoMiSS ≥ 12. This work showed that the accuracy of CoMiSS in diagnosis of CMA, it was 89 %. The percentage of sensitivity (87.7 %), specificity (92.6 %), positive predictive value

% (96.9 %) when the score is ≥ 12, negative predictive value % (73.5 %). CoMiSS is an easy-to-use and practical awareness tool for evaluating CM-related symptoms but cannot be considered a standalone diagnosis tool for CMA.

Recommendations: Based on the results of the current study, it is recommended that:

- Use of Cow's Milk Related Symptoms Score (COMISS) as a screening tool for cow's milk allergy not as a confirmatory tool.
- Further studied should be done with larger sample size.
- Use of updated CoMiSS, 2023 in further studied for more accurate assessment.
- More studies are needed to evaluate whether the factors such as bloody stool, failure to thrive should be included in CoMiSS.
- Support exclusive breast feeding during the first 6 month of life.

References

- Al-Beltagi, M., Saeed, N. K., Bediwy, A. S. & Elbeltagi, R. 2022. Cow's milk-induced gastrointestinal disorders: From infancy to adulthood. *World J Clin Pediatr,* 11**,** 437-454.
- Al Rushood, M., Al-Qabandi, W., Al-Fadhli, A., Atyani, S., Al-Abdulghafour, A. & Hussain, A. 2023. Children with Delayed-Type Cow's Milk Protein Allergy May Be at a Significant Risk of Developing Immediate Allergic Reactions Upon Re-introduction. *J Asthma Allergy,* 16**,** 261-267.
- Cronin, C., Ramesh, Y., De Pieri, C., Velasco, R. & Trujillo, J. 2023. 'Early Introduction' of Cow's Milk for Children with IgE-Mediated Cow's Milk Protein Allergy: A Review of Current and Emerging Approaches for CMPA Management. *Nutrients,* 15.
- Dupont, C. 2014. Diagnosis of cow's milk allergy in children: determining the gold standard? *Expert Rev Clin Immunol,* 10**,** 257-67.
- El-Asheer, O. M., El-Gazzar, A. F., Zakaria, C. M., Hassanein, F. A. & Mohamed, K. A. J. E. P. A. G. 2022. Frequency of gastrointestinal manifestations among infants with cow's milk protein allergy, Egypt. 70**,** 34.
- El-Desoky, M. A., Gad, S. S. & Omran, A. G. 2023. Malpractice in Cow's Milk Protein Allergy Management Canal Area. *Suez Canal University Medical Journal,* 26**,** 0-0.
- El-Sebay, H. M., Badr, E. A., El-Ghobashi, Y., Khalil, M. M. & El-Mashad, G. M. 2016. The role of specific IgE antibodies in infants with cow milk protein allergy. *Menoufia Medical Journal,* 29**,** 874.
- El-Shafie, A. M., Omar, Z. A., El Zefzaf, H. M. S., Basma, E. M., Al Sabbagh, N. M. & Bahbah, W. A. 2023. Evaluation of Cow's Milk Related Symptom Score [CoMiSS] accuracy in cow's milk allergy diagnosis. *Pediatric Research,* 94**,** 987-995.
- El Desouky, A. I., Anany, H. G. & Mohammed, I. S. I. 2021. Assessment of CoMiSS among Children with Cow's Milk Allergy at Zagazig University Hospital %J The Egyptian Journal of Hospital Medicine. 83**,** 838-843.
- Elghoudi, A. & Narchi, H. 2022. Food allergy in children-the current status and the way forward. *World J Clin Pediatr,* 11**,** 253-269.
- Eslamian, M. H., Moghtaderi, M. & Gharagozlou, M. 2018. IgE-mediated cow's milk allergy in Iranian infants and children: Predictive factors of early tolerance. *Iranian Journal of Pediatrics,* 28.
- Korol, D. & Kaczmarski, M. 2001. Positive family history of allergy in children with hypersensitivity to cow's milk. *Medical Science Monitor,* 7**,** 966-970.
- Maksoud, H. M. A., Al Seheimy, L. A. F., Hassan, K. A. G., Salem, M. F. & Elmahdy, E. A. A. M. 2019. Frequency of cow milk protein allergy in children during the first 2 years of life in Damietta Governorate. 17**,** 86-95.
- Pourhoseingholi, M. A., Vahedi, M. & Rahimzadeh, M. 2013. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench,* 6**,** 14-7.
- Prasad, R., Venkata, R. S. A., Ghokale, P., Chakravarty, P. & Anwar, F. 2018. Cow's Milk-related Symptom Score as a predictive tool for cow's milk allergy in Indian children aged 0-24 months. *Asia Pac Allergy,* 8**,** e36.
- Raziani, Y., Othman, B., Ahmad, A. & Qadir, S. 2022. Non-invasive diagnostic test for cow's milk allergy: A cross-sectional, descriptive study. 2022.

- Saad, K., Ahmad, A. R., El-Tellawy, M. M., El-Ashry, A. H., Nagiub, E. M., Abdelsalam, T. A. & Elhoufey, A. 2020. Cow milk protein allergy: clinical phenotype and risk factors. *Curr. Trend. Immunol.,* 21**,** 129-135.
- Samir, S., El Maraghy, N. & Azzam, M. 2020. Association between Delayed Speech in Children and Allergy. *Egyptian Journal of Medical Microbiology,* 29**,** 81-85.
- Schoemaker, A. A., Sprikkelman, A. B., Grimshaw, K. E. & Roberts, G. 2015. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. *Allergy,* 70**,** 963-72.
- Selbuz, S. K., Altuntaş, C., Kansu, A., Kırsaçlıoğlu, C. T., Kuloğlu, Z., Ilarslan, N. E. Ç., Doğulu, N., Günay, F., Topçu, S. & Ulukol, B. 2020. Assessment of cows milk-related symptom scoring awareness tool in young Turkish children. *Journal of Paediatrics Child Health,* 56**,** 1799-1805.
- Turnbull, J., Adams, H. & Gorard, D. A. 2015. The diagnosis and management of food allergy and food intolerances. *Alimentary pharmacology therapeutics,* 41**,** 3-25.
- Vandenplas, Y., Bajerova, K., Dupont, C., Eigenmann, P., Kuitunen, M., Meyer, R., Ribes-Koninckx, C., Salvatore, S., Shamir, R. & Szajewska, H. J. N. 2022. The Cow's Milk Related Symptom Score: The 2022 Update. 14**,** 2682.
- Warren, C. M., Agrawal, A., Gandhi, D. & Gupta, R. S. 2022. The US population-level burden of cow's milk allergy. *World Allergy Organ J,* 15**,** 100644.
- Zeng, Y., Zhang, J., Dong, G., Liu, P., Xiao, F., Li, W., Wang, L. & Wu, Q. 2019. Assessment of Cow's milk-related symptom scores in early identification of cow's milk protein allergy in Chinese infants. *BMC Pediatr,* 19**,** 191.