Retrospective and Prospective Determination of the Cow's Milk-Related Symptom Score (CoMiSS™) Values in Symptomatic Infants

Anna Kozłowska-Jalowska, Andrea Horvath, Yvan Vandenplas, and Hania Szajewska

1Department of Paediatrics, Medical University of Warsaw, Warsaw, Poland
2KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

ABSTRACT

Purpose: The Cow’s Milk-related Symptom Score (CoMiSS™) was developed as an awareness tool for evaluating cow's milk-related symptoms in otherwise healthy children. Using a convenience sample of participants, this cross-sectional study aimed to determine CoMiSS™ values of symptomatic infants based on retrospectively or prospectively obtained information.

Methods: CoMiSS™ values were determined in infants aged <12 months with symptoms suggestive of cow's milk protein allergy or functional gastrointestinal disorders. The exclusion criteria were previous diagnosis with acute or chronic disease, treatment with a therapeutic formula, and in case of breastfeeding, an elimination diet followed by the mother. Two CoMiSS™ values were assessed. A retrospective collection was defined as the collection of data after initial contact with the medical center but before the first medical consultation. A prospective collection was defined as the collection of data within 24 hours from the time of medical consultation but before starting any therapeutic intervention. The CoMiSS™ total and individual component scores obtained retrospectively or prospectively were compared between groups using the Wilcoxon signed-rank test.

Results: This study was performed between August and November 2019. Data of 110 children (62 males and 48 females), with a mean±standard deviation age of 18.2±11.7 weeks, were obtained. The total CoMiSS™ value (p<0.001) and some individual component scores (crying, regurgitation, and stool) were significantly lower when collected prospectively than when collected retrospectively.

Conclusion: CoMiSS™ values were retrospectively and prospectively determined. Lower CoMiSS™ values were obtained during prospective evaluation. Possible differences should be considered when using CoMiSS™ in clinical practice.

Keywords: Infants; Food hypersensitivity; Milk hypersensitivity; Milk

INTRODUCTION

Cow’s milk protein allergy (CMPA) is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to cow's milk protein [1]. The use of strict diagnostic criteria, as in the well-conducted EuroPrevall birth cohort study, reveals important geographic differences in national incidences of CMPA [2]. However, in
In many settings, CMPA remains a common food allergy in infants and children [3]. In many cases, especially those with non-immunoglobulin E-mediated manifestations, the diagnosis of CMPA may be challenging because of nonspecific symptoms and various skin, respiratory, and/or gastrointestinal tract manifestations. Moreover, many health care providers (HCPs) and parents confuse CMPA with lactose intolerance [4,5]. Without a correct diagnosis, children with CMPA will not be provided appropriate dietary treatment, which will adversely affect their growth and development [5]. Additionally, the similarity of CMPA symptoms to symptoms in children presenting with other diseases such as functional gastrointestinal disorders (FGIDs) can lead to underdiagnosis. Consequently, both overdiagnosis and underdiagnosis of CMPA may occur [6,7].

In 2015, a group of experts published a workshop report on the development of a Cow’s Milk-related Symptom Score (CoMiSS™). CoMiSS™ is an awareness tool for evaluating cow’s milk-related symptoms in otherwise healthy children [8]. It rates five different symptoms, including crying, regurgitation, stool, skin, and respiratory symptoms (Table 1). The total score ranges from 0 to 33. Crying, regurgitation, and cutaneous symptoms are scored from

| Symptom                  | Score | Symptom severity                              |
|--------------------------|-------|-----------------------------------------------|
| Crying*                  | 0     | ≤1 h/day                                      |
|                          | 1     | 1–1.5 h/day                                   |
|                          | 2     | 1.5–2 h/day                                   |
|                          | 3     | 2–3 h/day                                     |
|                          | 4     | 3–4 h/day                                     |
|                          | 5     | 4–5 h/day                                     |
|                          | 6     | ≥5 h/day                                      |
| Regurgitation             | 0     | 0–2 episodes/day                              |
|                          | 1     | >3–≤5 episodes of small volume                |
|                          | 2     | >5 episodes of >1 coffee spoon               |
|                          | 3     | >5 episodes of ≥half of the feed in ≤half of the feeds |
|                          | 4     | Continuous regurgitation of small volumes for >30 min after each feed |
|                          | 5     | Regurgitation of half to complete volume of a feed in at least half of the feeds |
|                          | 6     | Regurgitation of the complete feed after each feeding |
| Stools (Bristol scale)    | 4     | Type 1 and 2 (hard stools)                    |
|                          | 0     | Type 3 and 4 (normal stools)                  |
|                          | 2     | Type 5 (soft stool)                           |
|                          | 4     | Type 6 (liquid stool, if unrelated to infection) |
|                          | 6     | Type 7 (watery stools)                        |
| Skin symptoms            | 0 to 6| Atopic eczema                                 |
|                          |      | - Head/neck/trunk                             |
|                          |      | Absent: 0                                     |
|                          |      | Mild: 1                                       |
|                          |      | Moderate: 2                                   |
|                          |      | Severe: 3                                     |
|                          |      | - Arms/hands/legs/feet                        |
|                          |      | Absent: 0                                     |
|                          |      | Mild: 1                                       |
|                          |      | Moderate: 2                                   |
|                          |      | Severe: 3                                     |
|                          |      | 0 or 6                                       |
|                          |      | Urticaria (no 0/yes 6)                        |
| Respiratory symptoms     | 0     | No respiratory symptoms                       |
|                          | 1     | Slight symptoms                               |
|                          | 2     | Mild symptoms                                 |
|                          | 3     | Severe symptoms                               |

CoMiSS: Cow’s Milk-related Symptom Score.
*Crying was only considered if the child was crying for 1 week or more, assessed by parents, without any other obvious cause.
0 to 6, and respiratory symptoms are scored from 0 to 3. A cut-off score of ≥12 has been arbitrarily proposed to indicate the likelihood that the symptoms may be suggestive of CMPA [9]. Recent data also showed that while agreement between CoMiSS™ scores in presumed healthy infants obtained from the parent or HCP is excellent [10], the score differs if collected retrospectively or prospectively. However, in the previous study, there were two sources of variability between both CoMiSS™ assessments: (i) retrospective vs. prospective rating and (ii) different raters (HCP vs. parent) [10].

Therefore, the study determined CoMiSS™ values in symptomatic infants based on retrospectively or prospectively obtained information from a single rater (i.e., parent). We hypothesized that there was a difference in CoMiSS™ values and that the scores would be significantly lower for prospective evaluations.

MATERIALS AND METHODS

This cross-sectional study included a convenience sample of participants visiting three pediatric clinics (general pediatrics, allergology/pulmonology, and gastroenterology) of the Pediatric Hospital of the Medical University of Warsaw. Participants were parents of infants aged <12 months who were examined for consultation for symptoms suggestive of CMPA or FGID. The exclusion criteria were previous diagnosis with acute or chronic disease, treatment with therapeutic formula, and in case of breastfeeding, an elimination diet followed by the mother. The CoMiSS™ questionnaire and the study design were explained to the parents. Then, two CoMiSS™ value assessments, i.e., retrospective and prospective, were performed in which parents answered questions about symptoms in their children. A retrospective collection was defined as the collection of data after initial contact with the medical center but before the first medical consultation. The prospective collection was defined as the collection of data within 24 hours from the time of the medical consultation but before starting any therapeutic intervention. A medical consultation was defined as an outpatient visit and included a complete medical examination (history taking and full physical examination). Based on previous reports in the literature, data were analyzed at two cutoff values: CoMiSS total score ≥12 and CoMiSS total score >9 [9,11,12]. The first is the score currently considered suggestive of CMPA. The findings of one study documented a significant decrease in CoMiSS™ total score during the implementation of a cow's milk-free diet and an increase during oral food challenge [9]. Regarding the latter, the 95th percentile for the total CoMiSS™ score was 9 in a large series of healthy infants who had a high prevalence of positive oral food challenge when the ≥12 cut-off was used [11]. In contrast, a CoMiSS™ cut-off score of >9 was proposed to be more sensitive and more predictive of a response to a cow’s milk-free diet in a group of symptomatic infants than the cut-off score of ≥12 [12]. Ethical approval was obtained from the Bioethics Committee of the Medical University of Warsaw before starting the study (Approval No. AKBE/206/2019). Informed consent was obtained from all parents. The CoMiSS™ questionnaire, originally published in English, was translated into Polish.

Statistical analysis

The analysis was conducted using the statistical software R (version 3.5.1; http://cran.r-project.org). Differences between groups with respect to nominal secondary outcomes were assessed using the chi-square test or Fisher’s exact test. Data are expressed as means (95% confidence intervals, 95% CIs), medians (Q1–Q3), or numbers (n [% of total]). Data were assessed for
normality using the Shapiro–Wilk test. The CoMiSS total and individual components obtained retrospectively or prospectively were compared between groups using the Wilcoxon signed-rank test. Differences were considered significant at two-sided \( p \)-values <0.05.

**RESULTS**

This study was conducted between July and November 2019. Data of 110 children (62 males, 48 females) aged 2 weeks to 12 months with a mean±standard deviation age of 18.2±11.7 weeks were obtained.

Results of the total CoMiSS™ data analyses are presented in Table 2. The CoMiSS™ overall score collected prospectively was significantly lower than that collected retrospectively (median difference [MD], −1.5; 95% CI −2.0 to −1.0; \( p < 0.001 \)). Similarly, scores for three individual components of the CoMiSS™ collected prospectively were significantly lower than those collected retrospectively, including the scores for crying (MD −0.5; 95% CI −1.0 to −0.000006; \( p = 0.006 \)), regurgitation (MD −1.0; 95% CI −1.5 to −1.0; \( p < 0.001 \)), and stool (Bristol scale; MD −2.0; 95% CI −2.0 to −0.00002; \( p = 0.002 \)). There were no differences in the CoMiSS™ individual component scores for skin symptoms and respiratory symptoms collected retrospectively compared with the scores collected prospectively.

Seventeen of 110 (15.5%) infants had a CoMiSS total score ≥12 during the retrospective assessment. However, only 11 (10%) infants had a score ≥12 during the prospective assessment. This difference was not significant (\( p = 0.109 \)). Nine (8.2%) infants had a score ≥12 on both retrospective and prospective assessments. Eight of 99 (8.1%) infants with a prospective score <12 had a CoMiSS total score ≥12 during the retrospective assessment.

Thirty-two of the 110 (29.1%) infants had a CoMiSS total score >9 during the retrospective assessment. However, only 19 (17.3%) infants had a score >9 during the prospective assessment. This difference was significant (\( p = 0.004 \)). Sixteen (14.5%) infants had a score >9 on both retrospective and prospective assessments. Sixteen of 91 (17.6%) infants with a prospective score ≤9 had a CoMiSS total score >9 during the retrospective assessment.

**Post-hoc**, we analyzed the CoMiSS™ values in two age groups: infants younger than 6 months and infants older than 6 months (Table 3). The difference between the retrospective and prospective determinations of the CoMiSS total score was similar between children younger and older than 6 months. Differences between the retrospective and prospective determinations of the individual components of the CoMiSS™ were also similar between

| Table 2. CoMiSS™ data analyses (overall and individual components): retrospective and prospective analyses |
|---------------------------------|-------------------------------|-------------------------------|---------------------|---------------------|
| CoMiSS™ score                  | Retrospective CoMiSS™ determination | Prospective CoMiSS™ determination | MD               | 95% CI              | \( p \)-value   |
| Overall value                  | 7.0 (4.0–10.0)                 | 6.0 (3.25–9.0)                | −1.50             | −2.0 to −1.0        | <0.001         |
| Crying                         | 1.0 (0.0–3.0)                  | 1.0 (0.0–3.0)                 | −0.50             | −1.0 to −0.000006   | 0.006          |
| Regurgitation                   | 1.0 (0.0–3.0)                  | 1.0 (0.0–2.0)                 | −1.00             | −1.5 to −1.0        | <0.001         |
| stools (Bristol scale)          | 2.0 (2.0–4.0)                  | 2.0 (0.0–4.0)                 | −2.00             | −2.0 to −0.000002   | 0.002          |
| skin symptoms                  |                               |                               |                   |                     |                |
| Urticaria                       | 0.0 (0.0–0.0)                  | 0.00 (0.0–0.0)                | N/A               | N/A                 | N/A            |
| Atopic eczema                   | 0.0 (0.0–0.0)                  | 0.0 (0.0–1.0)                 | 0.35              | −0.5 to 1.5         | 0.446          |
| Respiratory symptoms            | 0.0 (0.0–1.0)                  | 0.50 (0.0–1.0)                | −0.000007 to 1.00 | 0.068               |                |

Data are presented as median (Q1–Q3); comparison of the groups using the Wilcoxon signed-rank test.

CoMiSS: Cow’s Milk-related Symptom Score, MD: median difference, CI: confidence interval, N/A: not applicable.
the groups with one exception. For atopic eczema, the difference was significantly lower in infants aged >6 months \((p=0.001)\).

**DISCUSSION**

**Principal findings**

This study demonstrated that the timing of determining CoMiSS™ values is important because CoMiSS™ total scores determined retrospectively and prospectively differed. Lower CoMiSS™ total scores and lower scores for some of the CoMiSS™ individual components (including those for colic, regurgitation, and stool) were obtained during the prospective assessment.

The study design did not allow us to conclude which type of evaluation of symptoms, i.e., retrospective or prospective, was superior. However, possible differences should be considered when using CoMiSS™ in clinical practice. For example, if the CoMiSS™ assessment is repeated during follow-up, the assessment should be performed in the same way. The same applies if CoMiSS™ is used to recruit patients in clinical trials.

This study was not designed to determine a CoMiSS™ cut-off value for identifying infants with CMPA. However, considering the ongoing discussion on optimal cut-off values, we analyzed two sets of CoMiSS™ values based on those previously reported. First, we used the originally proposed CoMiSS ≥12 [9]. It has been reported that using this CoMiSS™ cut-off is useful for identifying infants at risk for CMPA, and a good correlation exists between a positive score (≥12) and positive oral food challenge [13,14]. Oral food challenge is considered the gold standard for diagnosing food allergy [5,15]. More recently, a new cut-off value of >9 was proposed [11,12]. In our study, the difference between the retrospective and prospective assessments was significant only in the case of a CoMiSS total score >9. However, whether CoMiSS™ can be used as a potential diagnostic tool in infants with suspected CMPA remains to be determined [14,16,17].

*Post-hoc*, we also compared the difference in the CoMiSS™ total score and its individual components between infants younger and older than 6 months. The rationale for a 6-month cut-off was that it is likely to reflect children who do or do not receive complementary foods. In Poland [18], in line with the current European recommendations [19], exclusive or full breastfeeding should be promoted for at least 4 months (17 weeks, beginning of the 5th month of life), and exclusive or predominant breastfeeding for approximately 6 months.

| CoMiSS™ score                  | Children ≤6 months | Children >6 months | MD   | 95% CI          | p-value      |
|--------------------------------|--------------------|--------------------|------|-----------------|--------------|
| Overall value                  | -1.00 (-2.00–0.00) | -1.00 (-3.00–0.00) | 0.00 | -0.00004 to 2.00 | 0.143        |
| Crying                         | 0.00 (-1.00–0.00)  | 0.00 (-1.00–0.00)  | 0.00 | -1.00 to 0.0007  | 0.499        |
| Regurgitation                  | -1.00 (-1.00–0.00) | 0.00 (-1.00–0.00)  | -1.00 | -1.00 to 0.00001 | 0.194        |
| Stool (Bristol scale)          | 0.00 (-2.00–0.00)  | 0.00 (-2.00–0.00)  | 0.00 | -0.01 to 2.00   | 0.403        |
| Skin symptoms                  |                    |                    |      |                 |              |
| Urticaria                      | 0.00 (0.0–0.0)     | 0.00 (0.0–0.0)     | 0.00 | N/A             | N/A          |
| Atopic eczema                  | 0.00 (0.0–1.00)    | 0.00 (0.0–0.00)    | 0.000005 | 0.00002 to 1.00 | <0.001        |
| Head-neck-trunk manifestation  | 0.00 (0.0–1.00)    | 0.00 (0.0–0.00)    | 0.00003 | 0.00002 to 1.00 | <0.001        |
| Arms-hands-legs-feet manifestation | 0.00 (0.0–0.00)    | 0.00 (0.0–0.00)    | 0.00005 | 0.00005 to 0.00006 | 0.003          |
| Respiratory symptoms           | 0.00 (0.0–0.00)    | 0.00 (0.0–0.00)    | 0.00 | -0.0003 to 0.0003 | 0.247        |

Data show difference between prospective and retrospective CoMiSS values. Data are presented as median (Q1–Q3); comparison of the groups using the Mann–Whitney U-test.

CoMiSS: Cow’s Milk-related Symptom Score, MD: median difference, CI: confidence interval, N/A: not applicable.
is considered a desirable goal. Complementary foods should not be introduced before 4 months but should not be delayed beyond 6 months. However, with one exception, no differences were observed between the two age groups. Thus, it is unlikely that infant age significantly affects CoMiSS™ values.

Comparison with other studies

Our findings are consistent with those observed in healthy infants [10,11]. One previous study showed excellent agreement of CoMiSS™ values when scored by a parent or HCP and when performed on three consecutive days by the same assessor, but medium inter-rater variability was also noted between retrospective and prospective assessments [10]. The effect of retrospective versus prospective assessments of individual components was not assessed. However, discrepancies between retrospective and prospective collection of data on symptoms such as regurgitation and colic have been previously reported [20]. In line with our findings, a previous study showed that data on regurgitation and colic seem to be overestimated when collected retrospectively. Taken together, these studies document that in asymptomatic and symptomatic infants, CoMiSS™ values may differ depending on whether they were collected retrospectively or prospectively. One major reason for such differences, particularly for lower CoMiSS™ values obtained prospectively, may be the fact that the infant had now been examined by an HCP. Even if no medical intervention was initiated at this stage, as in our study, it may provide support and reassurance to caregivers. Consequently, their perception of symptoms, particularly subjective symptoms such as crying, may be affected [21]. Other studies evaluated the use of CoMiSS™ in presumed healthy infants in various populations [11] and the usefulness of CoMiSS™ in evaluating whether symptoms worsen or improve after medical interventions [22].

Strengths & limitations

A strength of our study was that it builds on the results of a previous study that found that while agreement between CoMiSS™ values in presumed healthy infants obtained from a parent or HCP was excellent, the score differed if collected retrospectively or prospectively. Our study isolated the two sources of variability in a previous study, i.e., retrospective vs. prospective rating and inter-rater differences (HCP vs. parent), by obtaining data solely from parents. Only subjects who visited clinics in a tertiary university hospital were included in the study. For pragmatic reasons, convenience sampling was used; i.e., the participants were selected based on their ease of recruitment. However, random sampling would reduce the risk of selection bias. This was a cross-sectional study; thus, it was subject to non-response bias; i.e., the participants/infants whose parents agreed to contribute could differ from those who were not approached; thus, the representativeness of the healthy infant population may be questioned.

CoMiSS™ is a potential awareness tool for use in infants with suspected CMPA. We showed that retrospective and prospective determination of CoMiSS™ values in symptomatic infants may affect results and thereby change diagnostic decisions and therapeutic procedures. Possible differences should be considered when using CoMiSS™ in clinical practice.

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