Validation of a Modified Cow's Milk-related Symptom Score (CoMiSS) for Screening of Lactose Intolerance in Adults

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ABSTRACT

Introduction: Lactose intolerance (LI) is the failure to digest foods and beverages containing the lactose present in milk. LI can present by many digestive symptoms. **Objective**: To validate the modified CoMiSS score for prediction of LI, that was confirmed by a stool acidity test. **Patients and Methods**: A cross-sectional study, was conducted at Ain Shams University Hospitals/ Gastrointestinal Clinics, and included one hundred adult participants during the period from December 2018 to December 2019. Enrolled patients had one or more gastrointestinal symptoms and were subjected to a stool acidity test (fecal PH test) as a reference test and modified CoMiSS as an index test. **Results**: The mean age of participants was 35.30 ± 10.714 years old; 55% were females, and their mean body mass index (BMI) was 23.08 ± 2.080 kg/m2, with no significant relation between LI and patients` gender or BMI. Out of the studied participants 24% had positive stool PH, LI diagnosed according to modified CoMISS was present among 19% of them. The mean value of modified CoMISS Score was significantly higher in positive cases (12.37) compared to negative LI participants (2.33) as $p<0.001$. Area under ROC Curve was 0.998, at the selected cut-off value 8, the sensitivity was 89.5% and specificity was 100% thus, levels of questionnaire scoring of 8 or higher would indicate presence of lactose intolerance. **Conclusion;** Modified CoMiSS is a simple, fast, and easy-to-use tool that can predict LI, with a cut-off value of > 8, the Area under the ROC Curve was 0.998, sensitivity 89.5%, and specificity was 100%.

Keywords: *LI, Modified CoMISS Score, Adults, Validity, Sensitivity, Specificity.*

INTRODUCTION

Lactose intolerance (LI) is a prevalent condition defined by failure to disassemble lactose to its ingredients.[1] It happens due to low lactase levels in the duodenum's brush border. Lactase defect is believed to affect roughly seventy percent of the worldwide people and both genders are affected in the same way.[2, 3]

LI differs from milk allergy; LI is the incapacity of digestive system to analyzed lactose due to the partial or total decrease in lactase, the main enzyme specialized in this action.[4] Cow's milk protein allergy (CMPA), on the other hand, is specialized by immune responses once the body comes into contact with cow's milk protein.[5]

Intolerance to lactose means the emergence of digestive problem such as gas, flushing, abdominal cramping and pain that may happen when eating huge amounts of lactose food, also nausea or vomiting may occur.[6] Several investigations were found to diagnose LI, such as genetic, endoscopic, and physiological investigations.[7] The widely used test is the lactose breathe hydrogen test. A blood test came next, as inability to elevate glucose levels more than 1.1–1.4 mmol/L implies lactose mal-digestion. Also other tests are available, and some are used more frequently in pediatrics than in adults.[8, 9]

LI is now over diagnosed, with clinical signs easily mistaken for other issues with the gastrointestinal tract, leading to unsubstantiated advice to prevent milk and dairies from consuming. There is therefore a good hope that non-invasive, easy-to-apply and one of cheap methods for diagnosis become available.[10]

Eighteen experts in the fourteen health centers worldwide reached agreement on CMPA signals and suggested the prediction of CMPA through Cow's Milk-Related Symptoms Score (CoMiSS).[11] CoMiSS is considered as a simple, quick, and convenient tool for raising awareness and assisting in the early detection of CMPA. CoMiSS can be used with medical treatment for evaluation and quantification CMPA development. CoMiSS was developed to assist general practitioners in better understanding and assessing symptoms associated with CMPA in various organ systems.[11,12]

CoMiSS evaluates five distinct symptoms of CMPA for the child: daily crying; regeneration occurrences in number and amount; consistency of stool; the occurrence and intensity of atopic and urticaria; and respiratory problems and their seriousness. The scale ranges of the CoMiSS are 0 to 33. [13]

For the assessment of an adult patient with LI, we developed a modified CoMiSS. The modified CoMiSS included five main symptoms presented in an adult patient with LI as nausea and vomiting, gas bloating flatulence symptoms, stool consistency, gurgling sound in the abdominal area, and pain cramps lower abdomen.

We aimed in current study to validate the modified CoMiSS as a predictor of LI in adults, as confirmed by a stool acidity test.

MATERIALS AND METHODS:

The current study was a cross-sectional study, conducted on Ain Shams University Hospitals/ Gastrointestinal Clinics, approved by Ain Shams University institutional Review Board (ASU-IRB) and written consent was taken from participants. This study enrolled 100 participants who met the following inclusion criteria; age >18 years old, with presence of ≥ 1 gastrointestinal tract (GIT) symptom with body mass index (BMI) range of 20-28 kg/m^2. The study excluded those using antibiotics, (except if antibiotics were stopped for seven days prior to enrolment), all infectious causes of diarrhea, people who had a medical problem or family situations that would prevent them from taking part in the study and individuals known to have a severe GIT disorder.

Study Tools:

All participants were assessed for GIT symptoms and BMI was calculated.

Laboratory investigations included complete blood count CBC for leukocytosis (diagnosed when white blood cell (WBC) count is typically above 11.0x10^9/L) [14] and anemia (In men, anemia is typically defined as a hemoglobin level of less than 13.5 gram/100 ml and in women as hemoglobin of less than 12.0 gram/100 ml) [15] and C-reactive protein CRP (positive level >1mg/dL) [16] and stool analysis for all participants to exclude other causes for GIT symptoms.

The stool acidity test (fecal PH test) was used for all the study participants to differentiate participants with LI and normal ones; before we begin the test, we make sure that the participants hadn't been exposed to any Barium procedures or

laxatives in the previous week. We gave our participants 50 gm lactose in the form of 1liter of milk, then waited for them to give us a fresh stool sample (at least 0.5 gm to 1gm) in a clean container; if the specimen was contaminated with urine or was on the outside of the container, it was rejected. The pH of the aqueous stool suspension was determined using pH paper, and the specimen was determined to be acidic at PH<7.

In healthy individuals all of the lactose is metabolized and absorbed from the GIT; however in lactose intolerant individuals, part or all of the lactose isn`t digested nor absorbed from the gastrointestinal and reaches the colon. The colonic bacteria cause the feces to be acidic. This acidity occurs after lactose consumption, so in case of acidic stool, the individual was diagnosed as lactose intolerant.[17]

Based on their stool PH results, the study participants were divided into normal adults and patients who had LI.

The study participants were then asked about the general features, history of any medical conditions, and clinical examination findings. After that a preformed questionnaire "modified CoMiSS" score for information gathering was fulfilled. This questionnaire included the following five major points: "Nausea and vomiting" were scored (0-6) from never to severe incapacitating vomiting, "Gas, bloating, and flatulence symptoms"; had score of (0-4) from never to very severe, "Fecal consistency" had been scored using the Bristol stool scale, with zero if normal stool was found (type 3 and 4), two points if soft stools was present (type 5), four points for hard stools (type 2) or liquid stools (type 6), five points for severe constipation (type 1) and six points for watery stools (type 7). "Gurgling sound" in the abdominal area was given a score 0-3 (absent to severe) and "Pain cramps in lower abdomen" were scored 0-4 (no pain to very severe). The modified CoMiSS is illustrated in table (1).

The CoMiSS questionnaire was used independently to assess our participants who

hadn't been diagnosed before as LI, neither had they been made aware of the relation between dairy intake and any GIT symptoms they suffered.

Table (1): Modified Cow's Milk-related Symptom Score (CoMiSS).

Symptoms	Score	Severity
Nausea and vomiting	0	Never
	1	Complains of nausea but tolerable
	2	Severe nausea needs medication
	3	Vomiting sometimes "small volume"
	4	Vomiting sometimes "large volume"
	5	Vomiting often most of time
	6	Severe incapacitating vomiting
Gas bloating flatulence	0	No
	1	Not very severe
	2	Quite severe
	3	Severe
	4	Very severe
Stool consistency	5	Type 1 severe constipation
	4	Type 2 "mild constipation lump sausage like"
	0	Type 3 and 4 "normal stool"
	2	Type 5 "soft stool"
	4	Type 6 "foamy frothy like stool
	6	Type 7 "watery stool"
Gurgling sound in abdominal area	0	Absent
	1	Mild
	2	Moderate
	3	Sever
Pain cramps lower abdomen	0	No pain
	1	Mild
	2	Moderate
	3	Severe
	4	Very severe

Scoring system for Modified CoMiSS tool ranges (0-23); the selected cut-off value was 8 (regarding operating characteristics ROC CURVE) which defines a 89.5%

and specificity was 100%. Thus, levels of questionnaire scoring of 8 or higher would indicate presence of lactose intolerance.

The local investigator team approved the translation of all study materials, including the Modified CoMiSS tool, into Arabic.

Statistical Analysis

The next descriptive analysis was conducted to characterize the sample: frequency, percentage, mean, and standard deviations. For continuous variables, Mann-Whitney and Wilcoxon Rank tests were used, and for categorical variables, the Pearson's Chi square test was used. The variables' normal distribution was checked using the Kolmogorov-Smirnov test before calculating their correlations using the Pearson's Correlation test.

Using the two values, the Cronbach Alpha test was used to determine the internal consistency of the Modified CoMiSS. Relying upon that prediction, the ROC curve for the Modified CoMiSS had been evaluated, and the area under the curve (AUC) of the ROC curve had been calculated. The ROC curve represented the relationship between true positive rate (sensitivity) and false positive rate (1-specificity) for various CoMiSS Thresholds (change from baseline).

The significance level was set at p level less than 0.05 ($P<0.05$). All data variables were encoded and computerized, and data was entered and statistical analysis was carried out by using Statistical Package for Social Science (SPSS) Version 23.0.

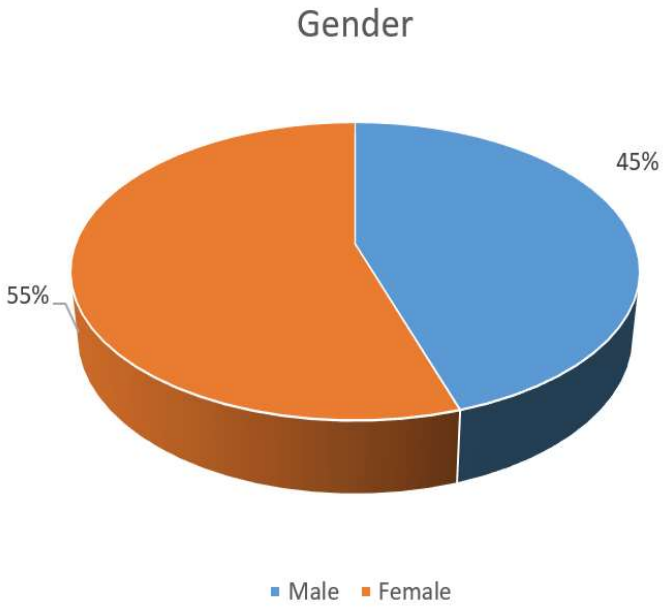
RESULTS

This cross-sectional study enrolled 100 participants. Table 2 summarizes mean age and BMI of participants. Female participants represent more than half of patients (55%) as demonstrated in Figure 1. No participants suffered from any chronic disease. Regarding laboratory finding; 16 % had leukocytosis, 14% had anemia and 24% had positive CRP and positive stool PH was found in 24% of our participants.

Table 2: Age, BMI and laboratory findings of the study participants

Age and BMI			
Variable	**Number**	**Mean ± SD**	**Range**
Age in years	100	35.30 ± 10.714	16 – 54
BMI	100	23.08 ± 2.080	20 – 27
Laboratory finding and stool acidity			
Variable		**Number**	**Percentage**
Leucocytosis		16	16%
Anemia		14	14%
Positive CRP		24	24%
Positive stool PH		24	24%

Figure 1: Gender distribution for the study participants.



LI according to modified CoMiSS was diagnosed in 19% of the study participants, the mean (SD) of score was 12.37(3.320). The mean of CoMiSS in positive cases detected by stool acidity was significantly higher than those negative for LI (Table 3).

Table (3): LI distribution among study participants regarding modified CoMISS Score

LI	Number	Mean	SD	P value (Sig)
Negative	81	2.33	1.877	0.001(HS)
Positive	19	12.37	3.320	

Student's t-test: -12.707, HS; Highly Significant.

There was no statistically significant difference between positive and negative LI patient (P> 0.05) regarding gender, age, CBC finding, or CRP finding, on the other hand there was statistically significant difference regarding stool PH and LI.

Table (4): LI frequency among study participants regarding gender, age, CBC finding, CRP positivity, stool analysis and PH of stools.

Variable	LI		Test	P value (Sig)
	Negative	Positive		
Male	36 (44.4%)	9 (47.4%)	Chi-square value: 0.053	1.00 (NS)
Female	45 (55.6%)	10 (52.6%)		
Age (mean ±SD)	35.06±10.966	36.32± 9.776	Student's t-test: -0.457	0.292 (NS)
CBC finding				
Normal	54 (66.7%)	16 (84.2%)	Chi-square value: 2.569	0.277 (NS)
Leucocytosis	15 (18.5%)	1 (5.3%)		
Anemia	12 (14.8%)	2 (10.5%)		
CRP findings				
Negative CRP	59 (72.8%)	17 (89.5%)	Chi-square value: 2.335	0.127 (NS)
Positive CRP	22 (27.2%)	2 (10.5%)		
Stool PH				
Negative	76 (93.8%)	0 (0%)	Chi-square value: 74.28	0.000 (VHS)
Positive	5 (6.2%)	19 (100%)		

Receiver operating characteristics ROC Curve was used to identify the cut-off point for modified CoMISS to diagnose LI among the study participants. Area under ROC Curve was 0.998, with cut-off value ≥8, Sensitivity was 89.5% and specificity was 100% (Figure 2).

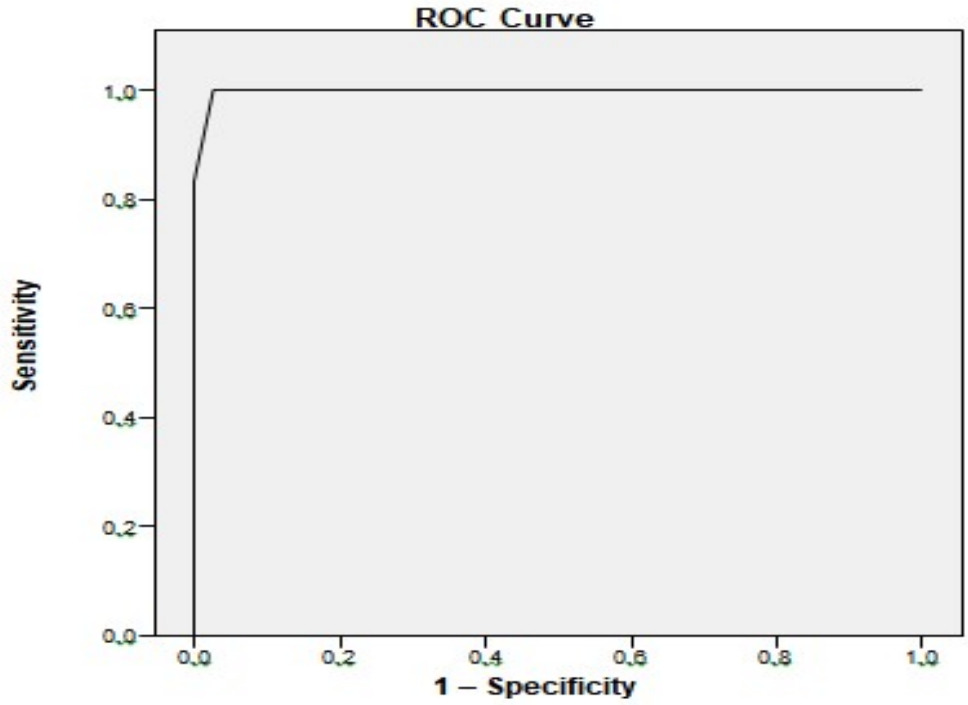


Figure (2): ROC curve showing Area under ROC Curve was 0.998, with cut-off value ≥8, Sensitivity 89.5% and specificity was 100%.

DISCUSSION

The Cow's Milk-related Symptom Score (CoMiSS) was designed to aid in the evaluation and quantification of related symptoms to cow milk protein allergy CMPA, also to ensure effective judgment and appropriate management.[12]

Various studies evaluated CoMiSS in children with CMPA, such as *El-Desouky et al.* [18] in 2021, who assessed CoMiSS in children had CMPA, and they demonstrated that there was a higher statistically significant total score of CoMiSS among confirmed CMPA than no CMPA. In the same line, *Prasad et al.* (2018) [19] considered the CoMiSS score as a CMPA predictor in Indian children.

These studies moreover discussed the validity of CoMiSS score in children as *El-Desouky et al.* [18] study, who showed that the accuracy of CoMiSS in the diagnosis of CMPA was 90.8%, with 86.4% for sensitivity and 93.4% for specificity when the score is >12, also *Prasad et al.* [19] study mentioned CoMiSS had a sensitivity and specificity of (77% and 66%) respectively at a cutoff value of 12 by CoMiSS.

In the current study, we developed a "modified CoMiSS score" to help in assessing symptoms that related to suspected LI in adults. As in medical practice, physicians frequently encounter patients who described some symptoms, as pain in abdomen, bloating, as well as diarrhea, after milk ingestion or ingestion of its derivatives, even in small amounts, as LI.[20]

The symptoms of LI and objective findings are poorly defined [21], which led to the unnecessary exclusion of milk as well as its derivatives from their diet, resulting in harmful health and psychological consequences.[22]

In the current study, Modified CoMiSS was used on 100 adult patient's complaint with one or more GI symptoms to reveal the association of this score and the diagnosis of LI after assessing the patients by stool acidity testing.

Many questionnaires assess digestive problems as Casellas et al. [23] (2009) who developed a validated questionnaire. However, other studies had examined symptoms with non-validated questions that directly explained the related symptoms, with the use of breath test.[10, 24]

Casellas et al. [23] (2009) questionnaire measured symptoms intensity in an adult participants using a 10 cm visual analog scale (VAS) to severity assessment of the main symptoms; diarrhea, vomiting occurrence, cramping, bowel related sounds, and flatulence occurrence or gases. Symptom severity was self-rated by subjects ranging from 0 – 10; by adding each result of the five VASs, the total score range was 0 -50 which differs from the current study score that ranged between 0-23.

In a recent study, Rocco et al.[25] (2021) used a *Casellas et al.* questionnaire to assess double-blind placebo challenge accuracy in diagnosing LI in patients with self LI reported symptoms. They give participants 25 grams lactose or 1 gram glucose as a placebo, patients with self-reported LI were enrolled in the study in random and blind way and subjected to a hydrogen breath test (HBT). All participates completed a validated questionnaire related to habitual consumption of dairy products at home and throughout the 4-h test after lactose or placebo administration. To minimize potential bias sources, one of the investigators administered all questionnaires while blinded to the experimental substrate used to perform HBT. They demonstrated that a blinded oral challenge with lactose and placebo is a viable and useful method for diagnosing LI.

In another recently published study by Ritter et al, [26] (2018) who used a new tool for assessing LI symptoms, including an eight-item LI symptom questionnaire, by using a LI composite symptom score; Cognitive interviews were used to implement and evaluate the LI symptom questionnaire, which was then subjected to psychometric analysis. The questionnaire includes response sets with Eleven-point numerical rating scale (NRS) and verbal rating scale (VRS) scales. This

study found that a LI symptom composite score made up of four abdominal symptom severity objects (abdominal pain, cramping, bloating, and gas) can be seen as a reliable and valid measure of LI symptom change over time. The four symptom severity items were clearly different but well related, consistent, and capable of supporting the calculation of a reliable symptom severity total score.

We used a stool acidity test as a reference test in this study, as the stools had a low pH when undigested lactose fermented into lactic acid [27]. However, *Casellas et al.* [23] questionnaire used the breath test as a reference test in which undigested lactose led to hydrogen production in the gut when the participants consumed large amounts of lactose. This test is mainly positive in 90% of patients with the condition. Results may be false-negative when the gut's normal bacterial flora is absent. Laxatives and recent antibiotic use can also affect the results.[28]

Using stool acidity test was considered as one of current study limitation; as the hydrogen breath test (gold standard test) wasn't available neither in location nor at time of our study, moreover the stool acidity test was available in our primary healthcare facilities as a primary diagnostic method.

By Modified CoMISS score; High sensitivity (89.5%) and specificity (100%) were found at cut off value $\geq$8 for LI diagnosis among this study participants; Our values are higher than those found by *Casellas et al.* [23] (2009) as they found lower sensitivity and specificity(0.75 and 0.67) respectively, in a cutoff point of 7. In the same line other study by Latorre et al. [29] (2014) assessed the prevalence of lactose intolerance in a double-blind placebo design using HBT as well as the symptoms questionnaire developed by *Casellas et al.* [30] (2010), A ROC curve was developed to predict lactose malabsorption utilizing HBT; a score of more than 6 proved : a sensitivity of 72%, a specificity of 81%, and an area under the curve (AUC) of 0.796 ($p< 0.001$). When diarrhea and vomiting were excluded from the symptom

score, the sensitivity was 67% and the specificity was 81% for predicting malabsorption.

The score developed by Ritter et al, [26] (2018) determined that a 3-point change had sensitivity of 75% and specificity of 68%, which are lower than the values obtained in the current study.

In comparison with our modified CoMiSS score; our score is easier , with less procedures and time which was appreciated by our participants than Rocco et al[25] and Ritter et al. [26] with better sensitivity and specificity than Ritter et al. [26], *and Casellas et al.*[23]

LI was defined as having symptoms after consuming 50 grams of lactose or less in a single dose [31], so in the current study we used 50 grams of lactose in the form of 1liter of milk; When lactose or milk was administered alone, most studies found that subjects with LI could ingest 12 grams (nearly 250 ml of milk) of lactose as a single dose with no or minor symptoms. LI became more noticeable as the dose was increased above 18 grams. [29, 32, 33]

LI is a common condition all over the world.[3] There were many studies from different countries that show a wide range of adult LI prevalence (15% to 70%) [34, 35], *Ramadan et al.* [36] (2020) found 65 % of adult Egyptian patients studied had LI, and *Rosado*[37](2016) reported that nearly half of the participants complained of discomfort in digestion caused by eating dairy products, and 70% of them had a positive test, indicating a deficiency in lactose digestion.

By using the stool acidity test in this study; LI was reported among 24% of patients' complaints with gastrointestinal symptoms, and a modified CoMISS score identified LI in 19%. These tests showed a highly statistically significant difference between LI patients and participants without LI. This difference in the finding was attributed to the fact that stool acidity test didn't specific for LI only

but also it contributed to other carbohydrate mal-absorption conditions so it can give false positive results, so we recommended further studies with a hydrogen breath test as a reference test.

The discrepancy in percentages among studies was caused by a lack of standardization in the amount of lactose prescribed for the tests, as well as the conditions under which they were performed and their interpretation, as well as genetic variability in the study populations. [17]

In our participants, there was no statistically significant difference regarding sex, gender, or BMI in line with *Ramadan et al.* [36] and *Rocco et al.*[25] (2021) who study LI diagnose. There is currently insufficient evidence to support an association between LI and gender, age, or BMI, other than differences due to LI genetic background.[37, 38]

Regarding our results, the modified CoMiSS can be viewed as a brief, easy-to-use tool and a practical method with high specificity and sensitivity to assist in reducing the delays and difficulties associated with LI, thereby reducing the prevalence of incorrect management among physicians and patients. CoMiSS could also be reliable in determining whether symptoms improve or worsen throughout a clinical treatment.

The current study has some limitations; as using stool acidity test as a reference test however this test wasn't the gold standard test, small sample size and conducting it in one health facility.

In conclusion, modified CoMiSS is a simple, quick, and simple-to-use tool that can predict Lactose Intolerance with a cut-off value of more than 8 with high specificity and sensitivity.

Conflict of interest:

No financial or personal association is confirmed by all authors with 3rd parties whose interests can be influenced positively or negatively by its content.

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REFERENCES

1. **Deng Y, Misselwitz B, Dai N, Fox M.** Lactose Intolerance in Adults: Biological Mechanism and Dietary Management. Nutrients 2015;7(9):8020-35.
2. **Facioni MS, Raspini B, Pivari F, Dogliotti E, Cena H.** Nutritional management of lactose intolerance: the importance of diet and food labelling. Journal of Translational Medicine 2020;18(1):260.
3. **Heine RG, AlRefaee F, Bachina P, De Leon JC, Geng L, Gong S, et al.** Lactose intolerance and gastrointestinal cow's milk allergy in infants and children - common misconceptions revisited. World Allergy Organ J 2017;10(1):41-.
4. **Rangel AHdN, Sales DC, Urbano SA, GALVÃO JGB, ANDRADE JCd, Macêdo CdS.** Lactose intolerance and cow's milk protein allergy. Food Science and Technology 2016;36:179-87.
5. **Baghlaf MA, Eid NM.** Prevalence, Risk Factors, Clinical Manifestation, Diagnosis Aspects and Nutrition Therapy in Relation to both IgE and IgG Cow's Milk Protein Allergies among a Population of Saudi Arabia: A Literature Review. Current Research in Nutrition and Food Science Journal 2021;9(2).
6. **Szilagyi A, Ishayek N.** Lactose intolerance, dairy avoidance, and treatment options. Nutrients 2018;10(12):1994.
7. **Misselwitz B, Butter M, Verbeke K, Fox MR.** Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management. Gut 2019;68(11):2080-91.
8. **Furnari M, Bonfanti D, Parodi A, Franzè J, Savarino E, Bruzzone L, et al.** A comparison between lactose breath test and quick test on duodenal biopsies for diagnosing lactase deficiency in patients with self-reported lactose intolerance. Journal of Clinical Gastroenterology 2013;47(2):148-52.
9. **Rana SV, Malik A.** Hydrogen breath tests in gastrointestinal diseases. Indian J Clin Biochem 2014;29(4):398-405.
10. **Dainese R, Casellas F, Mariné–Barjoan E, Vivinus-Nébot M, Schneider SM, Hébuterne X, et al.** Perception of lactose intolerance in irritable bowel syndrome patients. European Journal of Gastroenterology & Hepatology 2014;26(10):1167-75.
11. **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 paediatrica (Oslo, Norway: 1992) 2015;104(4):334-9.
12. **Vandenplas Y, Steenhout P, Järvi A, Garreau AS, Mukherjee R.** Pooled Analysis of the Cow's Milk-related-Symptom-Score (CoMiSS™) as a Predictor for Cow's Milk Related Symptoms. Pediatric Gastroenterology, Hepatology & Nutrition 2017;20(1):22-6.
13. **Vandenplas Y, Carvajal E, Peeters S, Balduck N, Jaddioui Y, Ribes-Koninckx C, et al.** The Cow's Milk-Related Symptom Score (CoMiSS(TM)):

Health Care Professional and Parent and Day-to-Day Variability. Nutrients 2020;12(2):438.
14. **Mank V, Brown K.** Leukocytosis. StatPearls [Internet](2020).
15. **Badireddy M, Baradhi KM.** Chronic anemia. StatPearls Internet](2018).
16. **Nehring SM, Goyal A, Bansal P, Patel BC.** C reactive protein (CRP). Treasure Island, FL: StatPearls(2020).
17. **Ugidos-Rodríguez S, Matallana-González MC, Sánchez-Mata MC.** Lactose malabsorption and intolerance: a review. Food & Function 2018;9(8):4056-68.
18. **El-Desouky AI, Anany HG, Mohammed ISI.** Assessment of CoMiSS among Children with Cow's Milk Allergy at Zagazig University Hospital. The Egyptian Journal of Hospital Medicine 2021;83(1):838-43.
19. **Prasad R, Venkata RSA, Ghokale P, Chakravarty P, Anwar F.** Cow's Milk-related Symptom Score as a predictive tool for cow's milk allergy in Indian children aged 0–24 months. Asia Pacific Allergy 2018;8(4).
20. **Jansson-Knodell CL, Krajicek EJ, Savaiano DA, Shin AS, editors.** Lactose intolerance: a concise review to skim the surface. Mayo Clinic Proceedings; 2020: Elsevier.
21. **Lomer M.** The aetiology, diagnosis, mechanisms and clinical evidence for food intolerance. Alimentary Pharmacology & Therapeutics 2015;41(3):262-75.
22. **Zhang X, Chen X, Xu Y, Yang J, Du L, Li K, et al.** Milk consumption and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses in humans. Nutrition & Metabolism 2021;18(1):1-18.
23. **Casellas F, Varela E, Aparici A, Casaus M, Rodríguez P.** Development, validation, and applicability of a symptoms questionnaire for lactose malabsorption screening. Digestive Diseases and Sciences 2009;54(5):1059-65.
24. **Casellas F, Aparici A, Pérez M, Rodríguez P.** Perception of lactose intolerance impairs health-related quality of life. European Journal of Clinical Nutrition 2016;70(9):1068-72.
25. **Rocco A, Compare D, Sgamato C, Martino A, De Simone L, Coccoli P, et al.** Blinded Oral Challenges with Lactose and Placebo Accurately Diagnose Lactose Intolerance: A Real-Life Study. Nutrients 2021;13(5):1653.
26. **Ritter AJ, Chey WD, Foyt HL, Lundy JJ, Coon CD, Savaiano DA.** Mo1048-A Novel Tool to Assess Symptoms of Lactose Intolerance and Define Meaningful Patient Benefit. Gastroenterology 2018;154(6):S-683.
27. **Morelli L, Amrani NE, Goulet O, Lukito W.** Lactose Intolerance: Clinical Symptoms, Diagnosis and Treatment. Global Diabetes Open Access Journal 2019.
28. **Vandenplas Y.** Lactose intolerance. Asia Pac J Clin Nutr 2015;24(Suppl 1):S9-13.
29. **Latorre G, Besa P, Parodi CG, Ferrer V, Azocar L, Quirola M, et al.** Prevalence of lactose intolerance in Chile: a double-blind placebo study. Digestion 2014;90(1):18-26.

30. **Casellas F, Aparici A, Casaus M, Rodríguez P, Malagelada JR.** Subjective perception of lactose intolerance does not always indicate lactose malabsorption. Clinical Gastroenterology and Hepatology 2010;8(7):581-6.
31. **Wilt TJ, Shaukat A, Shamliyan T, Taylor BC, MacDonald R, Tacklind J, et al.** Lactose intolerance and health. Evidence report/technology assessment 2010;192:1-410.
32. **Misselwitz B, Pohl D, Frühauf H, Fried M, Vavricka SR, Fox M.** Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. United European Gastroenterology Journal 2013;1(3):151-9.
33. **Dekker PJ, Koenders D, Bruins MJ.** Lactose-free dairy products: market developments, production, nutrition and health benefits. Nutrients 2019;11(3):551.
34. **Gil L, Scromeda MCP, Torres EE, Rott CM.** Intolerancia a la lactosa en pediatría. Revista de Posgrado de la VIa Cátedra de Medicina 2010;198.
35. **Vázquez SM, de Rojas JN, Troche JR, Adame EC, Ruíz RR, Domínguez LU.** The importance of lactose intolerance in individuals with gastrointestinal symptoms. Revista de Gastroenterología de México (English Edition)(2020)**.**
36. **Ramadan M, Eid AM, Seliem NM, Shokr HA.** Assessment of lactose intolerance in adult Egyptian patients with dyspeptic symptoms using lactase enzyme assay in duodenal biopsy. The Scientific Journal of Al-Azhar Medical Faculty, Girls 2020;4(2):300.
37. **Rosado JL.** Intolerancia a la lactosa. Gac Med Mex 2016;152(Supl 1):67-73.
38. **Lapides RA, Savaiano DA.** Gender, age, race and lactose intolerance: is there evidence to support a differential symptom response? A scoping review. Nutrients 2018;10(12):1956.