

Original Article



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Correspondence to

Yvan Vandenplas

KidZ Health Castle, UZ Brussels, Vrije
Universiteit Brussel (VUB), Laarbeeklaan 101,
1090 Brussels, Belgium.
Email: yvan.vandenplas@uzbrussel.be

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cited.

ORCID iDs

Nienke Knockaert
<https://orcid.org/0009-0000-8507-6802>
Koen Huysentruyt
<https://orcid.org/0000-0002-6402-1762>
Badriul Hegar
<https://orcid.org/0000-0002-5924-1664>
Jackeline Motta Franco
<https://orcid.org/0000-0003-3088-492X>
Victor Ravel Santos Macedo
<https://orcid.org/0000-0002-6483-0797>
Sarah Cristina Fontes Vieira
<https://orcid.org/0000-0002-0830-9657>
Yvan Vandenplas
<https://orcid.org/0000-0002-1862-8651>

Difference in Cow's Milk-Related Symptom Score (CoMiSS™) Among Presumed Healthy Infants in Indonesia and Brazil

Nienke Knockaert ¹, Koen Huysentruyt ¹, Badriul Hegar ²,
Jackeline Motta Franco ³, Victor Ravel Santos Macedo ⁴,
Sarah Cristina Fontes Vieira ³, and Yvan Vandenplas ¹

¹KidZ Health Castle, UZ Brussels, Vrije Universiteit Brussel (VUB), Brussels, Belgium

²Department of Child Health, Faculty Medicine Universitas Indonesia, Jakarta, Indonesia

³Reference Center for Food Allergies of Sergipe, Federal University of Sergipe, Sergipe, Brazil

⁴Department of Medicine, Federal University of Sergipe, Sergipe, Brazil

ABSTRACT

Purpose: The Cow's Milk-related Symptom Score (CoMiSS) improves the recognition of cow milk allergy (CMA) symptoms. A score of ≥ 10 should raise awareness of CMA. The median CoMiSS in healthy European infants aged < 6 months is 3. This study aimed to determine the impact of different regions on CoMiSS in healthy infants aged < 12 months to evaluate regional and age-related differences.

Methods: A prospective cross-sectional study was conducted at one hospital each in Indonesia (Jakarta) and Brazil (Sergipe). CoMiSS was assessed in healthy infants aged ~ 12 months old.

Results: In Jakarta, a total of 286 infants (50.7% boys) were included. The median (interquartile range) CoMiSS was 1.5 (0–4); the 95th percentile was 7. In Sergipe, 101 infants (60.4% boys) were included. The median (interquartile range) CoMiSS was 4 (4–6); the 95th centile was 10.9. Age (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.94–0.99; $p < 0.001$) and country (OR, 2.40; 95% CI, 2.06–2.79; $p < 0.001$) were significant independent predictors of changes in mean CoMiSS in a linear regression model ($r^2 = 0.27$).

Conclusion: Median CoMiSS in healthy infants differed between Jakarta and Sergipe (1.5 vs. 4.0). These findings highlight that the perceived normality of parents may be region-dependent.

Keywords: Cow's Milk-related Symptom Score; Healthy infant; Infant colic; Regurgitation; Stool consistency

INTRODUCTION

Cow's milk allergy (CMA) is a food allergy that occurs mainly in infants. The prevalence of CMA varies according to different assessment methods and predefined diagnostic criteria. In Europe, the reported prevalence ranges between 1.9% and 4.9% depending on feeding (formula vs. breastfeeding) and country [1,2]. A prevalence of 5.7% was reported in a recent systematic review [1], while the European Society of Pediatric Gastroenterology and Nutrition

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Conflict of Interest

YV has participated as a clinical investigator and/or advisory board member and/or consultant and/or speaker for Abbott Nutrition, Alba Health, Arla, Biogaia, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Pileje, and United Pharmaceuticals (Novalac). The authors have no financial conflicts of interest.

recently reported a prevalence of <1% [3]. In Indonesia, the prevalence of CMA is estimated to be between 2% and 7% [4]. A previous study did not reported differences in the prevalence of CMA between Western and Asian infants [5]. In Brazil, a cross-sectional study reported a prevalence of CMA of 5.7% [6].

Misdiagnosis of CMA is common due to the non-specificity of the symptoms and the lack of reliable diagnostic tests other than oral food challenge [3]. Underdiagnosis can cause nutritional deficiency and growth impairment, while overdiagnosis can be an economic burden [3]. Since infants on extensively hydrolyzed formula have a different taste preference than others [3], unnecessary elimination diets should be avoided.

The Cow's Milk-related Symptom Score (CoMiSS™) was developed in 2015 by a group of European experts and is intended to raise awareness regarding the recognition of CMA symptoms (**Supplementary Table 1**) [7]. This tool may help reduce over- and underdiagnosis while also aiding in the assessment of symptom evolution during treatment. A relevant percentage of infants with CMA have non-immunoglobulin (Ig)E-mediated CMA and, therefore, are negative for specific IgE for cow's milk while they are allergic to cow's milk [3,7]. Therefore, CoMiSS is of particular interest in non-IgE-mediated CMA.

CoMiSS incorporates various manifestations of CMA, including crying, regurgitation, stool consistency, skin manifestations, and respiratory problems. The scores range from 0 to 33 (**Supplementary Table 1**) [7]. In 2022, CoMiSS was updated after reviewing the evidence from 25 trials [8]. Infants at risk of CMA are identified using a cutoff value of ≥ 10 [8].

If, following an elimination diet, the initial CoMiSS decreases to ≤ 6 (the gold standard diagnostic test), oral food challenge yields positive results in 80% of cases [9,10]. Given that the score does not return to 0 during the diagnostic elimination diet, the data for CoMiSS in healthy infants has become relevant. Therefore, studies have been conducted to determine the age-related CoMiSS in healthy European infants. The overall median (interquartile range) CoMiSS in healthy European infants aged ≤ 6 months is 3 (1–5); the 95th percentile for this age group is 9 [11]. The overall median (interquartile range) CoMiSS in healthy infants aged 6–12 months is also 3 (1–5), with a 95th percentile of 8 [12]. Consequently, the CoMiSS in presumed healthy European infants aged 0–12 months is 3 (1–5) and is not age-dependent during infancy. The median CoMiSS in 808 Egyptian infants aged 0–12 months is 5 (5–6), with a 95th percentile of 7 [13].

To some extent, healthy infants have manifestations included in CoMiSS. Therefore, the determination of CoMiSS in presumed healthy infants is clinically relevant. We aimed to establish normal values in healthy populations with the intention of reassuring parents and providing healthcare professionals with information about normality. Among presumed healthy European infants aged 0–12 months, the crying time estimated by parents as normal differed between countries [11]. Therefore, it is relevant to determine CoMiSS in presumed healthy infants in different regions of the world. The relevance of this was highlighted by determining CoMiSS in 808 presumed healthy Egyptian infants [13]. It became relevant to evaluate CoMiSS in non-European infants to detect differences across continents. Therefore, this study aimed to determine the CoMiSS values in presumed healthy infants at a hospital in Indonesia (Jakarta) and another in Brazil (Sergipe).

MATERIALS AND METHODS

Study design and setting

A prospective cross-sectional study was conducted in presumed healthy infants in one hospital in Indonesia (Children Polyclinic, Private Hospital, Jakarta) and one center in Brazil (Santa Izabel Hospital, Sergipe), a reference center for normal pregnancies, with a dedicated outpatient follow-up setting for healthy term-born babies.

CoMiSS was developed as an awareness tool for healthcare professionals regarding the possibility that a combination of symptoms may be caused by cow's milk allergy [7]. CoMiSS collects information on the frequency and severity of regurgitation; stool consistency according to the Brussels Infants and Toddlers Stool Scale (BITSS); duration of crying; skin manifestations (e.g., atopic dermatitis, urticaria, and angioedema); and respiratory tract symptoms (e.g., runny nose, coughing) [7,8]. Each symptom has a maximum weight of 6, except for respiratory symptoms (which have a maximum of 3). The maximum score ranges from 0 to 33. A score of >10 should raise awareness about the possibility that CMA might be the cause of the combination of symptoms, while a score of <6 makes the diagnosis of CMA very unlikely [7,8]. As a consequence, CoMiSS will decrease during a diagnostic elimination diet if the suspected diagnosis of CMA is correct; however, the score will not decrease to 0 because many healthy infants present some of the manifestations listed in CoMiSS. Therefore, to evaluate the efficacy of a diagnostic elimination diet, it is important to determine CoMiSS values in a presumed healthy population. However, normal data in European infants have shown variability between countries for some subscores, especially for crying. Therefore, it is important to determine the normal range of CoMiSS in various parts of the world. In this study, CoMiSS was determined based on the information provided by the parents by experienced and trained pediatricians from a single center during a single visit to a welfare clinic or regular follow-up consultation in presumed healthy native children aged 0–12 months. Only infants born to native Indonesian or Brazilian parents were included from the respective countries. Additional information, including gestational age, sex, age, and feeding type was obtained. Exclusion criteria were as follows: i) parents of different ethnicities; ii) prematurity (<37 weeks of gestation at birth); iii) known or suspected diseases; iv) infants seeking medical consultation due to symptoms related to CMA; and v) infants using medication, therapeutic formula, or food supplements other than the recommended vitamins. Ethical approval was obtained from the corresponding ethics committees, including the Ethical Committee of UZ Brussels. No funding was received for this study.

Statistical analysis

IBM SPSS Statistics for Windows, Version 29.0 (IBM Co.) was used for statistical analyses. A *p*-value of <0.05 was considered statistically significant. To analyze the differences in proportions between groups, a chi-square test was used, and for continuous variables, a Mann-Whitney U or Kruskal–Wallis test was performed. The Kolmogorov–Smirnov test was used to check for a normal distribution. Normally distributed values are described using means and standard deviations; abnormally distributed values are described using medians and interquartile ranges. Regression analysis was used to assess the influence of age, sex, feeding type, and country on CoMiSS.

For age-dependent analysis, the categories—0–2, 2–4, 4–6, 6–8, 8–10, and 10–12 months—were compared and referred to as the first age category analysis. The categories of 0–6 and 6–12 months were also analyzed and referred to as the second age category analysis in this article.

RESULTS

JAKARTA

1. Population description

A total of 301 infants were included in the Indonesian database. Nine infants were excluded because they were not healthy, two were excluded because of incomplete data, one was excluded because of incorrect data, and two were excluded because their ages were >12 months.

Of the 286 remaining infants, 145 (50.7%) were boys and 141 (49.3%) were girls. Of these infants, 89.9% were breastfed (mixed+exclusively), 49.7% were exclusively breastfed, 32.9% received formula feeding (mixed+exclusively), and 30.4% had already started solid feeding. The overall median (interquartile range) age was 3 (1–6) months. There were no significant differences in age according to sex ($p=0.987$).

2. Overall results of the CoMiSS

The overall median (interquartile range) CoMiSS was 1.5 (0–4) (**Fig. 1**); the 95th percentile was 7. A CoMiSS of ≥ 10 was only observed in 0.7% (two infants had a score of 10; no work-up for CMA was performed). No significant differences in CoMiSS were observed according to sex ($p=0.212$) (**Supplementary Fig. 1**). None of the symptoms of CoMiSS were sex-dependent. A significant decrease in breastfeeding was observed with increasing age in both groups ($p \leq 0.001$). There was a significant difference in both age categories for formula feeding ($p \leq 0.001$), showing an increase in formula feeding with increasing age until months age of 10–12 months. Furthermore, a significant increase in solid feed was observed with increasing age ($p \leq 0.001$).

No significant overall differences in CoMiSS were observed according to breastfeeding (mixed+exclusively) ($p=0.544$), exclusive breastfeeding ($p=0.344$) (**Supplementary Fig. 2**), or formula feeding ($p=0.287$). When looking at the different age groups, only a significant difference was observed in CoMiSS according to formula feeding in the 4–6 ($p=0.047$) and 6–8 ($p=0.036$) months groups. There was a lower percentage of infants with a CoMiSS of 10 in the formula-fed infants in the 4–6 months group (0% vs. 2%), but a higher percentage of infants with a CoMiSS of 10 in the formula-fed infants in the 6–8 months group (5.5% vs. 0%). Overall, a significant difference in CoMiSS was observed according to feeding solids

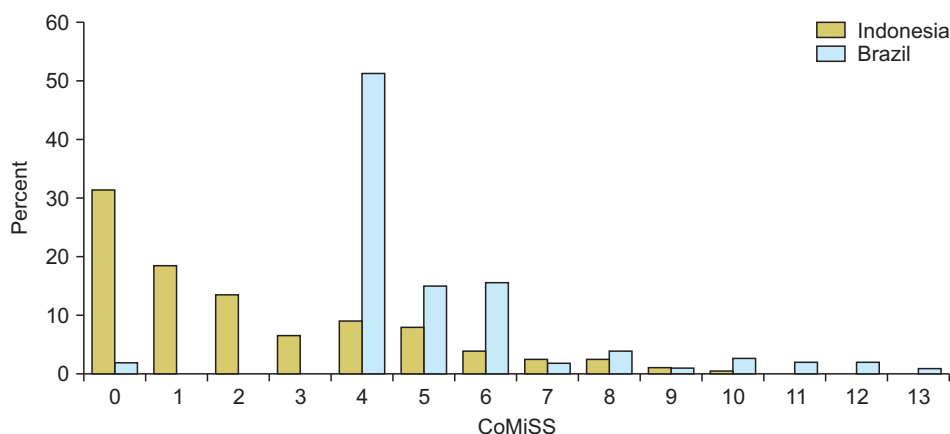


Fig. 1. Distribution of overall CoMiSS in Indonesian and Brazilian infants. CoMiSS: Cow's Milk-related Symptom Score.

($p=0.047$). A lower median (interquartile range) CoMiSS of 1 (0–4) was observed in the group already fed with solids compared to that of 2 (0–4) in the group not eating solids (**Table 1**). A significant difference was observed in the group that already ate solids only for regurgitation ($p\leq 0.001$). Only 5% of the infants who already ate solids had more than two episodes of regurgitation per day, compared to 23% of the infants who did not eat solids.

In the first age category analysis, there was a significant difference in CoMiSS ($p=0.001$), with the highest median of 3 in the 0–2 months group compared to a mean of 1 in the other age categories (**Table 1, Supplementary Fig. 3**). In the second age category analysis, there was a significant difference in CoMiSS ($p=0.037$), with a higher median (interquartile range) CoMiSS of 2 (0–4) in the 0–6 months group compared to that of 1 (0–4) in the 6–12 months group (**Table 1, Supplementary Fig. 4**).

Table 1. Descriptive statistics of CoMiSS in healthy Indonesian and Brazilian infants

Region (age)	N° infants	Median	Interquartile range	95th percentile
Overall CoMiSS				
Europe (0–6 mo) ²	891	3	1–5	9
Europe (6–12 mo) ³	609	3	1–5	8
Egypt (0–12 mo) ⁴	808	5	5–6	7
Indonesia (0–12 mo) ⁵	286	1.5	0–4	7
Brazil (0–12 mo) ⁶	101	4	4–6	10.9
Mexico (0–12 mo)	106	2	0–6	11
Crying/distress				
Europe (0–6 mo) ²	891	0	0–2	4
Europe (6–12 mo) ³	609	0	0–1	3
Egypt (0–12 mo) ⁴	808	0	0–1	2
Indonesia (0–12 mo) ⁵	286	0	0–1	1
Brazil (0–12 mo) ⁶	101	0	0–1	1
Mexico (0–12 mo)	106	0	0–2	4
Regurgitation				
Europe (0–6 mo) ²	891	0	0–1	3
Europe (6–12 mo) ³	609	0	0–1	2
Egypt (0–12 mo) ⁴	808	1	0–1	2
Indonesia (0–12 mo) ⁵	286	0	0–0	1
Brazil (0–12 mo) ⁶	101	0	0–1	5
Mexico (0–12 mo)	106	1	0–1	3
Stool consistency				
Europe (0–6 mo) ²	891	0	0–4	4
Europe (6–12 mo) ³	609	0	0–4	4
Egypt (0–12 mo) ⁴	808	4	4–4	4
Indonesia (0–12 mo) ⁵	286	0	0–0	4
Brazil (0–12 mo) ⁶	101	4	4–4	4
Mexico (0–12 mo)	106	0	0–4	6
Skin manifestations				
Europe (0–6 mo) ²	891	0	0–0	2
Europe (6–12 mo) ³	609	0	0–0	1
Egypt (0–12 mo) ⁴	808	0	0–0	0
Indonesia (0–12 mo) ⁵	286	0	0–1	3
Brazil (0–12 mo) ⁶	101	0	0–0	2
Mexico (0–12 mo)	106	0	0–0	1
Respiratory symptoms				
Europe (0–6 mo) ²	891	0	0–0	1
Europe (6–12 mo) ³	609	0	0–0	1
Egypt (0–12 mo) ⁴	808	0	0–0	0
Indonesia (0–12 mo) ⁵	286	0	0–0	1
Brazil (0–12 mo) ⁶	101	0	0–2	2
Mexico (0–12 mo)	106	0	0–0	1

N°: number, CoMiSS: Cow's Milk-related Symptom Score.

3. Contribution of each symptom to CoMiSS

1) Crying score

The most common classification in the crying sub-score was “crying ≤ 1 h/day,” accounting for 73.1% of the cases. None of the infants cried for >3 hours a day. The crying score was not significantly different in the first ($p=0.318$) nor the second age category analyses ($p=0.209$).

2) Regurgitation score

Most of the infants (82.5%) had 0–2 regurgitations a day. None of the infants had more than five episodes of regurgitation of more than half of the food. For feeding type, a significant difference was observed only in the regurgitation score according to solid feeding ($p<0.001$). As stated previously, infants who already ate solids had lower regurgitation scores, regardless of age. A significant difference was also observed according to the regurgitation score in the first age categories analysis ($p=0.006$) and the second age categories analysis ($p\leq 0.001$). A regurgitation score >1 was only observed in seven infants (2.4%) and was observed the most in the 2–4 months age group (5%) and not observed in those aged >8 months old.

3) Stools

Most of the infants had formed stools (78.7%). There was a significant difference in stool scores according to the first age category analysis ($p<0.001$) but not in the second age category analysis ($p=0.617$). Loose stools (30.7%) and watery stools (3.2%) were observed the most in the 0–2 months age category. There were no significant differences in stool scores for exclusive breastfeeding ($p=0.517$) or sex ($p=0.128$).

4) Skin symptoms

The most frequent skin score was 0 in 58.7% of infants. Only one infant had a skin score of 5. No urticaria or angioedema was observed. There was a significant difference in skin score according to the first age category ($p=0.025$) but not in the second age category ($p=0.230$).

A median (interquartile range) skin score of 1 (0–2) was observed in the 0–2 months group compared to that of 0 (0–0.25–1) in the other age categories.

5) Respiratory symptoms

The most frequent score was 0 (86.7%), which means no respiratory symptoms. None of the infants had severe respiratory symptoms; and only 1.7% had mild respiratory symptoms.

There were no significant differences in respiratory symptoms according to age ($p=0.879$ and 0.210 , respectively).

SERGIPE

1. Population description

Data were collected for 101 infants. There were 61 boys (60.4%) and 40 girls (39.6%). Of these infants, 64.4% were breastfed, 37.6% were exclusively breastfed, 44.6% received formula feeding, and 32.7% had started solid feeding. The median (interquartile range) age was 3.4 (1.8–7.6) months. There were no significant differences in sex according to age ($p=0.618$).

2. Overall results of the CoMiSS

The median (interquartile range) CoMiSS was 4 (4–6), with the 95th percentile at 10.9. A CoMiSS of ≥ 10 was observed in 8 (8%) of the infants. No significant differences in CoMiSS were observed according to sex ($p=0.579$) (**Supplementary Fig. 5**). No significant differences

were observed in CoMiSS according to breastfeeding ($p=0.924$), exclusive breastfeeding ($p=0.164$) (**Supplementary Fig. 6**), formula feeding ($p=0.281$), or solid feeding ($p=0.116$) across all age categories. A significant decrease in breastfeeding was observed with increasing age in the second age category ($p=0.010$). A significant increase in solid feeding was observed with increasing age in the first and second age category analyses ($p\leq 0.001$).

There were no significant differences in CoMiSS according to the first age category analysis ($p=0.417$) (**Supplementary Fig. 7**) or the second age category analysis ($p=0.260$) (**Supplementary Fig. 8**). However, a higher median CoMiSS was observed in the 4–6 and 8–10 months old groups in the first age category analysis and in the 6–12 months group in the second age category analysis.

3. Contribution of each symptom to CoMiSS

1) Crying score

For the crying sub-score, the predominant category was “crying ≤ 1 h/day” (88.1%). Only 1% of the infants cried >2 hours a day, and none cried >5 hours a day. Crying scores were not significantly different between the first ($p=0.682$) and second age category analyses ($p=0.573$).

2) Regurgitation score

For the regurgitation score, the most frequent score reported was “0–2 episodes/day” (75.2%). A regurgitation score >3 was observed in 7%. None of the infants experienced food regurgitation after each feeding. There were no significant differences in the regurgitation score between the first ($p=0.388$) and second age category analyses ($p=0.137$). No significant differences in regurgitation score were found according to sex ($p=0.342$) or feeding type ($p=0.899$, 0.650 , 0.262 , and 0.161 , respectively).

3) Stools

Regarding stool characteristics, most of the infants had “loose stools” (89.1%), hard stools were observed in 5.9% of the infants, watery stools in 3%, and formed stools in 2% according to BITSS. The stool scores differed significantly between the first age category ($p=0.021$) and the second age categories ($p=0.021$ and 0.028 , respectively). The group of 0–2 months had higher stool scores, with a minimum score of 4 and a maximum score of 6; the 10–12 months had lower stool scores, with a minimum score of 0 and a maximum of 4. Of the 0–2 months old group, 10.3% had watery stools, and none of the other age categories had watery stools. Stool scores did not differ significantly between the exclusive breastfeeding and non-exclusive breastfeeding groups ($p=0.569$).

4) Eczema

Eczema was reported in 6/101 (5.9%) of the infants. Only one infant scored moderately for eczema. Urticaria was observed in 2/101 (2%) of the infants. There was no significant difference in the skin score between the first ($p=0.560$) and second age category analyses ($p=0.601$). There was no significant difference in the incidence of eczema based on sex ($p=0.746$) or exclusive breastfeeding ($p=0.519$).

5) Respiratory symptoms

Regarding respiratory symptoms, most of the infants (75.2%) had no respiratory issues; only one infant had “severe respiratory symptoms.” There was no significant difference in the respiratory symptoms between the first age categories analysis ($p=0.259$) and second age groups ($p=0.451$). There was no significant difference in respiratory scores according to sex ($p=0.070$).

4. Overall results for Jakarta and Sergipe

When comparing CoMiSS among infants from Jakarta and Sergipe, age (odds ratio [OR], -0.061 ; 95% confidence interval [CI], -0.089 to -0.033 ; $p < 0.001$) and country (OR, 2.96; 95% CI, 2.56–3.379; $p < 0.001$; OR, 3.05; 95% CI, 2.80–3.29; $p < 0.001$) were significant independent predictors of a change in CoMiSS in a multiple linear regression model ($r^2 = 0.34$) (Supplementary Fig. 9).

DISCUSSION

In Jakarta, the overall median CoMiSS was 1.5; the 95th percentile was 7. A higher median CoMiSS of 3 was observed in the 0–2 months group. In Sergipe, the median CoMiSS was 4, with the 95th percentile at 10.9. A higher median CoMiSS of 5 was observed in the 4–6 months group, and the highest median CoMiSS of 6 was observed in the 8–10 months group.

Previous studies carried out in European infants aged 0–6 and 6–12 months showed a median CoMiSS of 3 [11,12]. In the study of healthy European infants from 0 to 6 months old, a weak trend was found for a higher CoMiSS with increasing age [11]. This is consistent with the Brazilian data, but contradicts the Indonesian data.

In the 6–12 months group of healthy European infants, a decrease in CoMiSS was reported with increasing age, which was not clearly seen in this study [12]. It should be noted that the total number of children from Jakarta and Sergipe was smaller than the number of children in the bundled European data.

This study highlights the importance of country and age in interpreting the CoMiSS. The variation in the CoMiSS according to the country may suggest a difference in promptness in seeking medical help between countries. The lower CoMiSS in infants from the hospital in Jakarta may suggest that medical help due to CoMiSS-related symptoms is sought earlier than in infants born in Sergipe. The “private hospital setting” in Jakarta versus the “public setting” in Sergipe may also have contributed to this difference.

The incidence of CMA is highly variable owing to the assessment methods and may also be influenced by geography [13,14]. Using and reporting the CoMiSS worldwide could provide more information on geographical differences in the future.

The observed differences in CoMiSS between the two groups may be related to the relatively small sample size of infants from Sergipe ($n = 101$). However, the difference in the reported stool consistency appears to be the most contributing factor: “loose stool,” which has a CoMiSS of 4, was observed more in infants in Sergipe (89.1% vs. 30.7%). Although breastfed babies are known to generally produce less-formed stools than breastfed babies, the proportion of breastfed infants was higher in Jakarta than in Sergipe (89.9% vs. 64.4%, respectively). Although detailed information on diversification was not collected, eating habits differed between Asia and South America. The introduction of rice as a solid food in Indonesia may have contributed to the difference in the appreciation of stool consistency. The description of “stool consistency” by parents is subjective. Overall, the stool became more formed with increasing age [15]. A broad application of a “stool-tracker” (e.g., one developed based on a convolutional neural networks algorithm created by analyzing a total of 11,001 stool photographs from 4,836 non-toilet-trained children) would increase the

objectivity of the collected information, since the decision about stool consistency would be delivered through artificial intelligence [16].

In infants in Jakarta, a decrease in regurgitation was observed when solids were introduced. A thickened feeding can help with regurgitation [17]. The highest regurgitation score in Indonesian infants was observed in the 2–4 months group. This is consistent with the literature in Indonesia showing less regurgitation in older infants [18]. In both countries, watery stools were observed most in the 0–2 months group, which is consistent with the literature, showing that stools become more formed with increasing age [19].

A limitation of this study is that the data provided by healthcare professionals were based on retrospective parental recollections during the consultation. It is acknowledged that retrospective recall of symptoms often leads to exaggerated perception compared to methodical recording in a diary [20]. Another shortcoming is that, as in Jakarta and Sergipe, the data were collected from only one specific center. Given the size of both countries, it is possible that CoMiSS may differ in different regions of these countries. It can also not be excluded that the differences in settings (private versus public healthcare) strongly influenced the severity of symptoms when parents decided to consult a healthcare professional.

As stated previously, it is essential to note that CoMiSS is not a diagnostic tool for CMA. However, it can help prevent under- and overdiagnosis and can be helpful in assessing the difference after an elimination diet by comparing the scores before and after elimination. Since the median CoMiSS did not differ between Egyptian and European infants, CoMiSS may be a reliable awareness tool for CMA, regardless of ethnicity [13]. The median CoMiSS in healthy infants collected in one center each in Jakarta and Sergipe was 1.5 and 4, respectively, suggesting regional differences in the concept of “normality” in infants. However, these findings confirm that a CoMiSS of ≤ 6 is likely to be a good indicator of normality [7]. A comment that is frequently made is that CoMiSS may increase awareness and, therefore, induce overdiagnosis. The goal of the CoMiSS group was to establish normal values in healthy populations to provide reassurance. We are in the process of consolidating all data and designing centile curves for the overall CoMiSS, regurgitation frequency, and crying time.

In conclusions, CoMiSS was assessed in healthy infants in Jakarta and Sergipe. For infants in Jakarta, the median CoMiSS was 1.5, while for healthy infants in Sergipe, the median CoMiSS was 4. The observed difference was age-dependent and was mainly determined by the different reported stool consistencies. Future research should investigate the possibility of obtaining more objective data using artificial intelligence to define stool consistency.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

CoMiSS [7,8]

Supplementary Fig. 1

Distribution of CoMiSS according to sex in Indonesian infants.

Supplementary Fig. 2

Distribution of CoMiSS according to exclusively breastfeeding in Indonesian infants.

Supplementary Fig. 3

Distribution of CoMiSS according to the first age category analysis in Indonesian infants.

Supplementary Fig. 4

Distribution of CoMiSS according to the second age category analysis in Indonesian infants.

Supplementary Fig. 5

Distribution of CoMiSS according to sex in Brazilian infants.

Supplementary Fig. 6

Distribution of CoMiSS according to exclusively breastfeeding in Brazilian infants.

Supplementary Fig. 7

Distribution of CoMiSS according to the first age category analysis in Brazilian infants.

Supplementary Fig. 8

Distribution of CoMiSS according to the second age category analysis in Brazilian infants.

Supplementary Fig. 9

Distribution of CoMiSS according to country.

REFERENCES

1. Spolidoro GCI, Amera YT, Ali MM, Nyassi S, Lisik D, Ioannidou A, et al. Frequency of food allergy in Europe: An updated systematic review and meta-analysis. *Allergy* 2023;78:351-68. [PUBMED](#) | [CROSSREF](#)
2. Vandenplas Y, Brough HA, Fiocchi A, Miqdady M, Munasir Z, Salvatore S, et al. Current guidelines and future strategies for the management of cow's milk allergy. *J Asthma Allergy* 2021;14:1243-56. [PUBMED](#) | [CROSSREF](#)
3. Vandenplas Y, Broekaert I, Domellof M, Indrio F, Lapillonne A, Pienar C, et al. An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy. *J Pediatr Gastroenterol Nutr* 2024;78:386-413. [PUBMED](#) | [CROSSREF](#)
4. Setiabudiawan B, Sitaresmi MN, Sapartini G, Sumadiono, Citraresmi E, Sekartini R, et al. Growth patterns of Indonesian infants with cow's milk allergy and fed with soy-based infant formula. *Pediatr Gastroenterol Hepatol Nutr* 2021;24:316-24. [PUBMED](#) | [CROSSREF](#)
5. Paquete AT, Martins R, Connolly MP, Hegar B, Munasir Z, Stephanus S. Managing cow's milk protein allergy in Indonesia: A cost-effectiveness analysis of hypoallergenic milk formulas from the private payers' perspective. *J Health Econ Outcomes Res* 2022;9:77-85. [PUBMED](#) | [CROSSREF](#)
6. Vieira MC, Morais MB, Spolidoro JV, Toporovski MS, Cardoso AL, Araujo GT, et al. A survey on clinical presentation and nutritional status of infants with suspected cow' milk allergy. *BMC Pediatr* 2010;10:25. [PUBMED](#) | [CROSSREF](#)
7. Vandenplas Y, Dupont C, Eigenmann P, Host A, Kuitunen M, Ribes-Koninckx C, et al. A workshop report on the development of the Cow's Milk-related Symptom Score awareness tool for young children. *Acta Paediatr* 2015;104:334-9. [PUBMED](#) | [CROSSREF](#)
8. Vandenplas Y, Bajero K, Dupont C, Eigenmann P, Kuitunen M, Meyer R, et al. The cow's milk related symptom score: the 2022 update. *Nutrients* 2022;14:2682. [PUBMED](#) | [CROSSREF](#)
9. Vandenplas Y, Althera Study G, Steenhout P, Grathwohl D. A pilot study on the application of a symptom-based score for the diagnosis of cow's milk protein allergy. *SAGE Open Med* 2014;2:2050312114523423. [PUBMED](#) | [CROSSREF](#)
10. El-Shafie AM, Omar ZA, El Zefzaf HMS, Basma EM, Al Sabbagh NM, Bahbah WA. Evaluation of Cow's Milk Related Symptom Score [CoMiSS] accuracy in cow's milk allergy diagnosis. *Pediatr Res* 2023;94:987-95. [PUBMED](#) | [CROSSREF](#)

11. Vandenplas Y, Salvatore S, Ribes-Koninckx C, Carvajal E, Szajewska H, Huysentruyt K. The Cow Milk Symptom Score (CoMiSSTM) in presumed healthy infants. *PLoS One* 2018;13:e0200603. [PUBMED](#) | [CROSSREF](#)
12. Jankiewicz M, Ahmed F, Bajero K, Carvajal Roca ME, Dupont C, Huysentruyt K, et al. Cow's Milk-related Symptom Score (CoMiSS) values in presumed healthy European infants aged 6-12 months: a cross-sectional study. *Eur J Pediatr* 2024;183:707-13. [PUBMED](#) | [CROSSREF](#)
13. Bahbah WA, Knockaert N, El Zefzaf HMS, Huysentruyt K, Vandenplas Y. The cow's milk-related symptom score (CoMiSSTM) in presumed healthy Egyptian infants. *Nutrients* 2024;16:2666. [PUBMED](#) | [CROSSREF](#)
14. Woods RK, Stoney RM, Raven J, Walters EH, Abramson M, Thien FC. Reported adverse food reactions overestimate true food allergy in the community. *Eur J Clin Nutr* 2002;56:31-6. [PUBMED](#) | [CROSSREF](#)
15. Baaleman DF, Wegh CAM, de Leeuw TJM, van Etten-Jamaludin FS, Vaughan EE, Schoterman MHC, et al. What are normal defecation patterns in healthy children up to four years of age? A systematic review and meta-analysis. *J Pediatr* 2023;261:113559. [PUBMED](#) | [CROSSREF](#)
16. Xiao F, Wang Y, Ludwig T, Li X, Chen S, Sun N, et al. Generation and application of a convolutional neural networks algorithm in evaluating stool consistency in diapers. *Acta Paediatr* 2023;112:1333-40. [PUBMED](#) | [CROSSREF](#)
17. Leung AK, Hon KL. Gastroesophageal reflux in children: an updated review. *Drugs Context* 2019;8:212591. [PUBMED](#) | [CROSSREF](#)
18. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. *World J Gastroenterol* 2004;10:1795-7. [PUBMED](#) | [CROSSREF](#)
19. Steer CD, Emond AM, Golding J, Sandhu B. The variation in stool patterns from 1 to 42 months: a population-based observational study. *Arch Dis Child* 2009;94:231-3. [PUBMED](#) | [CROSSREF](#)
20. van den Brink M, Bandell-Hoekstra EN, Abu-Saad HH. The occurrence of recall bias in pediatric headache: a comparison of questionnaire and diary data. *Headache* 2001;41:11-20. [PUBMED](#) | [CROSSREF](#)