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SYSTEMATIC REVIEW

Cow's Milk-related Symptom Score for cow's milk allergy assessment: a meta-analysis for test accuracy

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BACKGROUND: We aimed to assess the ability of Cow's Milk-related Symptom Score (CoMiss) in screening cow's milk protein allergy (CMPA) and assess validation of its sensitivity and specificity.
METHODS: We searched the PubMed, WOS, Embase, and Ovid databases using broad terms and keywords for the concepts of the symptom-based score (CoMiss) and cow's milk allergy. We performed the meta-analyses using a meta-package of R software and Meta-DiSc software.
RESULTS: Fourteen studies were included with a total of 1238 children. At cut-off value 12, CoMiss had a pooled sensitivity of 0.64 and a pooled specificity of 0.75. The PLR and NLR were 3.05 and 0.5, respectively. The AUC value of the sROC curve was 0.7866.CoMiss showed a significant difference in CMPA patients at baseline and after milk elimination for 2–4 weeks (MD, 7.18), as well as between the CMPA-positive group compared with the CMPA-negative group, however, the statistical significancy was obtained after leave study of Selbuz et al. out of the analysis (MD, 4.61).
CONCLUSIONS: CoMiss may be a promising symptom score in the Awareness of the symptoms related to cow's milk allergy and a useful tool in monitoring the response to a cow's milk-free diet.

Pediatric Research (2023) 93:772–779; https://doi.org/10.1038/s41390-022-02334-y

IMPACT:

- Cow's milk protein allergy (CMPA) is the most frequent food allergy in children under the age of 3 years. Cow's Milk-related Symptom Score (CoMiss) is a clinical scoring system to assist primary healthcare providers in early detection of CMPA
- We performed a meta-analysis of CoMiss test accuracy.
- Our findings reflect that CoMiss may be a promising symptom score in CMPA awareness and a useful tool in monitoring the response to a cow's milk-free diet.

INTRODUCTION

While infants are still rapidly growing and developing, poor immune function, in combination with other factors, can raise the likelihood of allergies, particularly food allergy.[1] Food allergy is an immune-mediated hypersensitivity reaction to any food, including non-IgE-mediated and IgE-mediated allergic responses. Food allergies often produce mild to moderate symptoms, but some may result in severe or fatal responses.[2,3]

Cow's milk protein allergy (CMPA), sometimes known as cow's milk allergy (CMA), is the most frequent food allergy in children under the age of 3 years, and its prevalence is rising in both developed and developing nations. CMPA is an immunologically induced unpleasant response caused by cow's milk proteins that is repeatable.[4,5] It affects 2–5% of newborns and causes skin symptoms such as atopic dermatitis (50–70%); gastrointestinal (GI) symptoms such as vomiting, diarrhea, and constipation (50–60%); and respiratory symptoms such as wheezing and sneezing (20–30%).[5] CMPA is often misdiagnosed as gastroesophageal reflux disease, infantile colic, lactose intolerance, or functional gastrointestinal problems, resulting in delayed diagnosis, many consultations, and ineffective treatment.[6]

Skin-prick tests and specific IgE antibodies are used as screening tests to diagnose CMPA. IgE-specific that may identify the existence of circulating anti-CMP antibodies. Positive IgE, however, cannot tell the difference between clinical allergy and sensitization. The diagnosis of CMPA that is not IgE-mediated cannot be made using a specific IgE assay.[7] A skin-prick test detects tissue-bound IgE antibodies. A positive test does not always indicate allergy,

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Received: 12 April 2022 Revised: 16 August 2022 Accepted: 13 September 2022
Published online: 17 October 2022

although it might be taken into account in IgE-mediated illness. Skin-prick tests often provide less response in infants. It is not verified in non-IgE-mediated CMPA and might lead to erroneous diagnoses, both positive and negative.[8] Despite the importance of medical history, diagnostic procedures (such as IgE and skin-prick tests) and physical examinations, the specificity, and sensitivity of these tests, as well as clinical symptoms, are inadequate for an accurate diagnosis of food allergy.[9] When diagnosing CMPA, the standard diagnostic approach is a 2- to 4-week exclusion diet followed by an oral food challenge. Although the gold standard for food allergy diagnosis is a double-blind, placebo-controlled food challenge, open challenges are often adequate in clinical practice, especially in infants and young children.[10] The Cow's Milk-related Symptom Score (CoMiss) takes 5–15 min to complete and includes overall indications, as well as dermatological, respiratory, and GI symptoms. It was created as a tool to raise awareness about the symptoms associated with cow's milk allergy.[11] CoMiss is a clinical scoring system that seeks to assist primary healthcare providers in identifying children who may have CMPA; therefore, it may be considered an Awareness tool. Infants with a symptom-based score of 12 or higher are thought to be at risk of developing CMPA.[5,11,12]

Given that CMPA has remained a source of dispute and controversy, as well as the absence of clear recommendations, it continues to be a significant clinical burden. As a result, since CMPA is so frequently overlooked, obtaining an accurate and timely detection of the patients while reducing the stress on the patient and family remains a problem.[5,13] We aimed to assess the ability of CoMiss in screening CMPA and the validation of its sensitivity and specificity.

METHODS

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[14] (Fig. 1).

Search strategy

We searched the following databases: PubMed, WOS, Scopus, Ovid, and Cochrane using a broad term and keywords for the concepts of the symptom-based score (CoMiss) and cow milk allergy up to July 15, 2022, as shown in Supplementary Appendix 1.

After duplicates removal, three authors screened all included studies according to our eligibility criteria by title and abstract. Any potentially relevant studies and conflict studies were moved to full-text screening. Conflicts in full-text screening were resolved in a discussion. An additional manual search was done by screening references of the included articles, literature reviews, and related articles in PubMed and Google Scholar.

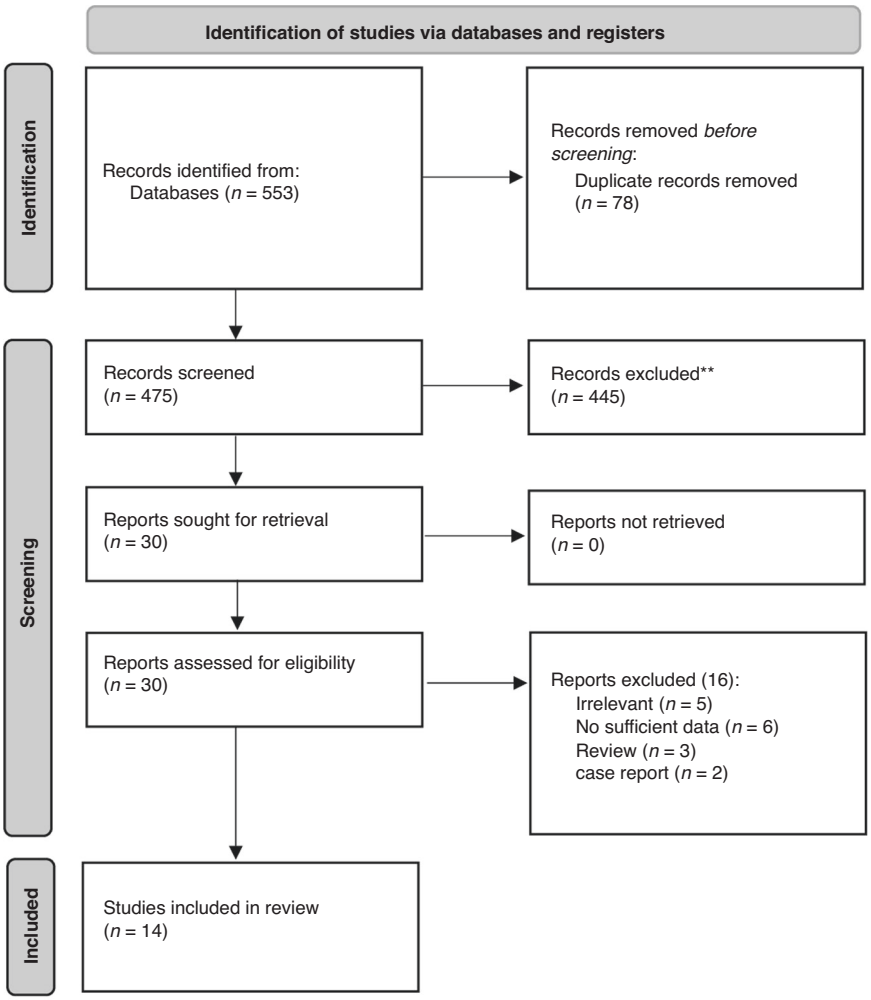

Fig. 1 The PRISMA flow diagram for the systematic review detailing the database searches, the number of records screened, and the full texts retrieved.

Eligibility criteria

Studies that assessed CoMiss in cow milk allergy patients, published in international peer-reviewed journals, were included without limits to language.

Exclusion criteria

Animal studies, reviews, case reports, and unretrieved full-text articles were excluded during the screening. Most of the included studies excluded children with congenital anomalies or chronic infection, infants with recent surgical intervention, and infants older than 24 months.

Data extraction

MA and MAA independently extracted data about baseline characteristics from the included studies using a standardized Excel sheet; first author name, publication year, study design, sample size, and characteristics of participants (sex and age). The same authors independently extracted data for the quantitative data analysis; change in CoMiss at baseline and after 2–4 weeks according to the study, test accuracy, and CoMiss in positive and negative allergy patients.

Risk of bias assessment

Risk of bias assessment of 14 included articles was performed by three independent reviewers who evaluated the quality of the included studies for bias using the National Institutes of Health (NIH) quality assessment tool.[14] The overall bias score was categorized as good, fair, or poor. Any disagreements were resolved by discussion and consensus. Whenever needed, a consultation of a senior reviewer was obtained. The articles are classified into three categories: good, fair, and poor.

Statistical analysis

We compared the CoMiss between the CMPA patients positive and CMPA patients negative, and the CMPA at baseline and after one month from cow's milk-free diet. We conducted a test accuracy for the CoMiss against other standard tests. Statistical analysis was conducted using the Meta-package of R statistical software version 4.1.0[15,16] and meta-disc software.[17]

We employed the random effect model in all analyzed outcomes. We calculated the mean difference with 95% CI For continuous variables. We pooled the sensitivity, specificity, positive likelihood, negative likelihood, and diagnostic odds ratio. The Summary receiver operating characteristics (sROC) curve was plotted. Heterogeneity was assessed using the I^2, chi-squared tests, and Spearman correlation for threshold analysis. Leave-one-out meta-analysis was done for each subset of the studies and leaving one study out at each analysis.

RESULTS

Study characteristics

We included randomized controlled trials, prospective cohort, and cross-sectional studies, as stated in the inclusion criteria. The fourteen studies included a total of 1238 participants who were children, comprising 587 boys and 550 girls. A total of 693 participants were CMPA-positive, and 321 were CMPA-negative. Of the studies included, three studies were randomized controlled trials, 10 were cross-sectional studies, and one study with pooled analysis. Most children were breastfeeding. Further details are shown in Table 1. The age range of the pediatric population included in the meta-analysis was from delivery up to 24 months. Almost all studies used the OFC-Oral food challenge test when CMPA is suspected, being positive when symptoms and signs reappear and negative when they don't.

In most of the studies, an elimination diet was implemented in these infants for 2–4 weeks. The elimination diet was given for 4 weeks according to the following feeding style: elimination of cow's milk and its products from the diet of the mother in exclusively breastfed infants. switching to extensive hydrolysed formula (ehf) in infants fed with only standard formula; and elimination of cow's milk-containing formula, cow's milk, and its products from infant's diet in non-breastfed infants who were also, on supplementary food. In most of the studies, the mothers avoided all milk and milk products from their own diet. The milk consumed during the elimination period in all studies was extensively hydrolyzed formula, except Zeng et al.[18] and Vandenplas et al.,[19] which used amino acid-based formula, and Prasad et al.,[6] which used soy protein isolate formula. Further details were reported in Supplementary Appendix 2.

Quality assessment

The risk of bias assessment of the 14 included articles used the NIH tool, which has three categories: good (nine studies), fair (four studies), and poor (one study). Eldesouky et al.[20] study was classified as poor because the study did not use randomization, state whether the treatment allocation was concealed, or mention the blindness of the assessors or participants. The score of each study is shown in Supplementary Appendices 3–5.

Awareness test accuracy of CoMiss

At cut-off value 12, CoMiss had an overall sensitivity of 0.64 (95% confidence interval [CI] 0.41–0.51), and the overall specificity was 0.75 (95% CI 0.69–0.80). The positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 3.05 (95% CI 1.06–8.77) and 0.5 (95% CI 0.27–0.93), respectively (Fig. 2).

We performed a subgroup analysis for children above and below 6 months, we found that sensitivity was higher for children above 6 months more than under 6 months children, 0.807 (0.723–0.875) and 0.336 (0.285–0.39), respectively. Also, specificity was higher for above 6 months children than below 6 months 0.899 (0.817–0.953) and 0.65 (0.564–0.729), respectively (Supplementary Appendix 6).

At cut-off value 9, CoMiss had an overall sensitivity of 0.47 (95% confidence interval [CI] 0.41–0.54), and the overall specificity was 0.77 (95% CI 0.64–0.87).

At cut-off value 5, CoMiss had an overall sensitivity of 0.88 (95% confidence interval [CI] 0.84–0.92), and the overall specificity was 0.47 (95% CI 0.32–0.62).

sROC curve

The sROC curve illustrates the trade-off between sensitivity and specificity and provides a global overview of the test's performance. The sROC curve in this study was symmetric, located in the top left corner, indicating that CoMiss had good test performance to detect CMPA, with an The Area Under the Curve (AUC) value of 0.79. The Q^* value was 0.7243, which indicates that the test has at least moderate predictive validity (>0.7; Fig. 2).

Threshold effect and The diagnostic odds ratio (DOR)

The threshold effect is a significant contributor to the heterogeneity between value diagnostic test accuracy (DTA) studies. When a threshold effect exists, the correlation coefficient between the false-positive rate and sensitivity is 0.6 or greater.[21,22] We found no statistical significance (Spearman's correlation coefficient = –0.200, $p = 0.747$) of heterogeneity due to the threshold effect. This proved that the threshold effect had no impact on heterogeneity. The DOR Forest plot revealed a non-threshold impact of 6.46 (CI 1.45–28.82; Fig. 2) at CoMiss > 12 (Figs. 3 and 4).

CoMiss for CMPA-positive and CMPA-negative patients

Figure 5 shows the CMPA-positive group compared with the CMPA-negative group with a mean difference of 3.21 (95% CI –0.14 to 6.57; $I^2 = 97\%$, $p < 0.01$), The pooled result was

Table 1. Characteristics of all included studies.

Study ID	Country	Study design	Total number		Age (range)	Sex Female/ male	CMPA + *n* (%)	CMPA– *N* (%)	Symptom (*N*)	Mode of delivery	Feeding mode	Family history of allergy (*N*)
El Desouky[20]	*Egypt*	Interventional	120		6.60 M[a] (0 :18 m)	66 (55%)/ 54 (45%)	44 (64.3)	76 (35.7%)	Mild to moderate (37) Severe (7)	Vaginal – CS	Breast (25) Fresh Cow Milk (9) Formula F (34) Mixed (52)	61
Vandenplas[39]	*Belgium*	RCT	116	Whey protein	80 days[a] (0.05 m:6 m)	15 (36%)/ 26 (64%)	26 (63.4%)	15 (36.6 %)	Crying (11) Eczema (12) Resp (6)	Vaginal (85%) CS (15%)	NR	NR
				Casein protein	64 days[b] (0.05 m:6 m)	22(49%)/ 22(51%)	33 (75 %)	11 (25%)	Crying (14) Eczema (13) Resp (9)	Vaginal (87%) CS (13%)	NR	NR
Vandenplas[5]	*Belgium*	Prospective	85		72 days[b] (2 w:6 m)	37(44%)/ 48(56%)	59 (69%)	26 (31%)	NR	Vaginal (86%) C-Section (14%)	NR	NR
Zeng[18]	*China*	Prospective	38		NR (1 m:12 m)	13/25	24	14	Eczema (18) Bloody stool (15) Diarrhea (15) Crying (1) Regurgitation (5) Resp (2)	Vaginal (20) C-Section (18)	Breast (18) Formula (7) Mixed (13)	NR
Selbuz[23]	*Turkey*	Observational	168		30 days[a] (0:12 M)	82/86	91 (54.2%)	77 (45.8)	GIT (67) Dermatological symptoms (48) Git + dermatological symptoms (6) Resp (2) Colic (17)	Vaginal (90) C-Section (78)	Breast (102) Formula (5) Mixed (42) Mixed + complementary (19)	109
Salvatore[37]	*Italy*	Prospective	47		3 m[b] (1:12 m)	21/26	9	NR	Crying (87) Regurgitation (92) Skin (32) Resp (38)	Vaginal (NR) C-Section (NR)	Breast (11) Formula (36) Breast +Complementary (4)	24
Prasad[6]	*India*	Cross-sectional	83		38.7[a] (0:24 m)	31/52	70 (84.3%)	13 (15.7)	GIT (41), Skin (50), Resp (64), Asthma (8), Eczema (18), Rhinitis (25), Urticaria/angioedema (18), Medication allergies (2), Food allergies (4)	Vaginal (NR) C-Section (NR)	Breast (26)	Asthma (11) Eczema (11) Rhinitis (9) Urticaria/ angioedema (4) Medication allergies (2) Food allergies (2)
Kose[40]	*Turkey*	Prospective cohort	112		4.7 m[a] (0:12 m)	56 (50%/) 56 (50%)	(69.4 %)	(30.6%)	Vaginal (NR) C-Section (NR)	Vaginal (NR) C-Section (NR)	NR	NR
Vandenplas[19]	*Multinational*	Mosaic	299		16.1 days[b] (9.9w:20.8w)	121(40.5%)/ 178(59.5)	217	33	Eczema 118 Rectal bleeding 35 Diarrhea 23 Vomiting 23 Constipation 6 other 2	Vaginal (151) C-Section (147)	Non-breastfed	NR
Ursino[26]	*Argentina*	*Validation study*	*32*		3 m[b] (2:4 m)	14 (45%)/ 18(55%)	NR	NR	50–70% of patients present with cutaneous symptoms. 50–60% with gastrointestinal symptoms. 20–30% with respiratory symptoms	NR	NR	NR
Vandenplas[25]	*Spain*	*Analyzing study*	148 Spain.		2.3 m[b] (2:6 m)	NR	NR	NR	NR	NR	NR	NR

Table 1. continued

Study ID	Country	Study design	Total number	Age (range)		Sex Female/male	CMPA + *n* (%)	CMPA– *N* (%)	Symptom (*N*)	Mode of delivery	Feeding mode	Family history of allergy (*N*)
	Belgium		72 Belgium.	3.7 m[b] (0:6 m)		35 (48%)/ 37(52%)	NR	NR	NR	NR	NR	NR
Jalowska[27]	*Poland*	*Cross-sectional*	110	18.2 w[a] (0:12 m)		48 (43.6%)/ 62 (56.4%)	NR	NR	NR	NR	NR	NR
Rossetti[24]	*Italy*	RCT	30	8.03 m[a] (1:36 m)		13(44.8%)/ 16(55.2%)	-	-	Digestive 10 Cutaneous 2 Digestive and cutaneous 3 Digestive and other symptoms such as crying, irritability, abdominal pain, and agitated sleep 5 Digestive symptoms and failure to thrive 6 Digestive, cutaneous and other symptoms such as crying, irritability, and agitated sleep 3	-	Breast Feeding 22	At least one parent or sibling with a medically confirmed allergy 14
Vandenplas[41]	*Belgium*	Pooled analysis	170	77 days[b] (2 w:12 m)	Original	41/59	69	31	NR	Vaginal (NR) C-Section (NR)	NR	NR
					Combined	45/55	75	25	NR			

m stands for months.
[a]Mean.
[b]Median.

insignificant, however, after leave study of Selbuz[23] out of the analysis the result became significant.

CoMiss in monitoring the response to a cow's milk-free diet

The comparison between CoMiss at baseline and after milk elimination is shown in Fig. 5. A significant symptom score reduction was found after 1 month of a cow's milk-free diet compared to the baseline. The mean difference was 7.18 (95% CI 5.41 to 8.95). All the studies included in the analysis used EHF except Vandenplas et al.,[19] however, on removal in the sensitivity analysis the pooled result did not change significantly (mean difference changed from 7.18 to 7.88).

Meta-regression

Meta-regression analyses for potential confounders like age, country, and design of the included studies were performed. A significant correlation with the country (p-value < 0.0001) was reported however, there is no other significant correlation for other covariates. The amount of heterogeneity accounted for in the analysis comparing Mean COMISS between CMPA positive and CMPA negative is 94.3% and about 97.8% in the analysis comparing mean COMISS between baseline and after milk elimination.

Leave-one-out analysis

A leave-one-out sensitivity analysis differentiating CMPA-positive from CMPA-negative patients revealed that the pooled result was affected by the study of Selbuz et al.[23] On its removal, the overall effect became significant, with a mean difference of 4.61 (95% CI 2.07–7.16). This due to Selbuz et al.[23] included infants with COMISS > 12 and excluded others with COMISS < 12, this criterion was not present in the other studies. A leave-one-out sensitivity analysis calculating the change in CoMiss on the elimination of milk showed that no single study had affected the overall result, and the combined mean differences obtained were steady and statistically significant despite excluding any specific study from the sensitivity analysis (Fig. 6).

Qualitative analysis

Rossetti et al.[24] tested the hypo allergenicity of a new thickened extensively hydrolyzed casein-based formula (TeHCF) in children with already diagnosed cow's milk allergy (CMA). The new TeHCF meets the hypo allergenicity criteria and achieved adequate growth. However, the other studies included in the analysis comparing the CoMiss between baseline and after elimination diet (Fig. 5), the elimination diet was implemented in the suspected CMPA patients. Vandenplas et al.[25] analyzed the inter-rater variability between a pediatrician, parents, and day-to-day variability and revealed a very low variability was observed when the CoMiSS is scored prospectively over three days. While Ursino et al.[26] validate the CoMiss from English to Spanish and demonstrated the reliability of the CoMiSS, being a simple and rapid tool that is easy to apply. Jalowska et al.[27] highlighted that Lower CoMiSS values were obtained during prospective evaluation than the retrospective evaluation and these Possible differences should be considered when using CoMiSS in clinical practice (Supplementary Appendix 7).

DISCUSSION

CMPA is a common disease in children, characterized by an allergic reaction to cow's milk. It manifests as a combination of symptoms and signs that can be a source of stress to the child and their family due to the need for a cow's milk-free diet. CMPA can cause some nutritional deficiencies if not managed appropriately.[28,29] The prevalence of CMPA ranges between 0.25% and 4.9%, with a higher tendency in children than adults.[1,3] It is an immune-mediated disease that can be classified as IgE-mediated and non-IgE-mediated; the latter is the most frequent.[30] However,

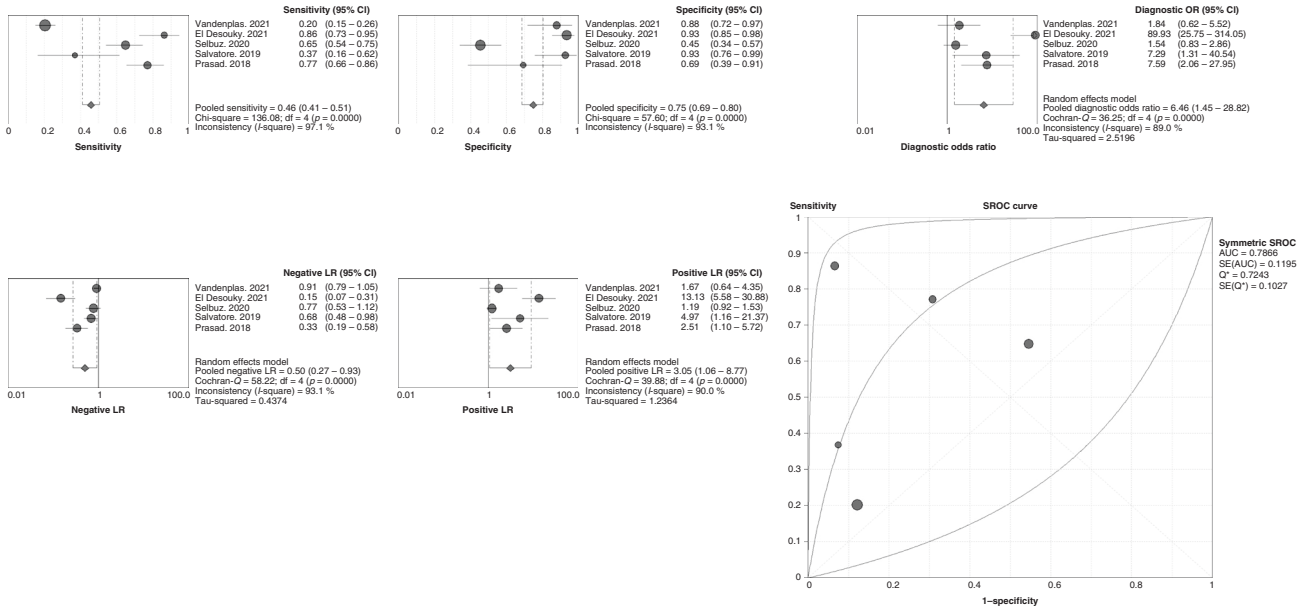

Fig. 2 Forest plot summarizing the test accuracy of CoMiss at cut-off > 12 for cow's milk allergy assessment.

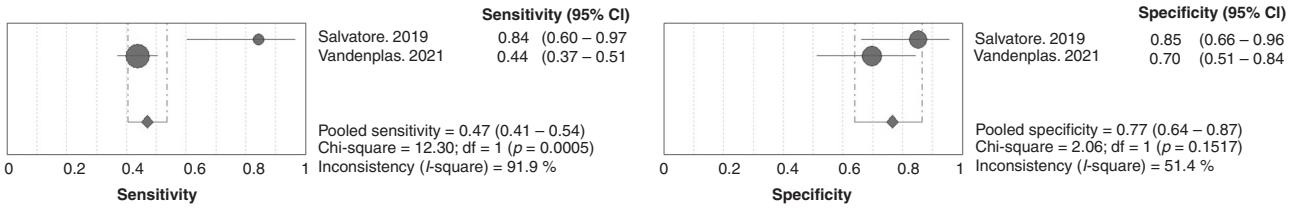

Fig. 3 Forest plot summarizing the test accuracy of CoMiss at cut-off > 9 for cow's milk allergy assessment.

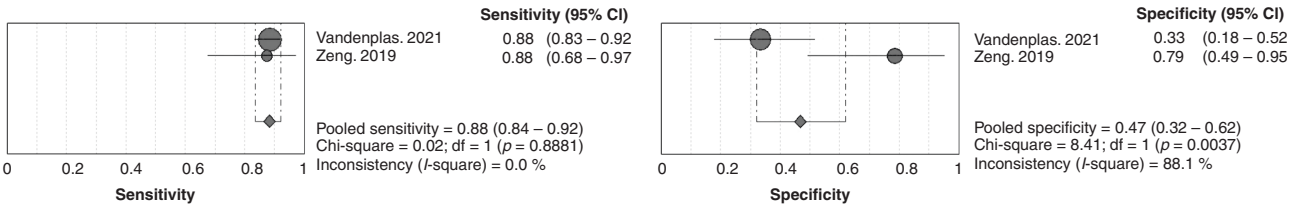

Fig. 4 Forest plot summarizing the test accuracy of CoMiss at cut-off > 5 for cow's milk allergy assessment.

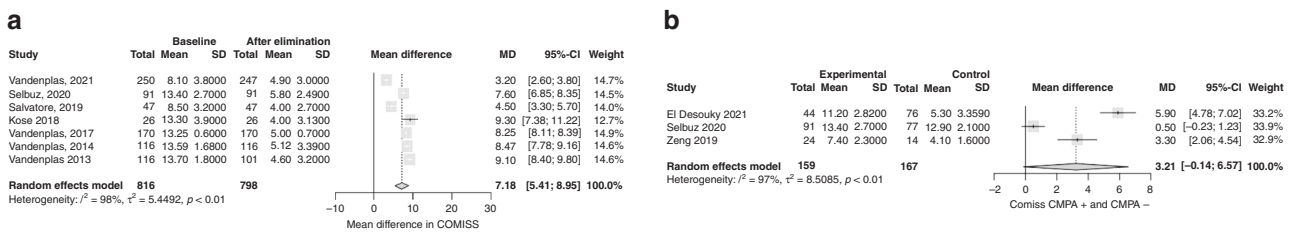

Fig. 5 The Forest plot of CoMiss summarizing. a Comparison between CoMiss at baseline and after milk elimination. **b** Mean difference in CoMiss between CPMA positive and CMPA negative. SD standard deviation, CI confidence interval.

errors of CMPA are frequent, and many families mislabeled their infants as being allergic to cow's milk, making them vulnerable to potential nutritional deficiencies; this can be explained by the frequency of guideline-defined symptoms.[31,32]

Belgian researchers created the CoMiss to easily identify infants with CMA, especially the non-IgE type characterized by symptoms such as crying, food regurgitation, stool pattern, and respiratory and skin symptoms. The scoring system is non-invasive and safe.[11] However, it doesn't include all symptoms of CMA like anaphylaxis, colic, hematochezia, failure to thrive, angioedema, and iron deficiency anemia.[12,30]

A double-blind, placebo-controlled oral food challenge is the reference standard test for diagnosis of CMPA. However, it is time consuming and expensive.[33] Therefore, the open challenge test is

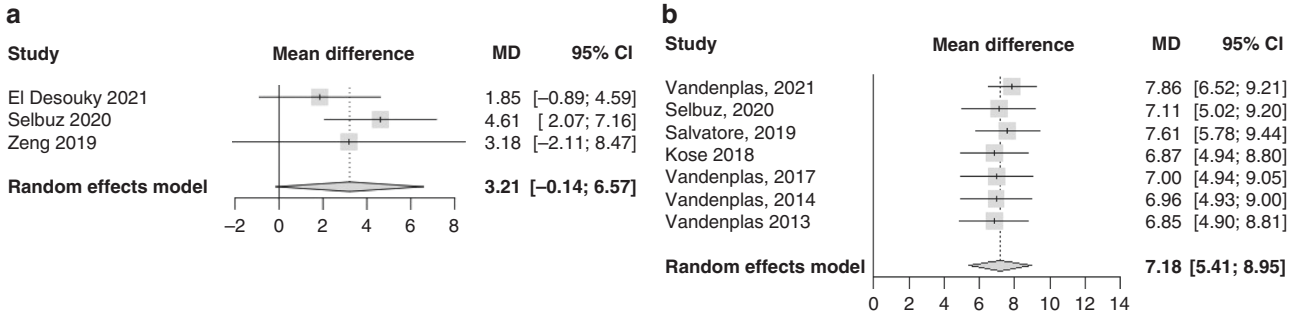

Fig. 6 Leave-one-out analysis. a Leave-one-out analysis for analysis comparing $CMPA^{+}$ and $CMPA^{-}$. **b** Leave-one-out analysis for analysis calculating mean difference between baseline and milk elimination.

usually the first step. This test is warranted if the diagnosis is uncertain, despite its potential complications. Furthermore, an open challenge cannot determine the severity of the disease because the tested food is discontinued when the reaction occurs.[34] Other tests usually used in IgE-type milk allergy are the IgE immunoassay test and skin-prick test. However, the specificity and sensitivity of these tests are inadequate for making an accurate diagnosis of food allergy; moreover, the tests for the IgE-mediated type are limited.[9,11]

We found two literature reviews discussed the CoMiss. Vandenplas et al.,[35] which gives a wide range of sensitivity and specificity (20% to 70%), (54% to 92%), respectively, and Thompson et al.[36] also give a wide range of sensitivity (37% to 98%) and specificity (38% to 93%). The two studies did not do any pooling for the results but just a qualitative analysis. Our study is the first to analyze and pool the sensitivity and specificity at different cut-off values. In our study at a cut-off value of 12, the sensitivity was 46%, and the specificity was 75%. The AUC value of the sROC curve was 0.79%. Furthermore, at a cut-off value of 12, we performed a subgroup analysis for the studies with a mean age greater than 6 months and under 6 months, and the sensitivity and specificity were higher for children above 6 months, however, this is limited by the small sample size. This highlights the need for future studies to validate the CoMiss at the age of more than 6 months. Furthermore, at a CoMiss cut-off value of 5, we found a higher sensitivity of 88% and a lower specificity of 47%. Interestingly, we found a lower sensitivity of 47% and a higher specificity of 77% at a cut-off value of 9, this indicates that CoMiss of cut-off > 9 is better than cut-off > 12 but more studies are needed to validate this cut-off value.

Our results showed a higher CoMiss score for CMPA-positive than CMPA-negative patients, with a pooled mean difference of 3.21 (–0.14 to 6.57). However, the result was statistically insignificant, possibly due to the small number of studies and small sample size. Therefore, we performed a leave-one-out meta-analysis that showed that the pooled result was affected by the study of Selbuz et al.[23] On its removal, the overall effect became significant, with a mean difference of 4.61 (95% CI 2.07–7.16). This displays the ability of CoMiss in differentiating CMPA-positive from CMPA-negative patients.

Our study supports using the CoMiss system in monitoring the response to a cow's milk-free diet. The analysis showed that on the elimination of cow's milk for 2–4 weeks, the CoMiss score decreased significantly, with a mean difference of 7.88 (95% CI 7.04–8.72). We suggest a CoMiss cut-off of 9 in the Awareness of the symptoms related to CMPA, as evaluated by Salvatore et al.[37] and showing the highest AUC of 91%. More studies are needed to validate the predictive ability of the CoMiss with this cut-off value. This is the first meta-analysis to evaluate the predictive ability of CoMiss and the first to analyze CoMiss in monitoring the response to a cow's milk-free diet.

The presence of substantial heterogeneity is considered the only limitation. This may be related to different populations in geographical constraints, and severity of symptoms. The high heterogeneity is usually common in this design. Plana et al.[38] analyzed 124 Cochrane DTA reviews. They found that most reviews described the subjective heterogeneity as moderate or extreme. However, we tried to address and treat this heterogeneity, firstly, we employed random effect models that consider the level of heterogeneity on pooling the overall effect, and we performed a leave-one-out meta-analysis to show the effect of every single study, which showed the effect of some studies as reported in the result, and threshold analysis to show the contribution of the different cut-off values to the heterogeneity (Insignificant Spearman's correlation test).

Following strategies suggested by Cochrane book part two 9.5.3 to explore the heterogeneity, we performed a meta-regression analysis for potential covariates with available data, which can be sources of heterogeneity like age, country, and design of the included studies, we found a significant correlation with the country (p-value < 0.0001), however, there is no other significant correlation for other covariates. The amount of heterogeneity accounted for covariate of the country in the analysis comparing Mean COMISS between CMPA positive and CMPA negative is 94.3% and about 97.8% in the analysis comparing mean COMISS between baseline and after milk elimination. Thus, we performed a subgroup analysis by the country, the heterogeneity decreased significantly from 98% to 65% in the subgroup of studies performed in Belgium. We also conducted a separate analysis for each cut-off value.

CONCLUSION

CoMiss may be a promising symptom score in the screening of cow's milk allergy and a useful tool in monitoring the response to a cow's milk-free diet for 2 weeks. However, it needs to be updated to include all symptoms of CMA like anaphylaxis, colic, hematochezia, failure to thrive, angioedema, and iron deficiency anemia. More studies are needed to validate the CoMiss in the age above 6 months.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author [KS], upon reasonable request.

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ACKNOWLEDGEMENTS

I would like to express my appreciation to Dr. Noha Yahia Ebaid, MD of radiodiagnosis Lecturer at Zagazig University for his support.

AUTHOR CONTRIBUTIONS

K.S., A.E., M.A.A., A.H.E., and E.E. designed the study and analyzed the data. M.A., A.M.A., F.A.A., S.F.T., M.G.A., and A.E. drafted the manuscript. All authors were involved in the critical analysis of the final version of the manuscript. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

FUNDING

No funding was secured for our study.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All protocols of our study followed the regulations of the research ethics committee of Assiut University.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-022-02334-y.

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