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ABOUT COVER

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AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (*WJCP*, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

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EDITORIAL

‘Prediabetes’ as a practical distinctive window for workable fruitful wonders: Prevention and progression alert as advanced professionalism

Sunil Jain

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Abstract

Diabetes is a devastating public health problem. Prediabetes is an intermediate stage in the disease processes leading to diabetes, including types 1 and 2 diabetes. In the article “Prediabetes in children and adolescents: An updated review,” the authors presented current evidence. We simplify and systematically clearly present the evidence and rationale for a conceptual framework we term the ‘3ASs’: (1) Awareness Sensible; (2) Algorithm Simple; and (3) Appealing Strategies. Policy makers and the public need to be alerted. The prevalence of prediabetes should send alarm bells ringing for parents, individuals, clinicians, and policy makers. Prediabetes is defined by the following criteria: impaired fasting glucose (100-125 mg/dL); impaired glucose tolerance (2 h postprandial glucose 140-199 mg/dL); or hemoglobin A1c values of 5.7%–6.4%. Any of the above positive test alerts for intervention. Clinical guidelines do not recommend prioritizing one test over the others for evaluation. Decisions should be made on the strengths and shortfalls of each test. Patient preferences and test accessibility should be taken into consideration. An algorithm based on age, physiological stage, health status, and risk factors is provided. Primordial prevention targeting populations aims to eliminate risk factors through public education and encouraging practices through environmental modifications. Access to healthy foods is provided. Primary prevention is for individuals with a prediabetes diagnosis and involves a structured program to reduce body weight and increase physical activity along with a healthy diet. An overall methodical move to a healthy lifestyle for lifelong health is urgently needed. Early energetic prediabetes action is necessary.

Key Words: Obesity; Overweight; Awareness; Algorithm; Lifestyle; Physical exercise; Screening; Primordial prevention; Primary prevention; Adolescents

Core Tip: Prediabetes provides a window for preventive action. The prevalence of prediabetes should send alarm bells ringing for parents, individuals, clinicians, and policy makers. Algorithms should delineate based on age, physiological stage, health status, and risk factors. Diabetes is dangerous and its management is difficult; hence, attention on prediabetes, which provides early opportunity for health promotion and prevention. Primordial prevention should target at-risk populations and primary prevention should target individuals for healthy lifestyles. Doctors should be proficient in modern technologies proficient to optimize prevention strategies.

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INTRODUCTION

Obesity is a global public health crisis. Prevalence rates are increasing among children and adolescents. Prediabetes identifies individuals at high risk of developing diabetes[1]. Prediabetes provides a preventive action window against progression and is considered an intermediate stage in all the disease processes leading to diabetes. The expanded list of diabetes etiologies is shown in Figure 1. All entities need necessary attention, particularly in prevention with increased efforts on identifying and acting on prediabetes.

"Discoveries many!
Necessitating strategies novel;
Innovative & inspiring".

In the article "Prediabetes in children and adolescents: An updated review" Ng *et al*[2] comprehensively present current evidence. They aim to provide pediatricians and primary care providers with an updated overview of this important condition. A clear understanding of the condition is essential for success with advancements professionally presented. Policy makers and the public need to be alerted and apprised. A simplified conceptual framework is presented as the '3ASs' in Figure 2.

AWARENESS SENSIBLE

As many as 34% or 88 million United States adults have prediabetes, as per the most recent estimate (2020) by the Centers for Disease Control and Prevention[3]. Children are likely to be similarly affected considering the increasing rate of obesity. Ng *et al*[2] reported a pooled prevalence of up to 8.84% from a recent systematic review and meta-analysis[2,4]. This increasing prevalence should send alarm bells ringing for parents, individuals, clinicians, and policy makers.

'Alarming statistics necessitate advanced strategies'.

Prediabetes is defined by the following criteria: Impaired Fasting Glucose (IFG) (100-125 mg/dL [5.6-6.9 mmol/L]), OR: Impaired Glucose Tolerance (IGT) (2 h postprandial glucose 140-199 mg/dL [7.8-11 mmol/L]), OR: Hemoglobin A1c (HbA_{1c}) values of 5.7%–6.4% (39-47 mmol/moL)[5].

Suspicions of prediabetes induce actions, and tests advance the actions to restore healthy status. Any of the above positive test alerts practitioners that intervention is necessary. Clear concepts are necessary for practitioners, and this should provide the impetus to the Core tip given by Ng *et al*[2] "child health practitioners are struggling with the definition".

'Knowing, understanding, & knack,
Testing, numbers, & tact'.

ALGORITHM SIMPLE

Evidence needs to be expertly incorporated into algorithms. We present an algorithm based on American Diabetes Association Professional Practice Committee recommendations (Figure 2)[6]. An algorithm based on age, physiological stage, health status, and risk factors is best.

The current comprehensive evidence is that: (1) 1 in 5 United States adolescents with obesity have prediabetes[7,8]; (2) The comorbidities of pediatric overweight and obesity are that prediabetes and diabetes occur more frequently among children ≥ 10 years of age, are in early pubertal stages, or have a family history of type 2 diabetes mellitus (T2DM)[8]; (3) The risk profile for diabetes mellitus and nonalcoholic fatty liver disease in children < 10 years of age is lower (especially in the absence of severe obesity). Hence, obtaining tests for abnormal glucose metabolism or liver function is not universally recommended for these children[8]; (4) Prediabetes is often associated with insulin resistance syndrome (also known as metabolic syndrome), which has dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both, and hypertension[5]; and (5) Progression of IFG to overt T2DM appears to be lower in the pediatric obese

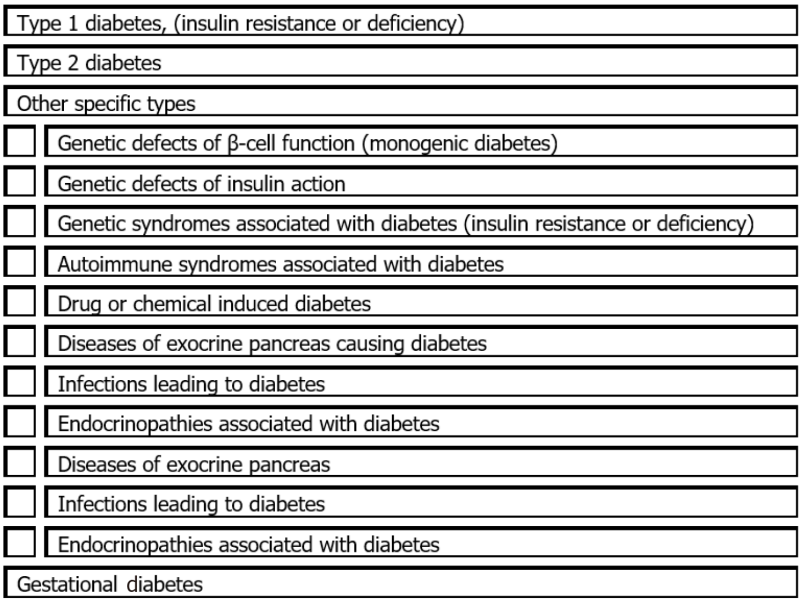

Figure 1 Etiologic classes of diabetes mellitus.

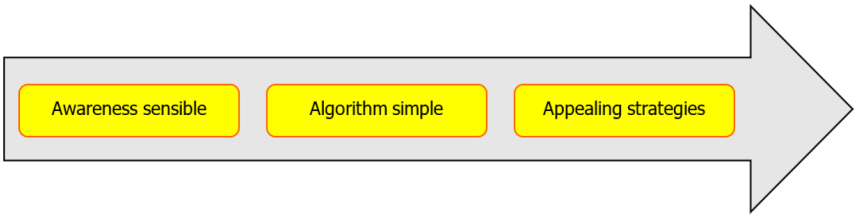

Figure 2 'Prediabetes' conceptual framework '3ASs'.

population than in adults[9]. However, the transition from IGT to T2DM is more rapid in children and adolescents than adults[10].

To encourage a pragmatic and efficient evaluation strategy (avoiding repeated testing), it is recommended that in children with obesity, evaluation for lipid abnormalities, abnormal glucose metabolism, and liver dysfunction be performed at the same time, beginning at 10-years-old[8].

Diagnostic tests for prediabetes are Fasting Glucose, Glucose Tolerance test, and HbA_{1c}. Clinical guidelines do not recommend preferring one test over the other for evaluation. Practitioners need to know and understand the strengths and shortfalls of each test for judicious use. Patient preferences and test accessibility should be taken into consideration [8].

In view of these, we recommend the following tests for abnormal glucose metabolism and discuss significance: (1) IFG: > 99 mg/dL (5.5 mmol/L) is the upper limit of normal, and alerts action because when left uncontrolled, it causes a progressively greater risk for the development of microvascular and macrovascular complications[5]; (2) IGT: Hyperglycemia when challenged with the oral glucose load, necessitates strict dietary measures, and adherence is improved when coupled with counselling; and (3) HbA_{1c}: The HbA_{1c} test is easy to obtain as it can be done anytime and fasting is not required. This provides stronger and more specific associations with cardiometabolic risk[11] (Figure 3).

Further, Ng *et al*[2] have provided a simplified approach algorithm, which leads with risk factors. One size does not fit all, especially in the growing pediatric age group. Ng *et al*'s[2] algorithm proposes oral glucose tolerance test or fasting plasma glucose, +/- HbA1C. Based on the definition above that states that any one positive test of the 'Tests for abnormal glucose metabolism' is sufficient to diagnose prediabetes, it is unclear what happens in the following situations: (1) Whether an IGT test will be performed in 'severely obese' children < 10-years-old when there are no risk factors and FBG is normal. Their algorithm suggests that the test should be performed only if risk factors are present. It should be performed, as (i) Individuals with IFG often manifest hyperglycemia only with the oral glucose load challenge, as in the standardized oral glucose tolerance test. Results will motivate a prevention rationale because (ii) subjects with both IFG and IGT have dangers of additive metabolic defects and are more likely to progress to overt T2DM[10]. Furthermore, should IGT be performed on overweight only patients with a positive IFG? No, as unnecessary testing is burdensome for individuals and healthcare institutions. Further, many individuals with IFG are euglycemic in their daily lives and may have normal or nearly normal HbA1c levels[5]. Thus, they have healthy diets, do not binge eat, and even if binging, their body is taking care of sugar levels. Lifestyle interventions for ideal weight should suffice, rewardingly!

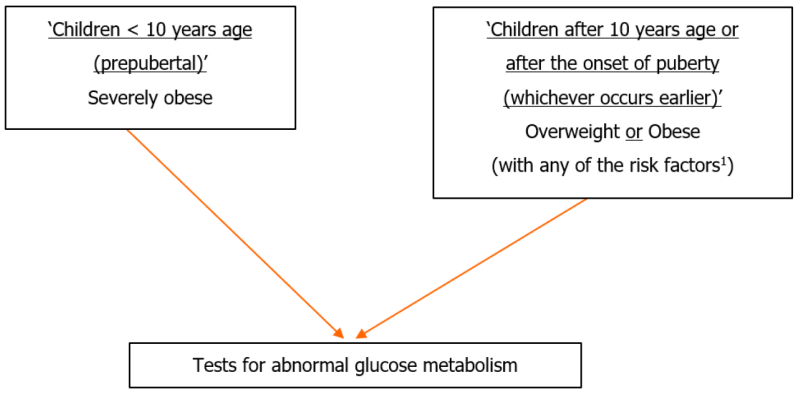

Figure 3 Algorithm for screening. [1]Risk factors: Maternal history of diabetes or gestational diabetes; Family history of diabetes in 1st- or 2nd-degree relative; Race/ethnicity (Native American, African American, Hispanic, Asian/Pacific Islander); Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome); Use of obesogenic psychotropic medications[1,8].

'Simple choices – comprehensive success'.

APPEALING STRATEGIES

Diabetes is dangerous, and its management can be difficult for good glucose control and complication prevention. Prediabetes provides an early opportunity for health promotion and prevention. Hence the need for energetic strategies with appeal that ensure success.

'Methods scientific, Motivation strong,
Success major over morbidity & mortality'.

Ng *et al*[2] write that "The lack of prospective long-term longitudinal data to inform evidence-based practice for disease prevention and complication avoidance is the real challenge and major gap in pediatric prediabetic research"[2]. Waiting for evidence is unpardonable. The Diabetes Prevention Program strikingly showed that lifestyle or drug intervention intensified in individuals with IGT prevents or delays the onset of T2DM[12]. Similar beneficial effects in obese adolescents with IGT are likely[5]! Such benefits necessitate large scale strategies for more benefits for many. The provision by Ng *et al*[2] of only individualistic strategies needs further expansion[2].

Prevention is most beneficial if it is early and energetic. Given the rising burden of lifestyle diseases and associated risks, we outline succinct strategies as appealing advancements: (1) Primordial prevention: Targeting an entire population is important, and this focusses on social and environmental conditions[13]. This aims at eliminating risk factors in general populations through public education and encouraging practice through modifications in the environment. Access to healthy foods is provided[1]. Breastfeeding should be encouraged and ensured, as it is associated with protection against childhood overweight and diabetes[14]. In mothers with gestational diabetes, breastfeeding protects against obesity and T2DM[15,16]. A sedentary lifestyle is to be avoided and the advice should be to be physically active for at least 60 min per day every day[17]; (2) Primary prevention: Interventions aiming at ameliorating risk factors reward favorably. Individuals with a prediabetes diagnosis should be promptly referred to a structured program for reducing body weight and increasing physical activity. A healthy meal plan is provided and intensive encouragement provided for compliance.

Appeal is ensured by education of long-term health burdens, which culminate in decreased life-expectancy. Health benefits of lifestyle modification are emphasized.

Attractiveness and compliance need to be ensured with motivational methods like health education and inspirational encouragement – 'healthy lifestyle favorable & must for lifelong happiness'.

In a recent Systematic Review, the benefits of using new information and communications technologies for improving health and preventing obesity were highlighted, with improvements in knowledge for nutrition habits and promotion of physical activity[18]. Therefore, doctors should be educated to be proficient in new technology use[19].

Ng *et al*[2] highlighted the use of metformin as a second-line management in individuals refractory to lifestyle interventions[2,20]. However, a recent systemic review was inconclusive as to the benefits of metformin to prevent the progression to overt T2DM in children and adolescents with prediabetes[21]. Hence, the focus should be on the continuation of lifestyle interventions.

Summary

Important points for professional impact are summarized in Figure 4.

CONCLUSION

In summary, the message is that if left unattended, the high incidence and higher risks of prediabetes will require the

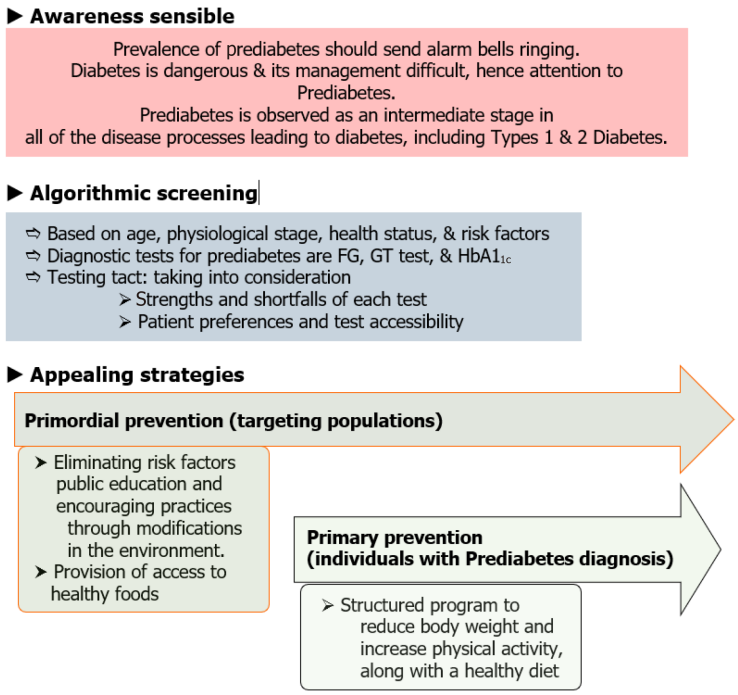

Figure 4 Visual summary.

highest level of major comprehensive professionalism. Patients transition to a healthy lifestyle for lifelong health needs practitioner attention and advancement.

"Progress for health, contemporarily, future favorable completely;
Prediabetes alerting professional tact timely;
Energetic and rationale, ensuring lifelong smiles surely".

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Imaging and endoscopic tools in pediatric inflammatory bowel disease: What's new?

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Abstract

Pediatric inflammatory bowel disease (IBD) is a chronic inflammatory disorder, with increasing incidence and prevalence worldwide. There have been recent advances in imaging and endoscopic technology for disease diagnosis, treatment, and monitoring. Intestinal ultrasound, including transabdominal, transperineal, and endoscopic, has been emerging for the assessment of transmural bowel inflammation and disease complications (*e.g.*, fistula, abscess). Aside from surgery, IBD-related intestinal strictures now have endoscopic treatment options including through-the-scope balloon dilatation, injection, and needle knife stricturotomy and new evaluation tools such as endoscopic functional lumen imaging probe. Unsedated transnasal endoscopy may have a role in patients with upper gastrointestinal Crohn's disease or those with IBD with new upper gastrointestinal symptoms. Improvements to dysplasia screening in pediatric patients with longstanding colonic disease or primary sclerosing cholangitis hold promise with the addition of virtual chromoendoscopy and ongoing research in the field of artificial intelligence-assisted endoscopic detection. Artificial intelligence and machine learning is a rapidly evolving field, with goals of further personalizing IBD diagnosis and treatment selection as well as prognostication. This review summarized these advancements, focusing on pediatric patients with IBD.

Key Words: Intestinal ultrasound; Endoscopy; Inflammatory bowel disease; Pediatrics; Imaging

Core Tip: Recent advances to imaging and endoscopic techniques and technology have improved the diagnosis, treatment, and monitoring of pediatric patients with inflammatory bowel disease. Options are now less invasive and can help avoid the repeat need for general anesthesia during endoscopy and imaging. Point-of-care ultrasound (transabdominal, transperineal, endoscopic), through-the-scope imaging (endoscopic functional lumen imaging probe) and treatment tools (balloon dilatation, injection, knife stricturotomy), unsedated transnasal endoscopy, virtual chromoendoscopy, and artificial intelligence were summarized in this current review.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder consisting of Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified[1,2]. The incidence of IBD continues to rise, including pediatric-onset disease, with most recent estimates approaching 1.5-2.0 per 10000 person years in areas with the highest rates of disease (Europe, North America)[3]. The youngest children, being diagnosed with very early onset IBD (< 6 years), are the fastest growing diagnosed population in Canada[4]. In the United States, nearly 1% of children and adults are living with IBD[5]. Recently, westernized countries, such as Asia and South America where IBD was rarely diagnosed, have seen a surge in newly diagnosed cases[3].

The gold standard of confirming a diagnosis of IBD includes macroscopic findings on endoscopy and microscopic findings on histopathology[6,7]. Imaging is a helpful additional tool, particularly in assessing bowel that is unable to be reached by upper and lower endoscopy. In addition to the initial diagnostic phase, endoscopy and imaging are essential tools in the ongoing monitoring and reassessment of disease activity in response to treatment. Disease monitoring has become a critical part of IBD patient care, particularly as mucosal healing has been identified as an important patient outcome to achieve[8].

The field of IBD has seen ongoing advancements in imaging and endoscopy over recent years. This is particularly of interest for pediatric patients, where better access to more noninvasive diagnostic, therapeutic, and monitoring tools could reduce the need for repeat general anesthesia for endoscopy and help alter the natural history of the disease by identifying when a treatment change is needed. Endoscopic advances may also now allow for the role of therapeutic endoscopy in place of surgery. Given how quickly technology has advanced in this area in the past several years, it is an important topic to review for training and practicing pediatric gastroenterologists. While there have been a few reviews of imaging or endoscopy in pediatric IBD (discussed below), there is a need to combine these topics and review all recent technology advances as a comprehensive approach in pediatric IBD. This review summarized these recent advances in imaging and endoscopy. This is not a systematic review but rather a focused review intended to summarize new changes and provide important clinical context.

IMAGING

Transabdominal intestinal ultrasound

Until recently, magnetic resonance (MR) and computed tomography enterography have been the mainstay of IBD imaging[9]. Gastroenterologist-performed point of care intestinal ultrasound (IUS) is now becoming more accessible in pediatric gastroenterology clinics worldwide, particularly since the implementation of the standardized International Bowel Ultrasound Group curriculum and available IUS scoring systems[10]. Bowel wall thickness, hyperemia, echogenicity, bowel wall stratification, and surrounding fat proliferation are some of the items that can be measured to assess bowel inflammation, with bowel wall thickness being one of the most relevant (Figure 1). Wall thickness has been shown to correlate well with MR and endoscopy[10]. It also allows for transmural assessment of the bowel, which endoscopy is unable to do. Importantly, IUS is well-received by pediatric patients and their caregivers, preferring it over other investigation modalities[11]. The optimal use of IUS in the decision-making tree during a patient's treatment course is under investigation. Whether or not IUS can replace repeat endoscopy is an important ongoing research question.

Transperineal ultrasound

Over a quarter of pediatric patients with IBD will have perianal disease in the form of fistulas and abscesses, most often associated with CD[12]. MR imaging (MRI) pelvis and exams under anesthesia (EUA) by a general surgeon are currently the only options for diagnosis and follow-up of both simple and complex perianal abscesses and fistula. Transperineal ultrasound, using microconvex and microlinear probes against the perineum, is a tool that is being explored in clinical practice for this use. Its use in clinic or at the same time as endoscopy may be a valuable means of perianal disease monitoring. Just like IUS, transperineal ultrasound (US) is more accessible than MR and avoids the general anesthesia

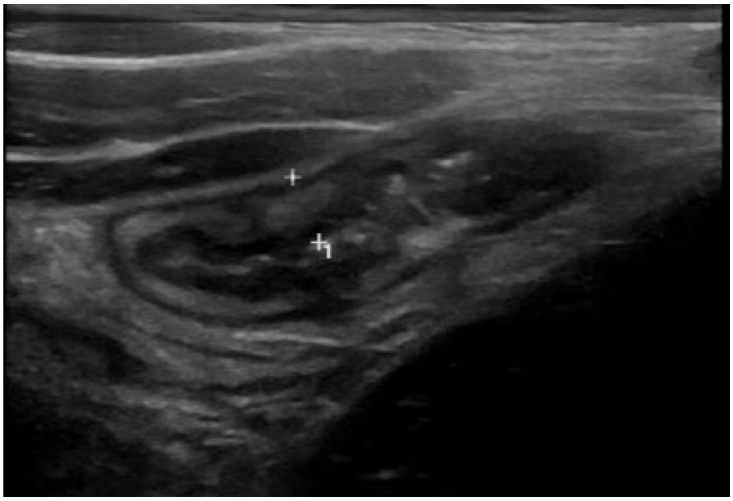

Figure 1 A transabdominal intestinal ultrasound image demonstrating an inflamed, thickened bowel wall of the terminal ileum in a pediatric patient with Crohn's disease.

associated with endoscopy and EUA, making it very favorable and accessible for repeated use in pediatric patients.

Another evolving utility is to use the transperineal probe to assess rectum mucosal disease activity in UC, an area that is very difficult to see on transabdominal IUS[13]. A recent study in pediatric patients with UC found transperineal US accuracy to be comparable to endoscopy[13]. It has also been shown to be able to distinguish between active IBD proctitis compared to non-IBD proctitis in children by detecting thicker bowel walls in those with inflammation[14]. Therefore, combining transperineal and transabdominal US would allow for a more complete assessment in UC, colonic CD, and IBD-associated perianal disease.

Endoscopic ultrasound

Mainly used for adult assessments, endoscopic ultrasound (EUS) has thus far been focused on pancreatic and biliary tree disease. The use of EUS in IBD has been limited mainly to assess bowel wall thickness[15] as well as perianal fistula tracts [9,16,17]. Similar to perineal US, its use to assess perianal fistulas and transmural inflammation, with the advantage of timing during colonoscopy, is an important area for further exploration. It may also be a helpful adjunct in guiding a surgical EUA and avoiding delay of the EUA by skipping the need for a preoperative pelvic MRI[17,18]. Future research is also needed to learn more about the EUS measurement of bowel wall thickness, similarly to IUS, and if this could help risk stratification or prognostication of patients at the time of their endoscopy.

ENDOSCOPY

Upper and lower endoscopy is an essential diagnostic and assessment tool in pediatric IBD[6]. It is the only IBD tool we have to assess mucosal disease both macroscopically and microscopically. Over recent years, there have been improvements in the quality of endoscopes (*e.g.*, more high-definition images) as well as available endoscopic tools such as balloon dilators and endoscopic needles[16,18].

Endoscopic balloon dilatation

Approximately 10% of pediatric IBD patients will present with an intestinal stricture at IBD diagnosis, with even more experiencing a stricture later in the disease course (inflammatory or fibrotic) or as a postsurgical anastomotic stricture [19]. In addition to surgery, through-the-scope balloon dilatation has become a therapeutic option for short (< 4 cm), single intestinal strictures in the setting of treated IBD (Figure 2). In the 1st year post-dilatation, surgery-free rates over 80% have been reported, although up to one-third may need repeat dilatation[6,20,21]. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition recently published a position paper on the use of endoscopic balloon dilatation for pediatric stricturing CD and highlighted the importance of an experienced endoscopist performing the dilation on short strictures (up to 5 cm) in the duodenum, terminal ileum, or colon with no associated fistula, phlegmon, or abscess[22]. Fluoroscopy at the same time could be considered but is not necessary for all patients. Both primary and postsurgical anastomotic strictures as well as inflammatory *vs* fibrotic strictures have had similar success rates with endoscopic dilatation[22].

Endoscopic injection

After dilatation disruption of strictured intestinal tissue, there is resulting inflammation that can lead to fibrosis and potentially reformation of the stricture. In an effort to reduce this inflammation and risk of re-stricturing, endoscopic intralesional anti-inflammatory medication injections (*e.g.*, steroids, infliximab) have been studied with mixed results[6].

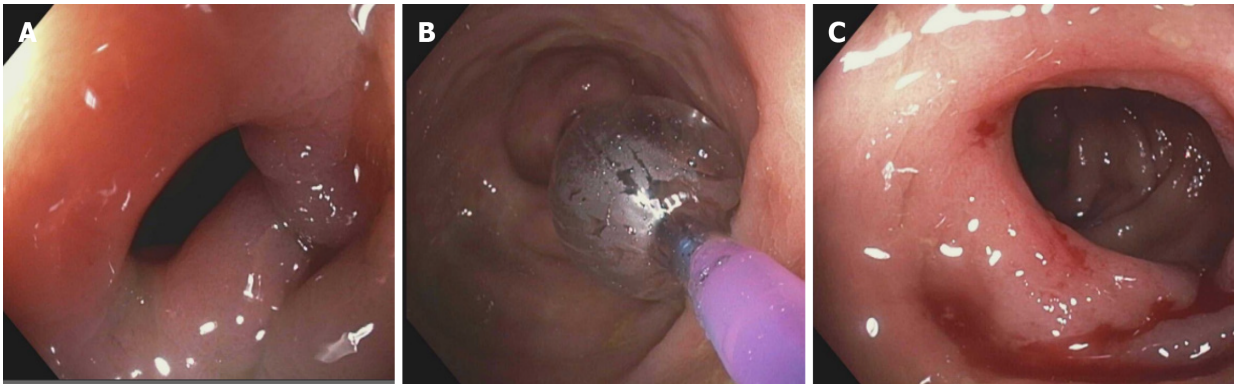

Figure 2 Endoscopic images demonstrating a through-the-scope balloon dilatation of an intestinal stricture in a pediatric patient with Crohn's disease. A: Predilatation; B: Balloon dilatation; C: Postdilatation.

One small pediatric randomized controlled trial found that compared to placebo injection, intrastricture injection of corticosteroid after endoscopic balloon dilatation had increased time free of re-dilatation and surgery[23]. Topical mitomycin, an antiproliferative agent, application post-dilatation has been reported for refractory esophageal strictures with mixed results[24] but is not yet widely explored in intestinal IBD strictures. Due to lack of sufficient evidence, intralesional injections and topical medication application during endoscopic balloon dilatation in pediatric IBD is not currently recommended[6].

Endoscopic stricturotomy

Endoscopic needle knife stricturotomy performed by an experienced endoscopist is an alternative for the treatment of persistent IBD strictures despite attempts at endoscopic balloon dilatation[25]. Circumferential or radial incisions are carefully made at the stricture site with the through-the-scope needle knife. One recent study of IBD patients with anastomotic strictures reported an improvement rate of 20% with this technique, with over 80% not needing surgical resection of the stricture[25]. Endoscopic stricturotomy has been reported in CD strictures, post-IBD surgery anastomotic strictures, and ileal-pouch strictures[26]. Comparison between stricturotomy and balloon dilatation in CD anastomotic strictures in adult patients found that stricturotomy appeared to be more effective, although both carry perforation and bleeding risks[27]. This has not yet been widely studied in pediatric IBD patients.

Endoscopic functional lumen imaging probe

Endoscopic functional lumen imaging probe (EndoFLIP) is a newer tool that is used at the time of endoscopy to assess lumen distensibility and stiffness, most commonly in the esophagus. It uses impedance planimetry to measure the cross-sectional area, lumen diameter, distension pressure, and overall motility[28]. Its reported uses have been in patients with achalasia, eosinophilic esophagitis (EoE), and pre-esophageal and postesophageal dilatation. The role of EndoFLIP in IBD-related intestinal strictures as well as preintestinal and postintestinal dilatation has not been widely described. A recent case report described its use in a 31-year-old IBD patient with a CD ileocolonic anastomotic stricture, demonstrating low lumen distensibility that improved after balloon dilatation[29]. This demonstrated its use in objectively quantifying the degree of fibrosis and the amount of improvement following a dilatation, similar to studies on EndoFLIP in esophageal strictures. Other potential uses include quantification of the length of the intestinal stricture and the lumen size, particularly in cases where the stricture is unable to be traversed by the scope. If this tool is able to confirm that a stricture is relatively short (< 4 cm), it may be amenable to treatment by endoscopic balloon dilatation rather than surgery, as discussed above.

Transnasal endoscopy

Unsedated transnasal endoscopy (TNE) has been gaining popularity in the last few years, particularly for follow-up of EoE[30]. Being able to perform awake TNE in the gastroenterology clinic allows for faster patient access and the avoidance of a general anesthetic. It also can help ease wait times for endoscopy and improve patient access. Its images and pathology specimens have been found to be comparable to standard peroral esophagogastroduodenoscopy[30]. Its use in IBD has not yet been explored. Approximately one-quarter of new pediatric IBD patients will have upper gastrointestinal (GI) tract involvement[19]. Esophageal disease and stricturing due to CD are rare but a possible disease complication, reported in up to 10% of adult patients with IBD[31]. In addition, patients with IBD have an increased risk of developing EoE[32]. Therefore, unsedated TNE may be a helpful clinic-based assessment tool in pediatric IBD patients presenting with dysphagia or upper GI symptoms or in the reassessment of known complex upper GI tract CD.

Virtual chromoendoscopy

The development of virtual chromoendoscopy (using a filter rather than a spray dye during endoscopy) has allowed for improved visual enhancement of the mucosal architecture during endoscopy. The majority of the literature has focused on its use in dysplasia detection, including colorectal adenocarcinoma[33]. Although rare in pediatric patients, colonoscopy for dysplasia surveillance is recommended annually starting at the time of diagnosis in patients with

concurrent primary sclerosing cholangitis as well as 8-10 years post-diagnosis of IBD affecting the colon (UC or colonic CD/IBD unclassified)[34]. Given the increasing rates of very early onset IBD (< 6-years-old at diagnosis), these patients will start undergoing dysplasia screening while still under the care of pediatric gastroenterology specialists. Increasing accessibility and training of this technology in pediatric IBD would be highly valuable.

ARTIFICIAL INTELLIGENCE

There has been a recent emerging role of artificial intelligence (AI) in gastroenterology to be able to improve endoscopic disease detection, diagnosis, and severity grading due to high endoscopic inter-rater variability that currently exists[35]. It has also been proposed as a potential IBD research tool to replace the need for a central endoscopy reader, which could help with the speed of trial completion[36]. In addition to diagnostic endoscopy, the use of AI to help detect small bowel ulceration and nonobstructive bowel stenosis in video capsule endoscopy is a developing field[37]. Furthermore, similarly to virtual chromoendoscopy, there is much interest in the use of AI to detect premalignant and malignant lesions in long-term IBD patients[38].

AI and its machine learning capabilities also holds promise in helping predict treatment response[38]. With the rapidly increasing number of available IBD biologics and small molecule medications, there is an important need for the development of personalized IBD care with the use of predictive markers. A recent systematic review of AI and machine learning in IBD identified 78 studies that have used clinical and microbiome data sets to aid in IBD diagnosis, disease course, and disease severity[39]. The number of recent publications on this subject has nearly doubled in the past 3 years, highlighting the growing interest[37]. Integrating AI at the time of patient diagnosis to help inform a treatment path with the highest likelihood of success would be of particular interest.

DISCUSSION

There have been exciting advances in imaging and endoscopic technology in pediatric IBD in recent years. Further development of less invasive diagnostic and therapeutic tools is always important for the pediatric population. There is new technology emerging from EoE and motility disorders that have not yet been explored in IBD (*e.g.*, EndoFLIP, unsedated transnasal endoscopy). The nature of a non-systematic review is a limitation of this current review. There is also a paucity of available pediatric literature given that the majority of research has focused on adult IBD patients.

CONCLUSION

The future of IBD will certainly benefit from diagnostic, assessment, and therapeutic tools that can aid in more personalized treatment to help establish early and sustained clinical, biochemical, and endoscopic remission. Future research should include prospective studies assessing efficacy, safety, and patient/caregiver satisfaction with these new imaging and endoscopic tools. It would also be of interest to identify if any of these tools are able to aid in the development of a treatment decision tree and eliminate the need for repeat sedated endoscopy or MRI in the pediatric IBD patient. Given the chronicity of IBD and with young pediatric patients being the fastest growing population with newly diagnosed IBD, there is a need to continue to develop these tools for use in patients that will live with this disease and potential disease-related complications for multiple decades.

FOOTNOTES

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MINIREVIEWS

Evolving strategies: Enhancements in managing eosinophilic esophagitis in pediatric patients

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Abstract

Eosinophilic esophagitis is a newly recognized disease first described about 50 years ago. The definition, diagnosis, and management have evolved with new published consensus guidelines and newly approved treatment available to pediatricians, enabling a better understanding of this disease and more targeted treatment for patients. We describe the definition, presentation, and diagnosis of eosinophilic esophagitis including management, challenges, and future directions in children. The definition, diagnosis, and management of eosinophilic esophagitis have evolved over the last 50 years. Consensus guidelines and newly approved biologic treatment have enabled pediatricians to better understand this disease and allow for more targeted treatment for patients. We describe the definition, presentation, diagnosis, management, and treatment in addition to the challenges and future directions of eosinophilic esophagitis management in children.

Key Words: Eosinophilic esophagitis; Esophagitis; Gastroesophageal reflux disease; Food allergy; Dysphagia

Core Tip: Eosinophilic esophagitis is a newly recognized disease described in the last 50 years. The definition, diagnosis, and management have evolved with new guidelines and medications available to allow for better understanding and treatment of pediatric patients. We describe the definition, presentation, diagnosis, and management including new biological treatment, long-term follow-up and the challenges of eosinophilic esophagitis in children. We discuss new management strategies and new future directions of monitoring eosinophilic esophagitis in children.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a persistent inflammatory disorder of the esophagus that arises in individuals with a genetic predisposition and is not associated with immunoglobulin E (IgE) mediation[1]. This condition ranks as the second most commonly encountered etiology of chronic esophagitis, behind gastroesophageal reflux disease. Furthermore, it is the primary culprit responsible for dysphagia among the pediatric and young adult population[2].

The initial instances of this condition were documented in the late 1970s and early 1980s[3-5]. Subsequently, the inaugural consensus guidelines outlining the diagnostic and therapeutic approaches for EoE were introduced in 2007, with subsequent updates provided in 2011[1,6]. The current guidelines establish the criteria for EoE as a persistent clinicopathological condition marked by the presence of eosinophils within the esophageal epithelium at a density of 15 or more eosinophils per high-power field (hpf), coupled with symptoms of esophageal dysfunction, after excluding other potential causes of esophageal eosinophilia[1].

In recent decades, EoE has emerged as a prevalent source of morbidity within the upper gastrointestinal (GI) tract, affecting both pediatric and adult populations. The epidemiology of EoE has experienced a substantial upswing, closely mirroring the heightened awareness and understanding of this condition. Most epidemiological data stem from population-based studies, primarily conducted in North America and Europe[2,7,8]. In developed nations, the incidence rates and prevalence of EoE in children exhibit geographic variation[7]. Incidence figures span from 2.1 cases per 100000 individuals annually in the Netherlands to 12.8 cases per 100000 individuals annually in Ohio, United States[9,10]. EoE can manifest at any age and is more prevalent in males[11]. It exhibits a strong connection with other atopic conditions including asthma, eczema, rhinitis, and food allergies.

EoE has a substantial effect on the daily lives of affected individuals. The symptoms have a noteworthy impact on school performance and participation in educational activities. While therapies may result in a better quality of life with reduced symptom severity, they may also introduce challenges in terms of dietary restrictions, potentially influencing overall quality of life.

CLINICAL PRESENTATION

Symptomatology in EoE can be widely variable, reflecting esophageal dysfunction and inflammation[12]. The esophagus is an obscure organ within the thoracic cavity, manifesting its ailments as vague symptoms and rarely results in specific physical signs[13]. The developmental stage of the child impacts the clinical manifestations; while adolescents typically exhibit symptoms akin to those observed in adults, such as dysphagia to solids and food impaction, younger patients tend to manifest more general and nonspecific complaints. These include abdominal or chest discomfort, vomiting, feeding difficulties, or extreme failure to thrive[12-14]. Interestingly, most children develop coping mechanisms, so feeding difficulty tends to be subtle and requires careful history to elicit positive findings[12,14]. Therefore, refusal to eat, inability to progress from liquids to solids, selective avoidance of hard consistencies after successfully tolerating a variety of solids, exaggerated chewing, prolonged meal time, or drinking excessive water to facilitate swallowing are all well-recognized patterns of coping mechanisms[12,13]. Another point worth discussing is that progressive symptoms are common and correlate strongly with transitioning from an inflammatory phenomenon in early childhood to a fibrostenotic remodeling process that significantly hinders esophageal compliance and function[13]. The relationship between symptomology progression and age is outlined in Figure 1.

Multiple symptoms can coexist, and some overlap with other diseases such as gastroesophageal reflux[15]. Subsequently, reflux symptoms that fail to respond to empiric proton pump inhibitor (PPI) trial warrants endoscopic evaluation for EoE[12,15]. Many patients have associated atopic disorders including eczema, allergic rhinitis, respiratory symptoms related to asthma, and allergic reactions to food[13,15]. It is postulated that EoE shares a common pathologic background with these conditions, most remarkably with allergic rhinitis, which was found to be in up to 90% in one report[6]. Historical remarks of family members with atopic disorders, dysphagia, or even a formal diagnosis of EoE should increase the suspicion in the index and prompt targeted evaluation[12,13,15].

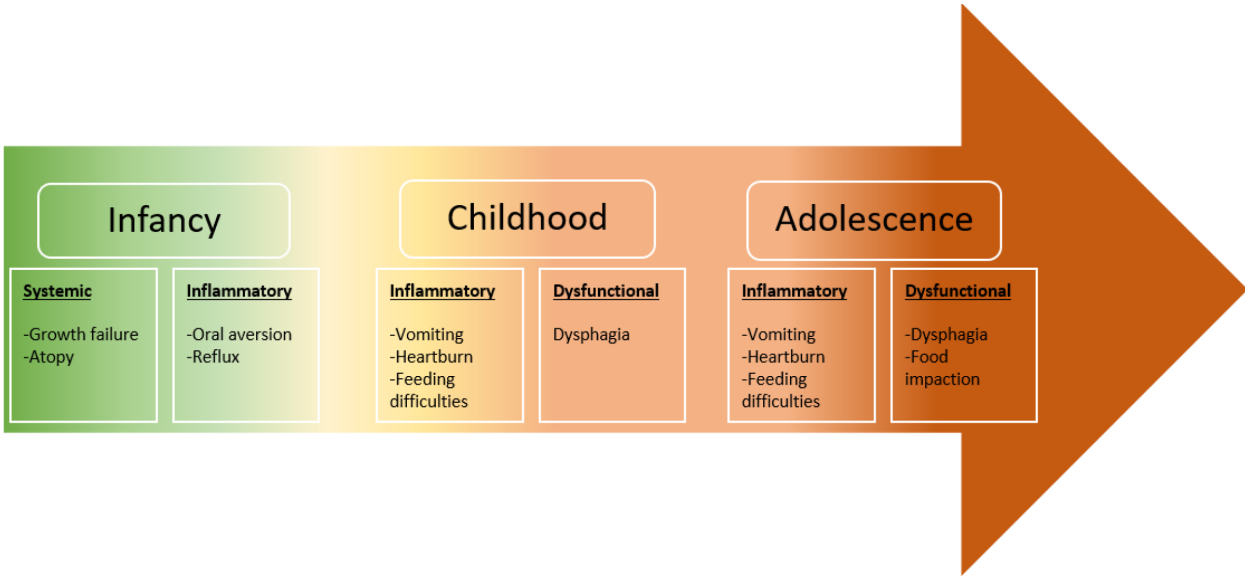

Figure 1 Relationship between symptomology progression and age.

DIAGNOSIS

The expanding research and literature available on EoE in the past 20 years has shaped our better conceptualization of the pathophysiology and natural history of EoE. Nevertheless, due to the nonspecific clinical picture in young children, EoE remains a diagnostic challenge to pediatricians who need a vigilant correlation between symptoms and endoscopic and histologic findings[12,13,15,16]. Consequently, an average 3 years to 5 years delay between symptoms onset and diagnosis was reported in one review, which was associated with a parallel increase in fibrostenotic complication rates [12]. Accordingly, guidelines have been revised several times to guide clinicians and help bridge this gap[12,17].

The consensus outlines the definition of EoE as a clinicopathologic entity, with evident esophageal impaired function, combined with histologic proof of esophageal eosinophilic predominant inflammation after ruling out other causes of eosinophilia (Figure 2)[12,13,15]. Upper GI endoscopy is the modality of choice for the gross examination of characteristic mucosal changes, obtaining biopsies for histological confirmation, and excluding other pathologies of the esophagus[12, 13,15,17]. Endoscopically, features of inflammation or fibrotic transformation features such as furrows, exudate, edema, rings, trachealization, and stricture, can be observed. The endoscopic findings of Edema, Rings, Furrows, Exudate, and Stricture (ERFES) are given a grade and have been grouped into a scoring system called EoE ERFES scoring system to aid in the diagnosis of EoE and monitoring patients' disease progression. However, confirmation requires histologic evaluation[14]. It is crucial to remember that as many as 17% of individuals with EoE may exhibit normal endoscopic findings. Therefore, it is recommended that for all pediatric patients with nonspecific upper GI symptoms severe enough to necessitate endoscopic examination, esophageal biopsies need to be collected[12,15]. A minimum of six biopsies should be obtained from various levels spanning from the proximal to the distal esophagus, focusing on areas of inflammation to enhance the likelihood of positive findings in the microscopic examination[12,13,15].

In histopathological assessment, eosinophilic infiltration is confirmed when it attains or surpasses a threshold of 15 eosinophils per hpf, excluding eosinophilia in the stomach or duodenum is a pre-requisite for diagnosing EoE[12,15,17]. Apart from mucosal esophageal eosinophil density, noteworthy histological characteristics in EoE encompass basal cell hyperplasia and the presence of eosinophilic layering[12].

The British Society of Pediatric Gastroenterology, Hepatology, and Nutrition revised its guidelines in 2022. It is recommended to stop PPI, if prescribed previously for the patient, for at least 3 wk before endoscopy[15]. The objective is to identify a subgroup of EoE patients referred to as PPI-responsive eosinophilia[12,15]. To elaborate further, PPI is uniquely anti-inflammatory in EoE by blocking interleukin 13 (IL-13)-mediated inflammatory cascade, masking the significant histological changes[12,15].

Additional laboratory testing, such as serum IgE levels and eosinophilic count, might serve as a clue to the atopic tendency of the patient. However, it has no diagnostic weight. Allergic testing could be sought and guided by an allergist based on initial assessment[15].

GENETICS

The multifactorial pathophysiology of EoE implicates a role in genetic susceptibility. Supporting evidence for the former can be found in the elevated risk observed among first-degree relatives of individuals with EoE in developing the condition[13]. Therefore, researchers have been adamant about mapping novel genetic loci involved in EoE[13,17]. A breakthrough finding revealed a distinctive genetic expression pattern in esophageal biopsies of EoE patients, involving

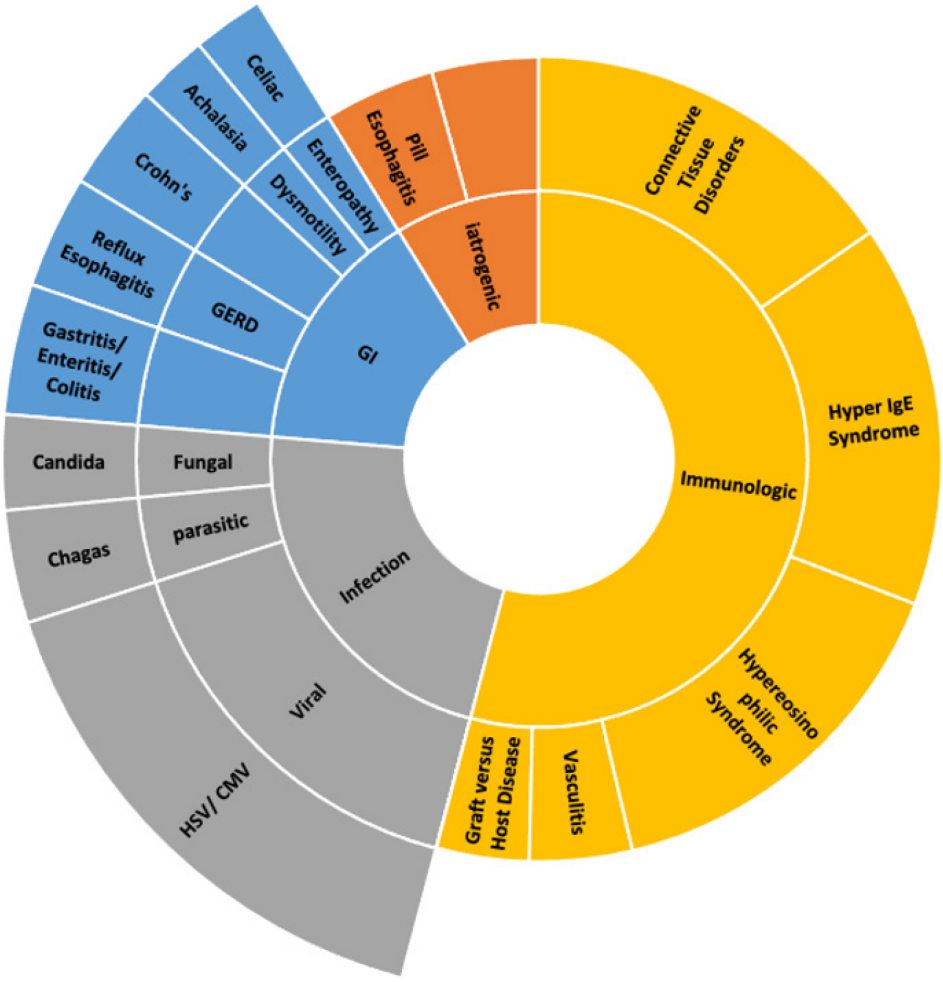

Figure 2 Differential diagnosis of eosinophilic esophagitis. CMV: Cytomegalovirus; GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; HSV: Herpes simplex virus.

96 genes, differentiating their biopsies from non-EoE[13,17]. This work and later research confirmed that the degree of genetic expression is directly related to the abundance of inflammatory cells and the presentation of its relevant genetic material in biopsy samples[12,13].

Genotyping can also be utilized in stratifying patients with EoE into inflammatory predominant or fibrostenotic phenotype[13]. However, evidence has yet to be validated through future research to guide the implementation of such a sophisticated molecular testing strategy[13,16].

MANAGEMENT

Treatment options for EoE include dietary elimination, and drug treatment in addition to esophageal dilatation in some advanced cases. Some scholars came up with the abbreviation of 3 "D" S, representing Drugs, Diet, and Dilatation[16]. Over the past year, dupilumab, a new biologic, a human monoclonal antibody that targets the IL-4 receptor alpha subunit of heterodimeric IL-4 and IL-13 receptors, has become the first United States Food and Drug Administration (FDA)-approved biologic treatment for EoE in adult and adolescent populations aged 12 years and older. EoE is one of those diseases that needs an individualized treatment plan for every patient. The decision of which treatment to start depends on the clinical picture, severity, practicality/suitability, other comorbid allergic disease, and the patient or parents' choice. Clinicians usually decide on the treatment on a case-by-case basis. Hence, the treatment formulation will rely on mutual agreement between the child or the child's family and the treating clinicians. Efficient treatment will help ease the signs and symptoms and reverse inflammatory damage to the esophagus and help the clinician liberate the child's diet, which could positively impact the nutritional status and well-being of the child[18]. Patients will benefit from being cared for by a multidisciplinary team, which should include the treating physician or the gastroenterologist, allergist, psychologist, general pediatrician, and dietitian to support patient care, avoid any conflicts regarding the advice given, and reduce the number of clinic visits. Gastroenterologists will lead the investigations, endoscopies, and treatments and perform esophageal dilation when needed. Allergists work with gastroenterologists to provide comprehensive care for patients with EoE and recommend elimination diets and treatments. Allergists also investigate the atopic co-morbidities common with EoE and provide additional treatment as necessary[15]. Dietitians are vital in arranging individualized dietary plans,

providing replacements for the eliminated food groups, and ensuring that patients receive appropriate nutritional intake. General pediatricians can follow the child's growth, nutritional status, and general well-being. Nevertheless, a psychologist can help patients and their families manage the psychological concerns of the disease.

Dietary elimination

Dietary therapy is based on EoE being a non-IgE-mediated food allergy. Thus, eliminating certain allergenic foods could induce disease remission. Three different methods are used in dietary therapy, full elemental diet, six food exclusion diet, and gradual food elimination diet. An elemental diet is administered by providing an elemental liquid formula; this formula should encompass all essential nutrients including carbohydrates, fats, vital minerals, and vitamins[13]. A systematic review by Rank *et al*[19] involving 431 patients, concluded that histological remission was achieved in 93.65% of patients on elemental diet, in contrast to the control groups in the studies where only 13.3% attained remission. This approach is generally not preferred for most children and care givers, because elemental milk has an unfavorable taste and can be relatively expensive. However, it remains a good option in infants with EoE especially that they are mostly dependent on milk for the 1st few months of their life. It is important to note that children with non-IgE-mediated food allergies have a potential risk of developing IgE-mediated allergies to the food eliminated, especially if food is excluded from their diet for an extended duration[19]. Therefore, allergy testing is required before introducing the common allergenic foods[20].

The most commonly recommended dietary therapy eliminates the six common allergenic foods commonly linked to food allergy in EoE. These foods are ranked based on their allergenicity as follows: cow's milk, wheat, egg, soy, peanuts/tree nuts, and fish. As expected, this six-food elimination is more effective than gradual food elimination, where one or two foods are eliminated for up to 12 wk, followed by endoscopy. However, six-food elimination is very challenging, especially for children, where compliance becomes an issue. Gradual food elimination diet focuses on excluding one or two types of food, which are thought to be the expected foods causing the patients eosinophilic esophagitis after thorough assessment by the pediatric allergist and gastroenterologist while considering starting with the most allergenic foods such as cow's milk and wheat followed by egg and Soya and finally peanuts/tree nuts and fish. It is vital to explain to the patient/carer that exclusive elemental diet, six-food elimination or gradual elimination required repeated endoscopy to document remission before food(s) are reintroduced in a reverse order of elimination based on the level of allergenicity. In the six-food elimination diet, fish and shellfish are introduced first, while cow's milk is usually the last to be reintroduced[21]. It is essential that a pediatric dietician is involved in the patient medical care to perform a comprehensive nutritional assessment and replacement of all deficient nutrients in the child's diet.

Pharmacological treatment

The medications that can be used for controlling inflammation in EoE include PPIs, corticosteroids, and dupilumab. PPIs are used for 8 wk as a therapeutic option for treatment. Numerous studies have substantiated its effectiveness as a primary therapeutic choice for managing EoE. In addition, it is used by some clinicians to rule out conditions such as reflux esophagitis, especially in children whose endoscopy is not done or delayed for different reasons. In a systematic review by Rank *et al*[19] with 1051 patients proved PPI's therapeutic effectiveness and efficacy.

Corticosteroids are known for their potent anti-inflammatory effect. They can be swallowed as a thickened solution or from the metered dose inhaler device. A systematic review encompassing trials demonstrated that topical corticosteroids led to histological remission in 64% of patients, a significant contrast to the 13.3% remission rate observed in the control groups of the study [confidence interval (CI:) 0.85-1.19][19]. Topical corticosteroids are proven to be very safe in children. Transient oral candidiasis is probably the most reported side effect reported. This can be avoided by mouth washing after administering swallowed corticosteroid treatment.

Biological treatments

In May 2022, dupilumab was approved by the FDA as the first and only drug specific for treating EoE for children aged 12 and above[22]. The biological drug is still not commonly used in children, and it is not clear where it fits in the stepwise approach for treating EoE in children. Nevertheless, the FDA's endorsement of it as the initial sanctioned treatment for EoE supports its consideration as a first-line medication. On the other hand, as it is a novel drug, certain healthcare providers contemplate its usage in instances where traditional therapeutic agents fall short in achieving both clinical and histological remission. Dupilumab is not a new medication; it has an established role in the management of moderate to severe asthma, challenging cases of atopic dermatitis, and chronic sinusitis with polyps in children. The Joint Task Force of The American Academy of Allergy, Asthma, and Immunology, American College of Allergy, Asthma, and Immunology, along with the American Gastroenterology Association, have recently issued expert opinion guidelines for the treatment of EoE. This paper guides healthcare professionals on using dupilumab in treating patients with EoE. It emphasizes the significance of the FDA approving dupilumab as the initial and sole pharmaceutical intervention for EoE management[20]. Furthermore, it states that dupilumab is to be considered in patients who refuse or are unsuitable for food elimination and swallowed corticosteroids, patients with esophageal dilatation, those who developed side effects to ongoing treatment, patients with strictures or narrow caliber esophagus, and patients with refractory EoE[22]. Dupilumab is currently licensed for 12-year-old children and above, and it has received FDA approval for use in Children over 1 year old with eosinophilic esophagitis in January 2024. However, in atopic dermatitis, it is licensed for treating children from 6 mo of age.

Mepolizumab is a biologic agent developed to treat asthma. It represents a humanized monoclonal antibody of immunoglobulin G1 κ type, which targets human IL-5 and thus prevents its interaction with the α-chain of the IL-5 receptor. A larger multicenter parallel group trial also demonstrated reductions in both peak and mean esophageal

eosinophil counts of greater than 50% after receiving three doses of mepolizumab in up to 77% of patients. In addition, peripheral blood eosinophil counts were also decreased. However, most mucosal biopsies did not return completely to normal (defined as fewer than four eosinophils per hpf for this study)[15]. Although it has shown promise in reducing both peak and mean esophageal eosinophil counts it has not been FDA-approved for treating eosinophilic esophagitis in children. Reslizumab was approved by the FDA in March 2016, and is indicated as an add-on maintenance therapy for adults with severe asthma with an eosinophilic phenotype. Reslizumab is a humanized monoclonal antibody that occupies the region glutamic acid, arginine, arginine, and arginine corresponding to amino acids 89–92 on IL-5, which is a region critical for its interaction with the IL-5 receptor on the eosinophil surface. Although reslizumab improves patients' clinical symptoms, the effect on lowering esophageal eosinophil level is modest. Other biologic agents including malizumab, cendaakimab, lirentelimab are potential treatments that may be used in the future to treat patients with eosinophilic esophagitis.

Endoscopic intervention

With the progression of eosinophilic esophagitis, children may develop esophageal narrowing, loss of elasticity, and stricture formation, especially when the inflammatory component of the disease advances to fibrosis. If the narrowing is not improved with medical treatment or is severe, esophageal dilatation may be required to improve patient symptoms. In addition, dilatation can also be used to release food bolus obstruction in the acute setting. Although esophageal dilatation can offer immediate symptom relief of dysphagia, esophageal dilatation cannot be considered an isolated treatment for EoE and must be used with appropriate medical therapy. Esophageal dilatation can be performed with balloon dilators or bougie dilators and is advised to be performed gradually with serial endoscopic sessions. There is not much data on esophageal dilatation in children, and most evidence is extrapolated from adult studies. The meta-analysis conducted by Dougherty and colleagues encompassed 37 studies, comprising 3 focused on pediatric populations and 2 encompassing children and adults[23].

A total of 977 patients underwent a combined 2034 dilations using either balloon or bougie dilators. Of these patients, 87% reported ameliorating dysphagia symptoms following esophageal dilation, although no concurrent improvement was observed in esophageal eosinophilia. Nine perforations were recorded during the procedures at a rate of 0.033% (95%CI: 0%-0.226%) per procedure. Notably, none of these perforations necessitated surgical intervention or led to any mortalities. Furthermore, a comprehensive systematic review and meta-analysis, encompassing 27 studies involving 87 pediatric patients of 845 with EoE, collectively underwent 1820 esophageal dilations[24]. This group's median number of dilations was three (range: 1-35). Clinical improvement was observed in 95% of patients in 17 studies. Notably, perforation occurred in 0.38% (95%CI: 0.18%-0.85%; I^2: 0% based on data from 27 studies), and hemorrhage was documented in 0.05% (95%CI: 0%-0.3%; I^2: 0% from 18 studies). Encouragingly, there were no reported fatalities. Therefore, esophageal dilatation in EoE is considered safe by using balloon or bougie dilators and improves dysphagia in patients with esophageal strictures. Dilatation will reduce the narrowing of the esophageal diameter. Still, it will not treat the inflammation and thus needs to be combined with medical treatment such as medication or food exclusion.

LONG-TERM CARE

The understanding of eosinophilic esophagitis is becoming increasingly evident in its natural progression. Pathogenesis starts with mucosal inflammation, leading to remodeling and fibrosis[17]. In a single center in Switzerland, two related studies were conducted on the progression of EoE in adults; these studies showed the persistence of dysphagia and eosinophilic inflammation, primarily observed in children, which subsequently progresses into subepithelial fibrosis in adults[25,26]. Therefore, EoE is classified as a chronic disease that can be persistent or relapsing, necessitating a comprehensive long-term monitoring and treatment plan.

The primary objectives in treating EoE are to effectively manage symptoms, mitigate the risk of complications associated with fibrostenotic remodeling, and improve patient quality of life[27]. To ensure treatment efficacy, it is advisable to schedule a follow-up endoscopy with esophageal biopsies within 6 to 12 wk after initiating therapy to evaluate the histological findings and adjust the treatment accordingly[1,28].

Given that the diagnosis relies on histology, symptoms, and endoscopic findings, a system has been implemented to evaluate the progress of patients within a spectrum that includes complete normalization, partial response, and nonresponse[29]. Patients are categorized to: (1) Nonresponders with persistent eosinophilia ≥ 15 eosinophils/hpf; (2) partial responders with reduced eosinophilia of 7-14 eosinophils/hpf OR 1-6 eosinophils/hpf; and (3) complete normalization with normal biopsy with < 1 eosinophils/hpf[29].

CHALLENGES

Clinicians and patients may face different challenges when managing eosinophilic esophagitis patients. Although diet therapy offers nonpharmacologic options for disease management, it can be difficult for patients to follow. This can result in noncompliance, isolation from peers, the extra cost of exceptional food alternatives, cross-contamination while preparing meals, or possibly nutritional deficiencies in poorly planned diets. In addition, repeated hospital visits and multiple endoscopies to identify the triggers during the elimination diet can lead to extra financial and psychological burdens on patients and their families. Symptoms do not fully reflect disease activity, which might demotivate patients

during the lengthy period of food elimination and re-introduction. Also, clinicians may find difficulty in interpreting biopsies of refractory disease *vs* noncompliance to the elimination diet[30].

The potential consequences of untreated or undertreated eosinophilic inflammation includes the development of fibrosis, thickened esophageal walls, and the formation of strictures. Ultimately, these structural and functional changes can damage the esophagus[31] resulting in complications such as esophageal stenosis, food impaction, esophageal perforation, and malnutrition. These complications will certainly affect patient QoL[17]. EoE harms the health-related QoL (HRQoL) of patients and their families while also imposing a significant burden on the healthcare system. Although there are limited data available, the currently accessible treatments seem to positively impact HRQoL[32]. Therefore, it is crucial to incorporate psychosocial support into patient care by actively engaging both the patient and their family in group support. Additionally, it is essential to ensure that they are well-informed about the appropriate resources available for EoE.

FUTURE DIRECTIONS

In addition to the well-established and approved biological treatment, dupilumab, some other drugs are now being explored for managing EoE and targeting type 2 inflammatory response with different cytokine pathways associated with EoE pathogenesis. Hirano *et al*[33] investigated anti-IL-13 with half of the patients having steroid-refractory disease. The trial demonstrated reduced eosinophil counts and the patient's reported disease severity with improvement in dysphagia symptoms, but it lacked statistical significance.

Also, a randomized control trial with chemoattractant receptor-homologous molecule expressed on Th2 cells antagonist showed a statistically significant reduction in eosinophil count compared to placebo[34]. Compared to placebo, anti-IgE monoclonal antibody (omalizumab) showed no substantial improvement in clinical symptoms or decrease in eosinophil count[35].

Other new therapeutic drugs under investigation include Siglec-8 blockers (lirentelimab). The KRYPTOS trial (Phase 2/3) showed that lirentelimab achieved a statistically significant eosinophil reduction. Despite improving dysphagia symptoms compared to placebo, it did not meet the primary endpoint of the change in daily Dysphagia Symptom Questionnaire score[36].

The new therapeutic options highlight the need for further comprehensive trials. Nonetheless, it provides hope for potentially treating many atopic conditions, including EoE, with a single medication.

EoE necessitates multiple endoscopies for diagnosing and monitoring the disease. Less invasive monitoring tools are needed. New minimally invasive methods are now being studied to assess EoE disease activity. Cytosponge is a sponge-containing capsule after being swallowed it collects esophageal tissue as it is pulled back, offering an easy method to assess EoE inflammatory activity[37]. Another monitoring tool currently being assessed is the Esophageal String Test, which assesses eosinophil-derived granule proteins from secretions for the esophagus that stick to the string as it is removed[38].

Additionally, a new way to perform serial endoscopies is through a transnasal endoscopy. It provides an effective and less invasive test that can be done without sedation while maintaining a visual assessment of the esophagus and histopathologic testing[39]. These investigations are still in the initial stages of assessment and need further validation and evaluation of effectiveness.

CONCLUSION

EoE is a persistent clinicopathological condition distinguished by eosinophilic infiltration within the esophageal epithelium, typically exceeding 15 eosinophils per hpf. This manifestation of EoE is associated with esophageal dysfunction symptoms, following the exclusion of alternative causes of esophageal eosinophilia[1]. Thorough clinical assessment and histological endoscopic biopsy remain the mainstay of diagnosis. Treatment is best achieved in a multidisciplinary setting after appropriate counseling. There is hope for targeted biologic therapy; these treatments are still in their infantile stages and more studies are required. New minimally invasive methods are being evaluated to aid in the monitoring of patients. However, endoscopy and tissue histology remain the only methods to assess response to treatment and monitor disease.

EoE continues to be a fascinating disease for clinicians. Despite the consensus and guidelines published on managing children with EoE[1,15,19,20,30], many unanswered questions still need to be answered, such as: What is the actual prevalence of the disease? What is the disease's natural clinical progression, and is complete recovery possible for patients? Which factors contribute to the development of fibrotic disease? What constitutes the most effective treatment approach? Lastly, what potential long-term side effects are associated with current biologic therapy? We hope to have readily available biomarkers that can help assess patients for response to treatment. Much research is still needed to answer all the remaining questions related to EoE.

FOOTNOTES

Author contributions: Elghoudi A and Bitar R made substantial contributions to the conception and design of the work, interpretation of

data, drafting, writing and revising the manuscript critically for important intellectual content and approved the final version to be published, and agrees to be accountable for all aspects of the work; Zourob A, Al Atrash E, Alshamsi F, Alkatheeri M, and Narchi H made substantial contributions to the design of the work, acquisition and interpretation of data and revising the manuscript critically for important intellectual content, and approved the final version to be published and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Case Control Study

Exclusive breastfeeding greater than 50%, success of education in a university hospital in Bogotá: Case-control study

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Abstract

BACKGROUND

Maintenance rates of exclusive breastfeeding (EBF) worldwide are low, thus, one of the objectives of the summary of policies on breastfeeding (BF) in world nutrition goals for 2025 are that at least 50% of infants under six months of age receive EBF that year. The Objective of this study is to document the rates of EBF in children born in San Ignacio University Hospital (HUSI) and identify factors associated with maintenance.

AIM

To document the percentages of EBF in those that were born at HUSI and identify factors associated to their maintenance.

METHODS

This is a study of cases and controls in an analytic, retrospective cohort that took children born alive between January 2016 and January 2019 at HUSI located in the city of Bogotá, Colombia.

RESULTS

Receiving information about BF at HUSI was able to maintain EBF up until 4 mo (OR = 1.65; 95%CI: 1.02-2.66). The presence of gynecologic and obstetric comorbidities (OR = 0.32; 95%CI: 0.12-0.83), having mastitis (OR = 0.56; 95%CI: 0.33-0.94), and receiving information from mass media (OR = 0.52; 95%CI: 0.31-0.84) are factors associated with not maintaining EBF.

CONCLUSION

Receiving education at a Women- and Child-Friendly Institution was the only significant factor to achieve EBF until 4 mo, with a frequency greater than the one reported in the country, which matches multiple studies where counseling and individualized support on BF achieve this purpose. Knowledge about BF and early detection of obstetric/gynecologic complications must be strengthened among the healthcare staff in charge of mothers during post-partum. Additionally, strategies must be promoted to continue BF such as creating milk banks with the objective of increasing BF rates even when mothers return to work.

Key Words: Breastfeeding; Women- and Child-Friendly Institutional Strategy; Strategies; Adherence; Education

Core Tip: Globally, exclusive breastfeeding (EBF) maintenance rates are low; therefore, one goal of the breastfeeding policy brief is to improve it. In the present study, we document that receiving information about BF in our hospital managed to maintain EBF up to 4 mo and that the presence of gyneco-obstetric comorbidities, having mastitis and receiving information from mass media were factors associated with non-maintenance of EBF.

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INTRODUCTION

The international community recognizes breastfeeding (BF) as the healthiest, most economic, and safe way of feeding a newborn and infant. The World Health Organization (WHO) defines exclusive BF (EBF) as the single intake of breastmilk without any other food or beverage, including water, during the first six months of life[1]. As for the European positions, European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) considers that 6 mo of EBF is the desirable objective, however, according to the nutritional needs of each child, complementary feeding, as defined by the WHO as the period in which BF is given together with other foods and beverages (including dairy formulas and breast milk substitutes), can be initiated earlier, but never in children younger than 17 wk of life[2].

Despite these positions, low rates of onset and maintenance of BF persist globally which becomes a public health problem[2]. Because of this, in 1990 international associations met with support of the WHO and UNICEF and created the Innocenti Declaration; a declaration intended to promote, protect, and support BF. This declaration established a series of criteria that each government must comply with to increase BF rates, which include the creation of a national BF committee, compliance to the "ten steps for healthy breast feeding," regulation of breast milk substitutes, and infant formulas, and the protection and BF rights for working women[3]. In addition, the WHO suggests that 50% of children under 6 mo must receive EBF by the decade ending on 2025[4].

The "2015 National Nutritional Situation in Colombia" (ENSIN) documented that in our country, EBF has presented a progressive reduction since 2005, where 46.9% of children under 6 mo received EBF while in 2015 only 36.1% did so, a level very inferior to the global average of 43%[4]. The 2010-2020 Ten-Year Plan from the Ministry of Health Promotes Institutions that apply the Women- and Child-Friendly Institution model (WCFI), adopted by San Ignacio University Hospital (HUSI) in 2013 which looks to promote BF and quality care for mothers and children through different political, family, educational, and other actions[5]. HUSI applies the WCFI strategy educating both the parents of newborns that are by the mother during postpartum as those that are hospitalized in the newborn unit about to be discharged. Taking this context into account, the objective of the study is to document the percentages of EBF in those that were born at HUSI and identify factors associated to their maintenance.

MATERIALS AND METHODS

Study design

Case study and controls in a retrospective, analytical cohort. The two definitions of the WHO and ESPGHAN were included. This was conducted between January 2016 and January 2019 through calls to mothers of newborns at HUSI in Bogotá, Colombia. The Research Ethics Committee at HUSI and the Faculty of Medicine of the Javeriana Pontifical University approved the study on June 28, 2018.

All newborns at HUSI between the dates mentioned were included in the study. 10 exclusion criteria were considered: mother with human immunodeficiency virus; documented type 1 herpes virus on the nipple; mother with severe diagnosed disease during the prenatal period that avoided feeding with breast milk; mothers that received medications

contraindicated in BF such as anticoagulants, cardiovascular (amiodarone, ergotamine), antineoplastic, psychologic drugs, iodides, amphetamines, cocaine, lysergic acid diethylamide, marihuana; patients with mothers that have received radioactive iodine-131 or that have received iodine or topical iodophors given the prolonged time of bioavailability; patients with galactosemia; maple syrup urine disease, phenylketonuria or newborn patients with weight below 1500 g, or less than 32 wk that require additional feeding (substitutes).

Size determination of the sample considered the prevalence of EBF documented in the 2015 ENSIN, the inclusion of the maximum association model of 20 parameters, and the possibility of 10 positive outcomes for every parameter with which a total of 583 surveys was calculated as 10% failed responses is added to the above (wrong telephone numbers, no response by the mother, incomplete information) for a total of 642 complete surveys to collect (Figure 1).

Measurement

A 25-question telephone survey was conducted, divided into 5 sections: the first includes social-demographic factors (maternal age, minor's age, place of residence, education level, parity, cigarette consumption, and monthly income). The second section was centered on the age of suspension of BF and the reasons why it was discontinued. Knowledge about BF and its benefits were part of the third section. The fourth section documented diseases during pregnancy and BF, and the last section gathered information received both before and after delivery about BF and places where that information was received.

Data gathering

Telephone calls where the interviewer indicated the purpose of the study in a clear language in order to obtain more consistent answers; guaranteed patient confidentiality, responses, and requested verbal consent from the mothers to conduct the survey.

Statistical analysis

The data were analyzed on STATA after correcting digitalization and inconsistencies. Quantitative variables were presented in percentages while qualitative variables were presented through standard deviations. A bivariate logistic regression model was conducted between EBF and each one of the possible factors that influence, reporting and OR with a 95%CI. Then, a multiple logistic regression model was conducted including significant variables ($P < 0.15$) and those considered clinically important. The presence of possible confounding variables was assessed.

RESULTS

Sociodemographic characteristics

The majority of mothers surveyed were between 19 and 35 years old (75.4%), followed by mothers older than 36 (13.1%) and the rest corresponded to those under 18 (1.1%). With regards to their homes, the majority lived in the urban area (86.9%), in comparison with 13.1% that liven the rural zone. In relation to their level of education, the majority of mothers had completed high school (27.9%), 3.6% had only attended Elementary school, 33.2% had technical or technologic studies, 24.6% had a professional degree, 10.6% had some type of graduate or post graduate degree, and only 0.2% didn't have any type of education. Regarding parity, almost half of those interviewed had only one child (49.7%), followed by 38% who had two children, and the remaining 12.3% referred having three or more children. With regards to the mother´s harmful habits during pregnancy, only 18 (2.8%) of the mothers were found to have consumed tobacco (Table 1).

BF

The report of EBF until 4 mo of age was 72% and until 6 mo 59% (Table 2). Amongst the questions asked there was one about the knowledge about the age recommended for EBF, 412 mothers (64.2%) affirmed to know about that age. Considering the definitions of the WHO and ESPGHAN, 53.7% of them affirmed that the age was up to 6 mo of life, compared to 1.2% who mentioned that was for those younger than 6 mo (Table 3).

Factors associated with maintenance and abandonment of EBF

The variables analyzed were adjusted by groups of maternal age and controlled by the following confounding factors: infant assisting to day care, maternal civil status, and mother's parity without documenting confounding effects.

Factors associated to abandonment of EBF

A univariate and multivariate analysis was conducted finding that the presence of obstetric/ gynecologic comorbidities (OR = 0.32; 95%CI: 0.12-0.83), having mastitis (OR = 0.56; 95%CI: 0.33-0.94) and receiving information from mass communication media (OR = 0.52; 95%CI: 0.31-0.84) are factors that were associated to not achieving EBF until 4 mo of age (Tables 3-5).

Factors associated to maintenance of EBF

Receiving information about BF at HUSI was the only factor that was significantly associated to maintenance of EBF until 4 mo (OR = 1.65; 95%CI: 1.02-2.66), see Tables 3-5.

Table 1 Sociodemographic characteristics (*n* = 642)

Variable	*n*	%
Maternal age (yr)		
≤ 18	7	1.1
19-35	484	75.4
≥ 36	151	23.5
Place of residence		
Urban	558	86.9
Rural	84	13.1
Level of education		
Elementary	23	3.6
High school	179	27.9
Technical	147	22.9
Technologic	66	10.3
Professional	158	24.6
Postgraduate/specialization	68	10.6
None	1	0.2
Multiparity		
One	319	49.7
Two	244	38.0
Three or more	79	12.3
Tobacco consumption		
Yes	18	2.8
No	624	97.2

Table 2 Duration of breastfeeding

Duration	*n*	%
Up until 4 mo		
EBF	461	72
Non-EBF	179	28
Up until 6 mo		
EBF	377	59
Non-EBF	263	41

EBF: Exclusive breastfeeding.

DISCUSSION

A systematic review published in the *Lancet* journal in 2016 identified that WCFI institutions in which counseling was provided on BF and support about it after delivery increased adherence to EBF by 49%[6]. Maintenance of EBF until 4 mo was the main finding of the study considering that HUSI is a WCFI institution since 2013. Having received information about BF during immediate postpartum increases its maintenance by the mother since it links feeding and attachment patterns which favors their learning[7]. In this study we effectively saw how the majority of mothers (53.7%) affirmed knowing which was the age recommended by the WHO.

Another aspect to consider is the duration of the maternity leave agreed on 18 wk for Colombia (approximately 4 mo), time that matches the duration of EBF documented in the study. This coincides with one the findings of Castrillón-García *et al*[8] who documented that one of the main factors for abandonment of EBF is mother's return to work.

Table 3 Mothers' response about the adequate duration of exclusive breastfeeding

Duration	*n*	%
Younger than 6 mo	8	1.2
6 mo	345	53.7
7 to 12 mo	37	5.8
13 to 24 mo	17	2.6
36 mo	1	0.2
More than 36 mo	4	0.6

Table 4 Univariate analysis

Variable	EBF for 6 mo			EBF for 4 mo		
	n	%	OR (95%CI)	*n*	%	OR (95%CI)
Univariate analysis						
Maternal age						
≤ 18 yr	16	4.2	2.2 (0.76-6.5)	18	3.9	2.5 (0.69-9.15)
19 to 35 yr	299	79.3	0.96 (0.63-1.48)	369	80	1.1 (0.67-1.69)
≥ 36 yr	72	19		74	16	
Multiparity						
1 child	180	47.7		222	48.1	
2 child or more	197	52.2	1.2 (0.9-1.7)	239	51.8	1.27 (0.9-1.8)
Cigarette consumption						
Yes	11	2.9	1.1 (0.4-2.9)	12	2.6	0.77 (0.28-2.09)
No	366	97		449	97.3	
Income						
Less than 1 million	91	24.1		101	21.9	
1 to 3 million	136	36	0.69 (0.4-1.1)	172	37.3	0.93 (0.59-1.47)
More than 3 million	116	30.7	0.77 (0.49-1.2)	143	31	1.01 (0.63-1.63)
No information	34	9		45	9.7	
Received help						
Yes	316	83.8		394	85.4	
No	61	21.4	0.87 (0.56-1.36)	67	14.5	1.28 (0.81-2.03)

mCRC: Metastatic colorectal cancer; KRAS: Kirsten rat sarcoma viral oncogene homolog; RAS: Rat sarcoma virus.

Likewise, another finding that influences abandonment of EBF is the presence of obstetric/gynecologic complications and mastitis. This was evidenced in the study conducted in 2017 in Milan, Italy, where they documented that two factors associated to abandonment of EBF were the presence of mastitis and cracked nipples[9].

Communication media are a controverted factor since there are studies such as the one mentioned in the review of the *Lancet* in which these are associated with an early start of BF *vs* a crosscutting study conducted in Laos in 2014 that found a negative association between the promotion of dairy formulas in the local media and BF, being congruent with the findings documented in this study[6,10,11].

According to all of the above, you can see that not only factors related to the mother, but also environmental factors and society influence the duration of EBF, that is why it is important to document them in order to create strategies and improvement plans that help its maintenance.

Table 5 Multivariate analysis

Variable	EBF for 4 mo	
	OR	95%CI
Pathologies during pregnancy		
Mastitis	0.56	(0.33-0.94)
Obstetric/gynecologic comorbidities	0.57	(0.3-1)
Medical comorbidities	0.43	(0.08-2.27)
Surgeries	1.40	(0.5-3.9)
Pathologies during BF		
Mastitis	1.17	(0.43-3.17)
Obstetric/gynecologic comorbidities	0.32	(0.12-0.83)
Medical comorbidities	1.74	(0.64-4.65)
Surgeries or accidents	0.40	(0.07-2.32)
Information		
Receive information at HUSI	1.65	(1.02-2.66)
Communication media	0.52	(0.31-0.84)

BF: Breastfeeding; HUSI: San Ignacio University Hospital.

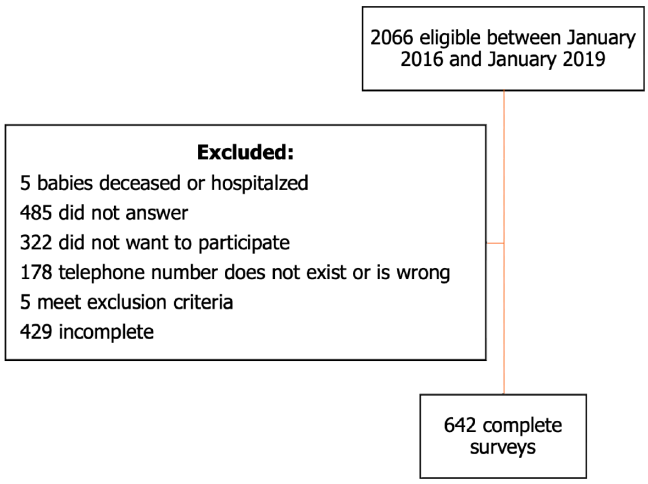

Figure 1 STROBE diagram of data collection.

CONCLUSION

The study showed that receiving education in a WCFI institution was the most influencing factor so that EBF was maintained until four months with a frequency higher than that reported in Colombia, and additionally, EBF was increased by 59% until 6 mo. What was found within the limitations was that when the interviewer was identified as working for the institution, the affirmative response of mothers could be induced from the information received previously. However, it is clear that when comparing the answers of mothers that reported having received information *vs* those that didn´t, the first group had greater adherence to the recommendation. Another limitation is that this study represents our hospital population but might not be representative of the global population since BF practices and associated factors can significantly vary between regions, cultures, and healthcare environments. Existing knowledge on the duration of EBF by mothers interviewed in the study coincides with what is presented in the 2010-2020 Ten-Year Plan assessment in which mothers from Quibdó, Leticia, Yopal, Tunja and Sincelejo were interviewed, which indicates that the information they have is clear and equivalent[5].

This study underscores the importance of the WCFI strategy for EBF maintenance. For that reason and considering that in Colombia there is a large population in rural areas, it is important to educate health professionals and staff in delivery rooms that work in the most remote areas about this strategy in order to increase adherence to and early recognition of gynecologic and obstetric complications. Additionally, this finding is useful as it opens up the possibility to conduct

national studies to assess the impact of this strategy regionally, and with that, suggest applying it internationally.

ARTICLE HIGHLIGHTS

Research background

The international community recognizes breastfeeding (BF) as the healthiest, most economic, and safe way of feeding a newborn and infant. Exclusive BF (EBF) of 6 mo is the desirable objective, however, supplementary feeding can be initiated earlier, depending on the nutritional needs of each child, but never in children younger than 17 wk.

Research motivation

Taking this context into account, the objective of the study is to document the percentages of EBF in those that were born at San Ignacio University Hospital (HUSI) and identify factors associated to their maintenance.

Research objectives

The Objective of this study is to document the rates of EBF in children born in HUSI (acronym in Spanish) and identify factors associated with maintenance.

Research methods

Case studies and controls in a retrospective, analytical cohort were analyzed between January 2016 and January 2019 through calls to mothers of newborns at HUSI in Bogotá, Colombia.

Research results

The study showed that receiving education in a WCFI institution was the most influencing factor so that EBF was maintained until four months with a frequency higher than that reported in Colombia, and additionally, EBF was increased by 59% until 6 mo.

Research conclusions

This study underscores the importance of WCFI strategies for EBF maintenance. Additionally, this finding is useful as it opens up the possibility of conduct national studies to assess the impact of the strategy in the region, and therefore recommends its application internationally.

Research perspectives

Additionally, this finding is useful as it opens up the possibility to conduct national studies to assess the impact of this strategy regionally, and with that, suggest applying it internationally.

FOOTNOTES

Author contributions: Murillo Galvis M, Ortegon Ochoa S, Plata García CE, Valderrama Junca MP, Inga Ceballos DA, Granados CM collaborated in drafting the protocol, data collection and analysis, design and writing of the article; Mora Gómez DM collaborated in drafting the protocol, data collection and analysis; Martín R collaborated in the data collection and analysis, design and writing of the article; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Research and Ethics Committee (No. 2018/105).

Informed consent statement: Telephone calls where the interviewer indicated the purpose of the study in a clear language in order to obtain more consistent answers; guaranteed patient confidentiality, responses, and requested verbal consent from the mothers to conduct the survey.

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ORIGINAL ARTICLE

Case Control Study

Childhood asthma biomarkers including zinc: An exploratory cross-sectional study

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Abstract

BACKGROUND

Childhood bronchial asthma (BA) is a chronic inflammatory respiratory disease. Nutritional conditions, including zinc deficiency, can affect such allergic disorders.

AIM

To outline the difference in serum zinc levels between asthmatic children and healthy controls.

METHODS

A cross-sectional study was carried out at Children's Hospital, Cairo University, investigating serum zinc levels in children with BA (n = 40) and healthy children (n = 21). Other markers included serum ferritin, iron, hemoglobin (Hb), and immunoglobulin E (IgE) levels. Independent t-tests and Mann-Whinny tests were used for comparisons. The Kruskal-Wallis test was applied to compare serum ferritin and IgE levels with regard to asthma severity. Spearman's rank correlation was performed to explore the relationship between serum ferritin levels and both iron and Hb levels in asthmatic children.

RESULTS

Children with BA had higher levels of zinc, yet the difference was not significant (P = 0.115). Serum ferritin and IgE levels were significantly higher in asthmatic children (P = 0.006 and 0.001, respectively), yet their levels did not differ

significantly by severity (P = 0.623 and 0.126, respectively). There was a nonsignificant weak correlation between serum ferritin levels and both serum iron and Hb levels.

CONCLUSION

Serum zinc levels do not seem to differ between asthmatic children and healthy children. Serum ferritin levels may be a marker of asthma control. Serum IgE levels are not markers of asthma severity.

Key Words: Children; Asthma; Zinc; Ferritin

Core Tip: Serum zinc levels were higher in asthmatic children than in nonasthmatic children. However, the difference was not significant. Serum ferritin levels were significantly higher in asthmatic children, which may be due to its immunosuppressive properties. Serum ferritin should not be considered in the diagnosis of iron deficiency anemia in asthmatic children. Serum immunoglobulin E should not be applied to diagnose the severity of childhood asthma. Further studies that track biomarkers such as ferritin during asthma progression are needed.

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INTRODUCTION

The most prevalent chronic respiratory condition in children is bronchial asthma (BA). BA is a chronic inflammatory disease of the lungs that causes airway inflammation and bronchial hyperreactivity; it may also be described as intermittent, reversible airway blockages[1]. Due to its immune-modulating properties, zinc has attracted much attention in relation to asthma and airway inflammation. Zinc is a crucial trace element for human metabolism and helps regulate gene expression, enzyme activity, and protein structure. Additionally, it is crucial for immune system regulation and functions as an antioxidant, anti-inflammatory, and antiapoptotic agent[2].

In the presence of continuous inflammation, free serum ferritin levels are elevated; in addition, free serum ferritin has a protective function in redox biology and iron homeostasis. In contrast, new research reveals that ferritin may have a causal role in the inflammatory pathology of illness, including rheumatologic, immunologic, neoplastic, and infectious diseases, and ferritin levels may be fundamental in the pathology of disease and help in predicting prognosis in addition to tracking disease activity[3].

Since the beginning of the 20th century, it has been known that immunoglobulin E (IgE) is different from other immunoglobulin isotypes in that it may both trigger extremely rapid pathological reactions and serve as a highly sensitive immunological amplifier. Furthermore, it is well known that patients with atopic diseases have higher IgE levels and that IgE serves as a vital link between the adaptive immune system's role in antigen recognition and the effector functions of mast cells and basophils at mucosal and cutaneous sites of environmental exposure. Due to these roles, IgE has become a desirable target for pharmacological intervention, and IgE blocking has clinical potential in a wide range of therapeutic fields[4,5].

Our study aimed to identify the difference in serum zinc levels between asthmatic children and healthy controls. Additionally, other labs of interest, such as serum ferritin and IgE levels, were studied. Moreover, the possible role of these findings as markers of controlled asthma was investigated.

MATERIALS AND METHODS

This exploratory cross-sectional study was carried out at Children's Hospital Cairo University between May 2022 and October 2022. Sixty-one children were enrolled [40 cases (asthmatic), 21 controls (non-asthmatic)]. The control group consisted of healthy children of comparable age and sex to the cases who had no disease based on history and physical examination and no history of BA or zinc deficiency. All asthmatic children who were attending in the asthma clinic, aged from 5-12 years, and whose parents or caregivers approved participation were included. Owing to the absence of the reliability of lung function tests in children under five, as they are rarely practical[6], children aged less than 5 years were excluded. Data on sociodemographic and clinical characteristics such as body mass index (BMI) and degree of asthma severity were collected. In addition, laboratory findings such as serum zinc, albumin, ferritin, and IgE levels were recorded and compared between cases and controls.

Case definition

The diagnosis of BA was considered using the medical history, family history, clinical examination, and symptoms including episodic dyspnea, coughing, wheezing, and tightness in the chest, as well as laboratory findings. The results of pulmonary function tests allowed for the confirmation of the diagnosis of BA and a determination of the severity and reversibility of airflow restriction[7,8]. Malnutrition was defined using World Health Organization definitions[9-12].

Control of potential bias

As our primary outcome was to compare cases and controls with regard to zinc levels, we essentially excluded participants with a drug history of zinc supplementation. We also excluded cases with a drug history of iron therapy, as our secondary outcome was to examine the difference between the two groups with regard to iron hemostasis.

Children admitted to the hospital were excluded because in-hospital admission could negatively affect their nutritional status and zinc level. Likewise, children with comorbidities that could affect their nutritional status were excluded.

Sample size calculation

The primary objective of the current study was to compare serum zinc levels between asthmatic children and healthy controls. Umar *et al*[13] reported that the mean serum zinc level in BA patients was 79.63 ± 9.62 μg/dL, while it was 93.27 ± 12.21 μg/dL in healthy controls. G*Power software (version 3.1.9.2) was used to estimate the required sample size. The alpha was set as 0.05, the power (1-β) was set as 0.99, and the case-to-control ratio was set as 2:1. Considering a nonparticipation rate of 10%, the minimum required sample size for the study was 60 patients, including 40 cases, and 20 controls.

Ethical concerns

All procedures were carried out in line with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 2013 and were approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University. The ethical approval number is MS-587-2021.

Statistical analysis

Data are statistically described in terms of the mean ± SD, the median and interquartile range, or frequencies (number of cases) and percentages when appropriate. Tests of normality were performed for all the numerical variables of interest using the Kolmogorov-Smirnov/Shapiro-Wilk test. The comparison of numerical variables between cases and controls was performed using the independent samples *t*-test for the parametric data and the Mann-Whitney *U* test for nonparametric statistics. When the analyses between more than 2 groups (between children with mild, moderate, and severe asthma) were needed, the Kruskal-Wallis test for nonparametric data was performed (as in the comparison regarding ferritin and IgE levels). Cross-tabulation was applied to compare the categorical variables using chi-square and Fisher's exact tests depending on whether more than 20% of the cells had expected cell counts less than 5. Spearman's rank correlation was applied if one or both of the numerical data of interest were not parametrically distributed, as in the case of the correlation between serum ferritin levels and both serum iron and hemoglobin levels. A two-sided *P* value less than or equal to 0.05 was considered statistically significant. A graphical presentation was also used to illustrate the difference between medians using a box plot and the difference between means using error plot graphs. Furthermore, a scattered plot was applied to clearly illustrate the possible linear relation between serum iron and ferritin levels. All statistical calculations were performed using the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, United States) release 27 for Microsoft Windows.

RESULTS

Our study aimed to describe the difference in zinc levels between children with BA and healthy controls without BA.

Preliminary analysis

Matching between cases and controls regarding age, sex, BMI, and the coexistence of malnutrition was performed (Table 1). Table 1 shows no significant differences, with *P* values more than 0.05

The normal distribution of the numerical variables of interest was tested using the Kolmogorov-Smirnov/Shapiro-Wilk test to identify the possible statistical methods of choice (Table 2). Age, serum ferritin levels, IgE levels, and BMI scores were not normally distributed. On the other hand, serum zinc, iron, hemoglobin (Hb) and albumin levels were normally distributed.

Sociodemographic criteria

Table 3 illustrates the sociodemographic criteria of the study participants. Among the study participants, male sex generally predominated, specifically in children with BA (Figure 1).

Characteristics of the study participants

Table 4 shows the distribution and level of significance of the biochemical laboratory assessments between cases and controls. The mean ± SD serum zinc level for asthmatic *vs* nonasthmatic children was 94.4 ± 24.7 and 85.2 ± 19, respectively, with no significant difference (*P* = 0.115). Similarly, no significant differences were observed regarding serum iron, Hb, and albumin levels in cases *vs* controls (*P* = 0.389, 0.857, and 0.391, respectively). In contrast, serum levels

Table 1 Matching between cases and controls

	Cases (*n* = 40)	Controls (*n* = 21)	*P* value
Gender distribution, *n* (%)			
Females	13 (32.5)	10 (47.5)	0.247[1]
Males	27 (67.5)	11 (52.5)	
Age in yr, median (IQR)	7 (4)	6 (4)	0.361[2]
BMI Z scores, median (IQR)	-1 (0)	-1 (0)	0.999[2]
Coexistence of malnutrition, *n* (%)			
Yes	35 (87.5)	21 (100)	0.154[3]
No	5 (12.5)	0 (0)	

[1]Chi-square test;
[2]Mann-Whitney test;
[3]Fisher's exact test.
BMI: Body mass index.

Table 2 Normality tests for numeric variables of interest

Studied numerical variables	*P* value	Distribution
Age of the study participants	0.000[a]	Non-parametric
Serum zinc	0.200	Parametric
Serum IgE	0.000[a]	Non-parametric
Serum iron	0.188	Parametric
Ferritin	0.000[a]	Non-parametric
Hb	0.200	Parametric
Albumin	0.212	Parametric
BMI Z scores	0.001[a]	Non-parametric

[a]*P* value is considered significant if ≤ 0.05.
BMI: Body mass index; Hb: Hemoglobin IgE: Immunoglobulin E.

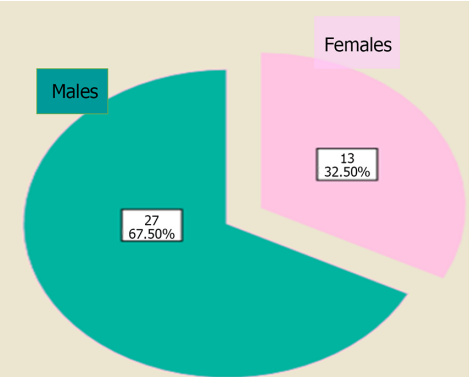

Figure 1 Pie chart showing the sex distribution among children with bronchial asthma.

of IgE and ferritin showed significant differences between cases and controls, with *P* values of 0.001 and 0.006, respectively.

Our primary objective was to compare zinc levels between asthmatic and nonasthmatic children. The mean difference was higher in asthmatic children, as shown in Figure 2.

Table 3 Sociodemographic criteria of the study participants

Sociodemographic criteria	
Age of the study participants, yr	
Median (IQR)	7 (4)
Min-max	5-12
Age of children with BA, yr	
Median (IQR)	7.4 (4)
Min-max	5-12
Sex distribution of the study, *n* = 61 (%)	
Males	38 (62.3)
Females	23 (37.7)
Sex distribution in children with BA, *n* = 40 (%)	
Males	27 (67.5)
Females	13 (32.5)

BA: Bronchial asthma; IQR: Interquartile range.

Table 4 Biochemical lab assessment in cases *vs* controls, mean ± SD

	Children with BA	Healthy controls	*P* value
Serum zinc Min-max	94.4 ± 24.7 47-142	85.2 ± 19 47.3-112	0.115[1]
Serum iron Min-max	68.8 ± 28.8 18.7-136.8	62.4 ± 26.4 26.5-116.9	0.389[1]
Serum ferritin, median (Q1-Q3) Min-max	53.1 (68.6-32.2) 4.2-329.2	30 (46-17) 2-71	0.006[a,2]
Serum Hb Min-max	12 ± 0.8 9.9-13.7	12 ± 0.8 10.3-13.6	0.857[1]
Serum albumin Min-max	3.9 ± 0.2 3.5-4.6	3.9 ± 0.19 3.5-4.2	0.391[1]
Serum IgE, median (Q1-Q3) Min-max	264 (229-37) 0.1-2302	33 (60.5-12.7) 6.7-91	0.001[a,2]

[a]*P* value is considered significant if ≤ 0.05.
[1]Independent *t*-test;
[2]Mann-Whitney test.
BA: Bronchial asthma; Hb: Hemoglobin; IgE: Immunoglobulin E.

Upon determining the serum levels of ferritin, median differences were higher in children with BA, as shown in Figure 3. This may disclose its role in inflammation, as higher serum ferritin levels do not necessarily mean higher serum iron levels. Spearman's rank correlation was performed and revealed a weak nonsignificant correlation between both serum ferritin and iron levels (*rs* = -0.077, *P* = 0.637), as shown in Table 5, which also yielded a similar weak nonsignificant correlation between serum ferritin and Hb levels (*rs* = 0.204, *P* = 0.208). In addition, a weak relation was observed in the scatter plot for ferritin and iron levels, as shown in Figure 4.

Upon checking the median difference in IgE levels, children with BA showed higher levels, as shown in Figure 5. However, serum IgE levels did not differ significantly in regard to the degree of asthma in children with BA, as shown in Table 6 and Figure 6. Likewise, serum ferritin levels did not show a significant difference regarding the grades of asthma severity (Table 6).

DISCUSSION

Our study included 61 children: 40 diagnosed with BA and 21 without BA. We examined zinc levels between the two

Table 5 Correlation between serum iron and hemoglobin levels and ferritin in asthmatic children

Studied covariates	Serum ferritin	
	rs	*P* value
Serum iron	-0.077	0.637
Hb	0.204	0.208

Hb: Hemoglobin.

Table 6 Serum immunoglobulin E with degree of severity of asthma in cases of bronchial asthma, mean rank

Study participants	Mild asthma, *n* = 24	Moderate asthma, *n* = 14	Severe asthma, *n* = 2	*P* value
IgE	21.5	19.7	13.5	0.623[1]
Ferritin	22	16	31.5	0.126[1]

[1]Kruskal Wallis test.
IgE: Immunoglobulin E.

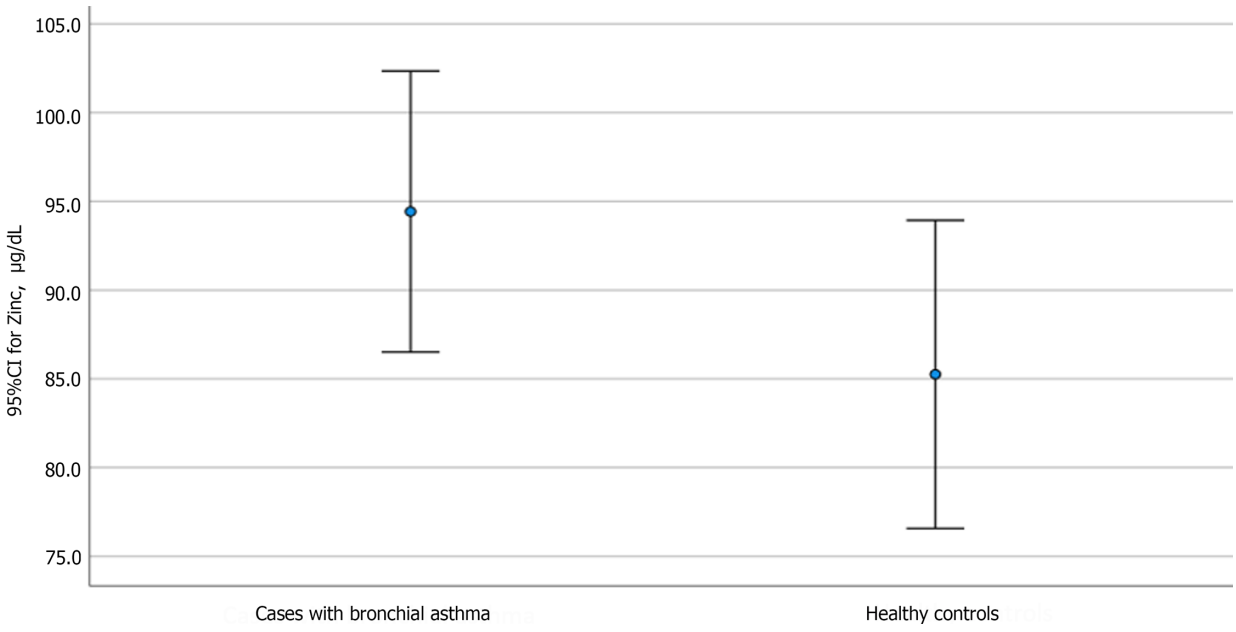

Figure 2 Error bar showing the mean difference between cases and controls, including the confidence interval regarding zinc levels.

groups. Yousef *et al*[14] detected significantly diminished levels in cases with BA in comparison to controls, and the *P* value was < 0.01. In addition, higher levels of serum zinc in control children were observed in another former study, yet the difference was not significant (*P* = 0.388)[15]. Our study showed a different result. For example, mean values of serum zinc were higher in cases with BA in our study. This difference may be because all cases were receiving asthma therapy such as inhaled steroids. Rahman *et al*[16] proposed that after steroid therapy, stimulation of glutathione (GSH) synthesis in the liver occurs due to a decrease in the generation of reactive oxygen species by neutrophils. Reduced GSH and GSH disulfide (GSSG) are critical modulators of both the rate of zinc transfer and the ultimate number of zinc atoms transferred. GSSG increases the rate of zinc transfer by 3-fold, and its concentration is the major determinant for efficient zinc transfer[17]. In another study, Raeve *et al*[18] showed that after corticosteroid therapy, macrophage oxidant production decreased, and the number of oxidant-generating cells present in the asthmatic airway mucosa also decreased; hence, the enhancement of GSH synthesis in the liver could subsequently occur. Considering that lower serum zinc levels indicate higher asthma severity[19], our finding of higher zinc levels in asthmatic children may suggest that lower serum zinc levels may indicate poor compliance with therapy and vice versa.

Other biochemical laboratory test results were assessed, all of which showed no significant difference between cases and controls except for serum ferritin and serum IgE levels. Serum ferritin appears to be a better biomarker for inflammation than iron status[20]. This may be the reason for the significantly elevated levels of ferritin in children with BA

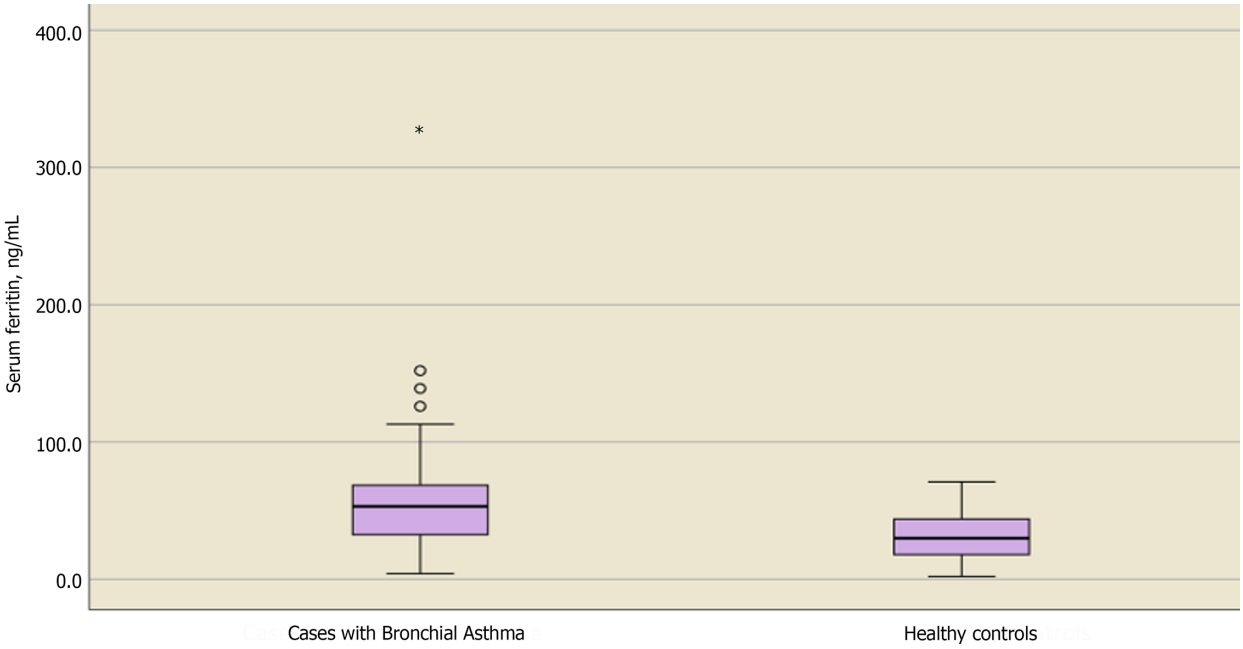

Figure 3 Box plot showing the median difference between cases and controls regarding ferritin levels.

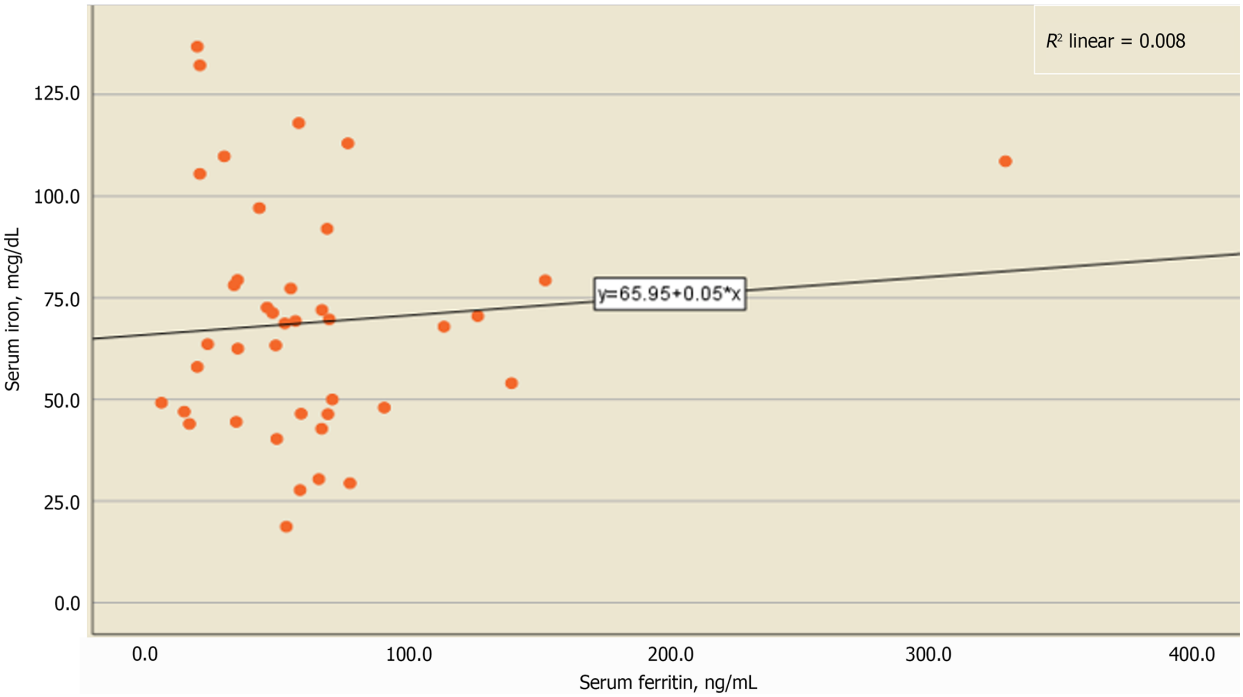

Figure 4 Scatter plot between serum iron and serum ferritin levels.

compared to controls in our study (P = 0.006). There is mounting evidence that circulating ferritin levels might not only reflect the acute phase response but also play a crucial role in inflammation. Its secretion is regulated *via* proinflammatory cytokines, and ferritin has immunosuppressive effects that are probably mediated by binding to its receptor. Although it is commonly accepted that circulating ferritin levels may reflect an acute phase response, the explanation for how and why serum ferritin is increased is unknown[21]. Higher ferritin does not essentially equal iron overload[22]. Ferritin can be a good biomarker of appropriate *vs* excessive inflammation, and previous research found that high ferritin in severe coronavirus disease 2019 pneumonia patients is associated with improved outcomes following steroid treatment[23]. Another study found that low ferritin levels in the course of steroid therapy were linked to greater mortality[24]. Therefore, our study may increase attention toward the possible use of ferritin as a marker of asthma control after steroid therapy. In addition, serum ferritin is not significantly correlated with Hb and iron. However, using serum ferritin as a marker of iron hemostasis or iron deficiency anemia in asthmatic children may be controversial.

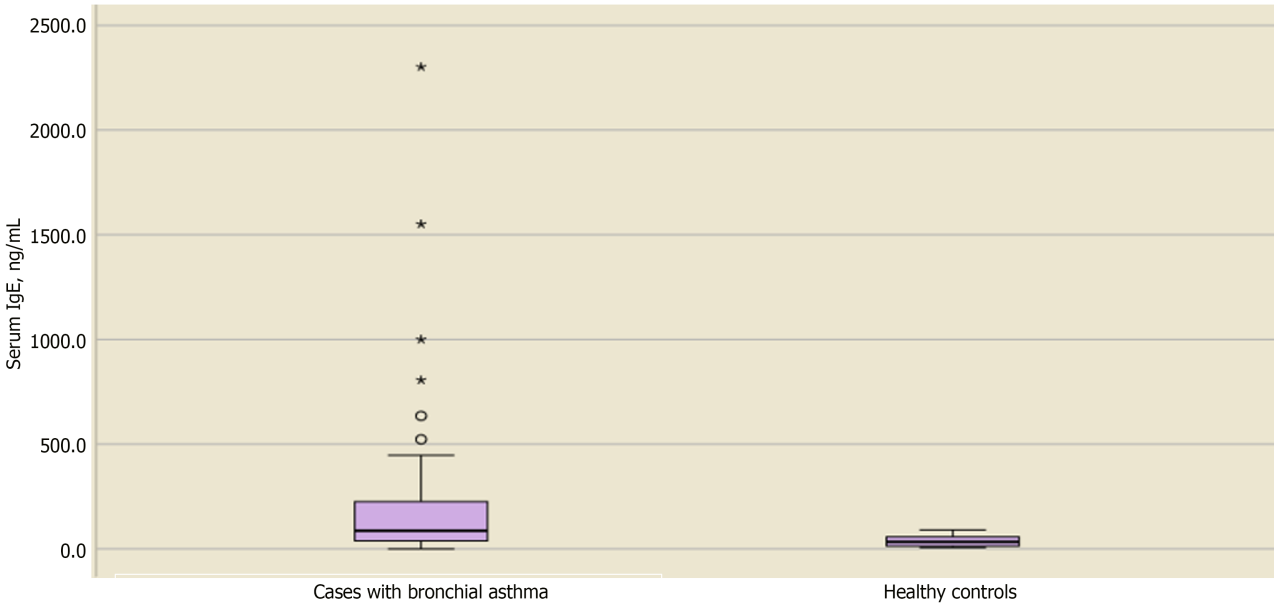

Figure 5 Box plot showing the median difference in serum immunoglobulin E levels between cases and controls.

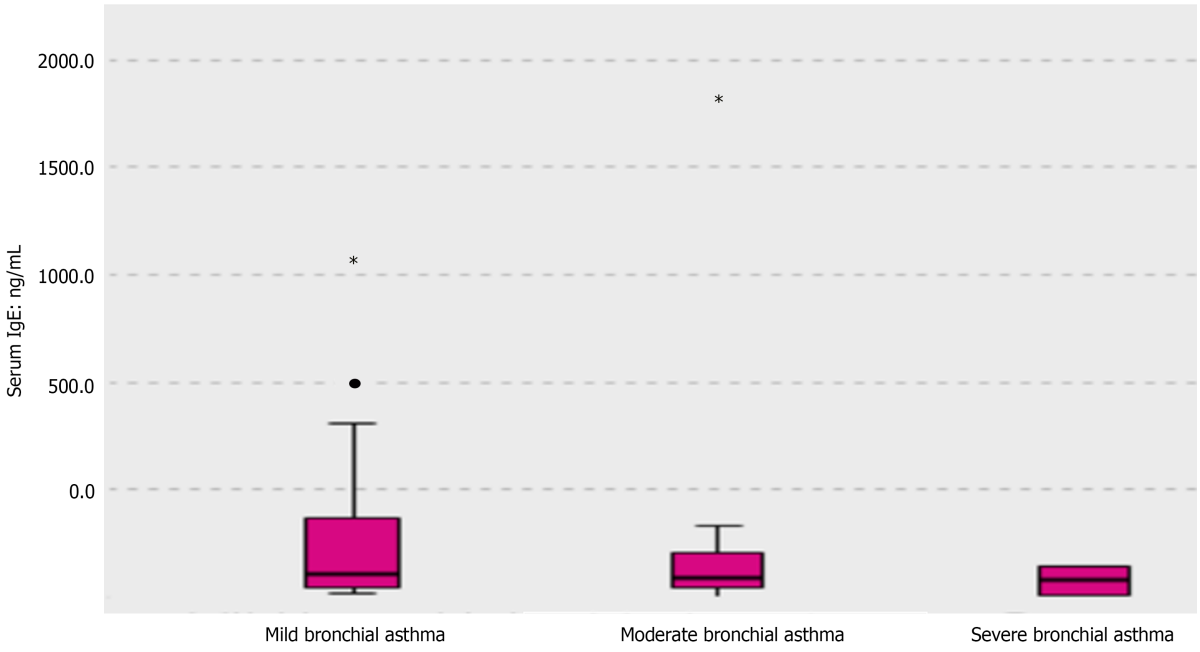

Figure 6 Box plot showing the median difference in immunoglobulin E levels between children with mild, moderate, and severe asthma.

Allergic diseases involving asthma are characterized by an increase in serum IgE levels[25,26]. Our study showed that there was a significant increase in serum IgE levels in patients with BA. However, there was no significant difference regarding the degrees of severity. Sandeep *et al*[27] reported a similar finding. It may be suggested that levels of IgE are quite high at the local inflammation site and that the serum levels do not essentially reflect the levels in the lungs or bronchus. Moreover, IgE is bound to mast cells with rather high affinity, and hence, circulating IgE may not provide conclusive evidence of the severity of inflammation[28].

CONCLUSION

Serum zinc levels did not show a significant difference between asthmatic children and nonasthmatic children. Serum ferritin may be a marker of controlled asthma. Serum IgE levels should not be used to stratify asthmatic children according to severity.

ARTICLE HIGHLIGHTS

Research background
Zinc levels might differ in asthmatic children.

Research motivation
The possible role of the biochemical nutritional assessment including zinc to be a biomarker for asthma severity.

Research objectives
To outline the difference in zinc levels between asthmatic and healthy children.

Research methods
A cross-sectional study was carried out investigating serum zinc levels in asthmatic and healthy children.

Research results
Zinc levels weren't different. Ferritin levels were significantly higher in cases with bronchial asthma.

Research conclusions
Ferritin could be used as a future biomarker for asthma controller therapy.

Research perspectives
Further studies investigating the possible role of ferritin and other possible biomarkers for asthma severity should be outlined.

FOOTNOTES

Author contributions: All the authors have read and approved the final manuscript. Conceptualization, material preparation, manuscript drafting/writing, editing, data interpretation and project methodology were performed by Atef Abdelsattar Ibrahim H; Resources were developed by Mohsen M, Salep Aziz Hanna B and Mahmoud D; The arrangement of diagnostic investigations and project administration were performed by Atef Abdelsattar Ibrahim H, Salep Aziz Hanna B and Mahmoud D; Supervision was performed by Atef Abdelsattar Ibrahim H, Mohsen M, Mahmoud D and Mohamed Abdelhamid El-Khashab K; Formal analysis was performed by Atef Abdelsattar Ibrahim H.

Institutional review board statement: The study was approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University, No. MS-587-2021.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: The dataset of this study is available from the corresponding author upon reasonable request.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

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ORIGINAL ARTICLE

Case Control Study

Salivary C-reactive protein and mean platelet volume as possible diagnostic markers for late-onset neonatal pneumonia

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Abstract

BACKGROUND

Neonatal sepsis, a formidable threat to newborns, is a leading cause of neonatal mortality, with late-onset sepsis manifesting after 72 hours post-birth being particularly concerning. Pneumonia, a prevalent sepsis presentation, poses a significant risk, especially during the neonatal phase when lung defenses are compromised. Accurate diagnosis of pneumonia is imperative for timely and effective interventions. Saliva, a minimally invasive diagnostic medium, holds great promise for evaluating infections, especially in infants.

AIM

To investigate the potential of serum C-reactive protein (CRP), salivary CRP (sCRP), and mean platelet volume (MPV) as diagnostic markers for late-onset neonatal pneumonia (LONP).

METHODS

Eighty full-term neonates were systematically examined, considering anthropometric measurements, clinical manifestations, radiology findings, and essential biomarkers, including serum CRP, sCRP, and MPV.

RESULTS

The study reveals noteworthy distinctions in serum CRP levels, MPV, and the serum CRP/MPV ratio between neonates with LONP and healthy controls. MPV exhibited a robust discriminatory ability [area under the curve (AUC) = 0.87] with high sensitivity and specificity at a cutoff value of > 8.8. Correlations between serum CRP, sCRP, and MPV were also identified. Notably, sCRP demonstrated excellent predictive value for serum CRP levels (AUC = 0.89), underscoring its potential as a diagnostic tool.

CONCLUSION

This study underscores the diagnostic promise of salivary and serum biomarkers, specifically MPV and CRP, in identifying and predicting LONP among neonates. These findings advocate for further research to validate their clinical utility in larger neonatal cohorts.

Key Words: Neonatal sepsis; Late-onset pneumonia; Salivary C-reactive protein; Mean platelet volume; Diagnostic markers; Newborn infections

Core Tip: This prospective study explores the potential of salivary C-reactive protein (CRP) (sCRP) and mean platelet volume (MPV) as diagnostic markers for late-onset neonatal pneumonia (LONP). Analyzing 80 neonates, significant differences in serum CRP levels, MPV, and the serum CRP/MPV ratio were observed between LONP cases and healthy controls. MPV demonstrated strong discriminatory ability with high sensitivity and specificity at a cutoff value of > 8.8. sCRP displayed notable predictive value for serum CRP levels. These findings highlight the diagnostic potential of salivary and serum biomarkers in identifying and predicting LONP among neonates.

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INTRODUCTION

Neonatal sepsis is a serious infection in newborns with a very high risk of neonatal death and occupies the third rank among the causes of neonatal death[1]. It can manifest in various forms, like septicemia, pneumonia, meningitis, osteomyelitis, arthritis, and urinary tract infections. Late-onset sepsis occurs after 72 hours of birth and is a significant cause of infant mortality[2]. Despite medical advances, diagnosing and managing neonatal infections remains challenging. Childhood mortality due to pneumonia carries the highest risk during the neonatal phase since the fetus and neonate have compromised lung defenses, making them more prone to infections[3]. Neonatal pneumonia can be classified according to its onset into early-onset (within the 1st wk of life) and late-onset (onset of symptoms after the 1st wk of life within the first 28 d). Late-onset neonatal pneumonia is further classified into hospital- or community-acquired. The community-acquired neonatal pneumonia occurs in term and near-term neonates who were discharged home after the initial birth hospitalization. Hospital-acquired late-onset pneumonia (LOP) occurs in newborns who remain hospitalized since birth (*e.g.*, preterm infants)[4,5].

It is crucial to accurately diagnose pneumonia to assess the disease's impact, implement suitable preventive or treatment measures, and develop more efficient interventions[6]. Saliva has been found to have excellent potential as a diagnostic fluid over the years. It's easy and non-invasive collection method makes it the most attractive diagnostic medium to examine vulnerable populations such as infants, toddlers and children[7]. C-reactive protein (CRP), which is a major acute phase protein, is a member of the pentraxin family and plays a central role in innate and adaptive immunity. It takes 10-12 h for CRP to rise significantly after the onset of an infection[8]. Since CRP shows an increase in several conditions, it is better to use it in combination with other biomarkers.

Platelets, small non-nucleated cells derived from precursor megakaryocytes, have multiple functions and play a vital role in hemostasis by forming blood clots. They are a natural source of growth factors, including platelet-derived growth factor and transforming growth factor-β, which are essential for connective tissue repair and regeneration[9]. Platelet-rich plasma has been used to increase the concentration of these growth factors and aid wound healing. Thrombopoiesis, the production of platelets, is driven by thrombopoietin and several transcription factors. In inflammatory states, interleukin-6 enhances the process of proplatelet formation by increasing thrombopoietin levels[10]. Mean platelet volume (MPV) is one of the hemogram parameters that is affected by many inflammatory conditions. In neonates, MPV can predict the development of sepsis and its severity[11]. Therefore, the combined measurement of CRP and MPV can be used to diagnose bacterial *vs* viral pneumonia and predict its complications[12]. This study aims to assess the effectiveness of salivary CRP (sCRP) and MPV in identifying LOP in newborns.

MATERIALS AND METHODS

The present research was a prospective case-control study conducted on eighty full-term neonates recruited serially from the Neonatal Intensive Care Unit (NICU) and Clinic, Pediatric Department, the tertiary care hospital of Tanta University between June 2021 and May 2022, to evaluate the usefulness of sCRP and MPV in identifying Late Onset Neonatal Pneumonia (LONP). The recruited neonates were divided into two comparable groups: Group I included neonates who developed late-onset neonatal pneumonia (who developed pneumonia after 3rd d and before 28th d of life). Group II included healthy neonates with no clinical manifestation of infection or other systemic diseases.

We included full-term neonates (gestational age ≥ 37 wk and birth weight ≥ 2.5 kg) with post-natal age between 7 and 28 d with clinical suspension of LOP. All eligible neonates underwent comprehensive assessments of their prenatal, perinatal, and postnatal history, thorough clinical examinations, a complete blood cell count including differential, evaluation of CRP levels, urine analysis and culture, blood culture, cerebrospinal fluid analysis and culture, and relevant infection markers. Blood gases, chest imaging (plain X-ray and/or ultrasonography), echocardiography, and abdominal X-ray were conducted based on specific clinical indications. We followed Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection for reporting neonatal infection[13] and Gerdes' sepsis screen (> 2) to screen for neonatal sepsis, including pneumonia[14]. Pneumonia was suspected in the presence of fever or temperature instability, irritability, lethargy, feeding difficulty, apnea, or respiratory distress. Other systemic manifestations, such as hepatomegaly, abdominal distention, convulsion, hypotonia, hemodynamic instability, and bleeding diathesis, were considered general manifestations of neonatal sepsis. We classified the patients as mild [degree of respiratory distress (RD) 1: Tachypnea > 60/min and flaring nostrils), moderate (RD 2: RD2 + intercostal and subcostal retractions), severe (RD2 + expiratory grunting), and advanced (RD 3 + central cyanosis); according to the degree of respiratory distress. Chest X-ray findings varied from normal chest X-ray to localized or diffuse alveolar densities, reticular opacities, homogenous ground glass opacities, and dense bilateral air space-filling process with air bronchograms. Any pneumonia complication findings were also recorded, such as interstitial emphysema, pleural effusion, pneumomediastinum, or pneumothorax.

We excluded premature infants and neonates with inflammation other than pneumonia, congenital heart conditions, hypoxic-ischemic encephalopathy, liver or kidney issues, hereditary coagulopathies, or any other systemic disorders unrelated to pneumonia that could impact CRP or platelet size levels. We also excluded neonates exposed to antibiotics before admission, neonates younger than 7 d, or infants older than 28 d of life. According to NICU protocol, all children with suspected pneumonia receive the appropriate management. All parents, guardians, or next of kin signed informed consent for the minors to participate in this study. The Institutional Ethical and Research Review Board of the Faculty of Medicine, Tanta University, approved the study.

Laboratory investigations included salivary and serum CRP measurement and MPV measurement. We collected salivary samples just before feeding to avoid milk contamination. With gentle handling of the baby, we stimulated the saliva secretion by allowing the baby to suck on a clean, sterilized pacifier for a few minutes. The head of the baby was elevated to allow the saliva to collect on the floor of the mouth, under the neonates' tongues, for accessible collection. The saliva samples were collected using a one-ml syringe without a needle with the suction pressure applied manually for about 10–15 s, collecting about 0.5 mL of saliva. Then, the samples were transferred to sterile polypropylene tubes to avoid contamination and stored at −20 °C until CRP analysis and measuring using ELISA. Serum CRP levels were determined using a fully automated auto-analyzer Cobas c501 (Roche Diagnostics, Manheim, Germany).

A peripheral blood sample was collected just before feeding (to avoid the effect of feeding on the platelet volume) into a clean, sterile EDTA vacutainer tube to measure MPV value. The sample was handled gently without unnecessary agitation to minimize platelet activation and analyzed using an automated blood cell counter (Cell-Dyn 3700, Abbott Laboratories, IL, United States) within 60 min of collection to avoid platelet swelling and pseudo increase in MPV value. The analyzer calculates the MPV by dividing the total platelet volume by the number of platelets in the blood sample.

Statistical analysis

We used the Power and Precision V3 program (http://www.Power-Analysis.com, Englewood, New Jersey) to determine the study's power level. The collected data were organized, tabulated, and subjected to statistical analysis using the SPSS version 20 (SPSS, Chicago, IL, United States) to determine the sensitivity, specificity, and predictive value of MPV, sCRP, serum CRP, and the serum CRP/MPV ratio for diagnosing LONP cases. We used the Shapiro-Wilk test to test the normality of data distribution. Mann-Whitney *U*-test assessed the differences between groups regarding nonparametric quantitative data. Receiver operating characteristic curves were used to identify optimal cutoff values for differentiating patients with LONP from healthy controls. We used the mean and standard deviation to characterize the quantitative data. We considered the findings to be statistically significant when the P *was* < 0.05.

RESULTS

In this study, we compared two groups of neonates: One with LOP comprising 40 neonates and a control group of 40 healthy neonates. Our analysis in Table 1 revealed no significant differences in sex distribution, age, mode of delivery, Apgar score, and the presence or absence of maternal illness during pregnancy between the neonates with LOP and the control group. However, notable variations in anthropometric measurements were observed, with the neonates with LOP neonates exhibiting lower weight, length, and head circumference than the control group. Additionally, the LOP group demonstrated substantially elevated levels of serum CRP, MPV, and the CRP/MPV ratio, indicating the potential

Table 1 Demographic and laboratory findings of neonates with late-onset pneumonia and the control group

Parameter		Neonates with LOP, *n* = 40	Control group, *n* = 40	*P* value
Sex	M	21	22	> 0.05
	F	19	18	> 0.05
	M:F	1.1:1	1.2:1	> 0.05
Age in d		15 ± 4.6	14 ± 5	> 0.05
Anthropometric measurements at admission	Weight in g	3454 ± 360	3728 ± 316	< 0.0001[a]
	Length in cm	51.42 ± 1.0	51.87 ± 0.57	< 0.05[a]
	Head circumference	36.21 ± 0.8	36.7 ± 0.60	< 0.05[a]
Type of delivery	Normal	14 (35%)	16 (40%)	> 0.05
	CS	26 (65%)	24 (60%)	> 0.05
APGAR score	At 1 min	7.1 ± 2.5	7.4 ± 2.3	> 0.05
	At 5 min	8.5 ± 3.2	9 ± 2.9	> 0.05
Maternal illness	Non	31 (77.5%)	32 (80%)	> 0.05
	DM	3 (7.5%)	2 (5%)	> 0.05
	hypertension	2 (5%)	5 (12.5%)	> 0.05
	UTI	4 (10%)	3 (7.5%)	> 0.05
Serum CRP in mg/L		38.58 ± 24.9	3.60 ± 2.25	< 0.0001[a]
sCRP in mg/L		6.17 ± 3.38	3.07 ± 1.24	< 0.0001[a]
MPV		9.99 ± 0.94	8.42 ± 0.83	< 0.0001[a]
Serum CRP/MPV		3.86 ± 2.29	0.42 ± 0.39	< 0.0001[a]

[a]*P* < 0.05.

Data are *n*, *n* (%), or mean ± SD. SCRP: C-reactive protein; CS: Caesarean section; DM: Diabetes mellitus; F: Female; LOP: Late-onset pneumonia; M: Male; MPV: Mean platelet volume; sCRP: Salivary C-reactive protein; UTI: Urinary tract infection.

diagnostic value of these markers for LOP among neonates.

Table 2 shows LOP's clinical and radiological features in a cohort of 40 neonates. Clinical manifestations were prominent, with 65% and 70% of neonates exhibiting fever and cough, respectively. Various degrees of respiratory distress were observed, ranging from RD 1 to RD 4 in 10% to 40% of neonates. Abnormal auscultatory findings were prevalent, including decreased air entry (82.5%) and fine crepitations (87.5%). Radiologically, pneumonic patches with an air bronchogram were the most common pattern (75%), followed by homogenous ground glass shadows (10.0%) and interstitial pneumonia (10.0%). A smaller percentage showed a complete white lung (2.5%), and complications were noted in 2.5% of cases. Oxygen support was crucial, with 77.5% requiring a nasal cannula, 12.5% supported by nasal continuous positive airway pressure, and 10% necessitating mechanical ventilation. These comprehensive findings offer valuable insights into LOP's clinical and radiological spectrum, enabling more precise diagnoses and tailored treatment approaches for affected neonates.

In addition to the clinical and radiological findings, the study evaluated the diagnostic validity of key markers in discriminating patients from controls, as shown in Table 3. The area under the curve (AUC), sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated for MPV, Serum CRP, and sCRP. MPV exhibited a high discriminatory ability (AUC = 0.87) with a sensitivity of 86.67% and specificity of 80.0% at a cutoff value of > 8.8. Serum CRP also showed good discriminative power (AUC = 0.81), with a sensitivity of 76.67% and specificity of 60.0% at a cutoff value of > 6. Similarly, sCRP demonstrated notable discriminatory ability (AUC = 0.80) with a sensitivity of 76.67% and specificity of 83.33% at a cutoff value of > 3.5. Furthermore, correlations were explored between serum CRP, sCRP, and MPV in Table 4, revealing significant positive correlations. The study also assessed the diagnostic validity of sCRP in predicting serum CRP levels, demonstrating a high AUC of 0.89 with a sensitivity of 91.3% and specificity of 71.4% at a cutoff value of >3.2, as shown in Table 5. These comprehensive assessments highlight the potential diagnostic utility of MPV and CRP markers, both serum and salivary, in discriminating and predicting disease severity in neonates with LOP.

Table 2 Clinical and radiological findings of neonates with late onset pneumonia

Finding	Number of 40 total	Percentage (%)
Clinical findings		
Fever	26	65.0
Cough	28	70.0
Degree of respiratory distress		
1	7	17.5
2	16	40.0
3	13	32.5
4	4	10.0
Decreases air entry	33	82.5
Fine crepitations	35	87.5
Radiological findings		
Homogenous ground glass shadow	4	10.0
Pneumonic patches and air bronchogram	30	75.0
Interstitial pneumonia	4	10.0
Complete white lung	1	2.5
Complications	1	2.5
Need for oxygen support		
Nasal canula	31	77.5
nCPAP	5	12.5
Mechanical ventilation	4	10.0

nCPAP: Nasal continuous positive airway pressure.

Table 3 Validity (area under the curve, sensitivity, specificity) of mean platelet volume, salivary C-reactive protein, serum C-reactive protein, and serum C-reactive protein/mean platelet volume to discriminate patients from controls

Parameter	AUC	95%CI	*P* value	Cut-off value	Sensitivity	Specificity	PPV	NPV
MPV	0.87	0.77–0.97	< 0.001[a]	> 8.8	86.67	80.0	81.2	85.7
Serum CRP	0.81	0.70–0.92	< 0.001[a]	> 6 mg/dL	76.67	60.0	65.7	72.0
sCRP	0.80	0.68–0.92	< 0.001[a]	> 3.5 mg/dL	76.67	83.33	82.1	78.1

[a]$P < 0.05$.

AUC: Area under the curve; CI: Confidence interval; CRP: C-reactive protein; MPV: Mean platelet volume; NPV: Negative predictive value; PPV: Positive predictive value; sCRP: Salivary C-reactive protein.

DISCUSSION

LOP in neonates is a critical condition, presenting unique challenges in diagnosis and management that demands a thorough understanding of its clinical, radiological, and biochemical features to enhance diagnostic precision, facilitate tailored therapeutic interventions and improve clinical outcomes[15]. This study aimed to comprehensively explore these aspects and evaluate the diagnostic potential of specific biomarkers in discriminating between neonates with LOP and healthy controls.

The clinical manifestations observed in neonates with LOP encompassed fever, cough, varying degrees of respiratory distress, decreased air entry and fine crepitations. These clinical findings align with the well-documented respiratory symptoms associated with pneumonia. These findings agreed with Omran *et al*[12], who studied 35 full-term neonates diagnosed with LOP and 35 controls. They found fine crepitation in 32 (91.4%), decreased air entrance in 24 (74.3%) and intercostal retractions in 25 (71.4%). Furthermore, the varying degrees of respiratory distress, observed as thoracic retractions in Omran *et al*'s[12] study and as RD1 to RD4 in our study, indicate the diverse respiratory involvement in

Table 4 Correlation of serum C-reactive protein with each salivary C-reactive protein and mean platelet volume, neonates with late-onset pneumonia (*n* = 40)

Parameter	*r* value	*P* value
Serum CRP *vs* sCRP	0.59	0.001[a]
Serum CRP *vs* MPV	0.66	< 0.001[a]
Salivary CRP *vs* MPV	0.54	0.01[a]

[a]*P* < 0.05.

CRP: Salivary C-reactive protein; MPV: Mean platelet volume; sCRP: Salivary C-reactive protein.

Table 5 Diagnostic validity (area under the curve, sensitivity, specificity) for salivary C-reactive protein to predict serum C-reactive protein > 6 (*n* = 31) from serum C-reactive protein ≤ 6 (*n* = 9) in the patient group (*n* = 40)

Parameter	AUC	95%CI	*P* value	Cut-off Value	Sensitivity	Specificity	PPV	NPV
sCRP	0.89	0.77-1.1	< 0.001[a]	> 3.2	91.3	71.4	91.3	71.4

[a]*P* < 0.05.

AUC: Area under the curve; CI: Confidence interval; NPV: negative predictive value; PPV: Positive predictive value; sCRP: Salivary C-reactive protein.

LOP. Additionally, radiological examinations provided valuable insights into the lung pathologies present in LOP, notably pneumonic patches with air bronchograms, ground glass shadows, and interstitial pneumonia. These findings agree with that of Haney *et al*[16], who found that bilateral alveolar densities were the most commonly identified X-ray abnormality, noted in 77% of cases. One-third of their patients had typically dense and extensive alveolar changes with frequent air bronchograms. Our findings resonate with existing literature, further validating the robustness of our study.

Intriguingly, our study delved deeper into the potential diagnostic value of biomarkers. MPV, serum CRP, and sCRP were identified as promising, readily available candidates for discriminating patients from controls. MPV, a marker often associated with inflammatory conditions, demonstrated high discriminative ability (AUC = 0.87) with significant sensitivity and specificity, suggesting its potential as a diagnostic tool for LOP.

Platelets play a significant role in neonatal sepsis-induced coagulopathy. During systemic inflammation, P-selectin is expressed on the surface of platelets, enhancing platelet adherence to leukocytes, platelet aggregation, and expression of tissue factor on monocytes[17]. MPV is considered a marker of platelet function and activation, associated with larger and more reactive platelets. During inflammatory states, platelets become activated, leading to an increase in MPV. This inflammation observed in LOP triggers platelet activation, resulting in larger platelets (higher MPV). Therefore, MPV could be used as a marker that indicates systemic inflammation and infection, including LOP[18]. It is being studied in various conditions in adults and children, including acute coronary syndrome and acute appendicitis[19,20]. In the current study, MPV was shown to have a high level of discriminative ability (AUC = 0.87), with a sensitivity of 86.67% and specificity of 80.0% at a cutoff value of > 8.8 for neonates with LOP. The high AUC score indicates that MPV is an excellent diagnostic tool for distinguishing neonates with LOP from healthy controls. An AUC of 0.87 signifies a strong ability to correctly classify patients and controls based on MPV levels. In addition, MPV has a sensitivity of 86.67%, which means it accurately identified the majority (86.67%) of neonates with LOP, reducing false negatives. On the other hand, the specificity of 80.0% suggests that MPV effectively excluded a significant portion (80.0%) of healthy neonates, reducing false positives. With a cutoff value of > 8.8 for MPV, neonates with MPV levels exceeding this threshold are likelier to have LOP.

Our results agree with many previous works. Omran and colleagues found a significant difference in MPV levels between neonates suffering from pneumonia and those who didn't and established a noteworthy association between MPV and CRP in both serum and saliva[21]. We have confirmed these findings. MPV, with a cut-off value of 9.0 fl exhibited an excellent diagnostic accuracy of 80% in identifying infants with pneumonia. Similarly, Pamudji and Kardana [22] reported that an MPV of 7.44 fl had 80% sensitivity and 84.2% specificity in diagnosing neonatal sepsis. In addition, Wang *et al*[23] conducted a meta-analysis which found that MPV was significantly higher in patients with neonatal sepsis than in the control group, suggesting that MPV could be used as an early indicator for diagnosing neonatal sepsis in clinical practice. This can help clinicians make diagnostic decisions based on MPV levels. With a high AUC and its balanced sensitivity and specificity, MPV holds promise as a diagnostic marker for neonatal LOP. It may offer a relatively simple and cost-effective method to diagnose neonatal pneumonia[24]. However, further research and validation in larger and more diverse cohorts are needed to definitively establish MPV's diagnostic accuracy and clinical utility.

CRP is one of the most utilized biomarkers to monitor infection and inflammation in the pediatric and neonatal populations[25]. Serum CRP, a well-established inflammation marker, exhibited a substantial discriminative ability (AUC = 0.81) and meaningful sensitivity and specificity, as observed in the current study. These findings are consistent with previous research indicating the diagnostic significance of serum CRP in respiratory infections. Kumar *et al*[26] found higher overall serum CRP accuracy in diagnosing late-onset neonatal sepsis, ranging from 96.5% in proven sepsis to

99.1% in probable sepsis with a specificity of 85.3 %, using a CRP cut-off value of 5 mg/L. This suggests that CRP has a high diagnostic accuracy in identifying neonates at risk of sepsis. In addition, Omran *et al*[27] found a significant increase in serum CRP with a mean of 29.4 ± 13 mg/L neonates with late-onset sepsis.

Serum CRP also exhibited considerable discriminative ability, with notable sensitivity and specificity for neonatal infection, including pneumonia. Its diagnostic significance in respiratory infections aligns with the observed potential in discriminating LOP. A meta-analysis by Xiao *et al*[28] revealed that infants with pneumonia exhibited higher serum CRP levels than healthy infants. Therefore, serum CRP levels might be an independent diagnostic tool for pneumonia in children. In addition, Li and Chen[29] found a close correlation between higher serum CRP levels and the progression of neonatal pneumonia. Several studies have reported different cut-off values for serum CRP levels in diagnosing neonatal sepsis. These values range widely, from 1.5 to 20 mg/L, and are associated with varying sensitivities and specificities. For instance, sensitivity values range from 74% to 98%, while specificities range from 71% to 94%, whether using a single measurement at least 12 h after the onset of symptoms or serial CRP determinations[30-33].

The detection of CRP in saliva is a new and promising diagnostic method that has recently gained attention as an emerging biomarker. It shows potential in diagnosing various medical conditions, such as pneumonia. One of the significant advantages of using sCRP in diagnosing neonatal pneumonia is its non-invasive nature. Saliva collection is less intrusive and more feasible than obtaining blood samples, especially in neonates, where it can be challenging to draw blood[34,35]. Iyengar *et al*[36] conducted a study on y sCRP detection and its usefulness in neonates. It is considered the first study to detect, quantify, and demonstrate that sCRP is a good measure of discrimination for clinically relevant serum CRP thresholds. The study included the most salivary samples obtained from neonates suffering from necrotizing enterocolitis or spontaneous intestinal perforation, infectious diseases, and post-operative monitoring. The median sCRP concentration was found to be 3.1 ng/mL, whereas the median serum CRP concentration was 106.1 mg/L[36]. Interestingly, we used sCRP in our study as a non-invasive alternative that displayed noteworthy discriminatory ability (AUC = 0.80) and strong correlations with serum CRP and MPV. Our results emphasize the potential of sCRP as a viable diagnostic marker in neonates with LOP and agree with many previous studies. A study conducted by Omran *et al*[27] found a result similar to ours. They observed a significant difference in the mean level of sCRP between septic neonates (12.0 ± 4.6 ng/L) and the control group (2.8 ± 1.2 ng/L). The sensitivity of sCRP was 94.3%, and specificity was 80% at a cut-off point of 3.48 ng/L[27]. Barekatain *et al*[25] also reported a significant increase in sCRP levels in neonates with sepsis compared to healthy controls. The AUC value was 0.63, with a sensitivity of 44.9%, specificity of 80%, PPV of 73.3%, NPV of 54.2%, and diagnostic accuracy of 61% at a cutoff of 4.55 ng/L[25].

The current study has shown a significant correlation (r = 0.59, P < 0.001) between serum CRP and sCRP levels in neonates with LOP. This suggests that sCRP levels reflect those in serum and can serve as a non-invasive diagnostic biomarker for neonatal LOP. sCRP can potentially be used as a proxy for serum CRP, indicating the systemic inflammatory response associated with pneumonia[37]. The positive correlation strengthens the case for considering sCRP as a reliable diagnostic tool for neonatal LOP. In a study by Iyengar *et al*[36], an sCRP concentration of 4.84 ng/L was found to have 64% sensitivity and 94% specificity for predicting a serum CRP of 5 mg/L. It was also found to have 54% sensitivity and 95% specificity for predicting a serum CRP of 10 mg/L. On the other hand, Tosson *et al*[38] found no significant correlation between sCRP and serum CRP levels in neonates with late-onset sepsis. To ensure consistent and accurate sCRP measurement across different studies, it is important to address various challenges that may affect its accuracy. For instance, screening for oral trauma and controlling the salivary flow rate is necessary to account for the salivary dilution effect. However, there are no available reliable strategies to make sCRP an accurate quantitative measure of serum CRP, which limits the use of point-of-care systemic inflammation testing[39].

The current study found a significant positive correlation (r = 0.66, P < 0.001) between serum CRP and MPV in neonates with LOP. This means that when serum CRP levels increase, MPV also tends to increase. The positive correlation between MPV and serum CRP suggests that MPV is associated with the inflammatory response and may reflect the level of inflammation present in pneumonia. In addition to this positive correlation between CRP and MPV in the current study, the serum CRP/MPV ratio in neonates with LOP (3.86 ± 2.29) was significantly higher than in the control group (0.42 ± 0.39) with a P value of less than 0.0001. The elevated serum CRP/MPV ratio in neonates with LOP signifies a higher inflammatory state. CRP is a key acute-phase protein that increases during inflammation. Concurrently, as a marker of platelet activation, MPV is influenced by the inflammatory response. The higher ratio suggests a greater inflammatory burden and platelet activation in neonates with LOP[40]. Using MPV as a diagnostic marker in combination with serum CRP could provide a more comprehensive understanding of the inflammatory status in neonates with LOP. Omran *et al*[12] found a significant increase of CRP/MPV in neonates with late-onset sepsis than in the control.

The current study reveals a statistically significant positive correlation between MPV and sCRP in neonates with LOP (r = 0.54, P = 0.01). This correlation indicates that as sCRP levels increase, MPV also tends to increase. Our findings agree with the work of Omran *et al*[27], who found a significant positive correlation between sCRP and MPV (P < 0.001). The positive correlation between MPV and sCRP suggests that both biomarkers are associated with the inflammatory response seen in LOP.

Elevated sCRP levels indicate systemic inflammation, and this correlation implies that higher levels of inflammation are associated with an increase in MPV. Understanding the correlation between sCRP and MPV is clinically valuable[41]. Monitoring both sCRP and MPV in neonates with LOP can provide complementary information about the severity of the inflammatory response[23,36]. If both sCRP and MPV are elevated, it could indicate a more pronounced inflammatory state, prompting close monitoring and possibly more aggressive treatment. The correlation between sCRP and MPV suggests that MPV, an easily measurable parameter, could serve as a supplementary diagnostic marker alongside sCRP. It may enhance the accuracy of diagnosing and monitoring the inflammatory status in neonates with LOP[42].

Moreover, the correlations between serum CRP, sCRP, and MPV underlined their interrelated nature, indicating the potential for a multi-marker approach in diagnosis and disease monitoring. The high AUC of sCRP in predicting serum CRP levels further advocates for its utility in disease assessment[38]. Understanding these correlations is critical for establishing the diagnostic potential of these markers. The strong correlations between serum CRP, sCRP, and MPV suggest their interlinked roles in reflecting the inflammatory response associated with LOP. Incorporating these markers collectively in diagnostic algorithms could enhance accuracy and offer a more holistic assessment of the inflammatory status in neonates with LOP, potentially leading to improved diagnostic and therapeutic approaches[43]. Further research should delve deeper into these correlations, exploring their clinical implications and potential for diagnostic integration.

Limitations of a study

It is crucial to provide possible limitation of the current study that limits the generalizability of its findings. The study's sample size is relatively modest, which may limit the generalizability of the findings to a broader neonatal population. The study being conducted in a single center may introduce institutional biases and limit the external validity of the results. The variability in the clinical presentation of LOP among neonates may introduce heterogeneity in the study population, potentially affecting the consistency and reliability of the observed clinical and radiological features. The study's cross-sectional design limits the assessment of temporal relationships and trends over time, which could be valuable for understanding the progression and outcomes of LOP in neonates. While MPV, serum CRP, and sCRP were evaluated as potential diagnostic markers, other relevant biomarkers that could contribute to a more comprehensive assessment were omitted. We also should consider the factors that could affect the SCRP levels, such as salivary flow rate, circadian rhythm, age, sex, type of salivary gland, salivary stimulation, feeding, and collection method. The study's exclusion of preterm neonates might limit the generalizability of the findings to the entire neonatal population, as preterm infants often have unique healthcare needs and susceptibilities. The study also employed specific radiological techniques (plain Chest X-rays); however, using advanced imaging modalities such as high-resolution computed tomography or other advanced imaging methods could have provided additional valuable insights into the lung pathology of neonates with LOP. In addition, the study's findings might be specific to a particular ethnic or geographical population. Caution should be exercised when generalizing the results to a more diverse or different population.

Suggestions for future research

Including a larger and more diverse cohort of neonates could provide a more comprehensive representation of LOP cases. Multicenter studies involving diverse healthcare settings could offer a more comprehensive view of LOP cases. We also must explore a broader array of biomarkers for a more accurate diagnosis.

CONCLUSION

This study offers a comprehensive understanding of the clinical, radiological, and biomarker profiles in neonates with LOP, aligning with the observations made by previous studies. The potential diagnostic utility of MPV, serum CRP, and sCRP was evident, opening new avenues for non-invasive diagnostic approaches. Integrating these biomarkers into clinical practice may enhance diagnostic accuracy and subsequently improve outcomes for neonates with LOP. Future research should focus on validating these findings in larger cohorts and exploring the prognostic implications of these biomarkers in guiding therapeutic strategies.

ARTICLE HIGHLIGHTS

Research background

Neonatal sepsis is a significant cause of neonatal mortality, and late-onset pneumonia (LOP) is a challenging form of sepsis to diagnose. Saliva has been identified as a potential diagnostic fluid for neonates. C-reactive protein (CRP) and mean platelet volume (MPV) are biomarkers that can indicate inflammation and are of interest in diagnosing neonatal infections.

Research motivation

The research is motivated by the need to improve the diagnosis of LOP in newborns, a serious condition that can lead to high mortality rates. Current diagnostic methods for neonatal infections, including pneumonia, can be challenging. The motivation is to find non-invasive and effective diagnostic tools that can aid in the early and accurate identification of LOP. Salivary CRP (sCRP) and MPV are being investigated as potential biomarkers to enhance the diagnosis and management of LOP, aiming to improve clinical outcomes for affected newborns.

Research objectives

We aimed to assess the diagnostic accuracy of sCRP and MPV biomarkers, analyzing their temporal trends, considering demographic factors, and exploring their clinical implications in diagnosing LOP in newborns.

Research methods

The study involved 80 full-term neonates divided into a group with LOP and a control group. Clinical assessments, blood tests, and imaging were conducted to diagnose LOP. Salivary and serum CRP levels, as well as MPV, were measured. Statistical analysis was performed to determine the diagnostic validity of these markers.

Research results

Neonates with LOP showed differences in weight, length, head circumference, serum CRP, MPV, and the CRP/MPV ratio compared to the control group. Clinical and radiological features of LOP were observed, including fever, cough, respiratory distress, and abnormal auscultatory findings. MPV, serum CRP, and sCRP exhibited good discriminative power for diagnosing LOP. Positive correlations were found between serum CRP, sCRP, and MPV.

Research conclusions

The study provides insights into the clinical, radiological, and biomarker profiles in neonates with LOP. MPV, serum CRP, and sCRP show potential for non-invasive diagnostic approaches. Integrating these biomarkers into clinical practice may enhance diagnostic accuracy and improve outcomes for neonates with LOP.

Research perspectives

Further research in neonatal LOP is needed to validate findings and assess generalizability across different populations and healthcare settings, investigate temporal trends and longitudinal studies, explore multi-marker approaches, assess ethnic and geographic variations, analyze the kinetics of sCRP and MPV, conduct studies on preterm neonates, compare diagnostic performance with other modalities, examine clinical implications, develop point-of-care testing methods, and investigate therapeutic implications. These research perspectives can lead to improved clinical practices and outcomes for affected neonates.

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FOOTNOTES

Author contributions: El-Mashad MA and Hamza MB provided the research idea and initiated the study design; Metwali WA and El-Mashad MA collected the patients and their information; Hamza M and El-Mashad MA were responsible for statistical analysis; Metwali WA and Hazzaa HM were responsible for the technical part of the study; Also, they performed data analysis; Al-Biltagi M analyzed the data and wrote the final manuscript; all authors revised and agreed on the final version of the manuscript.

Institutional review board statement: We performed the study according to the latest version of Helsinki's Declaration. The Institutional Ethical and Research Review Board of the Faculty of Medicine, Tanta University, approved the study.

Informed consent statement: All parents, guardians, or next of kin signed informed consent for the minors to participate in this study.

Conflict-of-interest statement: All the authors declare that they have no potential nor real conflicts to disclose.

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ORIGINAL ARTICLE

Case Control Study

BCD020 rituximab bioanalog compared to standard treatment in juvenile systemic lupus erythematosus: The data of 12 months case-control study

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Abstract

BACKGROUND

Systemic lupus erythematosus (SLE) is the most frequent and serious systemic connective tissue disease. Nowadays there is no clear guidance on its treatment in childhood. There are a lot of negative effects of standard-of-care treatment (SOCT), including steroid toxicity. Rituximab (RTX) is the biological B-lymphocyte-depleting agent suggested as a basic therapy in pediatric SLE.

AIM

To compare the benefits of RTX above SOCT.

METHODS

The data from case histories of 79 children from the Saint-Petersburg State Pediatric Medical University from 2012 to 2022 years, were analyzed. The diagnosis of SLE was established with SLICC criteria. We compared the outcomes of treatment of SLE in children treated with and without RTX. Laboratory data, doses of glucocorticosteroids, disease activity measured with SELENA-SLEDAI,

and organ damage were assessed at the time of initiation of therapy and one year later.

RESULTS

Patients, treated with RTX initially had a higher degree of disease activity with prevalence of central nervous system and kidney involvement, compared to patients with SOCT. One year later the disease characteristics became similar between groups with a more marked reduction of disease activity (SELENA-SLEDAI activity index) in the children who received RTX [-19 points (17; 23) since baseline] compared to children with SOCT [-10 (5; 15.5) points since baseline, $P = 0.001$], the number of patients with active lupus nephritis, and daily proteinuria. During RTX therapy, infectious diseases had three patients; one patient developed a bi-cytopenia.

CONCLUSION

RTX can be considered as the option in the treatment of severe forms of SLE, due to its ability to arrest disease activity compared to SOCT.

Key Words: Systemic lupus erythematosus; Children; Rituximab; Anti-B-cell therapy; Glucocorticosteroids

Core Tip: Rituximab (RTX), known as an anti-B-cells agent, is actively discussed as one of the main drugs for severe systemic lupus erythematosus. Various studies have been conducted to evaluate its effectiveness, but their results are ambiguous. We show the benefits of RTX above the standard-of-care treatment in children.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most frequent systemic connective tissue diseases, which is characterized by an unpredictable course, affecting different organs and systems, often simultaneously[1,2]. Juvenile SLE has a more aggressive and severe course in children compared to adults, due to a higher frequency of kidney, central nervous system, and blood involvement[2-5]. Macrophage activation syndrome (MAS) is a difficult-to-recognize life-threatening complication of SLE, belonging to the family of hemophagocytic lymphohistiocytosis influencing the disease course and outcomes[6]. The disease severity and outcomes related to lupus nephritis (LN) occur in about 40% of patients, most often during the first 5 years from the onset of the disease[7-9]. Reduced damage to organs and systems, flare prevention, and improved quality of life of the patients are the main treatment goals of SLE[1,2]. Standard of care treatment (SOCT) for SLE includes glucocorticosteroids, hydroxychloroquine, and cytostatic drugs such as cyclophosphamide, cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil (MMF) and usually associated with toxic side effects[2,4,5,10]. Despite the toxicity of glucocorticosteroids and the recommendations of the European Alliance of Associations for Rheumatology (EULAR) to minimize doses, there are no uniform schemes and rates of reduction of glucocorticosteroids, except for lupus nephritis[4,11]. The optimization of SLE treatment in children is necessary. The use of biological drugs makes it possible to achieve faster remission and reduce the toxic side effects of SOCT[12].

Rituximab (RTX) is one of the biologics used for the treatment of SLE. RTX is a chimeric mouse antibody directed against the CD20 antigen of B-lymphocytes. Depleting the pool of B-lymphocytes, RTX acts only on mature B-lymphocytes, without affecting stem and plasma cells[3]. RTX is proposed in some studies as an alternative or additional therapeutic approach for SLE[13-15]. In North America (United States, Mexico), Europe, and Australia, RTX is still used as an induction therapy for lupus nephritis off-label, despite the first successful reports in LN were published about 20 years ago[12,16]. The data about RTX efficacy in SLE are contradictory. RTX is still considered an off-label drug only if first-line therapy with cyclophosphamide or MMF fails, according to the EULAR2019 recommendations[17]. However, the position of using RTX as a starting therapy in combination with corticosteroids and non-biological disease-modifying antirheumatic drugs (DMARDs) remains open and requires more evidence of efficacy and safety[2,8,10,18,19].

Our study aimed to compare the safety and efficacy of RTX therapy in comparison with SOCT in children with systemic lupus erythematosus.

MATERIALS AND METHODS

Study design

A single-center retrospective cohort study included the data from the medical histories of 79 SLE children from 2012 to 2022.

Inclusion criteria

(1) The diagnosis of systemic lupus erythematosus in patients under 18 years of age was established according to the criteria of Systemic Lupus International Collaborating Clinic (SLICC) 2012[20]; and (2) patients were selected from the database if the data about at least 12 months of observation were available.

Exclusion criteria

Absence or incomplete information about the first 12-month course of the treatment.

Population and treatment arms

Nineteen children from the study group received RTX therapy in the first six months from the onset of the disease and were observed at least twelve months from the initiation of the RTX therapy. Sixty children received SOCT, which included glucocorticosteroid, hydroxychloroquine, non-biologic DMARDs, such as mycophenolate mofetil, cyclosporine, cyclophosphamide, and also were observed at least one year after the start of therapy.

Indications for the RTX were

(1) A highly active course of systemic lupus erythematosus with kidney and central nervous system involvement, including resistance to previous therapy; (2) a presence of a recurrent course of autoimmune hemolytic anemia or thrombocytopenia, requiring repeated doses of corticosteroids, replacement therapy (blood and platelet transfusion); and (3) a presence of signs of corticosteroid toxicity if it is impossible to reduce the dose of corticosteroids to 10 mg/d or 0.2 mg/kg/d, whichever is less.

RTX treatment protocol

RTX was prescribed at a dose of 375 mg/m^2 weekly, no more than 500 mg per infusion (2-4 infusions) with repeated courses every 6-12 months, depending on the degree of disease activity, the severity of B-cell depletion, the level of IgG. The decision about the treatment protocol was made by the group of the most experienced pediatric rheumatologists.

Assessments and outcomes

The assessment of the main characteristics of patients was carried out at the time of the initiation of RTX or SOCT, then after 12 ± 3 months from the start of therapy. At each time point, laboratory parameters were evaluated: complete blood cell, immunological tests - antinuclear antibodies (ANA), antibody against double-stained DNA (anti-dsDNA), complement level, assessment of urine protein excretion, presence of active lupus nephritis), the daily dose of glucocorticosteroids (GCS), the calculation of disease activity on the SELENA-SLEDAI scale, which allows to distinguish four degrees of disease activity: 0 points – no activity, 1-5 points – minimal activity, 6-10 points – moderate activity, 11-19 points – high activity, and > 20 points - very high activity[21]. MAS was diagnosed according to the previously published criteria by Parodi *et al*[22].

Methods of statistical data analysis

The analysis of the obtained data was carried out using the statistical software package Statistica v. 10.0 (StatSoft Inc., United States). Quantitative variables were assessed for compliance with normal distribution using the Kolmogorov-Smirnov test allows to use of nonparametric methods of analysis due to the absence of the normal distribution. The description of quantitative variables was expressed in the median and quartiles Me (Q1; Q3). The categorical variables were expressed in absolute numbers and parts (%). Comparison of two independent groups of quantitative variables was carried out using the Mann-Whitney test, categorical variables - using the Chi-square test, or Fisher's exact test, if the expected frequency was less than 5. Differences or relationships were considered statistically significant if $P < 0.05$.

RESULTS

Characteristics of the patients in the SLE onset

Patients, treated with RTX were older at the initial point of the study (baseline-start of the therapy), compared to patients from the SCOT group. They had frequently central nervous system involvement, hepatomegaly, lymphadenopathy, palmar erythema, proteinuria, decreased glomerular filtration rate (GFR), and higher SLEDAI (more patients with high activity, grade four) and higher frequency of using high-dose IV glucocorticosteroids. They also tended to more frequent development of pleurisy, and lupus nephritis. The incidence of MAS was also higher in the group of children treated with RTX. All cases of MAS developed during the disease onset. Early treatment with RTX allowed the use of fewer non-biologic DMARDs. The baseline characteristics of children from two groups are presented in Table 1.

Table 1 The characteristics of the patients at the time of the start of the treatment, *n* (%)

Parameter	Rituximab (*n* = 19)	SOCT (*n* = 60)	*P* value
Demography			
Sex, male	4 (21)	11 (18)	0.829
Onset age, years, Me (25%; 75%)	14 (12; 16)	12 (10; 14)	0.035
Clinical features			
Skin involvement	18 (95)	50 (83)	0.257
Oral mucosa involvement	8 (58)	16 (27)	0.203
Alopecia	3 (16)	16 (27)	0.334
Arthritis	15 (78)	42 (70)	0.449
Pleurisy	6 (32)	8 (12)	0.070
Pericarditis	5 (26)	8 (12)	0.184
Ascitis	3 (16)	3 (5)	0.122
Myocarditis	2 (11)	7 (12)	0.856
CNS involvement	9 (47)	13 (22)	0.030
Splenomegaly	5 (26)	12 (20)	0.560
Hepatomegaly	9 (47)	14 (23)	0.045
Lymphadenopathy	8 (42)	10 (17)	0.022
Lung involvement	3 (16)	3 (5)	0.122
Palmar erythema	5 (26)	5 (8)	0.040
Livedo	3 (16)	5 (8)	0.348
Fever	11 (58)	32 (53)	0.728
Trombosis	1 (5)	3 (5)	0.964
MAS	4 (21)	1 (2)	0.003
Renal involvement			
Nephritis	8 (42)	17 (28)	0.081
Kidney biopsy	3/8 (38)	7/17 (42)	0.670
Class of nephritis			
I	0 (0)	0 (0)	0.700
II	0 (0)	0 (0)	
III	1/3 (33)	3/7 (43)	
IV	2/3 (67)	3/7 (43)	
V	0 (0)	1/7 (14)	
Hematuria	8/8 (100)	17/17 (100)	0.124
Proteinuria	8/8 (100)	17/17 (100)	0.487
Proteinuria, g/L, Me (25%; 75%)	0,31 (0; 0,93)	0,1 (0,0; 0,3)	0.154
Proteinuria, g/24 h, Me (25%; 75%)	0,49 (0,12; 1,2)	0,17 (0,0; 0,3)	0.046
Urea, mmol/L, Me (25%; 75%)	5,8 (4,8; 9,6)	4,2 (3,5; 5,5)	0.003
Creatinine, mcmol/L, Me (25%; 75%)	58 (52; 94)	59 (54; 70)	0.856
GFR, mL/1.73/m^2	131 (72,0; 151)	130 (115; 147)	0.077
Decreased GFR	3 (16)	2 (3)	0.052
Dialysis	0 (0)	1 (2)	0.493
Laboratory features			

ANA-positivity	19 (100)	52 (87)	0.094
ANA level, titer, Me (25%; 75%)	1920 (1280; 5120)	2560 (640; 10240)	0.859
Anti-dsDNA antibodies	15 (79)	43 (72)	0.532
Anti-dsDNA, U/L (25%; 75%)	102 (12; 150)	63 (14; 237)	0.975
Positive Coombs	11/16 (69)	15/34 (44)	0.104
Low complement	11/14 (79)	15/30 (50)	0.073
Complement C3, g/L, Me (25%; 75%)	0.64 (0.35; 1.0)	0.84 (0.74; 0.94)	0.170
Complement C4, g/L, Me (25%; 75%)	0.1 (0,05; 0,17)	0.12 (0,1; 0,24)	0.610
Anaemia	12 (63)	31/59 (52,5)	0.418
Hemoglobine, g/L, Me (25%; 75%)	111 (98; 129)	111 (100; 126)	0,865
Thrombocytopenia	9 (47)	18 (30)	0.118
Platelets, 10^9/L, Me (25%; 75%)	232 (189; 285)	269 (178; 328)	0.454
Leucopenia	11 (58)	23 (38)	0.134
WBC, 10^9/L, Me (25%; 75%)	5.3 (4.2; 11.1)	5.4 (4.2; 8.3)	0.526
Lymphopenia	6 (33)	6 (10)	0.023
ESR, mm/h, Me (25%; 75%)	21 (8; 31)	18 (5; 37)	0.766
C-reactive protein (CRP), mg/L, Me (25%; 75%)	0.7 (0; 2.0)	1.0 (0.2; 3.7)	0.841
SLE activity			
SLEDAI onset score, Me (25; 75%)	22 (13; 26)	12 (9; 17)	0.002
SLEDAI onset, grade			0.005
0 grade	0 (0)	0 (0)	
I grade	0 (0)	5 (8)	
II grade	3 (16)	20 (33)	
III grade	5 (26)	25 (42)	
IV grade	11 (58)	10 (17)	
Treatment			
Intravenous corticosteroids	15 (79)	22 (37)	0.002
Corticosteroids, mg/kg, Me (25%; 75%)	1.0 (0.7; 1.0)	1.0 (0.4; 1.0)	0.854
Hydroxycholoquine	9 (47.4)	35/58 (60.3)	0.321
Non-biologic DMARDs	11 (58)	58 (97)	0.00001
Cyclophosphamide	5 (26)	23 (38)	0.340
Other DMARDs	6 (32)	37 (63)	0.054
Mycophenolate mofetil	2 (11)	20 (33)	0.630
Azathioprine	2 (11)	6 (10)	
Cyclosporine	0 (0)	2 (3)	
Methotrexat	2 (11)	9 (15)	

Anti-dsDNA: Antibody against double-stained DNA; ANA: Antinuclear antibodies; CNS: Central nervous system; DMARD: Disease-modifying anti-rheumatic drugs; ESR: Erythrocyte sedimentation rate; GFR: Glomerular filtration rate; MAS: Macrophage activation syndrome; Me: Median; SLEDAI: Systemic lupus erythematosus disease activity index; SOCT: Standard of care treatment; WBC: White blood cells.

Characteristics of the patients (outcomes) at the end of the study

At the end of the study, after twelve months, the disease characteristics between studied groups became equal, except for a tendency to higher levels of hemoglobin and lower part of patients having anti-dsDNA antibodies and low complement. Detailed characteristics of children at the end of the study are presented in Table 2.

Table 2 Characteristics of the patients (outcomes) at the end of the study, *n* (%)

Parameter	RTX (*n* = 19)	SOCT (*n* = 60)	*P* value
Laboratory features			
ANA positivity	16 (84)	42 (70)	0.222
ANA level, titer, Me (25%; 75%)	640 (320; 2560)	640 (160; 2560)	0.849
Anti-dsDNA antibodies	3 (16)	26 (43)	0.079
Anti-dsDNA U/L (25%; 75%)	5.1 (0; 12.0)	7.4 (0.6; 57.4)	0.166
Low complement	3 (16)	25 (42)	0.098
Complement C3, g/L, Me (25%; 75%)	0.92 (0.8; 11)	1.07 (0.72; 1.4)	0.409
Complement C4, g/L, Me (25%; 75%)	0.19 (0.14; 0.27)	0.17 (0.12; 0.25)	0.594
Hemoglobine, g/L, Me (25%; 75%)	133 (127; 138)	124 (111; 133)	0.06
Platelets, 10^9/l, Me (25%; 75%)	276 (240; 306)	269 (215; 335)	0.712
WBC, 10^9/l, Me (25%; 75%)	4.9 (4.4; 5.8)	5.5 (4,5; 6.5)	0.252
ESR, mm/h, Me (25%; 75%)	6 (2; 20)	7 (2; 18)	0.365
SLE activity			
SLEDAI onset score, Me (25; 75%)	3 (0; 4)	2 (0; 4)	0.599
SLEDAI onset, grade			0.804
0 grade	6 (32)	16 (26)	
I grade	9 (47)	34 (57)	
II grade	4 (21)	9 (15)	
III grade	0 (0)	0 (0)	
IV grade	0 (0)	1 (2)	
Kidney involvement			
Hematuria	6/8 (75)	4/17 (24)	0.015
Proteinuria	1/8 (13)	2/17 (12)	0.958
Active nephritis	1/8 (13)	5/17 (29)	0.356
Proteinuria, g/L, Me (25%; 75%)	0.07 (0; 0.1)	0 (0; 0.07)	0.209
Proteinuria, g/24 h, Me (25%; 75%)	0.15 (0.02; 0.3)	0 (0; 0.16)	0.066
Urea, mmol/L, Me (25%; 75%)	3.7 (3.1; 4.4)	3.84 (3.05; 4.66)	0.526
Creatinine, mmol/L, Me (25%; 75%)	0.06 (0.05; 0.07)	0.06 (0.05; 0.07)	0.78
Treatment			
GCS, mg/kg, Me (25%; 75%)	0.1 (0.07; 0.15)	0.13 (0; 0.2)	0.569
Hydroxycholoquine	15 (78)	37 (62)	0.167
Mycophenolate mofetil	9 (47)	33 (55)	0.824
Azathioprine	2 (11)	4 (7)	
Cyclophosphamide	3 (16)	9 (15)	
Cyclosporine	0 (0)	2 (3)	
Methotrexate	1 (5)	7 (12)	

Anti-dsDNA: Antibody against double-stained DNA; ANA: Antinuclear antibodies; ESR: Erythrocyte sedimentation rate; GCS: Glucocorticosteroids; SLEDAI: Systemic lupus erythematosus disease activity index; WBC: White blood cells.

During the 12-month study period the more impressive reduction of the SLEDAI, the number of patients with active LN, and daily proteinuria were observed. Data are in Table 3.

DISCUSSION

In our study, some benefits of RTX treatment for pediatric SLE were found. During the 12-month observation period, a more impressive reduction in disease activity and improvement in lupus nephritis was observed.

RTX has not received official approval either in adult or pediatric practice despite many years of experience in the treatment of systemic lupus erythematosus[8,10,17]. Numerous series of retrospective studies and published clinical cases have shown the effectiveness of RTX in patients with varying degrees of activity systemic lupus erythematosus, including forms with a catastrophic course, which, together with expert opinion, allowed to include RTX into the treatment algorithms for the of systemic lupus erythematosus both for children and adults[3,9,23].

Biological drugs, including RTX, are recommended for the treatment of SLE, but the study results are contradictory[24, 25]. Some randomized controlled trials showed improvement in blood tests (anti-dsDNA, normalization of complement levels of C3 and C4), without changes in the outcomes of the disease one year after the start of treatment[24]. In the largest randomized controlled trial the Lupus Nephritis Assessment with RTX study (LUNAR), there was no significant difference in achieving a complete response between patients receiving RTX and SOCT at the control time points, although the proportion of patients with a partial response was greater in patients, treated with RTX[24]. There was a significant improvement in serological markers of disease activity, such as a decrease in antibodies to DNA, an increase in complement levels, and a decrease in the degree of proteinuria in patients who received RTX, which was also noted in the non-randomized studies[3,10,25,26].

The results of the above-mentioned studies corresponded with our results: improvement of certain laboratory parameters has been achieved, but there is no statistically significant difference between the outcomes of the disease a year after the start of therapy. The analysis of various non-randomized studies from different countries of the world showed a positive effect of RTX in systemic lupus erythematosus in adults and children[3,5,10]. Reduction of the activity of the disease, increased hemoglobin level, decreasing ESR and levels of ANA and anti-dsDNA antibodies, and the part of children having cytopenia demonstrated in several studies[3,5,10,27]. RTX is effective for the treatment of lupus nephritis in children, whom increased C3 and C4 Levels, GFR, and serum albumin and decreased urine albumin/creatinine ratio and proteinuria and GCS dose detected[3,5,10,17,26-28]. Additionally, some studies reported a decrease in creatinine, but the data were statistically non-significant[17]. There is also conflicting data that the use of biological therapy for lupus nephritis did not lead to a decrease in the albumin-creatinine ratio[29]. A recent study on 14 pediatric LN showed the additional RTX therapy to conventional therapy improved proteinuria, eGFR, and serological markers. Three patients who required acute kidney replacement therapy became dialysis-free after RTX[30]. We found decreased activity and proteinuria in our study similar to previous. The absence of a significant effect in some randomized studies suggests to use of RTX not as a means of inducing remission, but as an auxiliary therapy in patients with SLE[31].

However, 27 studies demonstrated the positive effect of RTX in patients refractory to standard therapy, including cyclophosphamide and MMF[17]. The inclusion of patients with primary LN without preceding experience of cyclophosphamide or MMF in a large randomized LUNAR study did not show the superiority of RTX over non-biological DMARDs[24]. On the one hand, RTX has shown its effectiveness in patients who have not previously received any treatment, which does not allow us to evaluate the benefits of RTX in comparison with standard non-biological therapy. On the other hand, RTX was able to induce remission in cases where standard therapy with non-biological DMARDs failed and disease duration and treatment exposure were longer[17,32,33].

In our study, RTX was prescribed to children in the first year of the disease who had had a higher disease activity at the time of initiation of therapy. There was no statistically significant difference in the activity of SLE between the two groups at the end of the study, but at the same time, there was a more significant decrease in the activity of the disease in the RTX group. It allows us to conclude that RTX shows its effectiveness in a more severe course of the disease.

Limitations

Our study has limitations, related to retrospective study designs, initial differences between studied groups, missing data, and absence of a unique treatment protocol with administration and tapering of the drugs. Personal opinion about prescribing the RTX and all the abovementioned limitations may make the study results inaccurate and other-estimated.

CONCLUSION

RTX can be considered as the option in the treatment of severe forms of SLE, due to its ability to rapidly arrest the disease activity compared to SOCT. Faster and intensive reduction of the disease activity and better nephritis outcomes are the main benefits of RTX above the SOCT. Further pediatric randomized controlled trials are required to evaluate its efficacy and safety in comparison with standard therapy, with further consideration of the possible use of RTX as an induction therapy in children with high-moderate disease activity.

Table 3 Dynamics of the main indicators of the disease activity in studied groups

Reduction since the baseline of	Rituximab (*n* = 19)	SOCT (*n* = 60)	*P* value
Anti-dsDNA, U/L (25%; 75%)	-139.7 (106.4; 374.1)	-129.0 (81.0; 369.4)	0.75
Anti-dsDNA, U/L (25%; 75%)	-93.7 (93.1; 95.0)	-83.7 (63.2; 96.4)	0.29
SLEDAI, points	-19 (17; 23)	-10 (5.0; 15.5)	0.001
SLEDAI, %	86.9 (82.6; 100.0)	77.5 (60.0; 100.0)	0.147
Daily GCS dose, mg/kg	-0.8 (0.6; 0.9)	-0.57 (0.0; 1.0)	0.874
Daily GCS dose, %	-88 (85; 90)	-83.3 (66.7; 94.6)	0.525
Proteinuria, %	-96.7 (91.3; 100)	-100 (72.9; 100)	0.967
Daily proteinuria, g/24 h	-0.83 (0.27; 1.24)	-0.1 (0; 0.34)	0.031
Patients without active LN since BL, %	-7/8 (88)	-12/17 (71)	0.356

Anti-dsDNA: Antibody against double-stained DNA; BL: Baseline; GCS: Glucocorticosteroids; SLEDAI: Systemic lupus erythematosus disease activity index; LN: Lupus nephritis.

ARTICLE HIGHLIGHTS

Research background

Systemic lupus erythematosus (SLE) is a serious life-threatening disease. Systemic corticosteroids are the still basis of the treatment of SLE.

Research motivation

The side effects of corticosteroids required to change the treatment plans of SLE with biologic implementation.

Research objectives

The place of biologics in the treatment of SLE is not yet determined, despite a lot of clinical observations and studies.

Research methods

The comparison of 12-month course of treatment of pediatric SLE patients with rituximab (RTX) and standard of care treatment without RTX was done.

Research results

RTX worked effective in SLE patients with high activity with improvement of kidney disease.

Research conclusions

RTX might be added in the treatment protocol of the severe pediatric SLE.

Research perspectives

The following randomized controlled trials are required in pediatric SLE.

FOOTNOTES

Author contributions: Kostik M and Kalashnikova E contributed to conceptualization writing—original draft preparation, writing—review and editing; Kostik M and Chikova I contributed to methodology; Kalashnikova O contributed to software; Isupova E, Gaidar E, and Sorokina L contributed to validation; Raupov R contributed to formal analysis; Kaneva M, Masalova V, Dubko M, and Kornishina T contributed to investigation; Isupova E and Gaidar E contributed to resources; Kalashnikova O and Chikova I contributed to data curation; Kostik M, Lubimova NA, and Kuchinskaya E contributed to funding; Kaneva M contributed to visualization; Kostik M contributed to supervision, project administration; All authors have read and approve the final manuscript.

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Informed consent statement: All patients or patients' representatives (for patients under the age of 15) gave their consent in their case

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ORIGINAL ARTICLE

Retrospective Cohort Study

Fever assessment in children under five: Are we following the guidelines?

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Abstract

BACKGROUND

Fever is a common cause of medical consultation and hospital admission, particularly among children. Recently, the United Kingdom's National Institute for Health and Care Excellence (NICE) updated its guidelines for assessing fever in children under five years of age. The efficient assessment and management of children with fever are crucial for improving patient outcomes.

AIM

To evaluate fever assessment in hospitalized children and to assess its adherence with the NICE Fever in under 5s guideline.

METHODS

We conducted a retrospective cohort review of the electronic medical records of children under five years of age at the Department of Pediatrics, Salmaniya Medical Complex, Bahrain, between June and July 2023. Demographic data, vital signs during the first 48 h of admission, route of temperature measurement, and indications for admission were gathered. Fever was defined according to the NICE guideline. The children were divided into five groups according to their age (0-3 months, > 3-6 months, > 6-12 months, > 12-36 months, and > 36-60 months). Patients with and without fever were compared in terms of demography, indication for admission, route of temperature measurement, and other vital signs. Compliance with the NICE Fever in the under 5s guideline was assessed. Full compliance was defined as > 95%, partial compliance as 70%-95%, and minimal compliance as ≤ 69%. Pearson's χ^2, Student's t test, the Mann-Whitney U test, and Spearman's correlation coefficient (r_s) were used for comparison.

RESULTS

Of the 136 patients reviewed, 80 (58.8%) were boys. The median age at admission was 14.2 [interquartile range (IQR): 1.7-44.4] months, with the most common age group being 36-60 months. Thirty-six (26.4%) patients had fever, and 100 (73.6%) were afebrile. The commonest age group for febrile patients (> 12-36 months) was older than the commonest age group for afebrile patients (0-3 months) (P = 0.027). The median weight was 8.3 (IQR: 4.0-13.3) kg. Patients with fever had higher weight than those without fever [10.2 (IQR: 7.3-13.0) *vs* 7.1 (IQR: 3.8-13.3) kg, respectively] (P = 0.034). Gastrointestinal disease was the leading indication for hospital admission (n = 47, 34.6%). Patients with central nervous system diseases and fever of unknown etiology were more likely to be febrile (P = 0.030 and P = 0.011, respectively). The mean heart rate was higher in the febrile group than the afebrile group (140 ± 24 *vs* 126 ± 20 beats per minute, respectively) [P = 0.001 (confidence interval: 5.8-21.9)] with a positive correlation between body temperature and heart rate, r = 0.242, n = 136, P = 0.004. A higher proportion of febrile patients received paracetamol (n = 35, 81.3%) compared to the afebrile patients (n = 8, 18.6%) (P < 0.001). The axillary route was the most commonly used for temperature measurements (n = 40/42, 95.2%), followed by the rectal route (n = 2/42, 4.8%). The department demonstrated full compliance with the NICE guideline for five criteria: the type of thermometer used, route and frequency of temperature measurement, frequency of heart rate measurement, and use of antipyretics as needed. Partial compliance was noted for two criteria, the threshold of fever at 38 °C or more, and the respiratory rate assessment in febrile patients. Minimal compliance or no record was observed for the remaining three criteria; routine assessment of capillary refill, temperature reassessment 1-2 h after each antipyretic intake, and refraining from the use of tepid sponging.

CONCLUSION

This study showed that fever assessment in hospitalized children under five years of age was appropriate, but certain areas of adherence to the NICE guideline still need to be improved.

Key Words: Fever; Pediatrics; Admission patterns; Temperature measurement; Guidelines; Bahrain

Core Tip: Fever assessment in children is vital in clinical practice. This study examined the compliance with fever assessment in our hospital according to the National Institute for Health and Care Excellence guideline. We found that while certain aspects were adequate, namely the thermometer type, route, frequency of temperature and heart rate measurement, and appropriate antipyretic use, there were areas that needed improvement, including capillary refill routine assessment, temperature reassessment 1-2 h after antipyretic administration, and refraining from tepid sponging. These findings emphasize the importance of continuous quality improvements in pediatric care to enhance adherence to evidence-based guidelines and improve patient outcomes.

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INTRODUCTION

Fever is one of the most common reasons for medical consultations in children[1,2]. Fever is the physiological elevation in body temperature in response to various conditions[1]. Infections are the most common causes of fever. Fever due to an infection will most likely result in administration of an antipyretic, performance of investigations, and potentially prescription of an antibiotic. Accordingly, ensuring that we are dealing with fever in the first place is crucial.

Fever is defined by the National Institute for Health and Care Excellence (NICE) as an elevation in body temperature above the normal daily variations[1]. Despite being ambiguous, this definition takes into account that the core body temperature is subject to variations, as many factors can influence the body temperature, such as age, time of the day, level of activity, and meals[3]. In the pediatric age group, a temperature of 38 °C or higher is generally considered fever [1]. There is considerable controversy regarding the best anatomical site for temperature measurement and the best thermometer to use[4].

Although not convenient for repeated use, the rectal thermometer is generally considered an accurate reflection of the body's core temperature[5-11]. Choosing the instrument for accurate measurement can be difficult. Tympanic thermometry is regarded by some studies as the best alternative to rectal thermometry in terms of accuracy and convenience[5,8,9,11]. Axillary thermometry is easy to use, however it was found to provide the worst estimate of core body temperature [5], and it is still used in neonates[5]. On the other hand, the accuracy of an oral thermometer depends on patient compliance, which is difficult to ensure in children[5]. Forehead measurements, although the easiest method, are not

considered accurate in detecting fever[6].

The NICE Fever in under 5s guideline recommends the use of axillary electronic thermometers for temperature measurement in infants under the age of 4 wk[2]. For children aged 4 wk to 5 years, it is recommended to use axillary electronic thermometers, axillary chemical dot thermometers, or infra-red tympanic thermometers[2]. The guideline does not emphasize routine use of oral or rectal routes to measure body temperature in children aged 0-5 years[2]. The guideline recommends the assessment of temperature every four hours in children with fever and more frequently in high-risk patients[2]. As part of assessment of risk of serious illness, the NICE guideline recommends measuring and recording temperature, heart and respiratory rates, and capillary refill time as part of the routine assessment of a child with fever [2]. It recommends offering antipyretics to children with fever who appear distressed and emphasizes refraining from the use of non-pharmacological interventions such as tepid sponging to control fever[2].

Although many studies on the methods of measuring and managing fever in children have been reported worldwide, no studies on this topic have been reported in Bahrain. This study aimed to assess the current practice of fever measurement in the main hospital in Bahrain and compare it with the NICE guideline.

MATERIALS AND METHODS

Study design and setting

This was a retrospective cohort study based on the electronic medical records of patients admitted to the Department of Pediatrics, Salmaniya Medical Complex (SMC), Bahrain between June 1, 2023 and July 11, 2023. SMC is the main tertiary care hospital in Bahrain to which most pediatric cases are referred for admission. It has 30 wards and a total capacity of 1200 beds.

The Department of Pediatrics has four general wards for 75 patients. In each ward, three nurses per shift were responsible for the daily measurement of temperature and other vital signs, including blood pressure, heart and respiratory rates, and pulse oximetry. All measurements were performed by pediatric ward nurses and immediately entered into the electronic medical records. Temperature recordings were performed every 4 h for each patient regardless of the condition. In febrile patients, the temperature was also recorded 30-60 min after each antipyretic intake. For children less than one year of age, temperature measurements are usually performed using the axillary or rectal routes. For children above one year of age, temperature measurements are usually performed *via* oral or axillary routes.

Temperature measurements were performed using a Food and Drug Administration-approved electronic thermometer (Welch-Allyn SureTemp Plus Model 692, New York, United States). The thermometer contained a liquid-crystal display screen and several buttons: a button to toggle between Celsius and Fahrenheit scales, a pulse timer, a mode selection button to choose the site for measurement, and a recall button to display the last measured temperature. Two probes can be used to obtain measurements using this thermometer: a red probe for rectal measurements and a blue probe for oral or axillary measurements. The different routes and types of thermometers used to assess the temperature in children are shown in Figure 1.

Population

The study population comprised all children with ages ranging from birth to five years, who were admitted for 48 h or more to the pediatric ward during the study period. Premature babies, children with bleeding disorders, immunocompromised or neutropenic patients, children with burns or extensive skin diseases, children with anorectal pathologies, and patients in the neonatal intensive care unit were excluded from the study.

Data collection

Demographic data including sex, age, reason for admission, and weight (kg) on admission were collected. The anatomical site used for temperature measurement was noted. The first recorded temperature in the ward, along with heart and respiratory rates, were collected. These parameters were recorded for each patient during the first 48 h of admission. The threshold of fever was set to ≥ 38 ˚C, according to the recommendations set by NICE[1]. For each patient, the first and second indications for admission as well as the presence of an underlying disease were noted when applicable, and these indications were categorized based on the main system involved in the patient's disease.

Statistical analysis

Data were entered into an Excel worksheet and then analyzed using the Statistical Package for Social Sciences program version 28 (IBM Corp., Armonk, NY, United States). The children were divided into five groups according to their age in months (0-3, > 3-6, > 6-12, > 12-36, and > 36-60). Categorical variables were presented as frequency and percentage while continuous variables were presented mean ± SD or median and interquartile range (IQR), according to normality of distribution. Patients were divided into two groups (febrile and afebrile). Febrile group included any patient who had a spike in temperature ≥ 38 °C during the first 48 h of admission. Patients with and without fever were compared in terms of demography, indication for admission, route of temperature measurement, and other vital signs. Compliance with the NICE Fever in under 5s guideline was assessed. Full compliance was defined as > 95%, partial compliance as 70%-95%, and minimal compliance as ≤ 69%. Group data were compared using Pearson's χ^2 test for categorical variables, and Student's *t* test or Mann-Whitney *U* test for continuous variables. Body temperature measurements were correlated with heart and respiratory rates using Spearman's correlation coefficient (r_s). The coefficient of determination (r^2) and a simple regression equation were calculated. The confidence interval (CI) was set to 95%. *P* value < 0.05 was considered statist-

Figure 1 Routes and types of thermometers used for temperature measurement in children. A: Forehead strip thermometer; B: Individual axillary electronic digital thermometer; C: Infra-red tympanic thermometer; and institutional electronic digital thermometer; D and E: Axillary; F: Rectal. Forehead strip thermometer, axillary chemical dot thermometer; and oral/sublingual thermometer are not recommended to be used in children.

ically significant.

Ethical approval

This study was conducted in accordance with the principles of Helsinki Declaration, and it was ethically approved by the Research and Research Ethics Committee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 38020523, May 02, 2023).

RESULTS

The records of 136 patients were reviewed during the study period. The patient demographic data are shown in Table 1. Eighty (58.8%) patients were boys, and 56 (41.2%) were girls. Ninety-seven (71.3%) patients were Bahraini nationals, while 39 (28.7%) were non-Bahraini (11 patients were from Pakistan, nine from India, seven from Yemen, three from Egypt, two from the Philippines and Tunisia each, one patient from Nepal, Oman, Sri Lanka, Sudan, and Syria). The median age at the time of admission was 14.2 (IQR: 1.7-44.4) months. The most common age group was > 36-60 months (n = 43, 31.6%). Thirty-six (26.4%) patients had fever, and 100 (73.6%) were afebrile. Febrile patients were older in age [15.6 (IQR: 6.8-44.2) months] than afebrile patients [11.1 (IQR: 0.7-45.1) months], but this difference was not statistically significant (P = 0.097)**.** The most frequent age group among patients with fever was >12-36 months, whereas that among patients without fever was 0-3 months (P = 0.027). The median weight on admission was 8.3 (IQR: 4.0-13.3) kg. Patients with fever had higher median weight [10.2 (IQR: 7.3-13.0) kg] than those without fever [7.1 (IQR: 3.7-13.3) kg] (P = 0.034).

The indications for hospital admission are shown in Figure 2. The most frequent cause of admission was gastrointestinal disease (n = 47, 34.6%), followed by respiratory disease (n = 29, 21.3%), and hematological disease (n = 14, 10.3%). A comparison between patients with fever and those without fever regarding the indication for admission showed a significant difference (P = 0.006) (Table 2). Patients with central nervous system diseases and those admitted for fever of unknown cause were more frequent in the febrile group (P = 0.030 and P = 0.011, respectively).

The recorded body temperature and its relationship with the heart and respiratory rates are shown in Table 3. Most of the patients were afebrile (n = 100, 73.5%) while the remaining 36 (26.5%) patients had a temperature of 38 °C or above [10 (7.4%) were febrile on admission and 26 (19.1%) developed fever later during their hospital stay]. Patients in the febrile group had a higher mean heart rate than the afebrile group, 140 ± 24 *vs* 126 ± 20 beats per minute, respectively [P = 0.001 (CI: 5.8-21.9)]. There was a positive correlation between body temperature and heart rate, r = 0.242, n = 136, P = 0.004 while no significant correlation was detected between temperature and respiratory rate, r = -0.012, n = 135, P = 0.892 (Figure 3). None of the patients had capillary refill recorded while in the hospital ward. Paracetamol was administered to 43 (31.6%) patients. A greater proportion of febrile patients (n = 35, 81.3%) received paracetamol than afebrile patients (n = 8, 18.6%); (P < 0.001).

Table 1 Demographic data of pediatric patients with or without fever

Demographic data	Total, *n* = 136 (100)	Febrile[1], *n* = 36 (26.5)	Afebrile, *n* = 100 (73.5)	*P* value
Sex				0.325[2]
Male	80 (58.8)	24 (66.7)	56 (56)	
Female	56 (41.1)	12 (33.3)	44 (44)	
Nationality				0.285[2]
Bahraini	97 (71.3)	23 (63.9)	74 (74)	
Non-Bahraini	39 (28.6)	13 (36.1)	26 (26)	
Age at presentation (mo)				**0.027**[3]
0-3	39 (28.7)	4 (11.1)	35 (35)	
> 3-6	8 (5.9)	4 (11.1)	4 (4)	
> 6-12	17 (12.5)	5 (13.9)	12 (12)	
> 12-36	29 (21.3)	12 (33.3)	17 (17)	
> 36-60	43 (31.6)	11 (30.6)	32 (32)	
Weight on admission (kg), (*n* = 124)	8.3 (4.0-13.3)	10.2 (7.3-13.0)	7.1 (3.7-13.3)	**0.034**[4]
Anatomical site of temperature measurement, (*n* = 42)				1.000[2]
Axillary	40 (95.2)	16 (40)	24 (60)	
Rectal	2 (4.8)	1 (50)	1 (50)	

[1]Included any patient who had a spike in temperature ≥ 38 °C during the first 48 h of admission.
[2]Fisher's exact test.
[3]Pearson's χ^2 test.
[4]Mann-Whitney *U* test.
Boldface indicates a statistically significant difference with $P < 0.05$. Data are presented as *n* (%) or median (interquartile range).

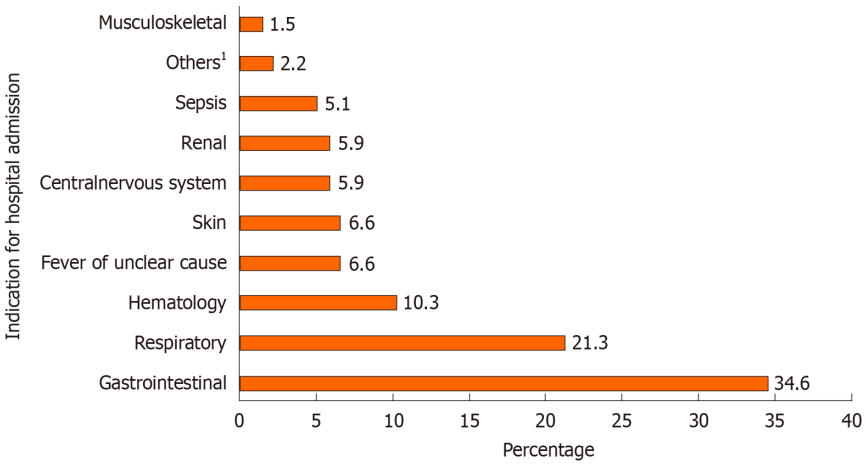

Figure 2 Indications for hospital admission of children included in the study. [1]Brief resolved unexplained episode (*n* = 2) and metabolic disease (*n* = 1).

The current practice of fever assessment in the pediatric department was compared with the NICE Fever in the under 5s guideline (Table 4). Full compliance (> 95%) was achieved for five key criteria: the type of thermometer used, route of temperature measurement, frequency of temperature and heart rate measurements, and use of antipyretics in children with fever who appear distressed. In contrast, partial compliance (70%-95%) was observed for two criteria; the threshold of fever at 38 °C or more (93%), and the respiratory rate assessment in febrile patients. Minimal compliance (< 65%) or no record was observed for the remaining three criteria (routine assessment of capillary refill, temperature reassessment 1-2 h after each antipyretic intake, and refraining from the use of tepid sponging).

Table 2 Proportion of patients with or without fever in relation to disease by body system

Diagnosis	Total, *n* = 136 (100)	Febrile, *n* = 36 (26.5)	Afebrile, *n* = 100 (73.5)	*P* value[1]
Gastrointestinal disease	47 (34.6)	8 (22.2)	39 (39.0)	0.101
Respiratory disease	29 (21.3)	11 (30.6)	18 (18.0)	0.154
Hematological disease	14 (10.3)	2 (5.6)	12 (12.0)	0.353
Fever of unknown etiology	9 (6.6)	6 (16.7)	3 (3.0)	**0.011**
Skin disease	9 (6.6)	1 (2.8)	8 (8.0)	0.444
Central nervous system disease	8 (5.9)	5 (13.9)	3 (3.0)	**0.030**
Renal disease	8 (5.9)	1 (2.8)	7 (7.0)	0.681
Sepsis	7 (5.1)	0 (0.0)	7 (7.0)	0.189
Musculoskeletal disease	2 (1.5)	1 (2.8)	1 (1.0)	0.461
Others[2]	3 (2.2)	1 (2.8)	2 (2.0)	1.000

[1]Fisher's exact test.
[2]Brief resolved unexplained episode (*n* = 2) and metabolic disease (*n* = 1).
Boldface indicates a statistically significant difference with $P < 0.05$. Data are presented as *n* (%).

Table 3 Distribution of the recorded body temperature and its relation to heart rate and respiratory rate

Parameter	Fever (≥ 38 °C), *n* = 36 (26.5)	No fever (< 38 °C), *n* = 100 (73.5)	*P* value (95%CI)
Temperature (degree Celsius)	38.2 (38.2-38.9)	37 (36.8-37)	**< 0.001**[1]
Heart rate (beat per minute)	140 ± 24	126 ± 20	**0.001** (5.8-21.9)[2]
Respiratory rate (breath per minute) (*n* = 135)	28 (24-34)	33 (24-40)	0.107[1]

[1]Mann-Whiteny *U* test.
[2]Student's *t* test.
Boldface indicates a statistically significant difference with $P < 0.05$. Data are presented as median (interquartile range) or mean ± SD.

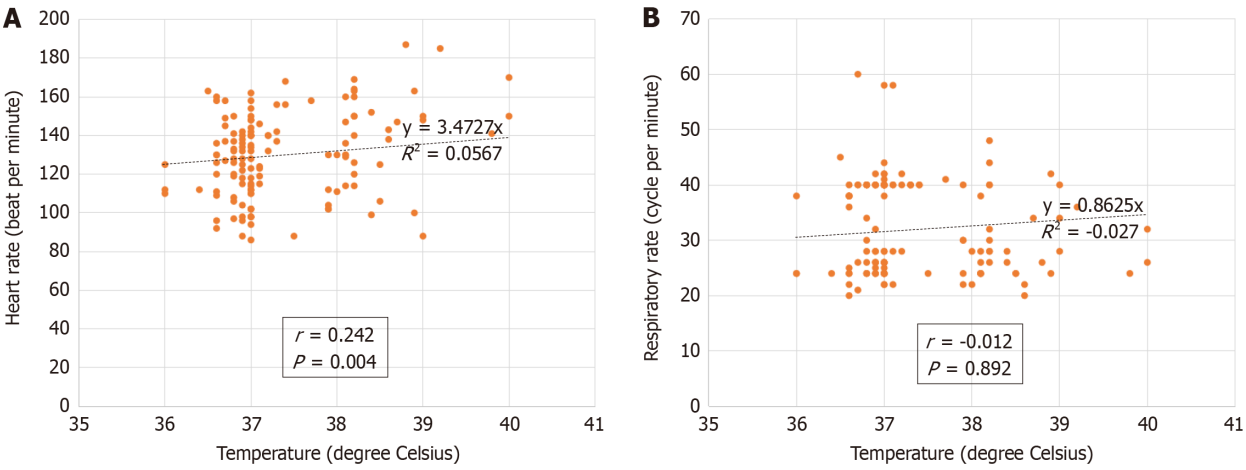

Figure 3 Correlation between body temperature and heart rate and respiratory rate of children included in the study. Spearman's correlation coefficient (r_s) was used. $P < 0.05$ was considered statistically significant.

DISCUSSION

This study found a male predominance (58.8%) among the children who required hospital admission. This trend is consistent with the results of other studies conducted in different countries. This percentage is similar to that reported by Mehdi *et al*[12] in Pakistan and Ambaye *et al*[13] in Ethiopia (58% each) and comparable with that observed by Alam *et al*[14] and George *et al*[15] in Bangladesh and Nepal (51% and 71%, respectively). However, the reason for this male

Table 4 Compliance with The National Institute for Health and Care Excellence guidelines

Criterion[1]	Compliance		
	Minimal (≤ 69%)	Partial (70%-95%)	Full (> 95%)
1: Fever is considered if temperature is 38 degrees Celsius or more	-	Yes	-
2: Do not routinely use oral or rectal routes to measure the body temperature of children 0-5 yr	-	-	Yes
3: In infants under the age of 4 wk, measure the body temperature with an electronic thermometer under the axilla	-	-	Yes
4: In children aged 4 wk to 5 yr, measure the body temperature by one of the following: Electrical thermometer to the axilla, chemical dot thermometer to the axilla, or infra-red tympanic thermometer	-	-	Yes
5: As part of routine assessment of children with fever: Record the heart rate	-	-	Yes
6: As part of routine assessment of children with fever: Record the respiratory rate	-	Yes	-
7: As part of routine assessment of children with fever: Record the capillary refill time	NR	NR	NR
8: Use of antipyretics in children with fever who appear distressed	-	-	Yes
9: In case of febrile patient, the temperature is reassessed 1-2 h after each anti-pyretic intake	Yes	-	-
10: The use of tepid sponging is not recommended for the treatment of fever	NR	NR	NR

[1]The National Institute for Health and Care Excellence guideline [NG143]: Fever in under 5s: Assessment and initial management. NR: Not reported.

predominance has not been extensively studied. A reasonable explanation for this may be the higher male birth rate in this population. With regard to live birth statistics from Bahrain's national registry, although there is a consistently higher birth rate of boys than of girls, the difference is relatively modest. According to the latest available records from 2016 to 2020, the difference in birth rates was between 50.5% and 51.7%[16]. While these percentages reflect a male predominance in the birth rate, they are unlikely to be the major contributing factor to the higher male predominance reported in our study. This male predominance may also be attributed to a sex bias in the health-seeking behavior of parents[14,17]. Other potential reasons include sociocultural variations and biological/genetic differences in disease susceptibility across the sexes. However, the sex distribution requires further investigation.

We observed a significant association between patient weight at admission and the presence of fever (P = 0.034). Patients with fever had a higher median weight than the afebrile patients. This finding raises questions about the potential relationship between a child's weight and their susceptibility to developing fever, and whether body weight itself could be a contributing factor leading to hospital admission.

The top three reasons for hospital admission in the current study were gastrointestinal (34.6%), respiratory (21.3%), and hematological (10.3%) diseases. Gastrointestinal disease predominance was similar to the findings of other studies published in Pakistan and Bangladesh, as reported by Mehdi *et al*[12] and Alam *et al*[14], respectively. In contrast, studies conducted in other countries have shown respiratory diseases to be the predominant cause of admission in this age group, including those conducted by Ambaye *et al*[13] in Ethiopia, George *et al*[15] in Nigeria, Bhurtel *et al*[18] in Nepal, and Merrill *et al*[19] in the United States of America. These differences might be the result of variations in healthcare availability, environmental factors, societal hygiene practices, vaccination rates, antibiotic use, dietary habits, population density, and migration patterns[20].

Temperature is a vital sign that is routinely measured in patients admitted for fever[1]. Assessing the accuracy and consistency of the routes used for temperature measurement is important because the presence of fever can significantly influence diagnostic and treatment decisions[1,3]. This study showed a preference for the axillary route (n = 40/42, 95.2%), followed by the rectal route (n = 2/42, 4.8%); the tympanic thermometer route was not utilized. This aligns with the existing literature regarding the ongoing debate regarding the optimal thermometer route for accurate temperature assessment[4-11]. While rectal thermometry is generally regarded as a reliable indicator of core body temperature, recent studies have suggested the limitations of this method, especially for repetitive use[4]. The limitations include the discomfort it causes to patients, time consumption, the slow rise and drop in its readings in relation to core temperature, the effect of local blood flow and stool on its accuracy, the risk of perforation and a general need for privacy. Research is exploring alternative routes[5-11]. Tympanic thermometry has been recognized by different studies for its accuracy and convenience compared with the rectal and axillary routes[10,11]. It measures the thermal radiation of the tympanic membrane using infrared radiation emission detectors, either through thermopile or pyroelectric sensors[4]. Due to the close proximity of the tympanic membrane's blood supply and the body's thermoregulatory sensor, the hypothalamus, tympanic temperature measurements were found to provide the closest measurement to the core body temperature[5-11]. Adding to that, tympanic thermometers are fast and easy to use, and are therefore cost-effective in terms of nursing time[4]. Axillary thermometry relies on the placement of thermometers over the axillary artery for more than four minutes for mercury-based and 40-80 s for electronic-based thermometers, which has an impact on nursing time[4]. Although simple to use, it has shown limitations in accuracy mainly because it requires proper placement and supervision, and local factors such as blood flow and sweat can affect precision[4,5,21,22]. Despite this, NICE still

recommends its use in children under five years of age[2]. Valuable information for optimizing temperature assessment in the pediatric population can be obtained from further evaluation of these routes.

A variable level of compliance was found in the current practice compared to the NICE Fever in under 5s guideline. Ten key criteria were used for evaluation. Our department demonstrated full compliance (> 95%) to certain guidelines, including routine assessment of heart rate, using antipyretics as necessary for temperatures ≥ 38 °C, and measuring temperatures using specific routes and types of thermometry. Conversely, partial compliance (70%-95%) was noted when considering fever exclusively for temperatures above a threshold of 38 °C (93%), as well as routine assessment of the respiratory rate. Additionally, our data point to minimal compliance (< 65%) with regard to the reassessment of temperature 1-2 h after each antipyretic intake (57%). The assessment revealed no record of compliance in the routine assessment of capillary refill time, as it is only performed in the pediatric emergency department before admission, together with refraining from the use of non-pharmacological interventions such as tepid sponging mainly because such interventions, if used, are not routinely entered into the electronic medical records. This analysis demonstrates the importance of a continuous quality improvement approach and highlights both the areas of adherence and those that need improvement. Addressing these gaps and maximizing compliance with the guidelines can potentially help improve patient care and outcomes.

Study strengths

The study's strengths are its approach to investigating current practices in a specific age group within a specific setting. Moreover, it provides a comprehensive analysis of a diversity of factors, including age, sex, reason for admission, and weight. Comparing the effects of these factors with those of other international studies has provided valuable information regarding the similarities and differences in pediatric admissions and fever assessment. The evaluation of compliance with the NICE guideline is a practical implementation of evidence-based recommendations and emphasizes the importance of quality improvement in healthcare. Furthermore, this study identified potential areas of investigation such as sex distribution, reasons for admission, and weight differences between febrile and afebrile patients, which opens the door for future research.

Study limitations

This study was limited by its retrospective nature and reliance on electronic medical records for data collection, which led to a lack of some relevant data. Additionally, despite SMC being the main hospital in Bahrain, this was a single-center study, which may limit the generalizability of its results. The study could not include records of capillary refill time, or use of non-pharmacological interventions, because they were incomplete due to customary record-keeping practices. Another limitation was that most patients were usually seen in the pediatric emergency department before admission; thus, records of the first true temperature and initial management were absent, as the data were inclusive only of pediatric inpatient records. Moreover, tympanic thermometers were not used in our patients, which might have limited the comparison between different types of temperature measurement routes. Despite these limitations, the present study is the first to evaluate fever in the Department of Pediatrics in Bahrain and can form a foundation for future studies.

CONCLUSION

This study provides valuable information regarding the patterns of pediatric admissions, temperature measurement routes, and compliance with the NICE guideline for Fever in under 5s, in the Department of Pediatrics at the Salmaniya Medical Complex in Bahrain. This revealed a male predominance in hospital admissions, with gastrointestinal diseases being the most common reason for admission in children below five years of age. The axillary route of temperature measurement was predominantly used, whereas tympanic thermometry was never utilized despite its recognized accuracy and convenience. The assessment of compliance with the NICE guideline revealed both areas of adherence and areas that needed improvement. Further studies that focus on exploring sex disparities in pediatric admissions, weight differences between febrile and afebrile patients, the use of tympanic thermometry for temperature assessment, and the impact of conducting regular audits to help track improvements in adherence to guidelines and their impact on patient care are needed.

ARTICLE HIGHLIGHTS

Research background

Fever is a common cause of medical consultations and hospital admissions in children. It is a physiological elevation in body temperature in response to various conditions. Recently, the United Kingdom's National Institute for Health and Care Excellence (NICE) updated its guidelines for assessing fever in children under five years of age. The presence of fever and proper fever assessment can have a significant impact on investigations, management plans, and the overall prognosis of patients.

Research motivation

Many studies on fever assessment in children have been reported worldwide; however, no such studies have been

conducted in Bahrain. This gap motivated us to evaluate the current practices of fever assessment.

Research objectives

To evaluate the current practice of fever assessment in hospitalized children under five years in the main hospital in Bahrain and to assess its adherence to the NICE Fever in under 5s guideline.

Research methods

We retrospectively reviewed the electronic medical records of children under five years of age admitted to the Department of Pediatrics, Salmaniya Medical Complex, Bahrain, between June and July 2023. Demographic data, vital signs during the first 48 h of admission, route of temperature measurement, and indications for admission were collected. The children were divided into five groups according to their age in months. The NICE Fever in under 5s guideline was used to define fever. Febrile and afebrile patients were compared in terms of demography, indication of admission, route of temperature measurement, and other vital signs. Compliance with the NICE guideline was assessed.

Research results

Of the 136 patients reviewed, 80 (58.8%) were boys. The median age at admission was 14.2 [interquartile range (IQR): 1.7-44.4] months. Thirty-six (26.4%) patients had fever, and 100 (73.6%) were afebrile. The commonest age group of febrile patients was higher (> 12-36 months) than for the group without fever (0-3 months) (P = 0.027). The median weight was 8.3 (IQR: 4.0-13.3) kg. Patients with fever had higher weight than those without [10.2 (IQR: 7.3-13.0) *vs* 7.1 (IQR: 3.8-13.3) kg, respectively] (P = 0.034). Gastrointestinal disease was the leading indication for hospital admission (n = 47, 34.6%). Patients with central nervous system diseases and fever of unknown etiology were more likely to be febrile (P = 0.030 and P = 0.011, respectively). The mean heart rate was higher in the febrile group than the afebrile group (140 ± 24 *vs* 126 ± 20 beats per minute, respectively) [P = 0.001 (confidence interval: 5.8-21.9)] with a positive correlation between body temperature and heart rate, r = 0.242, n = 136, P = 0.004. A higher proportion of febrile patients received paracetamol (n = 35, 81.3%) than the afebrile patients (n = 8, 18.6%) (P < 0.001). The axillary route was most commonly used for temperature measurements (n = 40/42, 95.2%), followed by the rectal route (n = 2/42, 4.8%). The department demonstrated full compliance with the NICE guideline for five criteria: type of thermometer, route and frequency of temperature measurement, frequency of heart rate measurement, and use of antipyretics as needed. Partial compliance was noted for two criteria, the threshold of fever at 38 °C or more, and the respiratory rate assessment in febrile patients. Minimal compliance or no record was observed for the remaining three criteria (routine assessment of capillary refill, temperature reassessment 1-2 h after each antipyretic intake, and refraining from the use of tepid sponging).

Research conclusions

The evaluation of fever in children under five years of age revealed areas of adherence to the guideline and areas that require enhancement. Specific noteworthy findings have emerged, such as a higher number of boys being admitted to the hospital, a common occurrence of gastrointestinal diseases, a significant difference in weight between febrile and afebrile patients, and an underuse of tympanic thermometry despite its established accuracy and convenience.

Research perspectives

Specific improvements in fever assessment in children under the age of five years should be implemented in accordance with international guidelines. Further studies exploring the sex disparities, indications for admission, and weight differences between febrile and afebrile patients are warranted. Furthermore, the use of tympanic thermometry for temperature assessment in children should be explored.

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FOOTNOTES

Co-first authors: Hasan M Isa and Ahmed J Isa.

Author contributions: Isa HM was the main contributor in study conceptualization, design, data curation, literature review, data analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, drafting manuscript, and over-sight for all phases of the project and the final approval of the version to be published; Isa AJ is the co-first author and was responsible for study design, acquiring and analyzing data, literature review, drafting and revising manuscript; Alnasheet MA and Mansoor MM participated in literature review and data collection; and all the authors have read and approved the final manuscript.

Institutional review board statement: This study was conducted in accordance with the principles of Helsinki Declaration, and it was ethically approved by the Secondary Care Medical Research Subcommittee, Salmaniya Medical Complex, Government Hospitals, Kingdom of Bahrain (IRB number: 38020523, May 02, 2023).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Systemic juvenile idiopathic arthritis–associated lung disease: A retrospective cohort study

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Abstract

BACKGROUND

Lung damage in systemic juvenile arthritis (sJIA) is one of the contemporary topics in pediatric rheumatology. Several previous studies showed the severe course and fatal outcomes in some patients. The information about interstitial lung disease (ILD) in the sJIA is scarce and limited to a total of 100 cases.

AIM

To describe the features of sJIA patients with ILD in detail.

METHODS

In the present retrospective cohort study, information about 5 patients less than 18-years-old with sJIA and ILD were included. The diagnosis of sJIA was made according to the current 2004 and new provisional International League of Associations for Rheumatology criteria 2019. ILD was diagnosed with chest computed tomography with the exclusion of other possible reasons for concurrent lung involvement. Macrophage activation syndrome (MAS) was diagnosed with HLH-2004 and 2016 EULAR/ACR/PRINTO Classification Criteria and hScores were calculated during the lung involvement.

RESULTS

The onset age of sJIA ranged from 1 year to 10 years. The time interval before ILD

ranged from 1 mo to 3 years. The disease course was characterized by the prevalence of the systemic features above articular involvement, intensive rash (100%), persistent and very active MAS (hScore range: 194-220) with transaminitis (100%), and respiratory symptoms (100%). Only 3 patients (60%) developed a clubbing phenomenon. All patients (100%) had pleural effusion and 4 patients (80%) had pericardial effusion at the disease onset. Two patients (40%) developed pulmonary arterial hypertension. Infusion-related reactions to tocilizumab were observed in 3 (60%) of the patients. One patient with trisomy 21 had a fatal disease course. Half of the remaining patients had sJIA remission and 2 patients had improvement. Lung disease improved in 3 patients (75%), but 1 of them had initial deterioration of lung involvement. One patient who has not achieved the sJIA remission had the progressed course of ILD. No cases of hyper-eosinophilia were noted. Four patients (80%) received canakinumab and one (20%) tocilizumab at the last follow-up visit.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

Key Words: Systemic juvenile arthritis; Interstitial lung disease; Canakinumab; Tocilizumab; Interleukin-6; Interleukin-1

Core Tip: We evaluated 5 patients with systemic juvenile arthritis and interstitial lung disease. This is an ultra-rare, unrecognized, life-threatening and potentially fatal complication of systemic juvenile arthritis. This complication is usually associated with early onset age, systemic features of the disease, especially with pleuritis, severe and long-term macrophage activation syndrome, lymphopenia, trisomy 21 syndrome, and biologic anaphylaxis. The recognition of these symptoms can help in early suspicion of this severe complication.

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INTRODUCTION

Juvenile idiopathic arthritis with systemic onset (sJIA) is the most life-threatening form of JIA due to macrophage activation syndrome (MAS) and internal organ involvement[1,2]. The lung disease is a rare, severe, potentially fatal manifestation of sJIA. Its prevalence has grown in the last 20 years from single cases at the beginning of 2000 to 5% nowadays[1]. Lung involvement in sJIA includes pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), presenting with pulmonary alveolar proteinosis, and lipoid pneumonia[1,2]. Patients may have a combination of ILD and PAH. The mechanisms of lung involvement in sJIA are still unclear. It is known that hyperproduction of interleukin (IL) 1, IL-18, and interferon (IFN) γ pathway signaling are the main key points of the pathogenesis of lung involvement in sJIA. Several risk factors, associated with lung involvement in sJIA were proposed: onset age < 2 years, prevalence of systemic features, chronic or recurrent or poor controlled MAS, persistent and progressed lymphopenia, anaphylaxis to IL-6 and IL blockers, trisomy on 21 chromosomes[3]. The outcomes of the patients with sJIA with lung diseases (sJIA-LDs) are extremely serious. In the first case series of 25 patients published by Kimura *et al*[4], 68% died in 8.8±11.4 mo after the lung involvement appeared. Several recent studies showed better outcomes with a mortality rate near 4.6% which is 7.5 times more than in sJIA patients without lung involvement[5]. There are no approved pathogenic medications for the treatment of lung involvement in sJIA patients. Treatment with IFN-γ direct blocker (emapalumab), indirect blockers (JAK-inhibitors), and anti-IL-18 blockers (IL-18 binding protein) seems to be promising but requires approval[6-8]. Additional treatment options might include corticosteroids (glucocorticosteroids), anti-IL-1 and anti-IL-6 biologics, cyclosporine A and tacrolimus, mofetil mycophenolate, intravenous immunoglobulin, and PAH for specific treatment to control the pulmonary blood pressure and oxygen supplementation[1,2,9]. Children with sJIA and chronic lung involvement are more susceptible to lung infections and require specific prophylaxis[4].

The Information about patients with lung involvement is scarce and related to patients whose chronic lung disease has already been diagnosed.

Our study aimed to describe the patients with sJIA-LD with a focus on the initial clinical and laboratory features.

MATERIALS AND METHODS

Population

In the present retrospective cohort study, we included available information about 5 pediatric patients (onset age < 18 years) with sJIA-LD. The diagnosis of sJIA was made according to the current 2004[10] and new provisional International League of Associations for Rheumatology (ILAR) criteria 2019[11]. If the patient did not fit one of the major criteria he/she was diagnosed with sJIA-like disease (probable"/"possible" sJIA).

ILD was diagnosed with chest computed tomography and the exclusion of other possible reasons for concurrent lung involvement.

MAS was diagnosed with HLH-2004[12] and 2016 EULAR/ACR/PRINTO Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis[13] and hScore was calculated during the lung involvement[14].

Statistics

The sample size was not calculated initially. We included all available cases in our center. We used only descriptive statistics (quantitative and categorical data).

RESULTS

Common symptoms at onset of sJIA

Diagnosis of sJIA was established in all patients. Two patients did not meet the current ILAR criteria in 2004, because patients 1 and 2 did not have arthritis at the onset. All patients corresponded to new provisional criteria for sJIA 2019. Patient 2 developed severe polyarthritis 2 years after the disease onset. The correspondence of the patients to current (2004) and new provisional (2019) ILAR criteria is shown in Table 1. Serositis was presented by pericarditis in 3 cases (patients 1, 2, and 4), pleurisy in 4 cases (patients 1,2,3 and 4), and peritonitis in patient 2. One patient (patient 5) developed leucopenia at onset due to MAS. The demographic characteristics of patients are in Table 2.

Lung involvement

All patients had dyspnea, but only 1 patient had a cough (patient 2). Clubbing (Figure 1) of the fingers was in 3 (60%) patients. Respiratory failure was diagnosed in 4 (80%) patients. They were admitted to the Intensive Care Unit for respiratory support.

In 2 cases, lung disease was diagnosed at the sJIA onset (patients 3 and 4) and in 3 cases, lung disease developed later in patients 1, 2, and 5 (Figure 2).

Two patients developed PAH, patient 1 had persistent PAH and required PAH-specific treatment, and patient 2 had temporary PAH at the lung disease onset and this was successfully resolved in 1 mo after high-dose systemic glucocorticosteroid treatment.

MAS and ILD development

All patients have met the above mentioned MAS criteria. Severe full-blown MAS had all 5 (100%) patients at the onset with a score range of 194-220 points. All patients had persistent/relapsed courses of MAS. In all cases, ILD was detected in patients with features of MAS. Interestingly, MAS was more aggressive and hardly controlled in patients with early onset (patients 1 and 2) and patients with trisomy 21 syndrome (patient 5).

Assessment of the known risk factors of LD-sJIA

We observed the risk factors which were previously described[1,3]. Infusion reaction on tocilizumab had 3 (60%) patients. Trisomy 21 syndrome had 1 patient (Patient 5). Four patients developed sJIA at the age of 2 years or younger, and patient 3 developed sJIA at the age of 10 years. All patients had severe MAS.

Treatment

All patients received corticosteroids. High doses of intravenous corticosteroids were received at the onset and with a major flare, including MAS. Inhalational corticosteroids (budesonide and fluticasone) were used in 1 case with lipoid pneumonia. All 5 patients have experienced tocilizumab treatment, and as we have already pointed out, infusion reaction was diagnosed in 3 cases (patients 1, 2, and 4). In 4 of 5 (80%) cases, tocilizumab was changed to canakinumab; abatacept was added to canakinumab therapy in patient 1. Patient 1 with PAH has received sildenafil with positive dynamic and stabilization in PAH.

Outcomes

The outcomes of our cases were different. Patient 5 with trisomy 21 (Down Syndrome) had a fatal outcome. The female developed a flare of sJIA with respiratory and heart failure. Two patients (patients 2 and 3) achieved sJIA remission with the improvement of ILD, but patient 2 initially had deterioration followed by improvement. Two patients had incomplete sJIA remission (patients 1 and 4) with ILD improvement in patient 4, but patient 1, despite the combination treatment of canakinumab and abatacept has not achieved ILD improvement. His PAH is under the control of sildenafil. Patients with early onset had more severe ILD. Demographic characteristics, clinical with ILAR criteria, radiological features, and

Table 1 Correspondence of our patients to current[10] and provisional International League of Associations for Rheumatology criteria for systemic juvenile arthritis[11]

No. ID	Major criteria			Minor criteria				Overall correspondence ILAR2004 criteria	Overall correspondence ILAR2019 criteria
	Fever	Erythematous rash	Arthritis	Lymphadenopathy/hepatomegaly/splenomegaly	Serositis	Arthralgia	Leukocytosis as/mm^3		
1	Yes	Yes	No	Yes	Yes	No	53.300	No	Yes
2	Yes	Yes	No	Yes	Yes	Yes	15.100	No	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	47.200	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	30,820	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	No	2.300	Yes	Yes

ILAR: International League of Associations for Rheumatology.

Table 2 Demographic characteristics of the patients

No.	Sex	Age of onset in yr	Age of last follow-up visit in yr	Time to sJIA-LD	Concomitant disease
1	Male	1	10	3 yr	--
2	Female	2	11	3 yr	--
3	Female	10	17	1 month	--
4	Male	2	11	4 months	Atopic dermatitis
5	Female	2	7	4 yr	Trisomy 21 syndrome

sJIA-LD: Systemic juvenile arthritis with lung diseases.

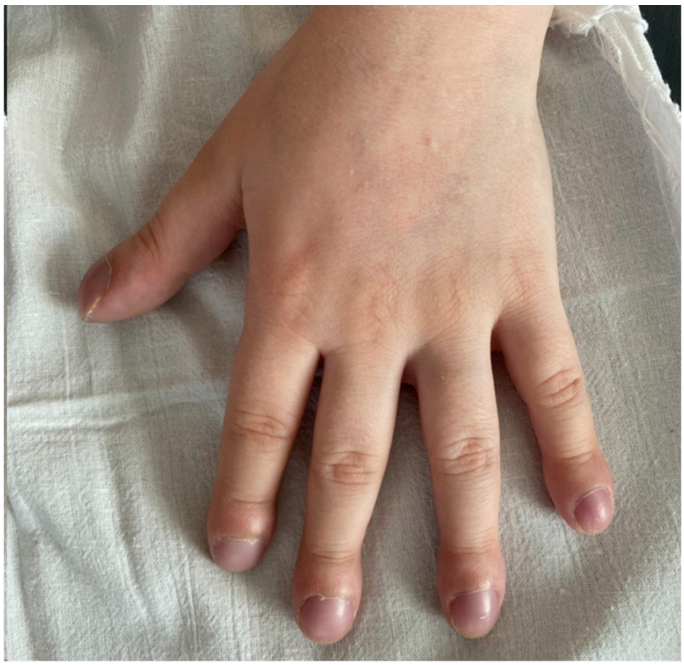

Figure 1 Clubbing of the fingers in patient 2. The changes of the distal phalanges and the nails are apparent.

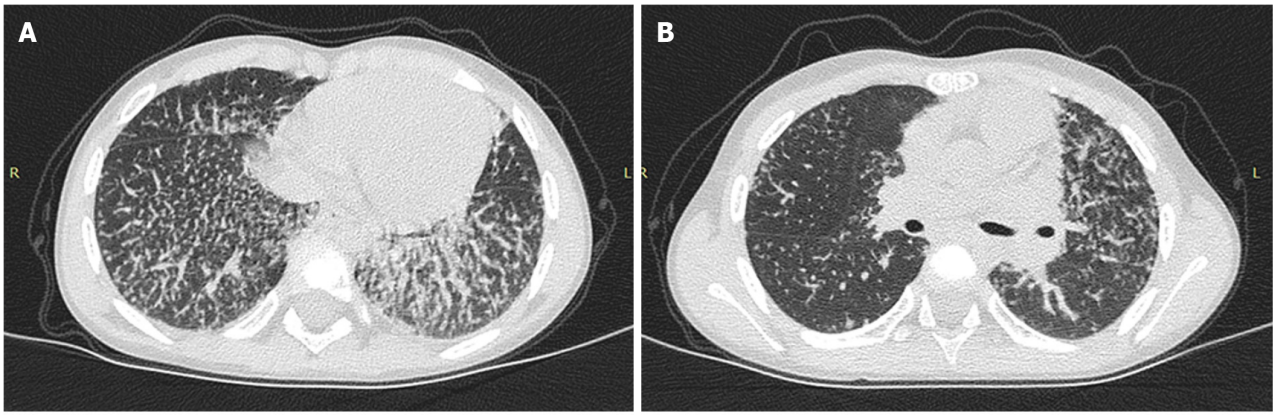

Figure 2 Chest computed tomography in patient 2 with lipoid pneumonia. A and B: Representative signs of interstitial changes in all lobes of the lungs with damage to the distal parts of the tracheobronchial tree. There are diffuse changes with the presence of multiple intralobular foci, with thickening of the peribronchovascular interstitium.

treatment outcomes are in Tables 1-4.

DISCUSSION

sJIA is an autoinflammatory disease that is characterized by fever, rash, arthritis, and damage to other organs[1].

MAS is a life-threatening complication in children with sJIA, related to the hyperproduction of proinflammatory cytokines, especially: IL-1, IL-6, IL-18, IFN-γ[2,9,15,16]. sJIA-LD is a troupe of nosology that is characterized by chronic lung disease in patients with sJIA[1] Now, it is clear, that lung involvement in sJIA patients is associated with persistent systemic inflammation, especially with MAS[1-3].

Clinical symptoms, associated with ILD

Unfortunately, typical respiratory symptoms at the beginning of the disease are usually absent or poorly expressed, and because of this, sJIA-LD occurs unexpectedly in many patients. For example, the cough was present in 33%-43%, tachypnea in 33%-38%, auscultative changes in the lungs in 30%, while hypoxemia was already registered in 43% of patients, and symptomatic PAH in 30%[1,3].

Sometimes, the main clinical symptoms indicating lung lesions are distal phalangeal dilation or the so-called clubbing symptom (61%) and erythema of the distal phalanges (34%).

Despite the diagnosis of sJIA, patients with lung involvement had unusual clinical presentations such as an itchy rash (56%), eosinophilia (37%), and unexplained intense abdominal pain (16%)[3].

In our group, patient 2 had a severe sJIA flare with aseptic peritonitis that required diagnostic surgery 1 year before the lung involvement.

Another important feature is the development of a hypersensitivity reaction (anaphylaxis) to 2-3 injections of tocilizumab in many children with JIA and lung damage[1,3,9]. The estimated probability of a hypersensitivity reaction during treatment with tocilizumab is up to 9.1%[17-19]. Three (60%) of our patients had a tocilizumab anaphylaxis. Hypersensitivity to biological agents was found to be a risk factor for ILD[1,3].

Laboratory symptoms associated with ILD

Lymphopenia (< 60% of the lower normal limit for age) was detected in sJIA patients with lung involvement. This could not be explained by the current MAS and was found in 42%. The combination of hyperferritinemia and severe lymphopenia serves as a marker of the risk of lung involvement in patients with sJIA[3]. Another important laboratory symptom is eosinophilia, associated with ILD in sJIA patients[3].

Interstitial lung involvement

Pulmonary alveolar proteinosis is a poorly studied disease manifested by the accumulation of lipid substances in the alveoli due to ineffective excretion of lipid substances by macrophages[20]. Macrophage dysfunction in sJIA-LD is not associated with congenital defects of macrophages, as in primary lung disease[1,20-22]. Patients with MAS have a highly active systemic inflammation that contributes to macrophage differentiation disturbances[1]. Similar cytokine transmission pathways in MAS and sJIA-LD explain the close similarity between both conditions. Several cytokines, such as IFN-γ and IL-18 are now the focus of MAS pathogenesis[6,23].

The persistence of high levels of IL-18 in patients with sJIA receiving canakinumab may explain the development of lung damage in children being in remission under the biological treatment[24].

In IL-18-dependent diseases, specific therapy with IL-18-binding protein is required, since other treatments may be ineffective[7].

Table 3 Clinical and radiological characteristics of the patients with systemic juvenile arthritis at the moment of diagnostics of lung involvement

No.	Rash	Hepatitis	Lymphadenopathy	Cough	Dyspnea	Clubbing	Respiratory failure	Infusion reaction on TCZ	PAH	MAS	hScorein points	Heart involvement	X-ray, CT, or MRI or US findings	Eosinophils as × 10^9/L
1	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	220	Pericarditis	ILD, pleurisy	0.63
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	209	Myocarditis, Pericarditis	Interstitial lung disease with intralobular foci, pleurisy	0.19
3	Yes	Yes	No	No	Yes	No	No	No	No	Yes	224	N	Alveolitis, diffuse focal lesions, pleurisy	0.29
4	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	194	Pericarditis	ILD, atelectasis, pleurisy	0.4
5	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	220	Heart Failure	ILD, pleurisy	0.12

CT: Computed tomography; ILD: Interstitial lung disease, MAS: Macrophage activation syndrome; MRI: Magnetic resonance imaging; PAH: Pulmonary arterial hypertension; TCZ: Tocilizumab; US: Ultrasound.

It is known that the lungs are the main source of physiological production of IL-1β and IL-6. These proinflammatory cytokines, as well as the levels of the endogenous antagonist of IL-1 receptors, are higher in children under the age of 4 years, which may explain the higher frequency of ILD in younger children[25-28].

IL-1β, IL-6, and IFN-γ are the main cytokines involved in the pathogenesis of sJIA and MAS[1]. The same cytokines play a key role in lung tissue damage, in particular, due to activation and/or dysfunction of macrophages in the pulmonary interstitium[20-22]. Hyperinfection and increased regulation of innate immunity lead to an increase in the production of IL-1β, which stimulates the levels of granulocyte-macrophage colony-stimulating factor, as well as hyperproduction of surfactant and its accumulation in tissues and impaired clearance. Elevated levels of IL-6 inhibit the production of type II bone morphogenetic protein receptors, which control cell growth and differentiation. IL-18, associated with the IFN-γ signaling pathway, is also associated with severe forms of MAS and ILD in patients with sJIA. The level of this cytokine remains elevated, despite the control of systemic inflammation by IL-1 or IL-6 blockade. This may explain lung damage in patients with sJIA who are in remission with IL-1 and IL-6 blockade[6,23,24]. Chronic lung inflammation with accumulation of surfactant and lipoproteins in the alveoli leads to interstitial pulmonary fibrosis, decreased elasticity of the pulmonary artery with the formation of pulmonary hypertension[1]. A brief pathogenesis of lung damage in sJIA is shown in Figure 3.

PAH

The pathogenesis of PAH is a result of systemic inflammation with proinflammatory cytokine disbalance. It's known, that the low expression of *BMPR2* (bone morphogenic protein receptor type II) associated with potential endothelial dysfunction and PAH, in turn, one of the central cytokines in the pathogenesis of systemic arthritis (IL-6) *in vitro* BMPR reduced its activity[29-31].

Radiological findings of the interstitial lung involvement

In clinical practice, radiological methods are often used to diagnose lung lesions. sJIA-LD is characterized by compaction/infiltration of lung tissue, thickening of the interlobular septa, and damage to the peripheral parts of several

Table 4 Main treatment outcomes of the patients with systemic juvenile arthritis and interstitial lung disease

No.	First biologic	Biologic at the ILD onset	Final therapy	Respiratory symptoms at the last follow-up visit	Dose reduction of non-biologic DMARDs	Dose reduction of BA	Discontinuation of GCS therapy	The outcome of sJIA-LD	The outcome of sJIA
1	TCZ	TCZ	CAN + ABT + CsA + GCS + SDF	No	No	No	No	Progression	Improvement
2	TCM	CAN	CAN + MMF + inhGS	No	Yes	No	Yes	Progression with the following improvement	Remission
3	CAN	CAN	TCZ + CsA	No	No	No	Yes	Improvement	Remission
4	TCZ	TCZ	CAN + MMF	No	No	No	Yes	Improvement	Improvement
5	TCZ	TCZ	CAN + GCS + IVIG	-	-	-	No	Death	Death

ABT: Abatacept; CAN: Canakinumab; CsA: Cyclosporine A; DMARD: Disease-modifying anti-rheumatic drug; GCS: Glucocorticosteroids; inhGCS: Inhaled glucocorticosteroids; IVIG: Intravenous immunoglobulin; ILD: Interstitial lung disease; SDF: Sildenafil; sJIA: Systemic juvenile idiopathic arthritis; TCZ: Tocilizumab.

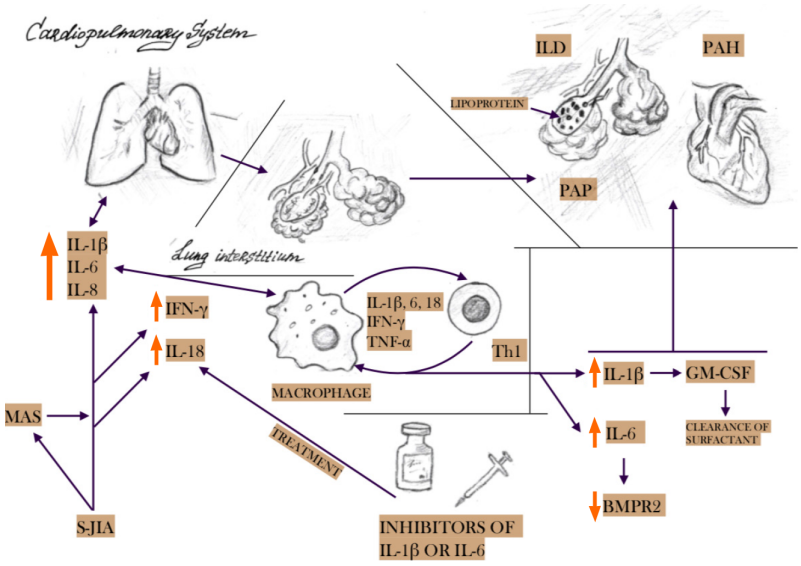

Figure 3 Brief summary of the pathogenesis of lung involvement in systemic juvenile arthritis. BMPR2: Bone morphogenetic protein receptor type II; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN: Interferon; IL: Interleukin; ILD: Interstitial lung disease; MAS: Macrophage activation syndrome; PAH: Pulmonary arterial hypertension; PAP: Pulmonary alveolar proteinosis; sJIA: Systemic juvenile idiopathic arthritis; TNF: Tumor necrosis factor.

lobes, mainly basal, para mediastinal, or anterior parts of the upper lobes in combination with the symptom of frosted glass, as well as the detection of enlarged lymph nodes with an increased density in CT of the chest with contrast[1,3].

Outcomes of the patients with sJIA-LD

The most alarming problem of sJIA-LD is the high mortality and a short life expectancy because of the development of lung damage. According to available data, 68% (n = 17) of patients died after 8.8 ± 11.4 mo from the onset of lung damage [4]. Unfortunately, mortality was about 40 times higher in the group of people with sJIA-LD[3]. In males, hypoxia at the beginning of lung damage, and neutrophilia in bronchial lavage (> 10 times higher) were considered the main predictors of death[3,31].

Management of the patients with LD-sJIA

In managing children with ILD, a multidisciplinary approach is required with the participation of specialists in various fields, including a rheumatologist, pulmonologist, infectious disease specialist, rehabilitation specialist, psychologist, transplant surgery, as well as comprehensive laboratory and instrumental support, including, in particular, spirometry,

pulse-oximetry, assessment of diffusion ability lung, computed tomography of the chest, echocardiography with assessment of pressure in the pulmonary artery, electrocardiography, assessment of sJIA and MAS laboratory activity. Sometimes, with chronic progressive hypoxemia, lung transplantation is the only method that can prolong the patient's life. Knowledge of the pathogenesis of this condition is important for the formation of potential prediction markers, targeted therapy, and prognosis. The following studies are needed to find the predictors, pathogenesis, and treatment options, for preventing and treating the ILD in sJIA patients.

Limits of the study

The main limitations of this study are related to the retrospective analysis and the very small sample size. The authors could not influence the treatment and could not if the treatment chosen in the past could influence the development of the complication and its severity or not. The absence of molecular studies decreased the value of this study.

CONCLUSION

ILD is a severe life-threatening complication of sJIA that may affect children of different ages with different time intervals since the disease onset. Extensive rash, serositis (especially pleuritis), full-blown MAS with transaminitis, lymphopenia, trisomy 21, eosinophilia, and biologic infusion reaction are the main predictors of ILD.

ARTICLE HIGHLIGHTS

Research background

Chronic lung involvement is an ultra-rare, unrecognized, poorly understood condition in children with systemic juvenile idiopathic arthritis.

Research motivation

To describe this ultra-rare complication and disease course in children with systemic juvenile idiopathic arthritis with interstitial lung involvement.

Research objectives

The clinical and laboratory data of these patients are not well-diagnosed. The number of patients is nearly a hundred.

Research methods

The clinical, radiological, and laboratory features were described in detail. The H score was applied to these patients for the first time.

Research results

The main clinical features of the disease are associated with early onset, chronic course of macrophage activation syndrome, pleuritis at onset, protracted lymphopenia, eosinophilia, and anaphylaxis drug-reaction on biologics.

Research conclusions

This life-threatening complication is associated with chronic, persistent macrophage activation syndrome, drug-associated anaphylaxis similar to DRESS syndrome.

Research perspectives

The future collection of information on these patients requires the following study of the features of the macrophage activation syndrome (cytokine profile, interferon signatures), and new target drugs are needed.

FOOTNOTES

Author contributions: Kostik MM and Belozerov KE contributed to the conceptualization, writing, review, editing and original draft preparation; Kostik MM and Kuznetsova AA contributed to the methodology; Belozerov KE contributed to the software and formal analysis; Solomatina NM and Isupova EA contributed to the validation and resources; Belozerov KE, Solomatina NM, and Isupova EA contributed to the investigation; Kuznetsova AA contributed to data curation; Kostik MM contributed to funding, supervision and project administration; All authors read and approve the final manuscript, were involved in drafting the article or revising it critically for important intellectual content.

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Institutional review board statement: The Ethics Committee of Saint Petersburg State Pediatric Medical University (18/01 from 27.10.2022) approved this retrospective study's protocol.

Informed consent statement: Written consent was obtained according to the Declaration of Helsinki. All patients or patient representatives (for patients under the age of 15 years) gave their consent in their case report forms authorizing the anonymous use of their medical information. All patients were appropriately anonymized.

Conflict-of-interest statement: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items.

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ORIGINAL ARTICLE

Observational Study

Prevalence of vitamin D deficiency in exclusively breastfed infants at Charoenkrung Pracharak Hospital

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Abstract

BACKGROUND

Vitamin D deficiency is a common problem in exclusively breastfed infants, with supplementation recommended by various international medical organizations. However, in Thailand, no advice for routine vitamin D supplementation is available. Thus, this study investigated the prevalence of vitamin D deficiency and its associated factors in exclusively breastfed infants in Bangkok, Thailand.

AIM

To investigated the prevalence of vitamin D deficiency and its associated factors in exclusively breastfed infants in Bangkok, Thailand.

METHODS

This descriptive observational cross-sectional study assessed 109 4-month-old infants at Charoenkrung Pracharak Hospital from May 2020 to April 2021. The 25-OH vitamin D level of the infants was measured using an electrochemiluminescence binding assay. Vitamin D deficiency was defined as 25-OH level < 20 ng/mL, with vitamin D insufficiency 20-30 ng/mL. The sun index and maternal vitamin D supplementation data were collected and analyzed using the independent *t*-test, univariate logistic regression, and multivariate logistic regression to identify the associated factors.

RESULTS

The prevalences of vitamin D deficiency and vitamin D insufficiency were 35.78% and 33.03%, respectively with mean serum 25-OH vitamin D levels in these two groups 14.37 ± 3.36 and 24.44 ± 3.29 ng/mL. Multivariate logistic regression showed that the main factors associated with vitamin D status were maternal vitamin D supplementation and birth weight, with crude odds ratios 0.26 (0.08–0.82) and 0.08 (0.01–0.45), respectively. The sun index showed no correlation with the 25-OH vitamin D level in exclusively breastfed infants (r = −0.002, P =

0.984).

CONCLUSION
Two-thirds of healthy exclusively breastfed infants had hypovitaminosis D. Vitamin D supplementation prevented this condition and was recommended for both lactating women and their babies.

Key Words: Breastfeeding; Sunlight; Vitamin D deficiency; Thailand

Core Tip: Vitamin D deficiency is a common problem in exclusively breastfed infants, so vitamin D supplementation was recommended by various international organizations but it has not been established in Thailand because of the limitation of study. This study showed high prevalence of vitamin D deficiency at 35.78% in exclusively breastfed infants at Charoenkrung Pracharak Hospital and its main associated factor was maternal vitamin D supplementation while the sun index in infants showed no correlation with the 25-OH vitamin D level. So, routine Vitamin D supplementation was recommended for both lactating women and their babies to prevent vitamin D deficiency.

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INTRODUCTION

Vitamin D3 is produced in human skin, whereas vitamin D2 is produced in plants and fungi from ergosterol[1]. This is subsequently metabolized by 25-hydroxylase in the liver and converted to 25-OH vitamin D, its storage form. 25-OH vitamin D is then catalyzed by 1-hydroxylase in the kidneys and converted to its hormonally active form, 1,25-dihydroxyvitamin D[2]. 25-OH vitamin D and other metabolites play a crucial role in maintaining calcium and phosphate homeostasis. Active vitamin D stimulates calcium absorption in the intestines and directly influences bones and growth plates as well as extraskeletal organs[2,3]. Vitamin D receptors and vitamin D metabolic enzymes are broadly expressed in the body. Several studies have shown that vitamin D has an effect on various organs and the immune system. Vitamin D deficiency causes osteopenia and rickets in infants and is associated with nonskeletal diseases such as allergies and autoimmune diseases, diabetes, cardiovascular disease, and cancer[3-5]. Lack of exposure to ultraviolet light is a risk factor for vitamin D deficiency, which is defined as 25-OH vitamin D levels of < 20 ng/mL[4]. However, several sunshine-rich countries, including Thailand, continue to report vitamin D deficiency cases despite the presence of abundant sunshine. Inadequate consumption of dairy products and low calcium intake are also causes of vitamin D deficiency[5]. Therefore, adequate ultraviolet light exposure and consumption of vitamin D-rich foods are crucial factors in maintaining normal vitamin D levels. Rickets, the most prevalent disease resulting from vitamin D deficiency, frequently occurs in children less than 2 years old. In 3-month-old infants, vitamin D is supplied through transplacental crossing, with the peak prevalence of rickets occurring in children aged 3–18 months[5,6]. Exclusively breastfed infants develop vitamin D deficiency rickets owing to inadequate sun exposure and low vitamin D content in breast milk (approximately 20 IU/Liter). The American Academy of Pediatrics has recommended that all breastfed infants should also be supplemented with 400 IU/d of vitamin D[5,7].

In Thailand, routine vitamin D supplementation guidelines for lactating mothers or infants have not been established, while in South East Asia, the amount of sun exposure required to maintain normal vitamin D levels in infants has not been quantified. A literature search recommended that infants wearing only a diaper should be exposed to sunlight for up to 30 min per week, while those fully clothed with no hat should be exposed to sunlight for up to 2 h per week[7].

This study investigated the prevalence of vitamin D deficiency and its associated factors in exclusively breastfed infants in Bangkok.

MATERIALS AND METHODS

This descriptive observational cross-sectional study was conducted at Charoenkrung Pracharak Hospital, a tertiary and breastfeeding-friendly hospital in Bangkok, from May 2020 to April 2021. During this period, 510 4-month-old infants visited the well-baby clinic in Charoenkrung Pracharak Hospital. The study was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (S008h/63) on April 20, 2020.

The sample size of the study was calculated using the equation below: The expected proportion was estimated at 93.3% to give the largest sample size with a 5% degree of precision. The alpha error was accepted at 0.05, and the calculated

sample size was 97, with 109 chosen after allowing for a 10% dropout rate.

A 10% value of the degree of precision was chosen due to financial and time limitations.

Four-month-old infants who were exclusively breastfed at the well-baby clinic in Charoenkrung Pracharak Hospital were included in the study. All the infants were born at 37-42 wk of gestation, weighed 2500-4000 g, and were of Thai descent. Infants who had received vitamin D supplementation and medications, had started using complementary foods, had been previously admitted to a neonatal intensive care unit, or those with other medical conditions (renal, gastrointestinal, hepatobiliary, genetic, and dermatological conditions) were excluded from the study.

After obtaining written informed consent from the mothers, demographic data including gestational age, birth weight, and length were recorded. Maternal demographic data, body mass index (BMI), education level, status of vitamin D supplementation (defined as the mother taking a Obimin-AZ tablet containing 400 IU of vitamin D once daily after delivery until the date of enrollment), and family income were recorded. Vitamin D levels in the breast milk were not measured. The sun index record form was created to calculate the sun index, using hours of sun exposure per week and percentage body surface area exposed to sunlight (full sun is not needed). Directions describing seven consecutive days of sun exposure were provided to the mothers, and the accuracy of the sun index record forms completed by the enrolled mother–infant pairs was validated. All the mothers completed the sun index record form correctly without any errors, ensuring that the case record forms were valid. The completed sun index record forms were collected, and the sun index was calculated using the following formula: Sun index = hours of sun exposure per week × fraction of body surface area exposed to sunlight.

Blood samples were drawn once *via* venipuncture from the infants to measure the 25-OH vitamin D levels on the day of visiting the well-baby clinic. Other blood chemistry measurements were not assessed. The 25-OH vitamin D serum levels were measured using an electrochemiluminescence binding assay (cobas®; CE number 05894913190). Vitamin D deficiency was defined as 25-OH vitamin D levels of < 20 ng/mL, with vitamin D insufficiency defined as 25-OH vitamin D levels between 20 and 30 ng/mL, and vitamin D sufficiency defined as 25-OH vitamin D levels of ≥ 30 ng/mL. Hypovitaminosis D was defined as the combination of vitamin D deficiency and vitamin D insufficiency[4]. The data were computerized and analyzed using SPSS version 26 (SPSS, IBM Corp., Armonk, NY, United States). Normally distributed data were presented as means ± standard deviation. A univariate analysis was performed to compare and define the differences between the groups, while associations between the significant factors for vitamin D deficiency and other factors including sun index and vitamin D supplementation in mothers were analyzed using multivariate regression. The Chi-square test was used for categorical data, with analysis of variance for quantitative normally distributed data, and the Kruskal-Wallis test for non-normally distributed data. The *P* value cutoff was set at < 0.05.

RESULTS

The flow diagram (Figure 1) shows demographic data for the 109 mother-infant pairs enrolled in the study. Incomplete case record forms were identified in five mothers and these were removed, with the remaining 104 maternal case record forms analyzed. Blood samples were drawn from 109 infants to measure 25-OH vitamin D levels, and a follow-up was conducted to collect the sun index record forms for analysis.

As shown in Table 1, the prevalences of vitamin D deficiency and insufficiency were 35.78% and 33.03%, respectively. The infants were categorized into three groups: Vitamin D deficiency (n = 39), vitamin D insufficiency (n = 36), and vitamin D sufficiency (n = 34). Among infants in the vitamin D deficiency group, 27 were male, and their mean weight and length were 6,956.92 ± 762.92 g and 62.28 ± 1.81 cm, respectively. Neonatal data showed that mean gestational age, birth weight, and birth length were 38.62 ± 1.09 wk, 3,110.51 ± 338.45 g, and 51.38 ± 2.09 cm, respectively. The demographic data of the infants were not significantly different between the groups, except that the mean birth weight of infants in the vitamin D insufficiency group was slightly lower than for infants in the other two groups (P = 0.008).

Infants in the vitamin D deficiency group were studied in the summer, monsoon, and winter seasons, with 11 (28.20%), 15 (38.46%), and 13 (33.33%) showing vitamin D deficiency, respectively. The sun index score for the vitamin D deficiency group was 1.44-10.95 h/wk and slightly higher than the vitamin D insufficiency and sufficiency groups. For example, the sun index in the vitamin D sufficiency group was 1.70-9.04 h/week. The mean 25-OH vitamin D levels in the vitamin D deficiency, vitamin D insufficiency, and vitamin D sufficiency groups were 14.37 ± 3.36, 24.44 ± 3.29, and 40.33 ± 8.69 ng/mL, respectively.

The demographic data of mothers in the vitamin D deficiency group for mean age, weight, and height were 29.56 ± 7.18 years, 60.03 ± 11.61 kg, and 158.24 ± 5.73 cm, respectively. The mean BMI among mothers in the vitamin D deficiency group was 23.95 ± 4.4, with nine mothers classified as obese (23.07%). Maternal education level and vitamin D status were not significantly different between the groups (P = 0.678 and P = 0.709, respectively). Overall, 42 out of 104 mothers reported that they received Obimin-AZ, and no significant differences were observed between the groups.

Univariate logistic regression identified male sex and vitamin D supplementation as two factors that were significantly associated with vitamin D status (Table 2), with crude odds ratios (ORs) 2.52 [95% confidence interval (CI): 1.1-5.76] and 0.36 (95%CI: 0.15-0.85), respectively. No significant differences were recorded in sun index scores and birth weights between the groups, with crude ORs 1.12 (95%CI: 0.89-1.39) and 0.46 (95%CI: 0.15-1.4), respectively. Multiple logistic regression analysis revealed that birth weight and vitamin D supplementation in mothers were significantly associated with vitamin D status, with adjusted ORs 0.08 (95%CI: 0.01–0.45) and 0.26 (95%CI 0.08–0.82), respectively. Vitamin D levels were not significantly correlated with the sun index [Pearson R-square = −0.002 (P = 0.984)] (Figure 2).

Table 1 Demographic data of infants and mothers (*df* = 2), *n* (%)

Parametric	Vitamin D deficiency (*n* = 39)	Vitamin D insufficiency (*n* = 36)	Vitamin D sufficiency (*n* = 34)	*P* value
Prevalence, %	35.78	33.03	31.19	0.326
Season of study				0.523
Summer	11 (28.20)	16 (44.44)	16 (47.05)	
Monsoon	15 (38.46)	10 (27.78)	12 (35.29)	
Winter	13 (33.33)	10 (27.78)	6 (17.65)	
Sun index (median – range)	**1.7-9.04**	**1.37-5.47**	**1.44-10.95**	0.053
Demographic data of infants				
Gender				0.053
Male	27 (69.2)	19 (52.8)	14 (41.2)	
Female	12 (30.8)	17 (47.2)	20 (58.8)	
Weight (g)	6956.92 ± 762.92	6880.28 ± 1036.99	6657.53 ± 540.74	0.008
Length (cm)	62.28 ± 1.81	62.03 ± 2.24	61.15 ± 2	0.105
Gestational age (wk)	38.62 ± 1.09	38.64 ± 1.1	38.68 ± 1	0.930
Birth weight (g)	3110.51 ± 338.45	3093.92 ± 345.04	3332.5 ± 362.05	0.008
Birth length (cm)	51.38 ± 2.09	51.33 ± 1.67	51.35 ± 2.04	0.105
Demographic data of mothers				
Age (yr)	29.56 ± 7.18	27.69 ± 6.6	29.10 ± 6.9	0.496
Age intervals				0.754
10-19 (yr)	5 (12.8)	4 (11.1)	3 (8.8)	
19-35 (yr)	26 (66.7)	26 (72.2)	21 (61.8)	
≥ 35 (yr)	8 (20.5)	6 (16.7)	10 (29.4)	
Body weight (kg)	60.03 ± 11.61	57.39 ± 9.27	57.39 ± 9.25	0.496
Height (cm)	158.24 ± 5.73	158.83 ± 5.39	160.54 ± 6.25	0.274
BMI (kg/m^2)	23.95 ± 4.4	22.76 ± 3.54	22.48 ± 3.87	0.251
Obesity	9 (26.5)	8 (22.2)	10 (25.6)	0.908
Education				0.678
Elementary school	3 (8.8)	2 (5.6)	3 (7.9)	
Junior High School	10 (29.4)	6 (16.7)	6 (15.8)	
High School	13 (38.2)	16 (44.4)	14 (36.8)	
Bachelor degree or above	8 (23.5)	12 (33.3)	15 (39.5)	
Family income (Dollars per month)	973.09 ± 719.64	890.97 ± 511.1	1061.92 ± 1445.85	0.777
Poverty	17 (43.58)	13 (36.11)	16 (47.05)	0.635
Not poverty	22 (56.41)	23 (63.88)	18 (52.94)	
Vitamin D supplement				0.001
No	29 (74.35)	23 (63.88)	10 (32.30)	
Yes	10 (25.64)	11 (30)	21 (67.70)	

Poverty is defined as having a monthly income of less than 600 dollars. BMI: Body mass index.

Table 2 Factors associated with hypovitaminosis D (vitamin D deficiency and vitamin D insufficiency) by univariate logistic regression and multivariate analysis (*df* = 1)

Univariate analysis	Hypovitaminosis D	Sufficiency	*P* value	Crude OR (95%CI)
Parametric				
Infants				
Male, *n*	27	33	0.028	2.52 (1.1-5.76)
Birth weight (kg)	3.11 ± 0.34	3.21 ± 0.37	0.170	0.46 (0.15-1.4)
Sun index (h/wk)	2.28 ± 2.14	1.84 ± 1.83	0.355	1.12 (0.89-1.39)
Mothers				
Vitamin D supplement, *n*	10	32	0.020	0.36 (0.15-0.85)
Multivariate analysis				
Parametric				
Infants				
Male, *n*			0.511	1.46 (0.47-4.49)
Birth weight (kg)			0.004	0.08 (0.01-0.45)
Mothers				
Vitamin D supplement, *n*			0.109	1.28 (0.95-1.73)

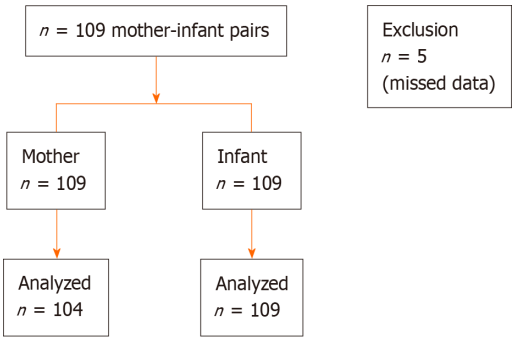

Figure 1 Flow diagram.

DISCUSSION

A high prevalence of hypovitaminosis D was recorded in 4-month-old infants whose vitamin D status was slightly confounded by transplacental vitamin D. An age of 2 months is generally considered appropriate for investigating vitamin D levels in infants as they are no longer dependent on their mothers for vitamin D supply[8]. In this study, vitamin D intake from complementary foods did not interfere with the analyses because the infants were exclusively breastfed. We found that two-thirds of healthy exclusively breastfed infants had hypovitaminosis D, concurring with a previous study conducted in Thailand, which reported the incidence of 25-OH vitamin D levels of < 20 ng/mL at 56.8% [9]. Our findings were also consistent with other studies, which found a high prevalence of vitamin D deficiency and insufficiency among exclusively breastfed infants in high-latitude and sunshine-rich countries[9-14]. Notably, the prevalence of vitamin D deficiency reported in this study in Thailand was lower than reported in India (83%)[12], Korea (90.4%)[15], Brazil (80.5%)[11], and the United Arab Emirates (82%)[16]. These differences can be attributed to multiple factors including the latitude of the country, air pollution, season, infant age, and study design. Numerous studies from different countries have reported that breast milk has low vitamin D content[13,17], with several international organizations, including the American Academy of Pediatrics, recommending routine vitamin D supplementation in exclusively breastfed infants[18]. A crucial source of vitamin D in humans is the ultraviolet radiation-dependent cutaneous synthesis of cholecalciferol[19], with the positive effect of sun exposure on vitamin D status previously described[20]. Several studies have shown a lower prevalence of vitamin D deficiency in summer, along with relatively large seasonal fluctuations in circulating vitamin D levels[19-21]. This study is the first report on sun index values in infants in Thailand. Sun exposure can be represented by the sun index, which is calculated from the exposed body surface area and the duration of sun exposure in hours per week. Sun index was expected to be a protective factor; however, the average sun index was low in all participants, and not significantly associated with vitamin D level (r = −0.002, P = 0.984). Sun index was also inversely related to vitamin D status. Low sun exposure was reported in infants living in Bangkok because parents

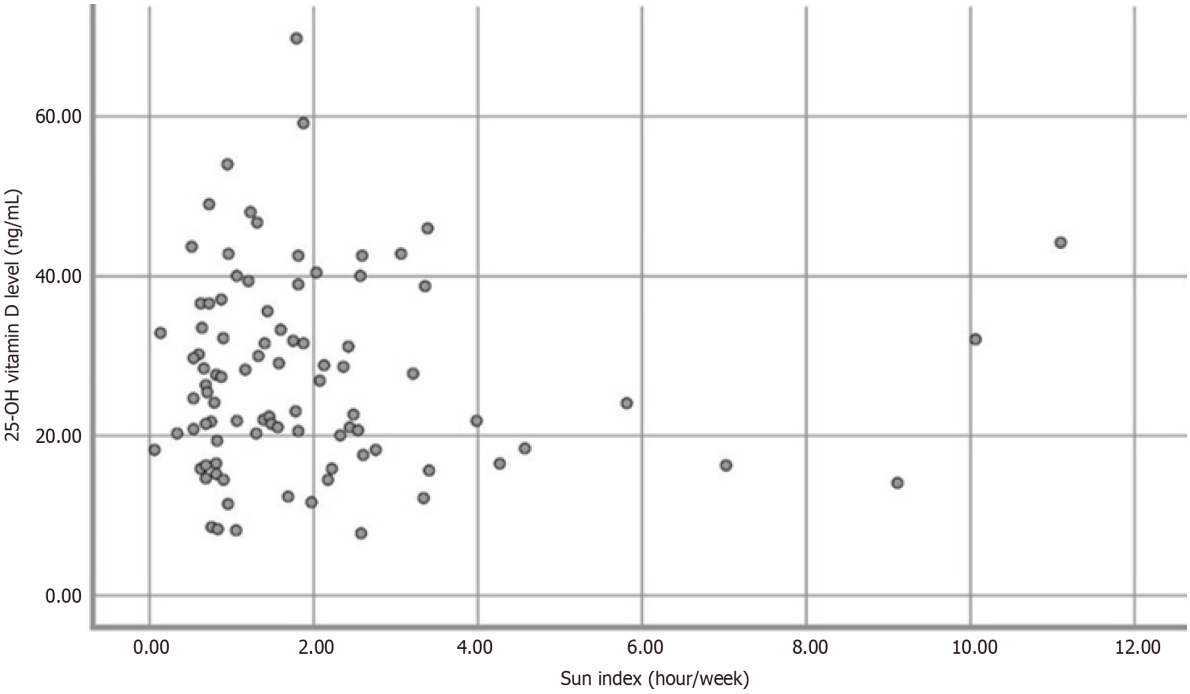

Figure 2 Association of the sun index and 25-OH vitamin D level.

avoided taking their children outside due to air pollution. Our study subjects were 4-month-old infants who spent most of their daytime indoors. Some parents believed that their babies were too young to be exposed to sunlight, and this belief resulted in inadequate sun exposure, which is the major natural source of vitamin D production. Our results showed that seasons were not associated with vitamin D status. Approximately 40% of the infants in the vitamin D deficiency group were studied during the summer season, and their characteristics were similar to those examined during the winter and monsoon seasons. Despite the presence of abundant sunshine throughout the year in South East Asian countries, including Thailand, various studies showed that more than 30% of children and adolescents had vitamin D insufficiency [22]. By contrast, an Indonesian study reported that although Indonesia is located in similar latitudes to other South East Asian countries, the prevalence of vitamin D deficiency was only 16.7%. The authors described a routine cultural practice among Indonesian mothers that involved exposing their newborns (without any cover) directly to the morning sun. This practice may have contributed to cutaneous vitamin D production in these infants[23]. Lactating mothers have increased nutritional demands, including vitamin D delivered from breast milk to their infants. As previously mentioned, vitamin D content in breast milk is low, and lactating women with vitamin D deficiency are more likely to have deficient vitamin D levels in breast milk[24]. Therefore, these mothers should receive supplemental vitamin D to prevent vitamin D deficiency in their infants[25]. Several studies reported a significant correlation between maternal and cord blood vitamin D levels[6,10,26], with maternal vitamin D levels correlating with vitamin D levels in breast milk[17]. Our findings were similar to previous studies[27,28]. In this study, mothers received vitamin D supplementation through Obimin-AZ tablets, which contained 400 IU of vitamin D. An amount of 400 IU/day of vitamin D showed a more protective effect against vitamin D deficiency in mothers than 6,400 IU/d of vitamin D[24]. Despite the lower dosage of vitamin D supplementation in mothers in this study, the occurrence of hypovitaminosis D decreased in infants. Therefore, efforts should be made to identify an optimal dosage of vitamin D supplementation for lactating women.

Female infants showed lower mean serum 25-OH vitamin D levels than male infants[15]. In this study, male sex was found to be associated with poor vitamin D status compared with female sex. However, sex does not influence vitamin D metabolism, and male sex cannot be a clinically significant factor. The birth weight of infants in the vitamin D insufficiency group was lower than in the vitamin D deficiency and vitamin D sufficiency groups and was also associated with hypovitaminosis D. Several studies have shown a correlation between low birth weight and vitamin D deficiency, especially in preterm infants[29-31]. Our study showed that the lowest mean birth weight was reported in the vitamin D insufficiency group. Therefore, other factors should be examined in future studies. We believe that this is the first study to determine the prevalence of vitamin D deficiency in exclusively breastfed infants in Thailand without the effects of transplacental vitamin D or vitamin D from complementary foods. This is also the first study in Thailand to evaluate the sun index, which represents sun exposure. Low vitamin D content in breast milk and inadequate sun exposure in infants are significant risk factors for hypovitaminosis D. This study presented new data from Thailand that can be used to develop guidelines for mothers of infants. Supplementation of vitamin D with a dosage of at least 400 IU/d for infants since birth has also been recommended by the American Academy of Pediatrics. Our findings concur with the Institute of Medicine that vitamin D supplementation should be provided for lactating women[4,32].

This study had certain limitations. First, the vitamin D status of mothers and vitamin D levels in their milk were not measured. Therefore, vitamin D deficiency in mothers was not identified and the correlation between serum vitamin D levels and breast milk was not evaluated. Further studies should explore the association between these factors. Second,

the sun index record form was difficult to understand and complete correctly for some mothers, resulting in incomplete reports with missing data. Following enrollment, the mothers were made aware that higher sun exposure resulted in increased vitamin D levels. Due to this knowledge and resulting behavioral changes, the sun index results could be artificially high, leading to bias. Additional studies, including a pilot for the sun index record form, should be conducted. Third, all the infants included in this study lived in Bangkok as an urban location, and the study was conducted in only one hospital. Therefore, the results cannot be considered representative of all Thai babies. Moreover, the air pollution in Bangkok is worse than in other provinces. And parents tend to avoid outside sun exposure for their children. A volunteer bias may also be present as a result of the sample population involved in the study, further limiting the generalizability of the results. Further studies that consider these limitations should be conducted to establish national guidelines.

CONCLUSION

Our results showed a high prevalence of vitamin D deficiency in exclusively breastfed infants. A 400 IU daily supplement of vitamin D in mothers was found to ameliorate vitamin D deficiency in infants. Sun exposure in infants was inadequate to maintain vitamin D levels and was not correlated with vitamin D status. Thai medical organizations should establish guidelines for routine vitamin D supplementation in exclusively breastfed infants.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is a common problem in exclusively breastfed infants. Therefore, vitamin D supplementation in infants is suggested by various international medical organizations. Due to limited available data in Thailand, there is no local recommendation for routine vitamin D supplementation. Thus, this study investigated the prevalence of vitamin D deficiency and its associated factors in exclusively breastfed infants.

Research motivation

Due to the limited number of studies on this issue in Thailand, routine vitamin D supplementation for lactating mothers or infants has not been established. In South East Asia, the amount of sun exposure required to maintain normal vitamin D levels in infants remains unknown. Few researchers have recommended that infants wearing only a diaper should be exposed to sunlight for up to 30 min per week and those with full clothes and no hat should be exposed to sunlight for 2 h per week. In addition, Charoenkrung Pracharak Hospital is a tertiary hospital which is a famous friendly breastfeeding hospital in Thailand and has a high rate of delivery. How big of vitamin D deficiency is a valuable thing to figure out in order to set up a proper guideline.

Research objectives

This study aimed to investigate the prevalence of vitamin D deficiency and its associated factors in exclusively breastfed infants in Bangkok. This study could not represent the overall Thai baby because we did a study in Bangkok which is the capital city of Thailand. So, enrolling the participants from all provinces is needed to study in the future in order to make an accurate prevalence of vitamin D deficiency in exclusively breastfed infants in Thailand.

Research methods

This descriptive observational cross-sectional study assessed 109 4-month-old infants at Charoenkrung Pracharak Hospital from May 2020 to April 2021. The 25-OH vitamin D level of the infants was measured using an electrochemiluminescence binding assay. Vitamin D deficiency was defined as 25-OH level < 20 ng/mL, with vitamin D insufficiency 20-30 ng/mL. This study is the first to report on the sun index in infants in Thailand. Sun exposure is represented by the sun index, which is calculated from the exposed body surface area and the duration of exposure in hours per week. It was expected to be a protective factor. Sun index and maternal vitamin D supplementation data were collected and analyzed using the inde-pendent t-test, univariate logistic regression, and multivariate logistic regression to identify the associated factors.

Research results

This study shows the high prevalence of vitamin D deficiency and vitamin D insufficiency (35.78% and 33.03%, respectively). The mean serum 25-OH vitamin D levels in both groups were 14.37 ± 3.36 and 24.44 ± 3.29 ng/mL, respectively. The associated factors were maternal vitamin D supplementation and birth weight. supplementation which were analyzed with multivariate logistic regression and showed crude odds ratios were 0.26 (0.08–0.82) and 0.08 (0.01–0.45), respectively. Sun index did not correlate with the 25-OH vitamin D level in the exclusively breastfed infants (r = −0.002, P = 0.984). In addition, the sun index record form should be revised and recorded for at least 1 wk before collecting the blood to prevent the bias.

Research conclusions

Our results showed a high prevalence of vitamin D deficiency in exclusively breastfed infants which is the risk factor of

vitamin D deficiency. Daily supplement of vitamin D in mothers was found to ameliorate vitamin D deficiency in infants while sun exposure in infants was inadequate to maintain vitamin D levels and was not correlated with vitamin D status. Although Thailand is rich in sunshine, the prevalence of vitamin D deficiency is high. Therefore, Thai medical organizations should establish guidelines for routine vitamin D supplementation in exclusively breastfed infants.

Research perspectives

The correlation of maternal vitamin D level, sun index, the dose of vitamin D supplement and vitamin level in exclusively breastfed infants should be evaluated in order to figure out the associated factors with vitamin D levels in infants. In addition, the vitamin D doses should be explored to set up proper vitamin D doses for prevention and treatment in exclusively breastfed infants who are diagnosed with vitamin D deficiency.

FOOTNOTES

Author contributions: Suksantilerd S perform the research, analyzed and wrote the manuscript; Rungrojjananon N and Thawatchai R collected and analyzed data.

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ORIGINAL ARTICLE

Observational Study

Effect of nutrition-related infodemics and social media on maternal experience: A nationwide survey in a low/middle income country

Marwa M Zein, Noha Arafa, Mortada H F El-Shabrawi, Nehal Mohammed El-Koofy

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Abstract

BACKGROUND

Undernutrition is a crucial cause of morbidity and mortality among children in low- or middle-income countries (LMICs). A better understanding of maternal general healthy nutrition knowledge, as well as misbeliefs, is highly essential, especially in such settings. In the current era of infodemics, it is very strenuous for mothers to select not only the right source for maternal nutrition information but the correct information as well.

AIM

To assess maternal healthy nutritional knowledge and nutrition-related misbeliefs and misinformation in an LMIC, and to determine the sources of such information and their assessment methods.

METHODS

This cross-sectional analytical observational study enrolled 5148 randomly selected Egyptian mothers who had one or more children less than 15 years old. The data were collected through online questionnaire forms: One was for the general nutrition knowledge assessment, and the other was for the nutritional myth score. Sources of information and ways of evaluating internet sources using the Currency, Relevance, Authority, Accuracy, and Purpose test were additionally analyzed.

RESULTS

The mean general nutrition knowledge score was 29 ± 9, with a percent score of 70.8% ± 12.1% (total score: 41). The median myth score was 9 (interquartile range: 6, 12; total score: 18). The primary sources of nutrition knowledge for the enrolled mothers were social media platforms (55%). Half of the mothers managed information for currency and authority, except for considering the author's contact information. More than 60% regularly checked information for accuracy and purpose. The mothers with significant nutrition knowledge checked periodically for the author's contact information (P = 0.012). The nutrition myth score was significantly lower among mothers who periodically checked the evidence of the information (P = 0.016). Mothers dependent on their healthcare providers as the primary source of their general nutritional knowledge were less likely to hold myths by 13% (P = 0.044). However, using social media increased the likelihood of having myths among mothers by approximately 1.2 (P = 0.001).

CONCLUSION

Social media platforms were found to be the primary source of maternal nutrition information in the current era of infodemics. However, healthcare providers were the only source for decreasing the incidence of maternal myths among the surveyed mothers.

Key Words: Nutrition; Infodemics; Maternal knowledge; Myth; Low/middle income country

Core Tip: Undernutrition is one of the principal causes of morbidity and mortality in children in low- or middle-income countries. The evaluation of maternal nutrition knowledge scores is crucial to improving practice. The infodemic era has significantly impacted the changing sources of nutrition information and myths. Consequently, this study aimed to assess healthy nutritional knowledge and nutrition-related misinformation and misbeliefs among a significant sample of Egyptian mothers. In addition, other objectives included determining the sources of nutritional information and how those mothers manage the sources of nutritional-related knowledge.

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INTRODUCTION

Undernutrition is one of the salient causes of morbidity and mortality among children less than five years old in low- or middle-income countries (LMICs)[1]. Accordingly, proper and adequate nutrition is vital for normal child's growth and development and prevention of long-term morbidity and subsequent mortality. Different previously published data support the effectiveness of variable nutritional interventions in improving the nutritional status of children and reducing mortality[2,3].

Mothers are the primary care providers for their children in all household affairs, especially nutrition[4]. Therefore, the level of maternal general nutritional knowledge usually impacts their nutrition behavior and practice[5]. Consequently, evaluation of maternal health understanding is crucial to filling the gap in training. This will help identify the most deficient points in this community's upcoming nutrition education programs. In addition to parental nutrition knowledge, nutrition myth is another essential factor previously reported in the literature as a determinant factor affecting their feeding style[6].

The phenomenon of infodemics refers to the abundant and widespread dissemination of information, whether accurate or not, through different media platforms, including mass media, social media, and online forums[7]. It can be challenging for mothers to select the correct information from the flow of sources. Different sources of nutrition education are available in this current era of infodemics, such as healthcare providers, family members, mass media, and social media. The sources of nutrition education, with the advent of internet technology and smartphones, have become much more diverse[8]. Despite the fact that this technology facilitates the delivery of information, acquiring the right information at the right time in the appropriate form is of greater importance[9].

To the researchers' knowledge, this is the first published study from Egypt evaluating this problem despite its significance in this LMIC.

This study's main objective was to assess healthy nutritional knowledge and nutrition-related misinformation and misbeliefs among a large sample of Egyptian mothers. In addition, this study aimed to determine the sources of nutritional information and how those mothers manage the sources of nutritional-related knowledge.

MATERIALS AND METHODS

Study design

A cross-sectional analytical observational study.

Sample type

A convenient sample (easy access).

Sample size and sampling technique

A sample size of 5100 was calculated using a formula for survey sample size calculation[10]. Here's a breakdown: n represents the sample size; z signifies the z-score, which is approximately ± 2.58 for a 99% confidence interval (CI); p stands for the degree of variability (proportion of outcome). In this case, 81.2% of mothers were found to have a high to moderate level of nutritional knowledge in a study conducted in Bangladesh[11]; e denotes the level of precision, set at 1%; N refers to the study population size, which mainly consists of females, likely mothers of children under 15, constituting 32% of the Egyptian population aged 15 to 60 years, totaling 32 million[12].

Study population

The study population consisted of Egyptian mothers with one or more children (age of at least one child under 15 years). The participants were recruited from many governorates all over Egypt: The upper Egypt governorates included Giza, Fayoum, Menia, and Assiut; the lower Egypt governorates included Dakahlia, Gharbia, and Kafr El-Sheikh; Cairo and Alexandria.

Data collection tool

A pre-tested e-questionnaire was used to collect data from the study participants. It included four sections: (1) Socio-demographic characteristics: Maternal, paternal, and siblings' age in years; sex of siblings; maternal and paternal education and occupation; residence; number of home bedrooms; and number of family members; (2) General nutrition knowledge questionnaire (GNKQ): It contains 41 questions that were derived from the validated general health questionnaire[13]. The questions of the original questionnaire were adapted to the Egyptian situation. Reliability analysis was conducted on the GNKQ, in which Cronbach's alpha was 0.73. Correct answers were coded with 1 and incorrect answers with 0. The total GNKQ score was 41. The percent score of the GNKQ was calculated, and the participants were categorized according to their responses into two groups: High to moderate knowledge (GNKQ percent score ≤ 70%) and low knowledge (GNKQ percent score > 70%)[14]; (3) Nutritional myths (misin-formation): 18 misinformation questions were derived from 45 pediatric nutrition consultants based on their clinical experience. The questions had five-level responses (Likert scale): Strongly disagree, disagree, neutral, agree, and strongly agree. The strongly agree, agree, and neutral levels were coded as 0, and disagree and strongly disagree responses were coded as 1. (N.B., the scales of the 2nd and 9th questions were reverted). Cronbach's alpha was 0.76 for the 18-item myth questionnaire. The respondents were categorized into two groups: Holding myths (below median score [≤ 9]) and not holding myths (above median score [> 9])[15]; and (4) The source of information and methods to evaluate internet sources were assessed using the Currency, Relevance, Authority, Accuracy, and Purpose test[16]. Two language experts translated the questions into Arabic and back-translated to English by another two independent language experts.

Data collection tool accuracy, validity, and reliability: A pre-test was performed to confirm the content validity of the questions and assure the validity of the results. In order to eliminate common mistakes and unclear wording and to ensure that the questions were understandable, a panel of 50 volunteers from various backgrounds reviewed the question construction. The final version of the questionnaire was updated to include the expert panel's comments. The questionnaires were distributed to the participants following this pilot study (the pilot results were not included in the final results). Reliability internal test (Cronbach's) was done for the 18-item questionnaire (nutrition misinformation), where Cronbach's alpha was 0.76 (high reliability).

Data collection technique: A Google form was created, and participants were invited through personal communication (*via* Facebook groups, WhatsApp contacts, and emails) with the researchers to complete and submit the form.

Statistical analysis: All the collected data were revised for completeness and logical consistency. The data were extracted from the Google form into the Microsoft Office Excel Software Program, 2019, and then analyzed in the Statistical Package of Social Science Software program, version 26 (SPSS, Chicago, IL, United States) for statistical analyses.

Quantitative variables are described as the mean ± SD, median, minimum, and maximum and compared using an independent *t*-test and a Mann-Whitney *U*-test for two groups, with the level of statistical significance set at $P < 0.05$. Qualitative variables are described as frequencies and percentages. Moreover, qualitative variables were compared using the Chi-square and Fisher exact tests, with the level of statistical significance set at $P < 0.05$. A binary logistic regression model was used to determine which source of knowledge could predict the likelihood of holding myths and be more knowledgeable in nutrition.

Ethical considerations

The study protocol was approved by the scientific committee of the Public Health and Community Medicine Department, Faculty of Medicine, Cairo University. It was approved by the International Ethical Committee at the Faculty of Medicine,

Cairo University (N 318-2023). Written informed consent was obtained from all study participants after thoroughly explaining the study's aim and the importance of the online form before data collection. Only those who agreed were included, and those who refused were excluded from the study by submitting an empty form after answering "Not willing to participate." All procedures for data collection were treated with confidentiality according to the Helsinki Declarations of Biomedical Ethics. Participants were informed that this was an anonymous survey and participation was voluntary. The assessment did not involve any invasive procedures or induce any change in dietary patterns.

RESULTS

The response rate for the online form was 99.4%. There were 5148 responses from mothers with one or more children aged less than 15 years. The sociodemographic background information was collected and is illustrated in Table 1. It was found that more than half of the mothers (56.9%) and fathers (52.5%) were aged from 30 to 40 years; extreme age was found in 2.2% of mothers and 0.5% of fathers aged less than 20 years; 1.6% of mothers and 5.7% of fathers aged more than 50 years. Mothers and fathers had higher university grades at 59.1% and 65.1%, respectively. However, the number of mothers and fathers who could only read and write was 64 and 59, representing 1.2% and 1.1%, respectively. The number of working mothers was 3321 (64.5%), and 96.3% (5061) of fathers were working. Most families were from urban areas (81.6%) and had a house crowding index of two or less (94.8%). Most mothers had fewer than five children; 23.2%, 43.7%, 24.9%, and 6.5% of mothers had one, two, three, or four children, respectively. The questions were asked about the gender and age of the children (from one child to seven children). Their sex distribution was almost the same; 1–5 year age was more evident with the 2nd, 3rd, 4th, 5th, and 6th child (Figure 1). The total general nutrition knowledge score was 41. It was found that the mean available nutrition knowledge score was 29 ± 9, with a percent score of 70.8% ± 12.1%. The median score was 27 (interquartile range [IQR]: 27, 33), with a percent score of 73.2% (IQR: 65.9%, 80.5%). The nutrition myth question score was 18. The mean score was 9 ± 4, and the mean myth percent score was 50.9% ± 23.7%. The median myth score was 9 (IQR: 6, 12), and the median myth percent score was 50% (IQR: 33.3%, 66.7%).

Figure 2 shows the percentage of mothers holding nutrition myths. As an example, it was found that 37% of mothers agreed that fish and milk should be avoided if the child is suffering from fever. Only 12% of mothers agreed that using candy to reward a child was a good idea.

The participants were categorized according to their responses to the GNKQ into the low knowledge group (≤ 70% GNKQ percent score) and the moderate to high knowledge group (> 70% GNKQ percent score). When comparing those groups based on their socio-demographic backgrounds, it was found that there was no statistical difference between the two groups regarding the socio-demographic backgrounds of the mothers and their families.

In the comparison between the mothers who held myths (with a median score of less than 9) and those who did not (with a median score of 9 or more) by their socioeconomic background, it was detected that there was no statistically significant difference except for maternal and paternal education and maternal occupation (P = 0.003, 0.004, and 0.013, respectively), as illustrated in Figure 3.

The primary source of nutrition knowledge for the enrolled mothers was social media (55%) (Figure 4).

Table 2 portrays how the mothers used to collect health information, with around half managing information for currency and authority except for viewing the author's contact information. More than 60% regularly checked information for its accuracy and purpose.

Table 3 shows ways of managing information among participants with low, intermediate, and high nutritional knowledge and participants who held and did not hold dietary myths. It was discovered that mothers with significantly high nutrition knowledge regularly checked for the author's contact information (P = 0.012). The nutrition myth score was considerably lower among mothers who periodically checked the evidence of the information (P = 0.016).

The bivariate analysis demonstrated that the likelihood of holding myths was significantly higher among those who did not depend on their study at school and university and among mothers who relied on knowledge from friends, relatives, television, radio, newspapers, and magazines (P = 0.037, < 0.001, and = 0.027, respectively). The multivariate analysis identified individuals depending on television, radio, newspapers, and magazines, consulting with friends and relatives, and using social media as independent predictors of holding myths (odds ratio [OR] = 1.15, 1.3, and 1.22, respectively). In addition to that, the bivariate analysis illustrated that the likelihood of being more knowledgeable in nutrition was significantly higher among those who did not depend on television, radio, newspapers and magazines, friends, relatives, and social media (P < 0.001) and among mothers who relied on knowledge from health care providers and scientific websites (P = 0.05). Furthermore, the multivariate analysis identified that individuals not depending on learning from television, radio, newspapers, and magazines, consulting friends and relatives, and using social media were independent factors for being more knowledgeable in nutrition (OR = 1.1, 1.2, and 1.4, respectively) (Tables 4 and 5).

DISCUSSION

The current study focused on evaluating healthy maternal nutritional knowledge and exploring nutrition-related myths among the surveyed mothers in the setting of an LMIC (Egypt), where the per capita income ranged between 1136 and 4465 dollars, according to the World Bank, 2023[17]. In addition, it determined the sources of this nutritional information and the assessment of their sources.

Table 1 Sociodemographic characteristics of enrolled mothers and their families (*n* = 5148)

	N	Percent
Maternal age		
Less than 20 yr	115	2.2
20-yr	1313	25.5
30-yr	2931	56.9
40-yr	708	13.8
50-yr	81	1.6
Paternal age		
Less than 20 yr	27	0.5
20-yr	693	13.5
30-yr	2704	52.5
40-yr	1431	27.8
50-yr	293	5.7
Maternal education		
Read and write	64	1.2
Primary school	28	0.5
Preparatory school	91	1.8
Secondary school	441	8.6
University	3042	59.1
Postgraduate	1482	28.8
Paternal education		
Read and write	59	1.1
Primary school	18	0.3
Preparatory school	63	1.2
Secondary school	433	8.4
University	3353	65.1
Postgraduate	1222	23.7
Maternal occupation		
Working	3321	64.5
Not working	1827	35.5
Paternal occupation		
Working	5061	98.3
Not working	87	1.7
Residence		
Urban	4202	81.6
Rural	946	18.4
Crowding index		
≤ 2	4878	94.8
> 2	270	5.2

Table 2 Management of knowledge source, *n* (%)

Domain	Question	Always	Usually	Often	Sometimes	Never
Currency	When was the information published or posted?	1216 (23.6)	1360 (26.4)	1611 (31.3)	805 (15.6)	156 (3.0)
	Has the information been revised or updated?	1181 (22.9)	1423 (27.6)	1549 (30.1)	802 (15.6)	193 (3.7)
Authority	Who is the author/publisher/source/sponsor?	1453 (28.2)	1351 (26.2)	1243 (24.1)	876 (17.0)	225 (4.4)
	What are the author's qualifications to write on the topic?	1399 (27.2)	1357 (26.4)	1219 (23.7)	907 (17.6)	266 (5.2)
	Is there contact information such as a publisher or e-mail address?	512 (9.9)	763 (14.8)	1300 (25.3)	1786 (34.7)	787 (15.3)
Accuracy	Is the information supported by evidence?	1625 (31.6)	1562 (30.35)	1264 (24.6)	530 (10.3)	167 (3.2)
Purpose	What is the purpose of the information? To inform? Teach? Sell? Entertain? Persuade?	1617 (31.4)	1561 (30.3)	1143 (22.2)	621 (12.1)	206 (4.0)
	Does the point of view appear objective and impartial?	1260 (24.5)	1697 (33.0)	1282 (24.9)	677 (13.2)	232 (4.5)
	Are there political, ideological, cultural, religious, institutional, or personal biases?	1214 (23.6)	1317 (25.6)	1160 (22.5)	987 (19.25)	470 (9.1)

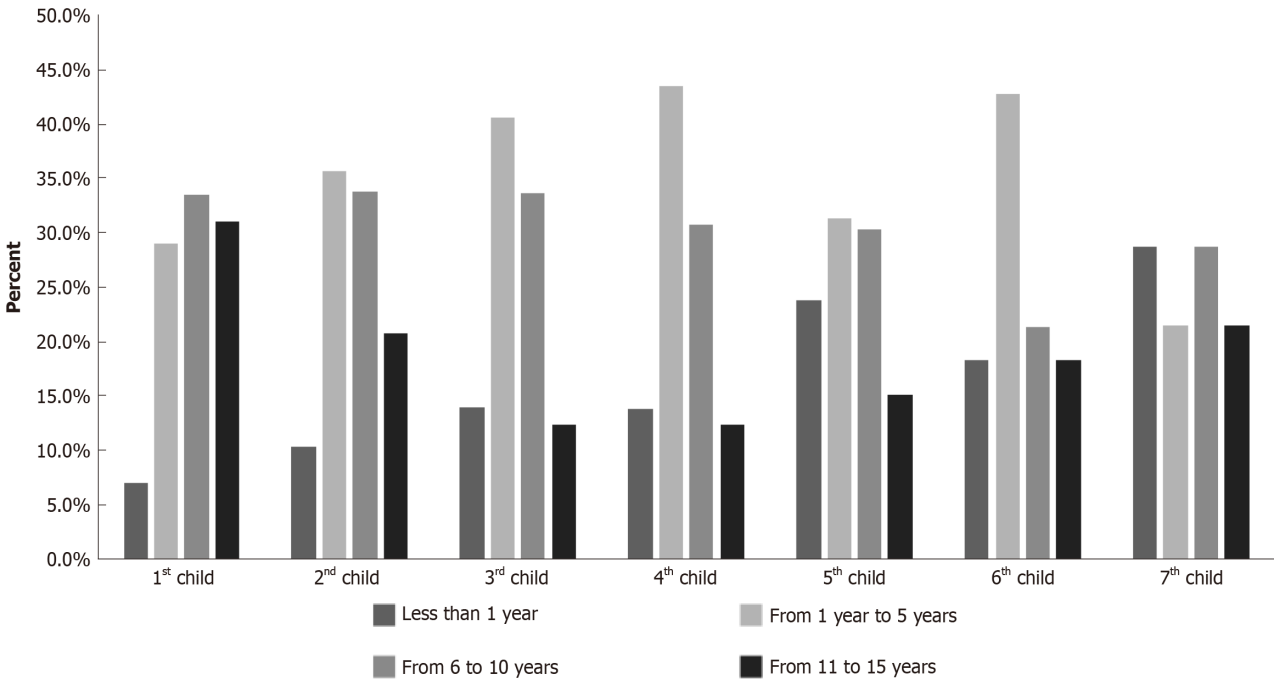


Figure 1 Percent distribution of age of children of enrolled mothers.

The response rate was 99.4% among the surveyed mothers, with 5148 maternal responses to the online survey. The present work reported that the median maternal nutritional knowledge score on the 13 identified questions was 27 out of 41 (73.2%). Accordingly, about half (57.6%) of the respondents had good nutritional knowledge.

The present study demonstrated that mothers referred to multiple sources of nutrition information. The primary source of nutrition information among the interviewed mothers was social media platforms (55%). At the same time, healthcare providers were the source for 22% of the surveyed mothers. Consistent with the results of this study, Griauzde *et al*[18] in 2020 found that 46.3% of recruited Hispanic mothers in Michigan (United States) used social media to explore feeding information for their children. However, other studies in Australia reported that mothers gained their knowledge mainly from their mothers and, to a lesser extent, from healthcare professionals[19,20].

Moreover, the parents' online health-seeking behavior about their children's general health was similarly reported in a systematic review by Kubb *et al*[21] in 2020. The current study reflects the significant impact of social platforms on disseminating nutrition-related information among mothers in the community. Additionally, it highlights the great need for the health care provider to make every visit a chance to provide education and revise already-known information

Table 3 Relationship between management of information sources and nutrition knowledge and myths

	Nutrition knowledge			Nutrition myths		
	Low nutrition knowledge	Intermediate to high nutrition knowledge	*P* value	Holding nutrition myths	Not holding nutrition myths	*P* value
Currency/When was the information published or posted?						
Always	417 (34.3)	799 (65.7)	0.852	528 (43.4)	688 (56.6)	0.441
Usually	447 (32.9)	913 (67.1)		581 (42.7)	779 (57.3)	
Often	559 (34.7)	1052 (65.3)		706 (43.8)	905 (56.2)	
Sometimes	278 (34.5)	527 (65.5)		377 (46.8)	428 (53.2)	
Never	55 (35.3)	101 (64.7)		70 (44.9)	86 (55.1)	
Currency/Has the information been revised or updated?						
Always	405 (34.3)	776 (65.7)	0.571	507 (42.9)	674 (57.1)	0.258
Usually	461 (32.4)	962 (67.6)		623 (43.8)	800 (56.2)	
Often	542 (35.0)	1007 (65.0)		664 (42.9)	885 (57.1)	
Sometimes	283 (35.3)	519 (64.7)		380 (47.4)	422 (52.6)	
Never	65 (33.7)	128 (66.3)		88 (45.6)	105 (54.4)	
Authority/Who is the author/publisher/source/sponsor?						
Always	495 (34.1)	958 (65.9)	0.988	636 (43.8)	817 (56.2)	0.947
Usually	459 (34.0)	892 (66.0)		605 (44.8)	746 (55.2)	
Often	427 (34.4)	816 (65.6)		541 (43.5)	702 (56.5)	
Sometimes	295 (33.7)	581 (66.3)		379 (43.3)	497 (56.7)	
Never	80 (35.6)	145 (64.4)		101 (44.9)	124 (55.1)	
Authority/What are the author's qualifications to write on the topic?						
Always	489 (35.0)	910 (65.0)	0.225	610 (43.6)	789 (56.4)	0.511
Usually	431 (31.8)	926 (68.2)		604 (44.5)	753 (55.5)	
Often	432 (35.4)	787 (64.6)		513 (42.1)	706 (57.9)	
Sometimes	306 (33.7)	601 (66.3)		413 (45.5)	494 (54.5)	
Never	98 (36.8)	168 (63.2)		122 (45.9)	144 (54.1)	
Authority/Is there contact information such as a publisher or e-mail address?						
Always	192 (37.5)	320 (62.5)	0.012[a]	229 (44.7)	283 (55.3)	0.786
Usually	250 (32.8)	513 (67.2)		323 (42.3)	440 (57.7)	
Often	474 (36.5)	826 (63.5)		575 (44.2)	725 (55.8)	
Sometimes	561 (31.4)	1225 (68.6)		778 (43.6)	1008 (56.4)	
Never	279 (35.5)	508 (64.5)		357 (45.4)	430 (54.6)	
Accuracy/Is the information supported by evidence?						
Always	553 (34.0)	1072 (66.0)	0.089	709 (43.6)	916 (56.4)	0.016
Usually	496 (31.8)	1066 (68.2)		664 (42.5)	898 (57.5)	
Often	457 (36.2)	807 (63.8)		542 (42.9)	722 (57.1)	
Sometimes	185 (34.9)	345 (65.1)		268 (50.6)	262 (49.4)	
Never	65 (38.9)	102 (61.1)		79 (47.3)	88 (52.7)	
Purpose/What is the purpose of the information? To inform? Teach? Sell? Entertain? Persuade?						
Always	562 (34.8)	1055 (65.2)	0.716	714 (44.2)	903 (55.8)	0.67
Usually	512 (32.8)	1049 (67.2)		669 (42.9)	892 (57.1)	

Often	400 (35.0)	743 (65.0)		498 (43.6)	645 (56.4)	
Sometimes	209 (33.7)	412 (66.3)		286 (46.1)	335 (53.9)	
Never	73 (35.4)	133 (64.6)		95 (46.1)	111 (53.9)	
Purpose/Does the point of view appear objective and impartial?						
Always	440 (34.9)	820 (65.1)	0.241	557 (44.2)	703 (55.8)	0.378
Usually	556 (32.8)	1141 (67.2)		755 (44.5)	942 (55.5)	
Often	448 (34.9)	834 (65.1)		534 (41.7)	748 (58.3)	
Sometimes	221 (32.6)	456 (67.4)		309 (45.6)	368 (54.4)	
Never	91 (39.2)	141 (60.8)		107 (46.1)	125 (53.9)	
Purpose/Are there political, ideological, cultural, religious, institutional, or personal biases?						
Always	433 (35.7)	781 (64.3)	0.559	533 (43.9)	681 (56.1)	0.343
Usually	428 (32.5)	889 (67.5)		565 (42.9)	752 (57.1)	
Often	400 (34.5)	760 (65.5)		492 (42.4)	668 (57.6)	
Sometimes	333 (33.7)	654 (66.3)		455 (46.1)	532 (53.9)	
Never	162 (34.5)	308 (65.5)		217 (46.2)	253 (53.8)	

[a]$P < 0.05$ is significant.

Table 4 Source of knowledge predictors of holding nutritional myths among mothers with children less than 15 years, *n* (%)

Predictor of holding nutritional myths		Holding nutrition myths	Not holding nutrition myths	Crude OR [95%CI][1]	Adjusted OR [95%CI][2]
Studying at school and university	No	1305 (45.2)	1581 (54.8)	0.95 [0.92-0.99]	0.95 [0.92-0.99]
	Yes	957 (42.3)	1305 (57.7)		
	***P* value**	0.037[a]			0.126
Television, radio, newspapers and magazines	No	1336 (42.7)	1792 (57.3)	0.93 [0.88-0.99]	0.93 [0.88-0.99]
	Yes	926 (45.8)	1094 (54.2)		
	***P* value**	0.027[a]			0.020[a]
Health care providers and scientific websites	No	1741 (43.6)	2255 (56.4)	1.03 [0.97-1.09]	1.03 [0.97-1.09]
	Yes	521 (45.2)	631 (54.8)		
	***P* value**	0.318			0.044[a]
Friends and relatives	No	1473 (42.4)	2002 (57.6)	0.89 [0.84-0.95]	0.89 [0.84-0.95]
	Yes	789 (47.2)	884 (52.8)		
	***P* value**	< 0.001[b]			< 0.001[b]
Social media	No	1051 (45.4)	1263 (54.6)	1.06 [0.99-1.13]	1.06 [0.99-1.13]
	Yes	1211 (42.7)	1623 (57.3)		
	***P* value**	0.053			0.001[a]

[a]$P < 0.05$ is significant.
[b]$P < 0.001$ is highly significant.
[1]Chi-square test.
[2]Binary logistic regression test.
OR: Odds ratio; CI: Confidence interval.

Table 5 Source of knowledge predictors of higher nutritional knowledge among mothers with children less than 15 years, *n* (%)

Predictor of good nutritional knowledge		Bad nutrition knowledge	Good nutrition knowledge	Crude OR [95%CI]	Adjusted OR [95%CI]
Studying at school and university	No	975 (33.8)	1911 (66.2)	1.02 [0.94, 1.04]	1.09 [0.98, 1.23]
	Yes	781 (34.5)	1481 (65.5)		
	***P* value**	0.577			0.126
Television, radio, newspapers and magazines	No	1132 (36.2)	1996 (63.8)	1.09 [1.05, 1.15]	1.15 [1.02, 1.29]
	Yes	624 (30.9)	1396 (69.1)		
	***P* value**	< 0.001[b]			0.02[a]
Health care providers and scientific websites	No	1403 (35.1)	2593 (64.4)	0.85 [0.76, 0.95]	0.87 [0.75, 0.99]
	Yes	353 (30.6)	799 (69.4)		
	***P* value**	0.005[a]			0.044[a]
Friends and relatives	No	1108 (31.9)	2367 (68.3)	0.9 [0.867, 0.943]	1.3 [1.14, 1.49]
	Yes	648 (38.7)	1025 (61.3)		
	***P* value**	< 0.001[b]			< 0.001[b]
Social media	No	683 (29.5)	1631 (70.5)	0.81 [0.756, 0.866]	1.22 [1.09, 1.38]
	Yes	1073 (37.9)	1761 (62.1)		
	***P* value**	< 0.001[b]			0.001[a]

[a]$P < 0.05$ is significant.
[b]$P < 0.001$ is highly significant.
OR: Odds ratio; CI: Confidence interval.

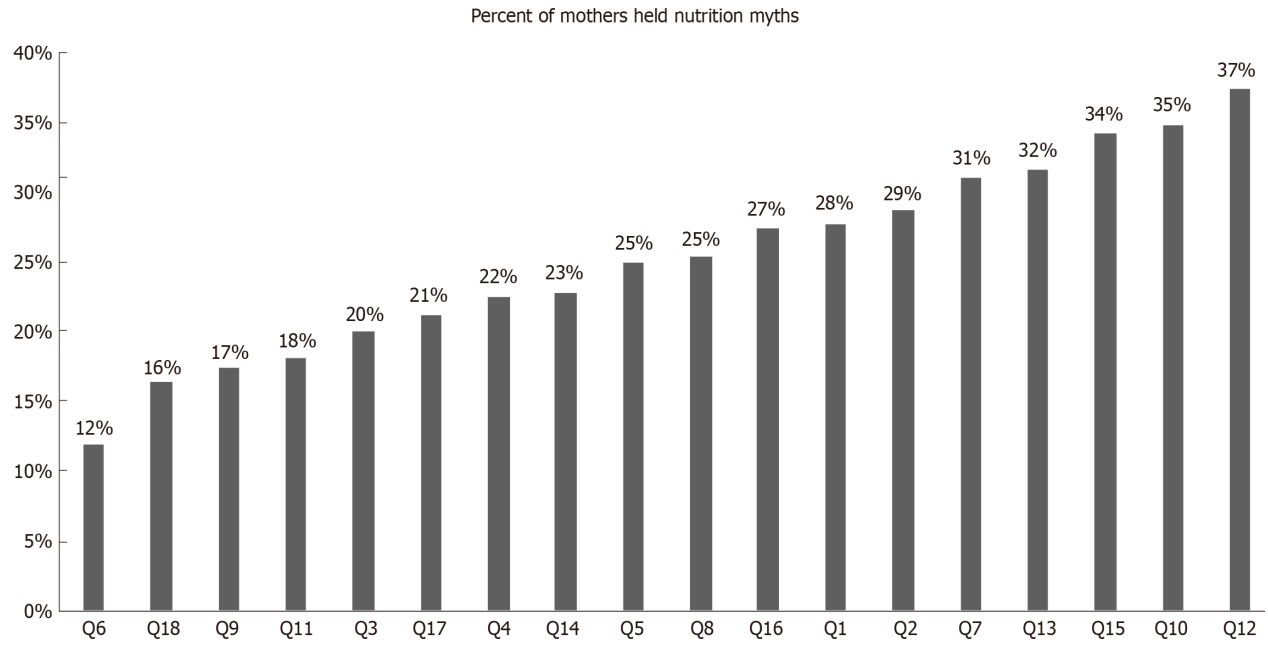
among those mothers. This continuous maternal education process through their healthcare providers will minimize the need to gain experience from untrusted resources.

Surprisingly, an evolving term in public health medicine, "infodemic," has emerged. This new term came out with the coronavirus disease 2019 pandemic[22]. An infodemic is defined as an epidemic of information[23]. This overflow of information is not always correct; some are accurate, and others are inaccurate (misinformation and misbeliefs). Unfortunately, in LMICs like Egypt, the unfavorable effects of such a phenomenon are aggravated by health illiteracy and limited resource settings. Therefore, defining the level of knowledge and the extent of myths is critical to outlining the best approach[24].

The complicated scientific information and sources that cannot easily reach the general public were the leading causes behind mothers' searching other channels for information, mainly social media platforms[25]. According to this study, this is the situation among the surveyed mothers and the reason behind their preference for social media as a source of nutrition information. It is very challenging for mothers to determine what is reliable and evidence-based.

In light of this unique phenomenon, we gained a more profound insight into how these mothers are dealing with the sources of information. The maternal behavior towards the sources of information was analyzed. It was found that 50% of mothers checked for information, currency, and authority except for contact details. Furthermore, more than 60% of mothers checked the accuracy of the information. Aligned with the data in this study, another study among low-income Hispanic mothers in the United States demonstrated that most social media users extracted feeding information from reliable websites to avoid doubtful information on that platform[18]. Consequently, it is vital to provide accessible and trustworthy sources of nutrition information through e-health education or smartphone health applications supplied by the Ministry of Health.

Further analysis of factors affecting maternal knowledge scores was conducted by comparing mothers with good nutrition knowledge to those with inappropriate nutrition knowledge. It was previously reported in Turkey that maternal age is one of the essential factors affecting knowledge, attitude, and behavior[26]. As expected, when getting older, the mother becomes more experienced and are able to gain and process information wisely. However, the data in this research demonstrated no significant differences between different maternal age groups regarding maternal knowledge scores ($P = 0.31$). A similar result from Turkey was found by Demir *et al*[27] in 2020, who reported that knowledge scores were almost identical among different maternal age groups except for those between 26 and 30 years, who had higher scores.



n	Question
1	Vitamins should be discontinued when a child has the flu
2	Giving the child food with added sugar or salt before he is one-year old causes kidney problems[1]
3	Introducing food to the child before the age of six months improves his appetite
4	Bananas should not be eaten in cases of diarrhea
5	Eating fish, milk, and eggs together causes allergies and the flu
6	Using candy as a way to reward a child is a good thing
7	Yogurt should be avoided if the child suffers from diarrhea or stomach aches
8	Natural juices are an alternative to eating fruit
9	Exposing vegetables to high temperatures during cooking will reduce their nutritional value[1]
10	Eating eggs causes high blood cholesterol
11	If the child has gastroenteritis, he or she should be given soda drinks, such as Seven Up
12	Fish and milk should be avoided for a child with a high temperature
13	Drinking water while eating affects the digestion of food
14	Giving formula milk to treat cases of high jaundice in newborns
15	Giving formula milk increases the feeling of satiety in infants and thus reduces the crying period of the infant
16	Fruit should not be eaten before meals so that it does not affect the appetite
17	Breast milk is not suitable for storage
18	A mother who is allergic to a certain type of food should not give it to her child.

[1]The scale was inverted.

Figure 2 Percent of mothers holding nutrition myths.

In addition, the maternal knowledge status was analyzed according to maternal education and paternal education, and it was not significantly different (P = 0.64 and 0.64, respectively). However, it was different from other reports from Ghana, the United Arab Emirates, and Turkey, where the level of knowledge score was positively correlated with maternal education level[27-30].

It is assumed that mothers acquire experience in nutrition and different health aspects when having more than one child or when children are getting older. However, this research discovered no difference regarding the nutrition knowledge scale according to the child's age, order, or sex.

A dietary myth is a negative or positive belief regarding nutritional concepts that cannot be supported or opposed by scientific evidence[31]. According to the extent of belief in myths, the healthy behavior of parents and, consequently, the nutritional status of their children are affected.

Regarding the nutrition myth score, the median score was 9 out of 18 (50%). Therefore, 56% of the mothers did not hold nutrition myths. This study found that the most frequent nutrition myth was reported by about 37% of respondents about avoiding eating fish and milk if the child was feverish.

However, the least frequently determined myth by only 12% of respondents was about rewarding children with candy. This behavior supports the recommendation of the American Academy of Pediatrics, which is against the administration of unnecessary additional calories as it increases the risk of obesity among children.

This study demonstrated that maternal education was significantly different between mothers with nutrition myths and those without (P = 0.003). Those with higher education (above the university) had substantially lower myth scores. Although the education level of mothers was not related to the maternal nutrition knowledge score, it was related to the lower myth group. This information emphasizes the importance of maternal education, even if only it positively reduces the myth belief. This differs from the results of Mrosková *et al*[32], who found that maternal education was related to food

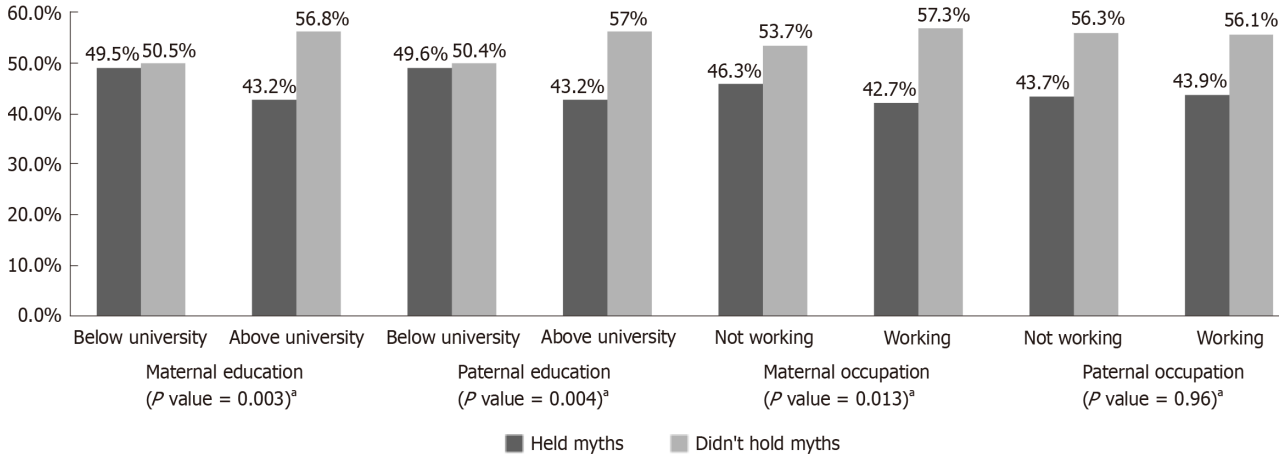


Figure 3 Relationship between participants according to holding myth score and their sociodemographic background (maternal and paternal education and occupation). [a]*P* value < 0.05 is significant.

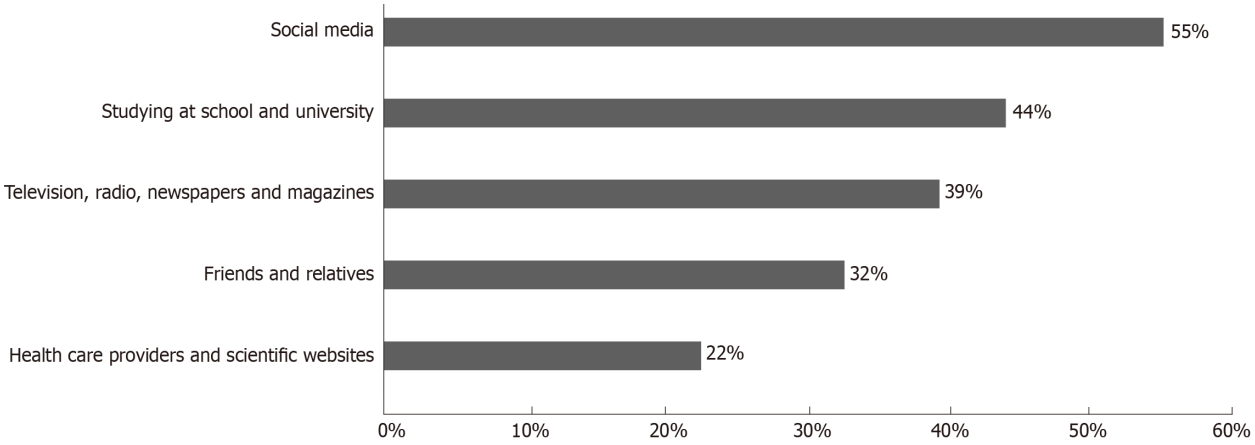


Figure 4 Main sources of nutrition knowledge for enrolled mothers.

choices, whether healthy or not, but not associated with paternal myth belief.

Further analysis of other factors related to nutrition myths revealed that maternal occupation was significantly different between the two groups. Substantially, more working mothers were not holding nutrition myths ($P = 0.013$). It could be assumed that employment raises socialization and awareness among mothers.

Additionally, logistic regression analysis was conducted to evaluate the impact of the five different sources of nutrition information on the development of nutrition myths. Interestingly, it was found that using social media, consulting with family members, and depending on knowledge from television, radio, newspapers, and magazines increased the likelihood of holding myths among mothers approximately 1.2, 1.3, and 1.14 times more than mothers who do not depend on those sources as a source of knowledge. However, mothers dependent on their health care providers and scientific websites are less likely to hold myths by 13%. This information emphasizes that informal sources of nutritional information increase the incidence of nutrition myths. However, using formal sources through health care providers and scientific websites positively decreased the misinformation rate. Regulatory health authorities should provide sufficient nutrition training for general pediatricians for that finding. In addition to that, adequate auditing for non-supervised nutrition training courses is deeply needed to minimize the incidence of myths among physicians and mothers.

Strengths and limitation

Since the survey was online, this gave the researcher more freedom to answer than a physical interview. Furthermore, it was less expensive and took less time. The study was a nationwide survey with randomly selected mothers from many governorates nationwide. The online survey involved only mothers who could access the Internet, which limited the conclusion. Future research, including all mothers, is needed to help identify the different sources and barriers of nutritional myths and knowledge among different socioeconomic levels.

CONCLUSION

In our LMIC setting, almost 50% of the mothers had good nutrition knowledge level scores. In the era of infodemics, social media platforms were the principal source of nutrition information, with more than 50% of mothers managing information currency and authority. For this finding, novel strategies are needed to raise maternal awareness for proper evaluation and selection of the suitable material offered through these platforms. In addition, updated maternal nutrition information sources should be developed and managed by different health authorities. Mothers holding nutritional myths represented 56% of the surveyed mothers. Maternal education and occupation reduced the frequency of myths and beliefs. Health care providers, as sources of nutritional information, are the only source of information, decreasing the mythic incidence among mothers.

ARTICLE HIGHLIGHTS

Research background

Nowadays, diversity of sources of maternal nutritional education becomes a fact in the light of infodemics era. Evaluation of these sources and the method of their assessment is crucial to improve the practice. To the best of our knowledge, this is the first published study from Egypt evaluating this problem in spite of its significance in this low/middle income country.

Research motivation

Healthcare providers, family members, mass media, and social media are different sources of maternal information. Technology enables faster delivery of information but cannot guarantee acquiring the right information. The results of the current study will help to innovate novel strategies to improve maternal awareness for proper evaluation and selection of the suitable material offered to them through different sources.

Research objectives

To assess the healthy nutritional knowledge and nutrition related myths among a large sample of Egyptian mothers, and to determine the sources of these information and how those mothers mange the sources of nutritional related knowledge.

Research methods

This cross-sectional analytical observational study enrolled 5148 randomly selected Egyptian mothers who had one or more children less than 15 years old. The data were collected through online questionnaire forms: One was for the general nutrition knowledge assessment, and the other was for the nutritional myth score. Sources of information and ways of evaluating internet sources using the Currency, Relevance, Authority, Accuracy, and Purpose test were additionally analyzed.

Research results

The main source of maternal nutrition knowledge was social media platforms (55%). Half of the mothers managed information for currency and authority, except for considering the author's contact information. The mothers with higher nutrition knowledge checked periodically for the author's contact information (P = 0.012). The nutrition myth score was significantly lower among mothers who periodically checked the evidence of the information (P = 0.016). Mothers dependent on their healthcare providers as the primary source of their general nutritional knowledge were less likely to hold myths by 13% (P = 0.044). However, using social media increased the likelihood of having myths among mothers by 1.2 (P = 0.001).

Research conclusions

In the era of infodemics, social media platforms are the principal source of nutrition information, with more than 50% of mothers managing information currency and authority. Health care providers, as sources of nutritional information, are the only source of information, decreasing the myth incidence among mothers.

Research perspectives

The online survey involved only mothers who could access the internet, which limited the conclusion. Future research, including all mothers, is needed to help identify the different sources and barriers of nutritional myths and knowledge among different socioeconomic levels.

FOOTNOTES

Author contributions: El-Koofy N designed the study; Zein MM and Arafa N participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; El-Shabrawi MHF and El-Koofy N revised the article critically for important intellectual content.

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ORIGINAL ARTICLE

Observational Study

Inpatient management of iron deficiency anemia in pediatric patients with inflammatory bowel disease: A single center experience

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Abstract

BACKGROUND

Screening for iron deficiency anemia (IDA) is important in managing pediatric patients with inflammatory bowel disease (IBD). Concerns related to adverse reactions may contribute to a reluctance to prescribe intravenous (IV) iron to treat IDA in this population.

AIM

To track the efficacy and safety of IV iron therapy in treating IDA in pediatric IBD patients admitted to our center.

METHODS

A longitudinal observational cohort study was performed on 236 consecutive pediatric patients admitted to our tertiary IBD care center between September 2017 and December 2019. 92 patients met study criteria for IDA, of which 57 received IV iron, 17 received oral iron, and 18 were discharged prior to receiving iron therapy.

RESULTS

Patients treated with IV iron during their hospitalization experienced a significant increase of 1.9 (± 0.2) g/dL in mean (± SE) hemoglobin (Hb) concentration by the first ambulatory follow-up, compared to patients who received oral iron 0.8 (± 0.3) g/dL or no iron 0.8 (± 0.3) g/dL (P = 0.03). One out of 57 (1.8%) patients that received IV iron therapy experienced an adverse reaction.

CONCLUSION

Our findings demonstrate that treatment with IV iron therapy is safe and efficacious in improving Hb and iron levels in pediatric patients with IDA and active IBD.

Key Words: Iron deficiency anemia; Pediatric inflammatory bowel disease; Intravenous iron therapy; Inflammatory bowel disease

Core Tip: In summary, in our single center study, we found oral iron generally ineffective in pediatric patients with inflammatory bowel disease and active inflammation. Parenteral iron met the primary clinical goal of the study (a 1g/dL increase in hemoglobin). Addressing inflammation without targeted therapy for iron deficiency is unlikely to correct the anemia associated with iron deficiency.

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INTRODUCTION

Anemia is one of the most common extraintestinal manifestations observed in patients with inflammatory bowel disease (IBD)[1]. Iron deficiency is the leading cause of anemia in these patients, and it is more prevalent in children and adolescents with IBD than adults[1,2]. Iron deficiency anemia (IDA) in pediatric patients with IBD is likely due to a combination of factors, including inadequate dietary intake, iron malabsorption, gastrointestinal (GI) blood loss, and reduced iron utilization[3]. Persistent IDA increases IBD-related morbidity, and its severity is inversely correlated with patient quality of life[4,5]. The clinical impact of IDA falls disproportionately on pediatric patients with IBD due to the potential for negative impact on physical and cognitive development during childhood[6].

There are published guidelines outlining the need to include IDA screening and treatment in managing pediatric patients with IBD[7-9]. Oral iron has been shown to be cost-effective in managing IDA[7]. However, this approach is limited by poor compliance[10,11], malabsorption, and decreased utilization of orally administered iron in the context of chronic inflammation[12,13]. Data from several comparative studies have demonstrated that intravenous (IV) iron therapy may be a better approach than oral iron to correct IDA, particularly in patients with active disease[14,15]. Nevertheless, there is mixed enthusiasm about the use of IV iron in children[16]. This reluctance likely arises from concerns about adverse reactions associated with IV iron administration and the lack of published data on the clinical efficacy and safety of newer IV iron formulations in this patient population[8].

The primary aim of this observational study was to prospectively evaluate the efficacy and safety of IV iron therapy for managing IDA in pediatric patients admitted to our center to manage clinical exacerbations of their IBD.

MATERIALS AND METHODS

Study design

This prospective, open-label, observational cohort study examined consecutive patients (≤ 23 years of age) admitted to Boston Children's Hospital (BCH) to manage clinically active IBD between September 2017 and December 2019**.** This study was approved by the Boston Children's Hospital Institutional Review Board (IRB #P00024515).

IDA was based on laboratory values and iron studies [ferritin, serum iron, and total iron-binding capacity (TIBC)] obtained on admission. Patients were screened using the electronic medical record to identify those with an established diagnosis of IBD using the Porto Criteria, including ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). Exclusion criteria included known or suspected concurrent infection, a history of small bowel resection or colectomy requiring packed red blood cell transfusion, or treatment with concurrent IV and oral iron therapy between admission and first follow-up visit (Figure 1).

Anemia was defined according to the World Health Organization criteria as hemoglobin (Hb) < 11.5 g/dL for patients 5-11 years of age, < 13 g/dL in males 12 years and older, and < 12 g/dL in females 12 years and older[17]. Iron deficiency was indicated by one of the following: Serum iron < 59 mg/dL, TIBC > 450 mg/dL, ferritin < 100 μg/dL in the presence of an elevated C-reactive protein (CRP) (> 1 mg/dL) or ferritin < 30 μg/dL in the presence of a normal CRP (0-1 mg/dL). These standards follow published guidelines for diagnosing and treating IDA in patients with IBD[18,19].

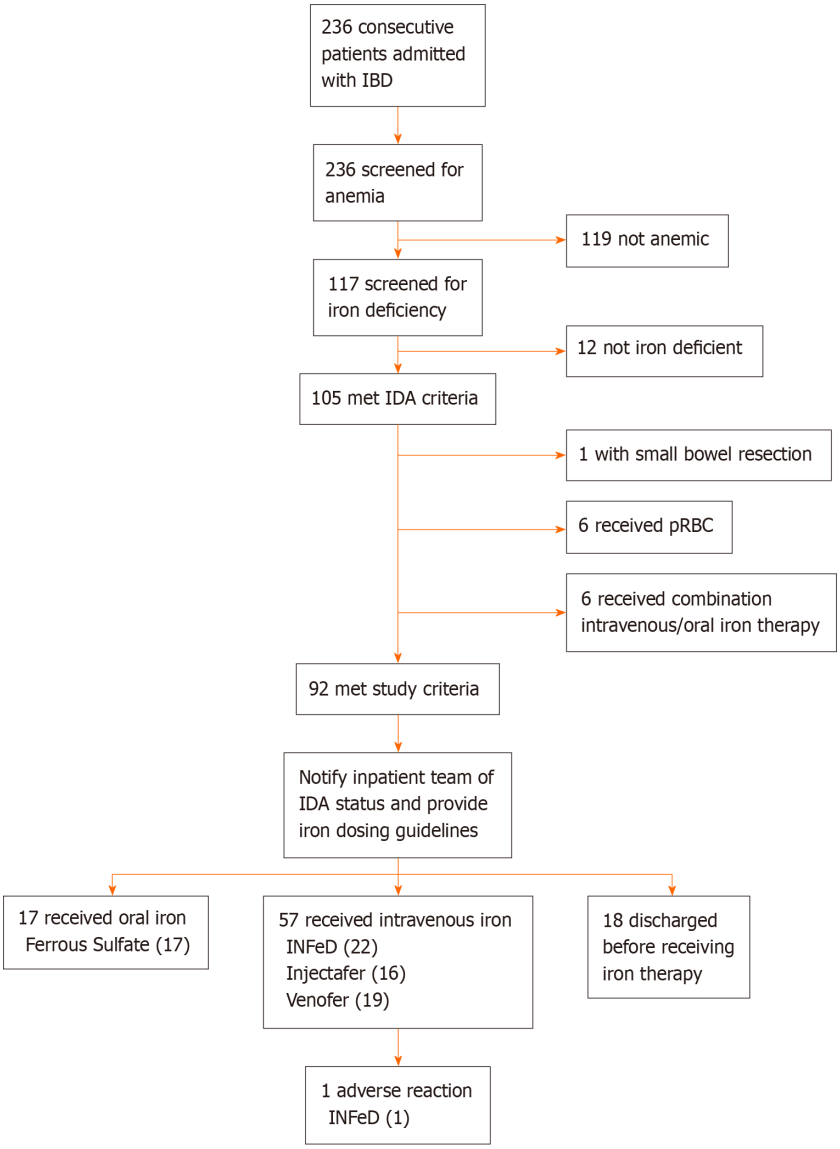

Figure 1 Study overview. IBD: Inflammatory bowel disease; IDA: Iron deficiency anemia; pRBC: Packed red blood cell; INFeD: Low-molecular-weight iron dextran.

Research Study Coordinators reviewed the inpatient census daily to assess patient laboratory studies. They notified clinical staff of patients meeting the criteria for iron deficiency and provided them with information about the parenteral IV formulations available on the hospital formulary and dosing guidelines using a standardized electronic template. The inpatient team subsequently made all decisions concerning the preparation and dose of parenteral or oral iron prescribed for individual patients. The recommended repletion dose of IV iron was based on a validated metric that took into account lean body weight (LBW), as well as measured and target Hb levels (Hb_0 and Hb_t g/dL, respectively) (Equation 1).

Dose (mg) = 0.0442 × LBW (kg) × (Hb_t-Hb_0) + [0.26 × LBW (kg)] × 50 mg/mL (1)

LBW was determined using each patient's total body mass and height[20]. Target hemoglobin (Hb_t) was determined from total body mass: If < 15 kg, Hb_t = 12.0 g/dL; if ≥ 15 kg, Hb_t = 14.8 g/dL[21].

Information provided to clinicians was made in conjunction with BCH Pharmacy staff and product insert guidelines. Iron sucrose (Venofer) was recommended for use in patients requiring a calculated repletion dose of elemental iron < 300 mg (to a maximum dose of 7 mg/kg). Ferric carboxymaltose (Injectafer) was recommended for patients requiring a repletion dose from 300-750 mg. Low-molecular-weight iron dextran (INFeD) was recommended for those patients requiring a repletion dose that was > 750 mg (to a maximum dose of 2000 mg) or in patients unable to receive iron sucrose due to the total dose being greater than 7 mg/kg. Study patients completed repeat iron studies during their first ambulatory follow-up visit after discharge.

This study was uncontrolled, and clinicians treated patients with whichever IV or oral iron supplementation they felt was clinically indicated. Some patients were discharged on no iron treatment at all. This decision was likely related to patient or provider preference or a conscious decision to focus clinical efforts on managing a patient's underlying IBD. Clinicians caring for patients admitted for a shorter duration had less opportunity to screen for iron deficiency, review the results, and initiate inpatient IV iron repletion therapy before discharge. Research Study Coordinators were not available to screen patients on the weekends. Nonetheless, data about these untreated patients were recorded and included for

comparative analysis (Figure 1).

Efficacy assessment

The efficacy of iron supplementation was defined as a ≥ 1 g/dL increase between pre-and post-treatment Hb and an improvement in iron status based on pre- and post-treatment iron studies (ferritin, serum iron, and TIBC).

Safety assessment

Safety was evaluated by reviewing the electronic medical record for adverse events from the onset of IV iron therapy administration to the first ambulatory follow-up after discharge.

Statistical analysis

Baseline characteristics, including age at admission, sex, IBD diagnosis and phenotype, and disease duration, are described by frequency count (and percentage) when categorical and by median (interquartile range; IQR) when continuous. Comparisons across iron therapy groups (no iron, oral iron, IV iron) were made by the Fisher exact and Kruskal-Wallis tests, respectively.

Changes in laboratory parameters from baseline assessment until the first follow-up visit were assessed with a repeated-measures linear regression model adjusted for the corresponding baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission follow-up labs. Estimates at admission, first follow-up, and change from admission to follow-up are presented as mean ± standard error (SE). Comparison between treatment groups (IV iron, oral iron, no iron) or within-group changes over time are shown as mean [95% confidence interval (CI)], and pairwise comparisons are corrected for multiple comparisons using the Holm's step-down Bonferroni procedure. Assessment of normality was made by the Shapiro-Wilk test. Data for labs that were not normally distributed were transformed using a rank-based inverse normal transformation[22,23]. The results were consistent with the non-transformed data in all cases, and only the latter were reported.

All comparisons were 2-sided, with $P < 0.05$ indicating statistical significance. Data analysis and figures were accomplished with SAS version 9.4 (Cary, NC).

RESULTS

Demographic data

A total of 105 patients (44% of those screened) met the criteria for IDA, of which 92 (40%) met the study criteria. The median age of patients in this cohort was 15 years (range: 1-23), and 41 (45%) were female. All patients included in the study met the criteria for active IBD, of which forty-seven patients (51%) had CD, 41 (45%) had UC, and 4 (4%) had IC. The median disease duration was 1.4 months (IQR: 0.1–31.2). Of the 47 patients with CD, 28 (60%), 10 (21%), and 9 (19%) had an inflammatory, penetrating, and stricturing phenotype, respectively. Of the 41 patients with UC, 34 (83%) had pancolitis, and 7 (17%) had left-sided colitis. Fifty-seven patients (62%) received IV iron therapy, 17 (18%) received oral iron, and 18 (20%) received no iron therapy (Table 1).

Hb and mean corpuscular volume

This was a longitudinal observational study of real-time clinical practice. The first ambulatory follow-up visit after discharge was not protocolized and was scheduled at the discretion of the discharging provider and contingent on physician and patient availability. The median follow-up time was 32 d (IQR: 20-58) following admission. Changes in lab assessments from baseline to first follow-up were examined by repeated-measures regression adjusted for baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. There was a significant change in Hb concentration observed in those who received IV iron therapy with a mean ± SE increase of 1.9 ± 0.2 mg/dL, compared to 0.8 ± 0.3 mg/dL ($P = 0.02$) and 0.8 ± 0.3 mg/dL ($P = 0.02$) in patients receiving either oral or no iron, respectively (Table 2). The mean Hb change met the study's predetermined criteria for efficacy (Hb increase ≥ 1g/dL) only in patients who received IV iron. Likewise, there was a statistically significant improvement in mean corpuscular volume of 6.0 ± 0.6 fL in patients treated with IV iron compared to those treated with oral iron 2.8 ± 1.1 ($P = 0.02$) or no iron 1.6 ± 1.1 fL ($P = 0.001$), respectively (Table 2).

Biochemical disease activity

There was no statistically significant difference in baseline erythrocyte sedimentation rate (ESR) ($P = 0.66$) and baseline CRP ($P = 0.67$) in patients subsequently treated with IV, oral, or no iron therapy. This was similarly the case concerning longitudinal changes in ESR and CRP. Although longitudinal changes in ESR were evident within each treatment group (IV: -16 ± 4 mm/h, oral: -20 ± 8 mm/h, and no iron therapy: -17 ± 8 mm/h), the changes were not statistically different from one another when compared across groups ($P = 0.94$). This was similarly the case for CRP (IV: -3.2 ± 0.7 mm/h, oral: -2.4 ± 1.4 mm/h, and no iron therapy: -1.8 ± 1.3 mm/h; $P = 0.63$) (Table 2).

Iron studies

Paired iron parameters, including TIBC, ferritin, and serum iron, were available in 64/92 (70%), 66/92 (72%), and 65/92 (71%) of patients in the cohort, respectively. IV iron therapy was the only treatment modality associated with an increase in ferritin (from 79 ± 15 μg/dL to 167 ± 18 μg/dL, $P = 0.0006$). In contrast, ferritin levels decreased in those patients

Table 1 Subject characteristics (*n* = 92)

	Overall (*n* = 92)	Iron therapy			*P* value
		No iron (*n* = 18)	Oral iron (*n* = 17)	IV iron (*n* = 57)	
Age (years), median (IQR)	15 (11–18)	13 (10–18)	15 (13–17)	15 (11–18)	0.70
Female sex, *n* (%)	41 (45)	10 (56)	7 (41)	24 (42)	0.63
IBD diagnosis, *n* (%)					0.008
CD	47 (51)	16 (89)	4 (24)	27 (47)	
UC	41 (45)	2 (11)	11 (65)	28 (49)	
IC	4 (4)	0 (0)	2 (12)	2 (4)	
Disease duration (months), median (IQR)	1.4 (0.1–31.2)	19.6 (0.1–82.3)	1.0 (0.2–16.6)	1.5 (0.1-24.6)	0.58
CD phenotype, *n* (%)					0.41
Inflammatory	28 (60)	9 (56)	1 (25)	18 (67)	
Fistula	10 (21)	4 (25)	2 (50)	4 (15)	
Stricture	9 (19)	3 (19)	1 (25)	5 (19)	
UC phenotype, *n* (%)					0.76
Pancolitis	34 (83)	2 (100)	10 (91)	22 (79)	
Left-sided colitis	7 (17)	0 (0)	1 (9)	6 (21)	

IQR: Interquartile range; IBD: Inflammatory bowel disease; IV: Intravenous; UC: Ulcerative colitis; CD: Crohn's disease; IC: Indeterminate colitis.

receiving either oral iron (from 82 ± 31 μg/dL to 15 ± 54 μg/dL, $P = 0.30$) or no iron (from 117 ± 30 μg/dL to 70 ± 58 μg/dL, $P = 0.45$) (Table 2). In addition, only treatment with IV iron increased ferritin levels above 100 μg/dL, thereby raising this parameter above the biochemical threshold supporting a diagnosis of iron deficiency. The mean ± SE increase in serum iron was greater in those treated with IV iron (30.3 ± 4.9 mg/dL) compared to those treated with either oral iron (26.8 ± 12.3 mg/dL) or no iron (10.7 ± 13.6 mg/dL). However, this difference did not reach statistical significance ($P = 0.41$) (Table 2). While there was an increase in TIBC among all three treatment groups in the interval between their admission and their first follow-up ambulatory visit, the increase in TIBC was smaller in patients treated with IV iron therapy (23 ± 15 mg/dL, $P = 0.15$)) compared to those who received either oral (108 ± 37 mg/dL, $P = 0.006$) or no iron (101 ± 39 mg/dL, $P = 0.01$) (Table 2); however, after adjustment for multiple comparisons, the changes from admission to first follow-up were not statistically different from one another.

Comparison of IV iron formulations

Among 57 patients who were treated with IV iron, 22 (39%) received INFeD, 19 (33%) were treated with iron sucrose (Venofer), and 16 (28%) with ferric carboxymaltose (Injectafer). Median (IQR) dose was 1119 (761-1320) mg for INFeD, 234 (120-300) mg for Venofer, and 750 (548-750) mg for Injectafer. After adjusting for baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs, all three parenteral iron therapies proved efficacious, resulting in an increase in Hb of at least 1 g/dL from pre- to post-treatment. Both Injectafer and INFeD elicited a greater change in mean ± SE Hb concentration (2.4 ± 0.3 mg/dL and 2.2 ± 0.3 mg/dL, respectively) compared to that observed in patients receiving Venofer (1.0 ± 0.3 mg/dL) ($P = 0.02$ for each comparison) (Table 3). Likewise, changes in serum iron levels were significantly higher in response to treatment with Injectafer (57.7 ± 9.7 mg/dL, $P = 0.001$) and INFeD (41.7 ± 7.3 mg/dL, $P = 0.006$) compared to those treated with Venofer (8.3 ± 7.1 mg/dL) (Table 3). Changes in ferritin levels observed in patients receiving the three different IV iron formulations resulted in a non-significant *P* value ($P = 0.30$) (Table 3). There were no significant differences in the change in Hb, serum iron, and ferritin between patients treated with Injectafer and those treated with INFeD.

Adverse events

Only 1/57 (1.8%; 95%CI: 0.04%-9.4%) of patients who received IV iron therapy had an adverse reaction noted in their electronic medical record. This patient was a three-year-old with very early onset IBD and no prior history of atopy. He was administered INFeD and developed an anaphylactoid reaction (Figure 1). There was no prior history of allergies noted in the patient's medical record, and he had not received any IV iron in the past. The patient was stabilized and required one additional day of inpatient observation prior to discharge.

Table 2 Iron studies (*n* = 92)

		Iron therapy			*P* value
		No iron (*n* = 18)	Oral iron (*n* = 17)	IV iron (*n* = 57)	
Hb (g/dL)	Admission	10.4 ± 0.2	10.0 ± 0.2	9.7 ± 0.1	
(*n* = 92)	Follow-up	11.2 ± 0.2	10.8 ± 0.2	11.6 ± 0.1	
	Change	0.8 ± 0.3[a]	0.8 ± 0.3[a]	1.9 ± 0.2[b]	0.003
MCV (fL)	Admission	78.8 ± 0.8	78.6 ± 0.7	78.2 ± 0.4	
(*n* = 92)	Follow-up	80.4 ± 0.8	81.4 ± 0.8	84.2 ± 0.4	
	Change	1.6 ± 1.1[a]	2.8 ± 1.1[a]	6.0 ± 0.6[b]	0.0004
CRP (mg/dL)	Admission	3.8 ± 0.8	3.2 ± 0.8	4.0 ± 0.4	
(*n* = 85)	Follow-up	1.9 ± 0.9	0.8 ± 0.9	0.8 ± 0.4	
	Change	-1.8 ± 1.3	-2.4 ± 1.4	-3.2 ± 0.7	0.63
ESR (mm/1h)	Admission	48 ± 5	42 ± 5	44 ± 3	
(*n* = 80)	Follow-up	31 ± 6	23 ± 6	27 ± 3	
	Change	-17 ± 8	-20 ± 8	-16 ± 4	0.94
TIBC (μg/dL)	Admission	284 ± 19	296 ± 19	301 ± 9.1	
(*n* = 64)	Follow-up	385 ± 35	404 ± 29	323 ± 10.7	
	Change	101 ± 39[a]	108 ± 37[a]	23 ± 15[a]	0.04
Ferritin(μg/dL)	Admission	117 ± 30	82 ± 31	79 ± 15	
(*n* = 66)	Follow-up	70 ± 58	15 ± 54	167 ± 18	
	Change	-46 ± 61[a]	-67 ± 61[a]	88 ± 23[b]	0.02
Iron (μg/dL)	Admission	34.5 ± 6.9	26.6 ± 6.7	23.7 ± 3.2	
(*n* = 65)	Follow-up	45.3 ± 12.8	53.4 ± 10.6	54.0 ± 3.8	
	Change	10.7 ± 13.6	26.8 ± 12.3	30.3 ± 4.9	0.41

[a]$P < 0.05$.
[b]$P < 0.01$.
Effects with different superscripts are statistically significant, mean ± standard error at admission, follow-up encounter, and change over time are shown. Results are from a repeated measures linear model adjusted for baseline outcome, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. After adjustment for multiple comparisons, the differences between total iron binding capacity and ferritin are not significant. Hb: Hemoglobin; MCV: Mean corpuscular volume; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TIBC: Total iron binding capacity.

DISCUSSION

Data collected from our single-center study demonstrate the safety and efficacy of parenteral iron administration in a population of children and young adults with IBD and IDA. Patients who received IV iron experienced a significant rise (greater than 1g/dL) in their Hb level in the interval between their admission and first post-discharge ambulatory follow-up visit. Only one adverse event was recorded during the study period.

The prevalence of IDA (44%) observed in this study is consistent with previous reports of IDA in pediatric patients with IBD[9,24-26]. After controlling for baseline Hb levels and the number of days between admission and the first ambulatory follow-up, we observed that the subset of patients with IDA who were not treated with iron or who were treated with oral iron experienced a minimal change in their Hb level. In contrast, patients receiving IV iron experienced significant increases in Hb levels by their first ambulatory follow-up visit, which occurred at a median duration of 32 d following discharge.

IV iron therapy was the only treatment modality that increased serum ferritin levels, whereas ferritin levels declined in patients receiving oral iron or no iron therapy. Serum ferritin is a non-specific acute-phase reactant that is elevated during periods of active inflammation[7]. The rise in ferritin levels observed in patients treated with IV iron and not with oral iron has been previously reported in a randomized controlled trial assessing these two treatment modalities in managing IDA in adults with IBD[14]. This suggests that tracking serum ferritin levels in the context of inflammation may be a misleading metric for assessing the response to oral or parenteral iron administration.

Table 3 Comparison of intravenous iron types (*n* = 57)

		Iron therapy			*P* value	Difference (95%CI)		
		Venofer (*n* = 19)	Injectafer (*n* = 16)	INFeD (*n* = 22)		Injectafer-Venofer	INFeD-Venofer	Injectafer-INFeD
Hb (g/dL)	Admission	9.4 ± 0.3	9.5 ± 0.2	9.4 ± 0.2				
(*n* = 57)	Follow-up	10.5 ± 0.3	11.9 ± 0.2	11.7 ± 0.2				
	Change	1.0 ± 0.3[a]	2.4 ± 0.3[b]	2.2 ± 0.3[b]	0.009	1.3 (0.2, 2.5)[a]	1.2 (0.1, 2.3)[a]	0.1 (-1.0, 1.2)
Ferritin (μg/dL)	Admission	117 ± 36	82 ± 33	73 ± 36				
(*n* = 43)	Follow-up	153 ± 39	183 ± 45	206 ± 42				
	Change	37 ± 43	101 ± 57	133 ± 44	0.3	64 (-118, 247)	96 (-61, 254)	-32 (-215, 151)
Iron (μg/dL)	Admission	19.2 ± 6.5	23.0 ± 5.8	25.3 ± 6.5				
(*n* = 43)	Follow-up	27.5 ± 7.0	80.7 ± 8.0	67.1 ± 7.4				
	Change	8.3 ± 7.1[a]	57.7 ± 9.7[b]	41.7 ± 7.3[b]	0.0006	49.4 (18.5, 80.2)[c]	33.5 (7.4, 59.6)[b]	15.9 (-15.0, 46.8)

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Effects with different superscripts are statistically significant at $P < 0.05$, mean ± standard error at admission, follow-up encounter, and change over time are shown. Results are from a repeated measures linear model adjusted for baseline outcome, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. The 95% confidence interval is adjusted for multiple comparisons using the Bonferroni step-down procedure. Hb: Hemoglobin; CI: Confidence interval; INFeD: Low-molecular-weight iron dextran.

The marginal improvement in hematologic and iron parameters observed in patients treated with oral iron therapy in this study may be explained by a combination of factors. Inflammatory cytokines released during chronic active inflammation can decrease iron absorption and utilization. Interleukin-6, in particular, upregulates hepatic production and release of hepcidin[27]. This signaling molecule impedes iron transport by inhibiting ferroportin channels in the enterocytes lining the small intestine[28,29]. It is also plausible that the blunted response to oral iron therapy could be related to ongoing GI blood loss. Furthermore, adverse GI side effects negatively impact long-term compliance with oral iron therapy, including nausea, diarrhea, abdominal pain, and pill fatigue[10]. Thus, the increased bioavailability of IV iron, combined with its lack of reliance on patient adherence, makes parenteral iron a more reliable alternative to addressing IDA in this vulnerable pediatric patient population and has been recommended as first-line treatment in patients with active IBD, severe anemia (Hb < 10g/dL), or previous intolerance to oral iron by the European Crohn's and Colitis Organization in 2015[18].

The reluctance to use IV iron in pediatric patients with IBD and IDA may be rooted in concern for serious adverse events, including anaphylaxis, which had been previously reported with the use of high-molecular-weight iron dextran [30]. However, newer low-molecular-weight and polysaccharide-based IV iron formulations, including those employed in the present study, have a much better safety profile in the pediatric IBD population[30-33]. We observed only one adverse event in this study, which coincided with administering INFeD.

Patients receiving INFeD and ferric carboxymaltose (Injectafer) experienced a greater increase in their Hb levels than those receiving iron sucrose (Venofer) in this study. This is likely related to the higher dose of infused iron permissible with INFeD and Injectafer. Of the IV iron formulations used in this study, we found INFeD and Injectafer more effective than Venofer for improving mean Hb and iron status by the time of a patient's first ambulatory follow-up visit. This is not surprising, as INFeD can be administered in doses as high as 2 g during a single infusion, while ferric carboxymaltose and iron sucrose are limited to 750 mg and 300 mg, respectively[34]. As such, patients receiving Venofer may require multiple infusions to achieve iron repletion. Injectafer allows for a more rapid IV iron infusion, taking only fifteen minutes to deliver a maximum dose[35]. There are reports of ferric carboxymaltose being associated with a higher incidence of hypophosphatemia than other IV iron preparations[36-39]. Previous meta-analysis revealed that patients receiving ferric carboxymaltose were at a significantly higher risk of hypophosphatemia related to those treated with iron sucrose [risk ratio (RR): 9.40, 95%CI: 2.30-33.0], iron isomaltose (RR: 7.90, 95%CI: 2.10-28.0), INFeD (RR: 6.60, 95%CI: 1.91-220.0), and ferumoxytol (RR: 24.0, 95%CI: 2.50-220.0)[38]. As such, phosphate monitoring may be warranted in patients receiving ferric carboxymaltose therapy to identify and address hypophosphatemia and its associated sequelae[39].

Our data demonstrate that patients with IBD and IDA who were not treated with IV iron therapy did not experience a significant change in their mean Hb level between their baseline and their first ambulatory follow-up visit. Of relevance, IDA did not resolve in patients who had otherwise responded favorably (comparable decreases in ESR and CRP levels) to medical therapy. In contrast to previous tenets suggesting that iron deficiency would resolve when the underlying inflammation was corrected, our data suggest that in the absence of targeted iron therapy, correction of the underlying inflammatory response is insufficient to resolve iron homeostasis in patients with IBD. Instead, many of these patients will likely experience a clinical or biochemical improvement (ESR and CRP) in the context of ongoing IDA. This

observation underscores the need for early recognition and active management of IDA in pediatric IBD care.

Our previous retrospective study found that only 32% of patients with UC and IDA admitted to our Center between 2003 and 2014 were treated with oral iron, and none had been treated with IV iron by discharge[40-43]. In contrast, 81% of patients with IBD and IDA admitted during the study period between 2017 and 2019 were identified and treated (77% with IV iron) during their hospitalization. It's likely that the engagement with Research Study Coordinators raised awareness of IDA in patients with IBD, educated providers about dosage calculations and the availability of parenteral iron preparations, and increased the level of provider comfort with respect to ordering parenteral iron therapy. Together, these factors likely contributed to a greater percentage of patients being identified and treated for IDA.

Our study's strength is derived from its sample size and observational longitudinal cohort design, which allowed us to evaluate changes in Hb and iron levels over time in individuals and groups of patients. This study has limitations, including the fact that this was a single-center, non-randomized design. As such, we could not actively control which patients received each treatment option nor the dosage of iron administered. Also, the ultimate choice of IV iron preparation used may have been affected by provider bias. As such, a more complete evaluation of the association between changes in Hb and iron levels in response to IDA therapy is clearly warranted.

CONCLUSION

In conclusion, our findings demonstrate that treatment with parenteral iron therapy is most likely to result in a significant improvement in Hb levels in pediatric patients admitted with IBD and IDA. Conversely, we found no significant changes in Hb levels in patients receiving oral or no iron therapy. Correction of IDA appears to occur independent of other biochemical responses to therapy, including changes in inflammatory (ESR and CRP) markers. As such, IDA may persist without directed therapy, even in patients who otherwise respond to effective corticosteroid, biologic, or other immunosuppressive therapies. IV iron therapy was safe and effective for managing IDA in our pediatric patients with IBD hospitalized for worsening disease activity. More extensive prospective studies are needed to investigate further the efficacy and safety of IV iron therapy in IDA in children with IBD.

ARTICLE HIGHLIGHTS

Research background

Screening for iron deficiency anemia (IDA) is uniformly recommended but may not always occur in the management of pediatric patients with acute exacerbation of their inflammatory bowel disease (IBD). In addition, clinicians may be hesitant to use intravenous (IV) iron in practice in the active IBD population due to concerns about adverse reactions reported in prior IV formulations. Our study sought to evaluate the efficacy and safety profile of IV iron therapy in pediatric patients with IDA admitted to our tertiary care center for their active IBD.

Research motivation

The significance of this research is that it provides additional data on the efficacy and safety profile of the newer IV iron preparations in pediatric patients with active IBD. This research will provide data in directing management of pediatric patients with IDA and active IBD.

Research objectives

The primary aim of this observational study was to prospectively evaluate the efficacy and safety of IV iron therapy for managing IDA in pediatric patients admitted to our center to manage clinical exacerbation of their IBD. The significance of achieving these objectives will allow providers caring for such patients to know the efficacy and safety profile of the newer iron preparations and possible expected outcomes.

Research methods

We performed a prospective, open-label, observational cohort study to evaluate our study aims. Research Study Coordinators reviewed the inpatient census daily to assess patient laboratory studies. They notified clinical staff of patients meeting the criteria for iron deficiency and provided them with information about the IV iron formulations available on the hospital formulary and dosing guidelines using a standardized electronic template. The inpatient team subsequently made all decisions concerning the preparation and dose of IV or oral iron prescribed for individual patients. The observational longitudinal cohort design allows us to evaluate changes in hemoglobin (Hb) and iron levels over time in individuals and groups of patients.

Research results

First, we found that IV iron is more efficacious than oral or no iron therapy in increasing Hb levels by their first ambulatory follow-up after receipt of iron therapy. This suggests that IV iron therapy is a more efficacious option in elevating Hb levels by the time of first ambulatory follow-up. Second, we found that IV iron was overall a safe option in the repletion of IDA in this pediatric IBD population with only 1/57 adverse events reported. This suggests that IV iron is a safe option in this patient population. Third, IDA did not resolve in patients who had otherwise responded favorably

(comparable decreases in erythrocyte sedimentation rate and C-reactive protein levels) to medical therapy. In contrast to previous tenets suggesting that iron deficiency would resolve when the underlying inflammation was corrected, our data suggest that in the absence of targeted iron therapy, correction of the underlying inflammatory response is insufficient to resolve iron homeostasis in patients with IBD.

Research conclusions

Our single-center study shows that IV iron is safe and efficacious in treating IDA in children with active IBD. Our data further demonstrate that addressing inflammation is insufficient to correct iron deficiency and that successful treatment of iron deficiency in pediatric patients with IBD warrants active management.

Research perspectives

More extensive prospective studies are needed to investigate further the efficacy and safety of IV iron therapy in IDA in children with IBD.

FOOTNOTES

Co-first authors: Krishanth Manokaran and Jonathan Spaan.

Author contributions: Manokaran K and Spaan J contributed equally to this work; Rufo PA conceptualized the study; Rufo PA, Manokaran K, and Spaan J conceived methodology; Mitchell PD performed formal statistical analysis; Manokaran K, Spaan J, Cataldo G, and Lyons C performed data collection; Manokaran K, and Spaan J prepared original draft; Rufo PA, Mitchell PD, and Zimmerman LA helped review and edit manuscript; Rufo PA and Sare T provided resources and project administration; All authors have read and agree to the published version of the manuscript.

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Observational Study

Gut microbiota predicts the diagnosis of ulcerative colitis in Saudi children

Mohammad El Mouzan, Ahmed Al Sarkhy, Asaad Assiri

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Abstract

BACKGROUND

Ulcerative colitis (UC) is an immune-mediated chronic inflammatory condition with a worldwide distribution. Although the etiology of this disease is still unknown, the understanding of the role of the microbiota is becoming increasingly strong.

AIM

To investigate the predictive power of the gut microbiota for the diagnosis of UC in a cohort of newly diagnosed treatment-naïve Saudi children with UC.

METHODS

The study population included 20 children with a confirmed diagnosis of UC and 20 healthy controls. Microbial DNA was extracted and sequenced, and shotgun metagenomic analysis was performed for bacteria and bacteriophages. Biostatistics and bioinformatics demonstrated significant dysbiosis in the form of reduced alpha diversity, beta diversity, and significant difference of abundance of taxa between children with UC and control groups. The receiver operating characteristic curve, a probability curve, was used to determine the difference between the UC and control groups. The area under the curve (AUC) represents the degree of separability between the UC group and the control group. The AUC was calculated for all identified bacterial species and for bacterial species identified by the random forest classification algorithm as important potential biomarkers of UC. A similar method of AUC calculation for all bacteriophages and important species was used.

RESULTS

The median age and range were 14 (0.5-21) and 12.9 (6.8-16.3) years for children with UC and controls, respectively, and 40% and 35% were male for children with UC and controls, respectively. The AUC for all identified bacterial species was 89.5%. However, when using the bacterial species identified as important by

random forest classification algorithm analysis, the accuracy increased to 97.6%. Similarly, the AUC for all the identified bacteriophages was 87.4%, but this value increased to 94.5% when the important bacteriophage biomarkers were used.

CONCLUSION
The very high to excellent AUCs of fecal bacterial and viral species suggest the potential use of noninvasive microbiota-based tests for the diagnosis of unusual cases of UC in children. In addition, the identification of important bacteria and bacteriophages whose abundance is reduced in children with UC suggests the potential of preventive and adjuvant microbial therapy for UC.

Key Words: Ulcerative colitis; Microbiota; Area under the curve; Children; Saudi Arabia

Core Tip: This study reports the predictive power of fecal microbiota, bacteria and bacteriophages, in predicting the diagnosis of ulcerative colitis in children. This was demonstrated by the calculation of the area under the receiver operating characteristic curve (AUC). High values of the AUC up to 97.6% and 94.5% for bacteria and bacteriophage, respectively, indicate excellent predictive power in differentiating children with ulcerative colitis (UC) from controls. This finding may lead to the development of noninvasive microbiota-based test for the diagnosis of unusual cases of UC in children.

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INTRODUCTION

Ulcerative colitis (UC) is an immune-mediated inflammatory bowel disease. Although the incidence of this disease is highest in Western populations, it is increasing globally[1-3]. The etiology of UC is unknown; however, multifactorial factors involving interactions between genetics, host immunity, the mucosal barrier, and the gut microbiome are highly suspected[4-6]. The role of the microbiota has been extensively reported mainly in Western populations, with strong evidence of an association with UC.

In Saudi Arabia, a developing country in transition, the incidence and clinical patterns of UC have been reported[7-10]. In addition, the microbiota profile of Saudi children with Crohn's disease (CD) has been reported to be significantly associated with not only the presence of bacteria but also the high area under curve (AUC) for bacteria in fecal samples, suggesting high accuracy in predicting the diagnosis of CD[11,12]. However, there are no reports on the predictive power of the microbiota for the diagnosis of UC. The objective of this study was to evaluate the role of the microbiota in predicting the diagnosis of UC in Saudi children.

MATERIALS AND METHODS

Study population

Children with a confirmed diagnosis of UC were enrolled in the study. The children were recruited from multiple hospitals in Riyadh, Kingdom of Saudi Arabia. The inclusion criteria included new-onset and untreated disease, as well as no antibiotic exposure for at least 6 months before stool collection. Fecal samples from the children with UC were collected before bowl preparation. Healthy school children were randomly selected as controls. Stool samples from children with UC and controls were collected in cryovials without fixatives or stabilizers and immediately stored at −80°C until analysis.

DNA extraction and sequencing

Bacterial and viral DNA from fecal samples was isolated using the QIAGEN DNeasy PowerSoil Pro Kit according to the manufacturer's protocol. DNA libraries were prepared using the Nextera XT DNA Library Preparation Kit (Illumina) and IDT Unique Dual Indexes with a total DNA input of 1ng. Library were subsequently sequenced on an Illumina NovaSeq S4 platform.

Statistical and bioinformatics analysis

Shannon alpha diversity metrics were calculated in R using the R package "vegan". Wilcoxon rank-sum tests were performed between groups using the R package ggsignif[13,14]. Bray-Curtis dissimilarity was calculated in R using the

vegan package with the function vegdist, and PCoA tables were generated using the ape function pcoa. PERMANOVA tests for each distance matrix were generated using the vegan's6 function adonis2, and beta dispersion was calculated and compared using the ANOVA method for the betadispering function from vegan[15]. DESeq2 was used to estimate differential abundance between cohorts based on count data[16]. The random forest classification algorithm was applied to the relative abundance data to predict bacterial and viral species biomarkers that might improve prediction[17].

The receiver operating characteristic (ROC) curve was used to determine the difference between the UC and control groups. The area under the curve (AUC) represents the degree of separability between the UC group and the control group. The AUC was calculated for all identified bacterial and bacteriophage species in this study and for bacterial and bacteriophage species identified by the random forest classification algorithm as important potential biomarkers of UC [18].

Ethical aspects: The study was approved by the Institutional Board Review of the College of Medicine, King Saud University in Riyadh, Kingdom of Saudi Arabia [No: 10/2647/IRB,26/6/2010]. Guardians and/or children signed informed consent and/or assent before enrollment in the study.

RESULTS

The median age and range were 14 (0.5-21) and 12.9 (6.8-16.3) years for children with UC and controls, respectively, and 40% and 35% were male for children with UC and controls, respectively. A high number of significant bacterial and bacteriophage dysbiosis events were found (unpublished data). Among these, 11 bacterial species biomarkers were identified. These included the *Bifidobacterium angulatum*, *Alistipes putredinis, Bacteroides caccae, and Bifidobacterium adolescentis* (Table 1). Similarly, among the high number of bacteriophages, four were identified as biomarkers. These included the *Salmonella phage SEN4*, *Streptococcus phage YMC-2011*, and *uncultured crAssphage* (Table 2).

The AUC for all identified bacterial species was 89.5% (79.1%-100.0%), but when based on the biomarkers, the accuracy increased to 97.6% (94.2%-100.0%) indicating very good to excellent predictive power (Figure 1). Similarly, the AUC for all the identified bacteriophages was 87.4% (75.9%-98.8%), but the AUC increased to 94.5 % (87.8%-100%), when the identified important species were used, indicating very good to excellent predictive power (Figure 2).

DISCUSSION

Shotgun metagenomic analysis of bacterial and viral bacteriophage species in fecal samples of children with new-onset untreated UC revealed significant differential abundances between the UC group and the control group, indicating significant dysbiosis (unpublished data). The AUC of the ROC curve represents the degree of separability between the UC group and the control group, indicating the predictive power of the ROC curve for UC diagnosis.

In this study, we calculated the AUC based not only on the entire bacterial species and bacteriophages but also on important species identified by the random forest classification algorithm. The calculated AUC based on the abundance of all the bacterial species increased from 89.5% to 97.6% when only 11 bacterial species biomarkers were considered, indicating increased predictive power of the important bacterial species biomarkers. Similarly, the AUC calculated based on the bacteriophages increased from 87.4% to 94.5% when only four biomarkers were considered, indicating that the use of these bacteriophage biomarkers has greater predictive power for distinguishing UC patients from controls. The excellent predictive power of these biomarkers indicates the potential for the development of microbiota-based diagnostic tests. Among the bacteria and bacteriophages, *Bifidobacterium angulatum* and *uncultured crAssphage* had the highest median importance scores. *Bifidobacterium angulatum* is a species that belongs to the Bifidobacterium genus that is known to modulate the immune system and may be considered protective against UC[19,20]. *Uncultured crAssphage* is the most abundant human-associated virus and is found in the gut virome in approximately 50% of humans. This virus infects species of Bacteroides with mostly beneficial effects on health. Accordingly, *Bifidobacterium angulatum* and uncultured *crAssphage* could constitute the basis of prophylactic or therapeutic options[21-24].

The excellent predictive diagnostic power for UC in this report is slightly greater but consistent with the 93% accuracy for UC diagnosis reported within a multiclass disease in an adult study in Hong Kong[25] and the 91% accuracy in a group of children with UC in which shotgun metagenomic bacterial species-level abundance was used[26]. Finally, the 84.4% to 95% predictive power of the bacteriophage species identified in this study has not been reported thus far and deserves further study.

Study limitations: This study had a relatively small sample size, but it may be acceptable for this is the first study to use metagenomic analysis in a non-Western childhood population to determine the accuracy of the microbiota in predicting the diagnosis of UC.

CONCLUSION

The very high to excellent AUCs of fecal bacterial and viral species indicate the potential for the development of noninvasive microbiota-based tests for the diagnosis of UC and for preventive and adjuvant microbial therapy for UC. In addition, the identification of important bacteria and bacteriophages whose abundance is reduced in children with UC suggests the potential of preventive and adjuvant microbial therapy.

Table 1 Bacterial microbiota biomarkers importance score

S. No.	Bacterial species	Mean	Median	Minimum	Maximum	Decision
1	*Alistipes communis*	3.199	3.222	1.528	5.055	Confirmed
2	*Alistipes putredinis*	6.748	7.094	3.605	8.565	Confirmed
3	*Bacteroides caccae*	5.914	6.28	2.717	7.552	Confirmed
4	*Bifidobacterium adolescentis*	5.843	6.123	3.073	7.578	Confirmed
5	*Bifidobacterium angulatum*	8.89	9.47	4.265	10.827	Confirmed
6	*Bifidobacterium bifidum*	4.138	4.293	1.512	5.794	Confirmed
7	*Bifidobacterium catenulatum*	5.544	5.823	2.246	7.352	Confirmed
8	*Dialister succinatiphilus*	3.418	3.594	-0.47	4.86	Confirmed
9	*Peptostreptococcus stomatis*	3.367	3.411	1.358	4.983	Confirmed
10	*Prevotella copri*	3.826	3.812	1.463	5.595	Confirmed
11	*Streptococcus_u_s*	3.987	3.93	1.595	6.232	Confirmed

Table 2 Viral microbiota biomarkers scores

S. No.	Bacteriophage	Mean	Median	Minimum	Maximum	Decision
1	*Salmonella phage SEN4*	5.311	5.474	2.349	8.294	Confirmed
2	*Siphoviridae_u_s*	7.224	7.591	3.16	10.1	Confirmed
3	*Streptococcus phage YMC-2011*	7.989	8.611	3.409	11.18	Confirmed
4	*uncultured crAssphage*	18.35	20.11	6.433	23.25	Confirmed

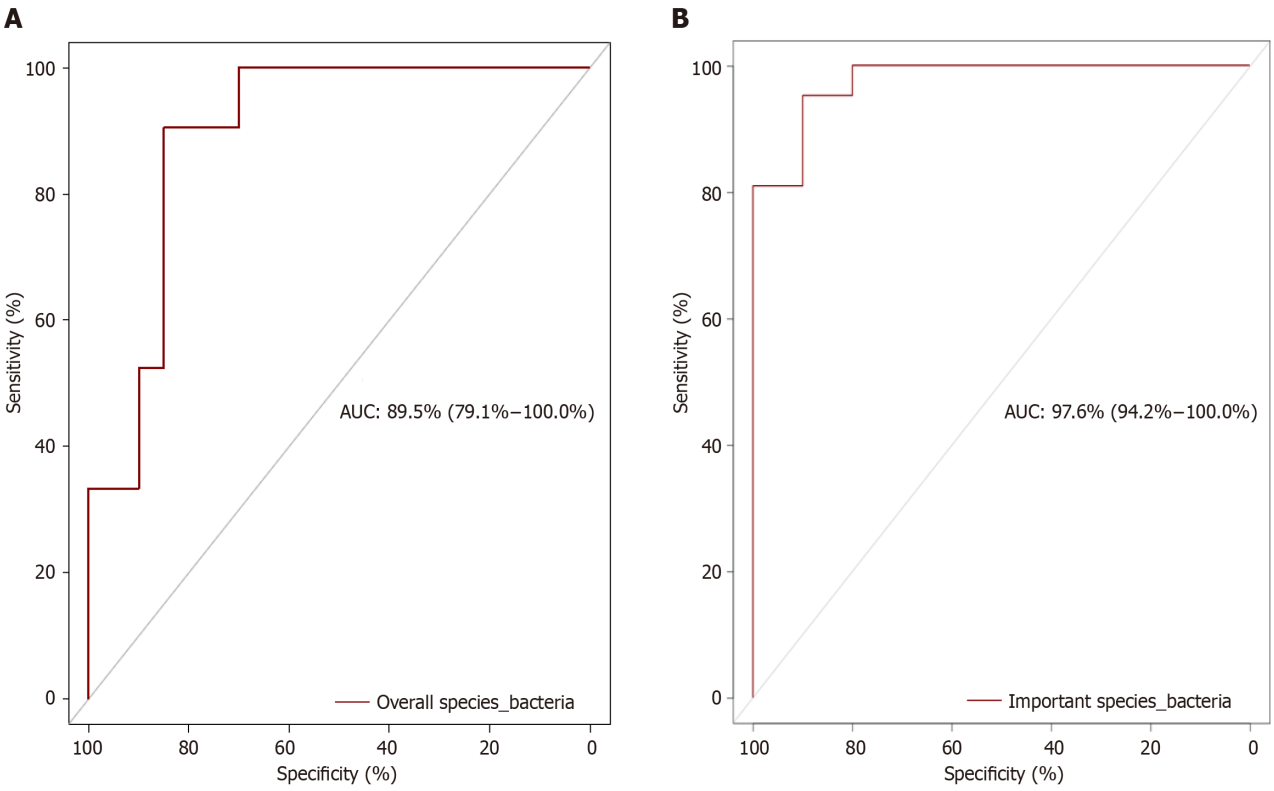

Figure 1 The predictive power of fecal bacteriome. A: Area under the curve (AUC) based on the entire bacterial species shows 89.5% (79.1%-100%CI) accuracy in predicting ulcerative colitis (UC); B: Random forest algorithm was performed on the entire dataset to identify important features significantly predictive of UC increased the AUC to 97.6% (94.2-100%CI).

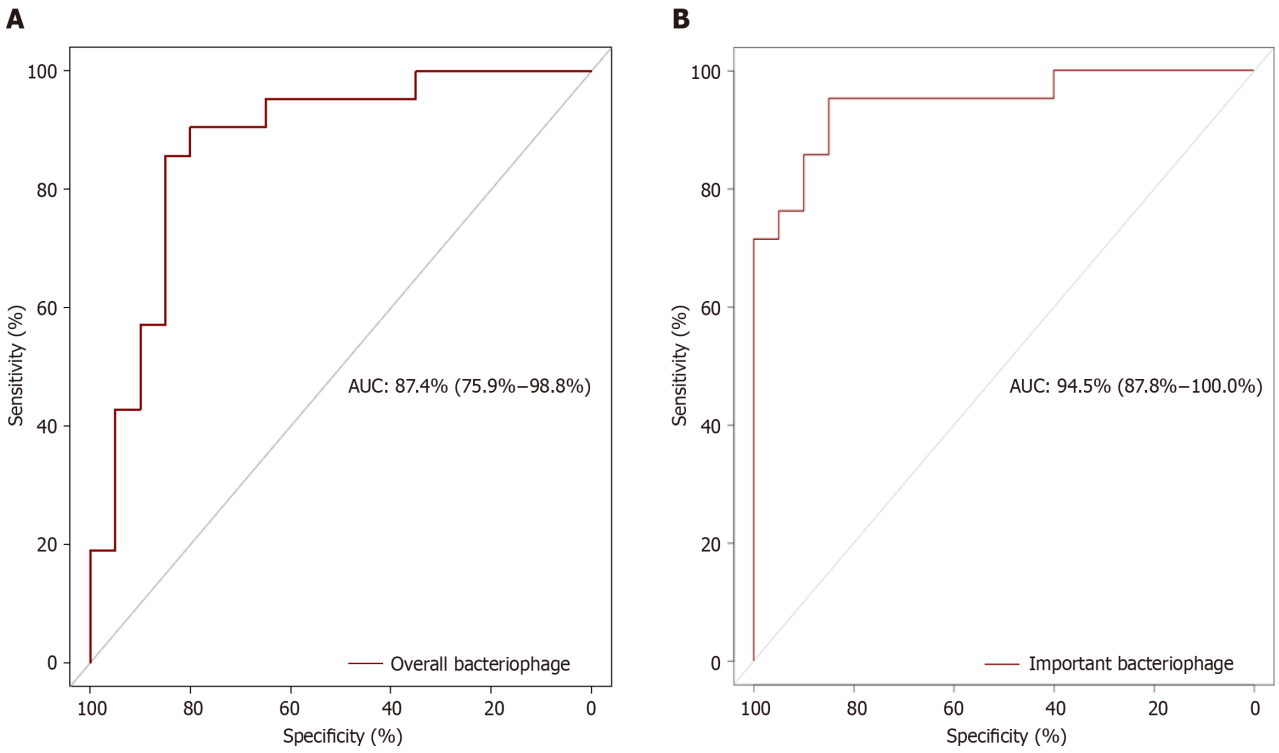

Figure 2 The predictive power of fecal bacteriophage. A: Area under the curve (AUC) based on the entire bacteriophage shows of 87.4% (75.9%-98.8%) in predicting ulcerative colitis (UC) in stool samples; B: Random forest algorithm was performed on the entire dataset to identify important features significantly predictive of UC increased the AUC to 94.5% (87.8%-100%CI).

ARTICLE HIGHLIGHTS

Research background

Microbiota dysbiosis has been reported in patients with ulcerative colitis (UC).

Research motivation

The role of the microbiota in predicting UC has rarely been reported.

Research objectives

To evaluate the predictive power of fecal bacteria and bacteriophages for diagnosing UC in children.

Research methods

Metagenomic analysis of bacterial and bacteriophage DNA in the stool of children with newly diagnosed UC. The area under the curve (AUC) was calculated to evaluate the predictive power of the total bacteria and bacteriophages, and random forest analysis was used to identify important microbes for distinguishing UC patients from controls.

Research results

The discriminatory power of the entire bacterial species (AUC: 89.5%) and bacteriophages (AUC: 87.4%) was very high. The random forest classification algorithm analysis revealed the excellent predictive power of important bacterial species (AUC: 97.6%) and bacteriophages (AUC: 94.5%).

Research conclusions

The very high to excellent AUCs of fecal bacterial and viral species indicate the potential for the development of noninvasive microbiota-based tests for the diagnosis of UC in children. In addition, the identification of important bacteria and bacteriophages whose abundance is reduced in children with UC suggests the potential of preventive and adjuvant microbial therapy for UC.

Research perspectives

Future research in this area with larger sample sizes is needed to clarify the role of the microbiota in the diagnosis, prevention, and treatment of UC.

FOOTNOTES

Author contributions: El Mouzan M designed and supervised the study and wrote the manuscript; Al Sarkhy A and Assiri A participated equally in recruiting participants and revising the manuscript draft; All authors have read and approved the final manuscript.

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Informed consent statement: Guardians and/or children signed informed consent and/or assent before enrollment in the study.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

Data sharing statement: Datasets are available from the corresponding author at email: drmouzan@gmail.com.

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SYSTEMATIC REVIEWS

Gastrointestinal tolerability of organic infant formula compared to traditional infant formula: A systematic review

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Abstract

BACKGROUND

Infants' nutrition significantly influences their growth, development, and overall well-being. With the increasing demand for organic infant formula driven by the perception of health benefits and growing awareness of natural feeding options, it is crucial to conduct a comparative analysis of the gastrointestinal tolerability between organic and traditional infant formulas.

AIM

To provide a concise and precise analysis of the gastrointestinal tolerability of organic infant formula compared to traditional infant formula. Due to limited direct comparisons, the review synthesizes available literature on each formula type, presenting insights into their potential effects on infants' digestive health.

METHODS
An extensive literature search was conducted, compiling studies on organic and traditional infant formulas, their compositions, and reported effects on gastrointestinal tolerability. We searched academic databases such as PubMed and Google Scholar and specialized nutrition, paediatrics, and infant health journals using relevant keywords till October 1, 2023.

RESULTS
Although specific comparative studies are scarce and formula heterogeneity is a significant limitation, this systematic review provides an in-depth understanding of organic infant formulas' composition and potential benefits. While scientific evidence directly comparing gastrointestinal tolerability is limited, organic formulas strive to use carefully selected organic ingredients to imitate breast milk composition. Potential benefits include improved lipid profiles, higher methionine content, and decreased antibiotic-resistant bacteria levels. Understanding the gastrointestinal tolerability of organic and traditional infant formulas is crucial for parents and healthcare providers to make informed decisions.

CONCLUSION
Despite limitations in direct comparisons, this systematic review provides insights into the composition and potential benefits of organic infant formulas. It emphasizes the need for further research to elucidate their gastrointestinal effects comprehensively.

Key Words: Organic infant formula; Traditional infant formula; Gastrointestinal tolerability; Formula ingredients; Digestive health; Infant nutrition; Organic farming

Core Tip: This systematic review focuses on the growing demand for organic infant formula, highlighting its potential benefits and impact on gastrointestinal health compared to traditional infant formula. Although there are limited direct comparative studies, an analysis of available literature suggests that organic formulas aim to replicate the composition of breast milk, providing improved lipid profiles, higher methionine content, and potentially reducing antibiotic-resistant bacteria. To make informed decisions about infant nutrition, it is crucial to understand the digestive effects of these formulas. Therefore, further comprehensive research is needed to elucidate their gastrointestinal implications fully.

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INTRODUCTION

Infants require proper nutrition for their growth, development, and overall well-being. Nutrients like protein, fat, carbohydrates, vitamins, and minerals are essential for the body to develop tissues, organs, and systems. Adequate nutrition strengthens their immune system and helps in brain development and cognitive function. Calcium and vitamin D assist in building strong bones. Breast milk or formula provides the necessary calories and nutrients, and introducing allergenic foods may reduce food allergy risk[1,2]. Inadequate nutrition increases the risk of illness in infants and children and is responsible for one-third of deaths in children below 5 years of age. Improper childhood nutrition can lead to obesity, a severe public health problem worldwide[3]. Malnutrition during early life, particularly in the first two years, leads to stunting, causing short stature during adulthood. Research has shown that malnourishment during early childhood can lead to long-term impaired intellectual performance during adulthood[4]. Breastfeeding promotes a strong emotional bond, and optimal nutrition reduces the risk of health problems later in life. Some infants may require specialized formulas due to medical conditions or specific dietary needs[5]. Infant formula is an essential alternative to breast milk for infants who cannot breastfeed or when it is unavailable. In such cases, healthcare professionals can help parents choose the most appropriate feeding option. Providing optimal nutrition during infancy is crucial for promoting healthy growth and development, supporting the immune system, and laying the groundwork for a healthy and thriving life. Parents, caregivers, and healthcare providers all play critical roles in ensuring that infants receive the nutrition they need to reach their full potential[6].

The demand for organic infant formula is increasing as parents become more aware of the potential health benefits. The term "organic" reflects a farming method that agrees with nature and is sustainable. Organic formula is considered a healthier option because it's free from synthetic additives, pesticides, genetically modified organisms (GMOs), and artificial additives[7]. Its market share has been steadily increasing in many regions. Organic infant formula is highly sought after as parents look for natural and safe baby products. More companies are entering the market, offering various products that meet strict regulations and certification standards. Organic infant formula is in higher demand in developed countries due to higher income and awareness of organic products. It is more expensive due to the costs of organic farming and production, but the most critical factor for parents is to ensure their child's nutritional needs are met [8]. Organic products are becoming more popular due to their potential health benefits. The products must contain at least 95% of their components as organic ingredients to be labeled as organic. They should be made without synthetic pesticides and may have higher nutrient content. They are often non-GMO, antibiotic and hormone-free, and produced sustainably. Some people choose organic to avoid allergens and ensure food safety. While scientific evidence is still evolving, informed choices based on reliable sources are recommended[9].

This systematic review aims to provide a concise and comprehensive analysis of the gastrointestinal tolerability of organic infant formula compared to traditional infant formula. The review examines the existing literature on both formula types and their impact on infants' digestive health. By comparing the gastrointestinal effects of organic and traditional infant formulas, the systematic review provides a comprehensive overview of the importance of proper nutrition for infants, the rising demand for organic infant formula, and the regulatory frameworks surrounding organic milk and infant formula. It also offers valuable insights for parents, caregivers, and healthcare professionals in making informed decisions when choosing between these two types of infant formulas.

MATERIALS AND METHODS

We conducted a comprehensive literature review to gather data on organic and conventional infant formula. We searched academic databases such as PubMed and Google Scholar and specialized nutrition, paediatrics, and infant health journals using relevant keywords till October 1, 2023. These keywords included "organic infant formula," "conventional infant formula," "gut tolerability," "nutritional composition," and related terms. Our review only included peer-reviewed articles, conference papers, and reputable publications. Our inclusion criteria focused on studies that examined the composition, gut tolerability, and nutritional aspects of organic and conventional infant formulas. We included studies that directly or indirectly compared these aspects, and only studies available in English were considered. We prioritized studies with transparent methodology, appropriate sample sizes, and a focus on infant populations. We also checked reference lists and conducted citation searches on the included studies. Articles with a possible commercial background were excluded. In total, we included 78 articles consisting of 45 research articles, two meta-analyses, three systematic reviews, 23 narrative reviews, two consensus guidelines, two book chapters, and one letter to the editor. We extracted data on formula compositions and nutritional profiles from producers' websites and end-products. Gut tolerability findings and related outcomes were extracted from the selected studies. We comprehensively compared the organic and conventional formulas, noting any discrepancies or variations in findings for further analysis and discussion. We evaluated the quality of each study, considering factors such as study design, sample size, methodology, and statistical significance. We identified and documented the limitations of each study. We assessed the overall quality of evidence for each aspect using established grading systems to ensure a robust analysis. Our comparative analysis focused on gut tolerability and nutritional composition differences between organic and conventional infant formulas. We paid specific attention to protein levels, lipids, lactose composition, and the presence of prebiotics and probiotics. We summarized the results, highlighting key findings from the literature. We identified research gaps and areas requiring further investigation based on the limitations and discrepancies observed in the reviewed studies. We also proposed recommendations for future research to enhance our understanding of gut tolerability and nutritional implications associated with organic and conventional infant formulas. We included a total of 175 full-text articles, including 102 research articles, nine meta-analyses, four systematic reviews, 58 narrative reviews, and two consensus guidelines. Figure 1 shows the PRISMA study flow chart.

RESULTS

From a systematic review of the included studies, we can summarize the findings into the following points as elaborated in Tables 1-5.

Organic vs non-organic infant formulas

A comparison between organic and non-organic infant formulas showed clear differences in various aspects. Organic formulas, usually obtained from organically raised animals, prioritize natural ingredients and strict regulations, ensuring a composition of at least 95% organic material. On the other hand, non-organic formulas may contain synthetic additives, GMOs, and non-organic components, which are typically sourced from conventionally raised animals and can have varying nutrient levels and processing methods.

Table 1 Compares the European and American organic infant formulas

	European organic infant formula	American organic infant formula
Regulations	EC has stricter standards than the United States FDA. For instance, all infant formulas must be organic, and there is a limit on certain ingredients, such as pesticides and antibiotics	The FDA regulates infant formulas through USDA & NOP, which have less strict standards than the EC. Not all infant formulas are required to be organic, & the FDA does not limit certain ingredients
Cultural attitudes toward the formula	Very strong positive attitude across the countries	Less than in Europe
Guidelines & regulations	Updated yearly	Not as frequent as European guidelines
Labelling and claims	Must meet standardized requirements, and products displaying the EU Organic Logo adhere to these regulations	Must comply with the NOP guidelines. The USDA Organic seal signifies adherence to these standards
Ingredients	It is more likely to be made with organic ingredients, such as milk from grass-fed cows or goats. They are also more likely to contain probiotics, beneficial bacteria that can help support gut health	It is more likely to contain added iron, which is essential for preventing iron deficiency anemia. They may also have other ingredients not allowed in European formulas, such as corn syrup solids
Probiotics	It is more likely to contain probiotics, which are beneficial bacteria that can help support gut health	Less likely to contain probiotics
Percentage of organic ingredients	Not less than 95%	Not less than 70%
Calories sources	Must have at least 30% of calories from lactose	Not required
	The inclusion of sucrose is prohibited, except in small quantities in some specialty formulas, such as premature or hypoallergic formulas	It may contain Sucrose, glucose, and maltodextrins
Added iron	It is less likely to contain added iron, which is vital for preventing iron deficiency anemia	More likely to contain added iron
Synthetic additives, pesticides, steroids, hormones, & GMOs	Strictly prohibited	Synthetic additives and GMOs are also prohibited, but specific regulations may differ
Taste	Some parents say that European formulas taste better than American formulas. This is likely because they are made with more natural ingredients	There is no consensus on whether European or American formulas taste better. Some parents prefer the taste of European formulas, while others prefer the taste of American formulas
Cost	Typically, they are more expensive than American formulas. This is because they are made with higher-quality ingredients & have stricter regulations	Typically, they are less expensive than European formulas. This is because they are made with less expensive ingredients and have less strict regulations

EC: The European Commission; EFSA: European Food Safety Authority; FDA: Food and Drug Administration; GMOs: Genetically modified organisms; NOP: The National Organic Program; USDA: The United States Department of Agriculture.

Organic formula composition

Organic baby formulas are designed to replicate the composition of human milk, with a focus on using organic lactose as the primary source of carbohydrates and organic dairy-derived proteins, with a balanced ratio of whey and casein (usually 60/40). These formulas also prioritize organic and natural fats, particularly vegetable oils, to balance omega-3 and omega-6 fatty acids, similar to that found in breast milk.

Nutritional variances

Organic and non-organic formulas aim to fulfil infants' nutritional requirements, but there are some differences between them. Non-organic formulas maintain similar nutrient levels but may differ slightly in components like fat content (which can range from 3.0-3.5 g/100 mL), carbohydrate sources, and protein characteristics. Although non-organic formulas meet regulatory standards, they may not perfectly match the nutrient ratios found in organic formulations.

Factors influencing gastrointestinal tolerability

Different factors can affect the ability of an individual to tolerate food. These factors include the composition of the food, the presence of prebiotics and probiotics, and the amount of lactose in the food. Individual sensitivities, medical co-morbidities, and hydration levels are also factors that can influence gastrointestinal tolerance. Additionally, how the food is prepared and fed can impact its tolerability. Factors such as the milk's temperature, the bottle's flow rate, and the feeding technique can all play a role in how well someone can tolerate their food.

Environmental considerations and consumer preferences

Organic formulas emphasize environmentally conscious farming practices and reduce chemical use, catering to parents

Table 2 The different compositions between the main organic infant first-stage regular formulas

	Brand	Country of origin	Protein source/100 mL	Fat source/100 mL	Carbohydrate source/100 mL	Other ingredients
1	Arla Baby & Me Organic	Denmark	1.4 g, Whey Protein Concentrate, Whey/Casein Ratio 60/40	3.6 g, vegetable oils (sunflower, soy)	6.7 g, Lactose	GOS, FOS, DHA of algal oil origin, ARA of fungal oil origin, Lecithin, choline, inositol, L-carnitine, tocopherol-rich extract
2	HiPP Organic	Germany	1.2-1.5 g, Whey protein concentrate, W/C Ratio 60:40	3.5-4.4 g, Palm olein oil, rapeseed oil, coconut oil, sunflower oil	6.5-7.5 g, Lactose	DHA, ARA, choline, taurine, nucleotides, lactoferrin, Metafolin, symbiotics (L. fermentum and GOS)
3	Kendamil Organic	United Kingdom	1.4 g, Whey protein concentrate, W/C Ratio 60:40	3.5 g, Whole milk fat and reduced levels of Organic vegetable oils (sunflower, coconut, rapeseed). No palm oil	7 g, Lactose	Marine algae-derived DHA, ARA, choline, taurine, nucleotides, lactoferrin, inositol, L-Carnitine, Organic GOS, 3'GL - Galactosyllactose
4	Holle Organic	Germany	1.4 g, contains the A2 protein. W/C Ratio 60:40	3.4 g, vegetable oils (palm, sunflower, rapeseed oil), oil from the microalgae Schizochytrium sp.2, Mortierella Alpina oil (No palm oil)	7.7 g, Lactose	Algae-derived DHA, ARA, choline, taurine, nucleotides, lactoferrin
5	Bellamy's Organic	Australia	1.5 g, Whey protein concentrate, W/C Ratio 60:40	3.4 g, Palm olein oil, soybean oil, sunflower oil	7.6 g, Lactose	Dried DHA and ARA oils [fish oil (tuna), choline, taurine, nucleotides, a Prebiotic GOS, 16 essential vitamins & minerals
6	Bubs Australia	Australia	1.56 g, Organic Whey Protein Concentrate, Whey/Casein Ratio 60/40	3.7 g, Organic Vegetable Oil Blend (High Oleic Sunflower, Coconut, Soy, Canola)	7.3 g, Organic Lactose	Organic GOS, DHA, from Algae, ARA, Probiotic Bifidobacterium longum BB536
7	Similac Organic with A2 milk	United States	1.55 g, Whey Protein Concentrate, A2 beta-caseins, W/C of 48:52	4.2 g, Organic High Oleic Sunflower Oil, Soy Oil, Coconut Oil	8 g, Organic Lactose	DHA, lutein, Choline, Beta-Carotene, Lycopene, Inositol, Nucleotides, Taurine, L-carnitine, L-methionine, Short-chain FOS
8	Happy Family Organics	United States	1.38 g, Organic Whey Protein Concentrate, W/C ratio of 30:70	3.4 g, Organic Palm Olein or Palm Oil, Soy Oil, Coconut Oil, High Oleic (Safflower or Sunflower) Oil	8 g, ORGANIC LACTOSE	DHA Algal Oil, Organic FOS and GOS, Choline, soy Lecithin, Beta-Carotene
9	Baby's Only Organic	United States	1.54 g, Organic Whey Protein Concentrate, A2 Protein, W/C Ratio 60:40	4.2 g, Organic High Oleic Sunflower and/or Organic High Oleic Safflower Oils), Organic Soybean Oil, Organic Coconut Oil	7.76 g, Organic Lactose	Choline, Taurin, Organic, Inositol, Non-Hexane Extracted Source of DHA & ARA
10	Plum Organics	United States	1.38 g, Organic Whey Protein Concentrate W/C Ratio 60:40	3.7 g, Organic Palm Oil Or Palm Olein, Soy Oil, Coconut Oil, High Oleic (Safflower or Sunflower) Oi	6.9 g, Organic Lactose	Plant-based DHA, & ARA. Tocopherol, Choline, Taurine, Lecithin
11	Honest Company Organic	United States, there was an issue about containing 11 non-organic elements	1.6 g, Organic Whey Protein Concentrate, W/C Ratio 60:40	3.9 g, Organic Palm Oil or Palm Olein, Soy Oil, Coconut Oil, High Oleic (Safflower or Sunflower) Oil	7.9 g, Organic Lactose, Organic Glucose Syrup Solids	Sodium Selenite, Taurine, Choline, Beta carotene, and Inositol Do not disclose the DHA/ARA extraction method
12	Enfamil Simply Organic	United States, the first organic formula that has certified USDA	1.49 g, Organic nonfat milk W/C Ratio 20:80	3.6 g, organic vegetable oil (organic palm, organic coconut, organic soy, and organic high oleic sunflower oils)	7.5 g, Organic Lactose, organic maltodextrin	Omega-3 DHA, Inositol, Choline, taurine, L-carnitine, & organic GOS
13	Nature's One Baby's Only	United States	1.5 g, Organic Whey Protein Concentrate W/C Ratio 60:40	4.2 g, Organic High Oleic Sunflower, Soybean Oil, Coconut Oil	7.7 g, Organic Lactose	Choline, Inositol
14	Bobbie Formula	United States	1.47 g, organic whey protein concentrate, W/C Ratio 60:40	3.9 g, organic high oleic (sunflower or safflower) oil, canola oil, coconut oil, linoleic sunflower or safflower) oil	8 g, Organic lactose	Choline, Inositol, Biotin, DHA, ARA
15	Earth's Best Organic	United States	1.64 g, Whey protein concentrate, W/C Ratio of 70/30	4 g, Palm olein oil, soy oil, coconut oil, sunflower oil, Linolic acid 750 mg	8 g, Lactose	DHA, ARA, choline, lutein, taurine, carnitine, selenium nucleotides, Iron, prebiotic FOS fiber

ARA: Arachidonic acid; DHA: Docosahexaenoic acid, FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; W/C ratio: Whey/Casein ratio.

Table 3 Comparison between human milk and organic formula

Feature	Human milk	Organic infant milk
Source	Produced by lactating mothers	Derived from organic cow's milk
Composition	Complex and ever-changing, tailored to the individual baby's needs	Mimics the composition of human milk but may not be identical
Nutrients	Contains all the nutrients a baby needs for optimal growth and development, including antibodies, enzymes, hormones, and growth factors	It contains most of the nutrients a baby needs but may not be as high in certain nutrients as human milk
Digestibility	Easily digestible, less strain on baby's digestive system, and well-absorbed	It may be more difficult to digest than human milk, especially for preterm babies. Generally easy to digest but may be more difficult to digest than human milk, especially for preterm babies. Some babies may have sensitivities
Allergies	It may help protect against allergies	Despite being organic, it may not offer the same protection against allergies as human milk
Infections	It may help protect against infections	It may not offer the same protection against infections as human milk
Growth Factors	Contains growth-promoting factors	Contains growth factors for the development
Probiotics	Contains beneficial bacteria	It may contain added probiotics
Cost	Free (if breastfeeding)	Varies, but typically more expensive than conventional infant formula
Availability	Available from any mother who is breastfeeding; no preparation is needed	Available at most grocery stores and online retailers, Requires preparation and storage
Environmental Impact	Minimal carbon footprint, no packaging waste	It may have a higher carbon footprint and packaging waste
Emotional Bonding	Promotes bonding between mother and baby	Less direct emotional bonding

prioritizing natural, organic ingredients and the absence of synthetic additives, pesticides, and GMOs. Conversely, non-organic formulas might involve more intensive chemical use, potentially impacting the environment, and were chosen based on diverse factors, including cost, availability, and perceived nutritional quality.

DISCUSSION

Organic milk development and regulation

It is interesting to note that the use of animal milk for infant feeding dates back to around 2000 BC. However, the concept of organic milk is relatively new and emerged much later[10]. During the mid-1940s, there was a global need to increase agricultural practices due to a food shortage after World War II[11]. In dairy production, this was achieved through genetic selection for higher productivity and improved nutrition, including a greater proportion of grains in animal diets. This led to a significant increase in milk yields per cow in the United Kingdom, from 4099 liters per cow per year in 1975 to 7916 liters per cow per year in 2014[12]. Total milk production also increased by 9%, from 13407 million liters to 14649 million liters. However, this intensive farming had some drawbacks, such as poor fertility and longevity in dairy cows and an increased incidence of mastitis due to antibiotic use[13]. As a result, consumers in affluent, developed countries began to demand food from less intensive production systems, including milk and meat[14]. This new socio-economic marketplace provided an excellent platform for developing organic production and commercializing organic milk. Organic milk is produced under strict regulations prohibiting the use of synthetic pesticides, herbicides, fertilizers, and antibiotics on farms that meet specific animal welfare standards[15].

The organic food industry in Europe has grown significantly since the beginning of the 21st century. The dairy sector has been the largest and fastest-growing segment. In 2018, organic dairy sales in Great Britain represented 3.9% of total dairy sales, with the organic milk market valued at £351 million. This accounted for 29% of total organic food sales[16]. The organic liquid milk market is growing at an annual rate of 1.8%, and 25% of households in Great Britain buy organic milk. The United Kingdom's organic dairy market is expected to grow further due to various factors such as strong sales, high-profile private labels, improved distribution chains, rising export demand, and farm conversions. The number of organic farms and cows is also increasing all over Europe, with Germany, Austria, France, and Great Britain having the largest numbers of organic dairy cows[17]. People buy organic food for various reasons, including their beliefs that it is better for the environment, animals, and human health. A recent study found that people primarily purchase organic food because they perceive it as more nutritious and safer than conventional food[18]. However, other factors such as animal welfare, price, availability, freshness, appearance, and taste also play a role in consumer decision-making. In the

Table 4 The main differences between the organic and non-organic formulas

	Organic	Non-organic
Dairy source	Milk often comes from organically raised cows or other organic animal sources	Milk may come from conventionally raised cows with potential hormone and antibiotic use
Ingredients	The certified organic formula must be at least 95% organic, including the milk, vitamins, minerals, and other nutrients—no synthetic pesticides, antibiotics, hormones, herbicides, GMOs, or artificial additives	It may include non-organic ingredients, synthetic pesticides, GMOs, artificial additives, non-organic corn syrup solids, soy oil, and palm oil
Nutrient levels	Provides essential nutrients for infant growth and development	Meets similar nutritional needs as the organic formula
Fat	3.5-4.0 g/100 mL	3.0-3.5 g/100 mL
	Emphasis on organic and natural ingredients, including organic vegetable oils (palm, coconut, soy, sunflower, *etc*.)	Similar use of vegetable oils as fat sources may not be organic
	Aim for a closer resemblance to breast milk in terms of balanced omega-3 and omega-6 fatty acids. Slightly higher content of omega-3 fatty acids	Aim to provide appropriate ratios of fatty acids essential for infant development
CHO	Formulated to meet the nutritional needs of infants. Organic lactose is the primary milk CHO mimicking breast milk in most organic formulas, especially the European formula. The American formula may add other CHO, such as corn syrup, glucose Syrup, and maltodextrin. The lactose amount is typically around 40% of the total calories, about 6-7 g/100 mL. Is easier to digest. Has a better texture & provides a creamy consistency	Formulated to meet the nutritional needs of infants. Lactose is the pr imary CHO source, designed to mimic the CHO composition of breast milk, especially the European formula. The American formula may add other CHO, such as corn syrup, glucose Syrup, Brown Rice Syrup, and sucrose. The lactose amount is typically around 40% of the total calories, about 8-9 g/100 mL
Proteins	It comes from organic dairy sources and contains easily digestible whey and casein proteins with smaller size molecules in a ratio (usually 60/40) and an amino acid pattern that mimics breast milk, supporting optimal digestion and balanced growth	Dairy sources are from conventionally raised cows, with whey and casein proteins with large-sized molecules, but the ratio might differ from breast milk. The amino acid pattern is designed to provide essential amino acids for infant growth
Flavors and colors	It may contain natural flavors & colors, such as vanilla or strawberry	It may contain artificial flavors and colors
Processing methods	Gentler processing to preserve nutrient content	It may undergo more intensive processing, potentially leading to some nutrient loss
Regulations	Subject to regulations set by health authorities (*e.g*., FDA in the U.S., EFSA in the EU	Subject to regulations set by health authorities (*e.g*., FDA in the U.S., EFSA in the EU)
Consumer preferences	Chosen by parents who prioritize natural and organic ingredients, absence of synthetic additives, pesticides, and GMOs	Chosen based on many factors like cost, availability, and a high standard of nutritional quality
Environmental considerations	Emphasizes organic farming practices and reduced chemical use	It may involve more intensive chemical use with potential environmental impacts

CHO: Carbohydrates; EFSA: European Food Safety Authority; EU: The European Union; FDA: Food and Drug Administration; GMOs: Genetically modified organisms; U.S: United States.

United Kingdom, a case study found that the primary reason for purchasing organic milk is the perceived health benefits, with other important factors being better taste, perceived environmental benefits, and avoiding genetically modified ingredients[19]. In 2018, organic cow milk production in the European Union accounted for 3.40% of European dairy cows' production, which is double the figure since 2008[20]. On the other side of the ocean, retail purchases of organic milk products in the United States have increased fivefold since 2002, reaching more than $6 billion in 2020[21].

Organic milk production triggered the development of organic infant formula, which began to be produced and sold in Europe in the early 1990s due to the growing need for organic food products. Many people in Europe believe that organic infant formulas are healthier and more nutritious than conventional formulas. However, the United States did not introduce organic infant formula until 2006. Over the years, the organic infant formula market has grown significantly [22]. In 2000, the European Union introduced the Organic Food Regulation, establishing strict standards for ingredients, processing, and labeling of organic infant formulas. Due to these regulations, the European market for organic infant formula has grown significantly and was worth €2.5 billion in 2021. This growth is expected to continue due to the increasing demand for natural and sustainable products, rising awareness of the benefits of organic food, and health concerns about conventional infant formulas[23,24].

Regulation of organic infant formula in the United States was relatively delayed compared to Europe. The National Organic Program was established by the United States Department of Agriculture in 2009 to regulate the production and labeling of organic infant formula. The program enforces strict criteria for ingredients, production, and processing methods to ensure safety and nutritional value. Other federal regulations, including the Food, Drug, and Cosmetic Act, the Federal Trade Commission Act, and the Consumer Product Safety Improvement Act, also play crucial roles in maintaining the quality of organic infant formulas[21]. As demand for organic infant formula grows, regulatory agencies must remain vigilant and make necessary adjustments to ensure ongoing safety and quality. Countries such as China,

Table 5 The factors that affect the gastrointestinal tolerability of infant formula

Item	Possible factor
Formula-related	Protein source and composition
	Lactose content
	Fat source and composition
	Presence of prebiotics and/or probiotics
	Fiber content
	Osmolality and osmolarity
	Additives and nutrient density
Infant-related factors	Presence of individual sensitivities
	Medical Co-morbidities. *e.g.*, prematurity
	Hydration status
Feeding procedure factors	Milk temperature
	The flow rate of the bottle
	The amount of the milk/feed
	The feeding technique

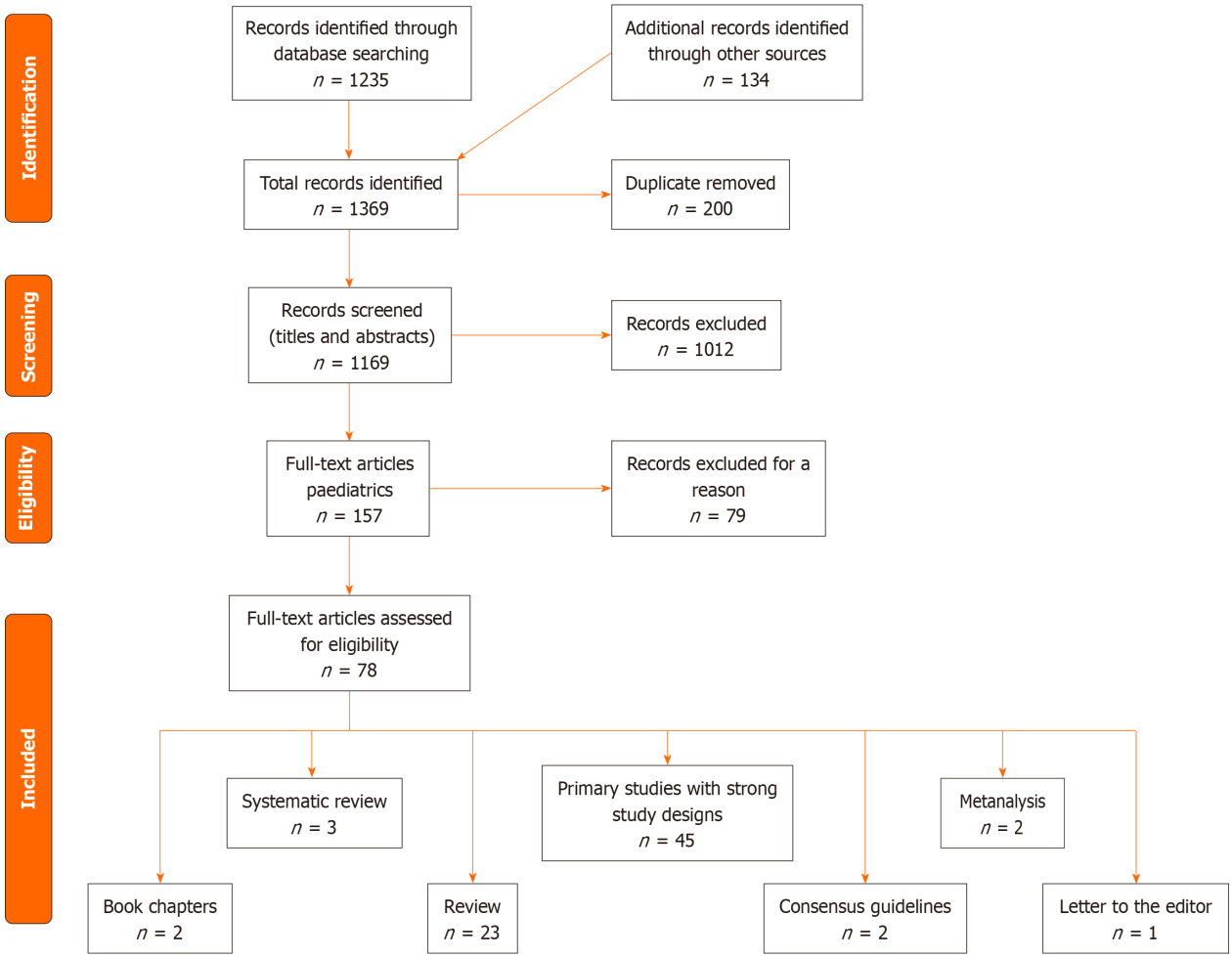

Figure 1 The PRISMA flow chart of the included studies.

Korea, Japan, and Australia have also developed their own standards and regulatory bodies for organic infant formula. Table 1 compares the European and American Organic Infant Formulas[25].

Differences in processing organic and conventional formula

Organic and conventional infant formula manufacturers follow strict regulations and procedures to ensure their safety and nutritional adequacy. However, the processing methods and ingredients used in both types of formula may differ significantly due to differences in sourcing, production standards, and regulations[23]. Organic formula is made in a certified organic facility that meets specific environmental sustainability and social responsibility standards. The formula is made from ingredients sourced from organic farms that follow strict farming practices, excluding synthetic pesticides, GMOs, and synthetic fertilizers[26]. Organic processing methods emphasize natural and minimally processed methods, and the formula may undergo additional testing and quality control measures[27].

In contrast, conventional formulas can combine organic and non-organic ingredients, with some coming from farms that use synthetic pesticides, GMOs, and other conventional farming methods. Conventional formulas may include a broader range of additives, preservatives, and synthetic nutrients to achieve desired characteristics and shelf stability. Conventional processing methods may involve using various processing aids and solvents[28]. It is important to note that regulations and practices can vary between countries and regions[29]. When choosing an infant formula, parents should consider their values and priorities.

Composition of organic infant formula

Organic infant formula is designed to provide infants with the essential nutrients for healthy growth and development. Although there may be slight variations in the specific ingredients among different brands or formulations, most organic infant formulas contain all the necessary nutritional components for infants and young children. The fatty acid profile in organic milk can vary significantly depending on the cows' diets, while protein composition has a more substantial genetic basis. Most studies on milk quality focus on fat composition, proteins, antioxidants, minerals, and other constituents such as terpenes and polyphenols[30]. Table 2 compares the composition of the main components of popular brands of organic first-stage infant formulas according to the companies' official sites. The primary source of protein in organic infant formulas is typically cow's milk, which may also be substituted with goat milk or plant-based proteins that have been modified and broken down to make them easier for infants to digest. Most organic formulas contain whey to a casein ratio of 60:40, which mimics breast milk. However, some organic formulas, especially United States ones, have higher casein ratios. Other formulas may contain type A2 beta-casein protein, which is known to be more digestible than type A1 beta-casein protein. The amino acid pattern in organic and conventional formulas differs significantly. Corbu *et al* [31] found that organic formulas had significantly higher Methionine content than conventional formulas. Methionine is essential for protein synthesis, cellular growth, repair of damaged cells, neurotransmitter synthesis, and antioxidant activity[32].

Organic lactose is commonly used as the main carbohydrate source due to its easy digestibility for infants and is naturally found in breast milk. It also enhances texture and adds a creamy consistency to products. Some organic companies have used organic brown rice syrup as a carbohydrate source. Still, it may contain inorganic arsenic levels up to six times the American standards for safe drinking water. To address this issue, these companies developed organic-compliant technology that filters and removes inorganic arsenic from organic brown rice syrup to undetectable levels[33].

Organic vegetable oils such as palm, coconut, soybean, or sunflower are added to provide essential fatty acids for brain development and energy. Tsiafoulis *et al*[34] discovered that organic milk has a significant increase in the percentage of (9-cis, 11-trans) 18:2 linoleic, linoleic, and α-linolenic acids - compounds that contain allylic protons and unsaturated fatty acids. Moreover, Tsiafoulis *et al*[34] found a significant decrease in the amount of caproleic acid found in organic milk compared to conventional milk. Additionally, Mazzei *et al*[35] found that organic milk has more unsaturated lipids and phosphatidylcholine than conventional milk.

Organic formulas are enriched with vital nutrients such as vitamins A, B, D, E, and K and essential minerals like calcium, phosphorus, iron, zinc, potassium, magnesium, and selenium. These nutrients support various body functions, promote overall growth, and facilitate bone development, red blood cell formation, and metabolic processes. Some organic formulas may contain prebiotics (like oligosaccharides) and probiotics (like *Bifidobacteria* and *Lactobacillus*) that help sustain a healthy gut microbiome and improve digestion. Nucleotides in breast milk are believed to promote infant immune development. Consequently, some formulas also include nucleotides and critical fatty acids like docosahexaenoic acid (DHA), arachidonic acid (ARA), and omega-6 fatty acids that are necessary for brain and eye development. Most organic formulas have DHA and ARA, which are often derived from algae and fungal sources[36].

Research studies have shown that organic milk contains higher levels of calcium, potassium, phosphorous, and molybdenum but lower levels of copper, iron, manganese, zinc, and aluminum when compared to conventional milk. There is also significant seasonal variation in the nutrient content of organic milk[37]. Additionally, some researchers have found that organic milk has lower levels of trace elements such as copper, zinc, iodine, and selenium when compared to conventional milk[38,39]. Organic infant formula should be supplemented with these trace elements, especially iodine, to prevent sub-optimal iodine status in infants. However, the iodine deficiency may depend on the location of organic farming[40]. Therefore, many companies fortify their organic formulas with organic iodine and selenium to ensure that infants receive adequate nutrition. It is important to note that the composition of organic infant formulas can vary between brands and formulations and is subject to change as manufacturers update their products[41]. However, government agencies regulate the composition of infant formulas to ensure that they meet the nutritional needs of infants and comply with organic certification standards. While organic formulas try to mimic human milk, their composition has significant differences, as shown in Table 3.

Benefits of the organic components of the organic formula

The organic formula is similar to the conventional formula in that it varies from company to company. However, certain minimum requirements must be met for a product to be labeled as organic. Table 4 compares the organic formula to conventional formulas. Although individual experiences may vary, the organic component of organic formulas offers several potential benefits. The fat profile is the most significant difference between organic and conventional milk. Organic milk has increased levels of mono- and poly-unsaturated fatty acids such as oleic, linoleic, conjugated linoleic, and α-linolenic acids. This leads to a reduction of atherogenic indices in organic milk. The improved lipid profile of organic milk is due to the excellent feeding strategies employed in organic dairy farms[42]. According to Ortman *et al*, organic milk also has higher levels of unsaturated fatty acids than conventional milk[43]. Gortzi *et al*[43] found that the milk fat and fatty acid profile are affected by animal feeding strategies, regardless of whether they are conventional or organic. Additionally, Ferreiro *et al*[44] discovered significantly higher levels of phosphatidylethanolamine, phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and the sphingophospholipid sphingomyelin in organic milk than in conventional milk. These phospholipids are vital functional foods and primary structural components that affect many organs, especially the central and peripheral nervous systems.

The high methionine content found in organic baby formula allows for better formation of neurotransmitters, such as serotonin and dopamine. This improves brain development, mood regulation, and overall cognitive function[45]. Organic milk has been found to have better heat stability than conventional milk, according to a study by Čuboň *et al*[46]. This heat stability makes organic milk proteins more resistant to denaturation and provides better microbial control, resulting in a longer shelf-life than conventional milk[47]. Milk stability is also important to maintain consistent levels of DHA during formula storage[48].

Many organic infant formulas contain DHA derived from algae. A study by Yeiser *et al*[49] revealed that algal-derived DHA is safe, well-tolerated, and associated with normal growth in infants. DHA is crucial for developing brain grey matter and retinal photoreceptor cell membranes and accumulates considerably in the central nervous system[49]. Algal oil is preferred over fish oil due to its higher purity of DHA and safety. It is commonly used in food and healthcare products and interacts synergistically with other ingredients[50].

Evidence suggests that organic infant formula can reduce the risk of newborns developing bacterial resistance. Studies have shown that organic milk has lower levels of antibiotic-resistant bacteria than conventional milk[51]. In particular, a study by Neri *et al*[52] found that bacterial isolates in milk from organic farms had lower antibiotic resistance, especially to ampicillin and tetracycline, compared to milk from conventional farms[52]. This could be due to several factors, including the lower disease caseload in organic farms, lower use of antimicrobials, and exclusion of sick animals who were given antibiotics until no antibiotic excretion was expected in their milk[53]. However, the use of organic fertilizers may increase the risk of increasing antibiotic resistance gene abundance. Therefore, before using organic formula, it is important to conduct a thorough microbial evaluation to ensure the safety of the organic milk[54]. However, more research is needed to confirm whether the difference in bacterial resistance is due to the organic ingredients in the formula or other factors.

Factors affecting gastrointestinal tolerability for infant formula

Several factors can affect how well an infant tolerates a particular formula. These factors can be related to the formula, how it is fed, or the infant's characteristics. It's essential to remember that each formula is unique, and each baby responds differently to it. Table 5 outlines the factors that can impact how well an infant tolerates a formula. The formula's type and source of protein can significantly affect gastrointestinal tolerability. Some babies may have difficulty digesting cow's milk protein, while formulas with whey protein or Casein A2 are easier to digest. Casein A2 has a different amino acid composition than Casein A1, making it easier to digest and more similar to breast milk[55]. Hydrolyzed protein formulas are recommended for babies with protein sensitivities[56]. Lactose-free or low-lactose formulas may be necessary for babies with lactose intolerance, but organic lactose is more tolerable than conventional lactose[57]. The type of fats in the formula also affects digestion, and a blend that resembles human milk is better tolerated. Prebiotics and probiotics can improve gastrointestinal function, and formulas with these additives may positively impact tolerability[58]. Specialized formulas with added dietary fibers can influence bowel movements, but fiber content must be balanced[59]. Osmolality and osmolarity affect gastrointestinal tolerability, with high osmolality leading to discomfort. Additives, vitamins, and minerals in the formula can also impact gastrointestinal function, and babies with sensitivities to specific additives may experience digestive issues[60].

It is important to note that not all infants are the same regarding formula feeding. Some infants may be sensitive to certain components, so finding the right brand may require trial and error[61]. This is especially true for babies with medical conditions such as reflux, colic, prematurity, or gastrointestinal disorders, who may need specialized formulas to manage their symptoms. Transitioning from breast milk to formula may take some time for the infant's gastrointestinal system to adjust, so it is essential to ensure that the infant is adequately hydrated while being fed formula[61]. By slowly introducing formula and monitoring the infant's response, you can determine the best formula suitable for their unique needs[1].

Effective formula feeding requires attention to several key factors that can impact gastrointestinal tolerability. Overfeeding or feeding too quickly can lead to discomfort or spitting up, while formula that is too hot or too cold can be challenging for infants to digest. It is best to warm the formula to body temperature before feeding to ensure an optimal temperature. The milk flow rate from the bottle is also crucial for gastrointestinal tolerability, as the formula that flows too quickly can cause gas and bloating. Adjusting the flow rate to ensure a slow and steady flow is important. Poor infant latching or hard sucking can also lead to air being swallowed along with the formula, causing gas and bloating. Proper latching and gentle sucking can help to achieve better milk tolerability. Finally, overfeeding can also cause gas and

bloating, so it is essential to feed on demand and ensure that the proper feeding amount is achieved. Parents can help ensure that their infants are comfortable and well-nourished by paying attention to these factors[1,62-64].

Gut tolerability in organic and conventional infant formula

Ensuring good tolerance in infant formula is of utmost importance as formula intolerance can lead to symptoms such as spit-ups, vomiting, fussiness, cramps, or constipation, which can significantly impact an infant's well-being and comfort. Commercially available formulas vary widely in their processing methods, sources, and levels of key components like protein, lipids, and micronutrients. These compositional differences are known to affect the formula's tolerability and can influence the health outcomes of the infants being fed[65]. It is worth noting that organic formulas are subject to regulatory guidelines and individual company protocols, which can affect their composition. Additionally, there are differences in the compositions of European and American organic formulas due to geographical and regulatory factors [66,67].

It has been found that the nutritional value of lactose in organic and conventional formulas is quite similar. However, new studies suggest that organic lactose may be better tolerated and more digestible, especially in cases of mild lactose intolerance. This could be because organic farming practices do not use synthetic pesticides and herbicides that may contaminate conventional milk[68]. However, there is insufficient evidence to prove that organic lactose is more beneficial than conventional lactose. Further research is needed to confirm these findings. Additionally, organic lactose is usually more expensive than conventional lactose[69]. However, conventional and organic formula producers provide low or free-lactose formula to manage severe lactose intolerance, a common cause of gastrointestinal problems in infants [70]. Unfortunately, no studies compare the effectiveness of organic and conventional lactose-free or low-lactose formulas in managing lactose intolerance.

Including organic zinc in formulas can improve the digestibility of essential components like crude protein, fat, and fiber compared to non-organic zinc[71]. Infant formula fat and protein contents are critical in determining stool consistency. For example, whey protein softens the stool, while casein makes it firmer. Moreover, the fat content in organic milk, especially if it is rich in polyunsaturated fatty acids (PUFA), can contribute to a softer stool consistency compared to standard fat content. Additionally, high lactose, magnesium, and galactooligosaccharides (GOS) can help to soften the stool consistency. Magnesium is a laxative and can stimulate intestinal motility by inducing cholecystokinin secretion and acetylcholine production[72].

It is essential to recognize that infant formula and human milk have different gut microbial colonization compositions that affect the gut microbiome of infants. Human milk, which is rich in nutritional and bioactive components such as lactoferrin, human milk oligosaccharides (HMOs), and immunoglobulins, is crucial in promoting growth and immunological development[73]. To make up for this difference, manufacturers often supplement formulas with prebiotics and probiotics to simulate the healthy gut microbiome seen in breastfed infants. These additives have bifidogenic properties and can regulate the immune system. Research has shown that adding prebiotic oligosaccharides to infant formula is well-tolerated by healthy infants. Including prebiotic oligosaccharides in infant formula results in softer stools, decreased fecal pH, and increased levels of Bifidobacteria when compared to formulas that lack this supplementation[74].

Table 2 indicates that many organic formulas contain prebiotics like organic GOS, FOS, 3'GL - Galactosyllactose, and probiotics such as *L. fermentum* and *Bifidobacterium longum BB536*. Conventional formulas have been using prebiotics and probiotics for a long time now to imitate breast milk. Some traditional formulas also add HMOs to aid gut microbiota development and facilitate gut maturation. However, HMOs are artificially produced in the lab with the same structure and function as those found in breast milk. Only Kendamil Organic formula is known to contain 3'GL – Galactosyllactose HMO, but its source is unclear. Researchers have found thirteen molecules in bovine colostrum that mimic breast milk HMOs, indicating that cow milk could be a potential source of organic HMOs[75].

Understanding and optimizing gut tolerability in infant formulas is paramount to ensure infants' well-being and comfort. Organic formulas may have better gut tolerability due to their composition and farming practices[76,77]. Still, comparative studies between organic and conventional formulas are needed to understand the nuanced effects of various components on the gastrointestinal system of infants. Including HMOs and using advanced prebiotic and probiotic supplementation can improve gut tolerability and overall health benefits of organic and conventional infant formulas[78].

Recommendations

Before recommending any infant formula, it is important to ensure that it meets specific ingredients, farming practices, and processing standards. A valid certification by a reputable certification body such as USDA, EFSA, or an equivalent organization should be available. The formula should also match the baby's nutritional needs according to their age and circumstances. The ingredient list should avoid artificial additives, synthetic preservatives, and unnecessary fillers. Whenever possible, ingredients should be sourced from organic farms. The formula should provide a balanced nutrition with essential nutrients such as vitamins, minerals, and fatty acids (*e.g.*, DHA and ARA) to support the baby's physical growth and mental development.

The source of protein should be organic, for example, organically raised cows. This helps to minimize the risk of exposure to antibiotics, synthetic hormones, or pesticides. The formula should also use natural sweeteners like lactose and avoid any added sugars or high-fructose corn syrup. Supplementing the formula with prebiotics, probiotics, or both are recommended to support gut health and digestion. If the organic formula contains brown rice syrup, the healthcare professional should be sure of the arsenic content of the formula.

The list of non-organic ingredients allowed to be included in the formula should be stated, including its percentage, especially for the American formula. The packaging should be free from bisphenol-A to avoid potential human health risks, especially the increased risk of developmental disorders in the growing brains. It is also important to ensure that the formulas are labeled as non-genetically modified organisms (non-GMO), as this indicates that the ingredients used in

the formula have not been genetically engineered.

Limitations of the study

There are several limitations to the current study. One of the biggest limitations is the lack of specific scientific studies directly comparing the gastrointestinal tolerability of organic and traditional infant formulas. The lack of available research restricts the depth and breadth of the review. Organic and traditional infant formulas are not standardized across brands or regions, resulting in different ingredients, nutrient composition, and processing methods. This variety makes it difficult to draw comprehensive conclusions that apply to all formulas within each category. Infants have different health conditions, dietary needs, and tolerances. The review may not include the full range of health conditions, which could result in bias or incomplete population representation. Some studies examining the gastrointestinal tolerability of infant formulas might have small sample sizes, reducing the statistical power and generalizability of their findings. This limitation affects the strength of the conclusions drawn from these studies. Studies assessing gastrointestinal tolerability may vary in duration, and some may be of short duration. Long-term effects and tolerability may not be adequately captured in shorter studies. Reports from parents on their experiences using infant formula could introduce reporting bias, as parents may perceive organic formulas more positively due to preconceived beliefs about their benefits. This bias could impact the interpretation of the results. Conducting controlled, randomized clinical trials directly comparing organic and traditional infant formulas can raise ethical concerns, particularly regarding exposing infants to possible risks associated with formula intolerance. Studies reporting significant differences or favorable outcomes may be more likely to be published, leading to publication bias. This could skew the overall conclusions of the review. The systematic-review is based on information available up to a specific knowledge cutoff date. More recent studies or developments in the field beyond that date may not be included, which could affect the comprehensiveness and accuracy of the review. It is essential to acknowledge these limitations to maintain transparency and ensure a balanced interpretation of the study's findings.

CONCLUSION

Understanding infant formula's impact on gastrointestinal tolerability is crucial for parents and healthcare providers. While factors like formula composition, feeding techniques, and individual differences affect how well infants tolerate formula, specific aspects of organic formulas might offer potential benefits. The comparison between organic and conventional formulas highlights differences in digestibility, prebiotic and probiotic contents, and potential advantages of organic lactose. However, more robust research is needed to establish these differences and their impact on infant health definitively. When selecting a formula, certifications, ingredient sources, nutritional balance, and the presence of natural additives should be considered. Organic formulas, often incorporating organic protein sources and beneficial supplements, represent a promising option, yet further studies are necessary to clarify their distinct advantages. Addressing these aspects holistically, alongside ongoing research and regulation enhancements, will support informed choices for parents seeking the best formula suited to their infant's unique needs and well-being.

ARTICLE HIGHLIGHTS

Research background

The demand for organic infant formula has surged, driven by heightened parental awareness of health benefits and a growing organic product market. Differences in regulatory standards and cultural attitudes globally have shaped variations between European and American organic infant formula.

Research motivation

The increasing popularity of organic infant formula raises critical questions regarding its composition, regulatory frameworks, and potential impact on infants' gastrointestinal health, especially when compared to traditional formulas.

Research objectives

To conduct a comprehensive analysis comparing the gastrointestinal tolerability and nutritional compositions of organic and traditional infant formulas, exploring the existing literature and regulatory disparities between European and American organic formulas.

Research methods

A systematic review was conducted, spanning multiple databases and reputable publications. Seventy-eight articles were included, comprising research papers, meta-analyses, systematic reviews, narrative reviews, and consensus guidelines. Data extraction covered formula compositions, nutritional profiles, and gastrointestinal tolerability findings from infant populations.

Research results

European organic infant formulas, regulated by the European Commission, exhibit stricter standards than American

organic formulas regulated by the USDA & NOP. Variations were evident in regulations, ingredients, nutritional content, and cultural attitudes toward these formulas.

Research conclusions

While both types of formulas aim to provide essential nutrients, disparities exist in ingredient sources, regulations, and nutrient levels. European formulas tend to prioritize organic ingredients and stricter regulations, while American formulas may contain additional ingredients like added iron and different carbohydrate sources.

Research perspectives

The findings highlight the need for continued investigation into the long-term effects of organic versus traditional formulas on infants' gastrointestinal health. Future research could focus on refining regulations and examining the real-world impact of these differences on infant health outcomes.

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SYSTEMATIC REVIEWS

Sociodemographic determinants associated with breastfeeding in term infants with low birth weight in Latin American countries

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Abstract

BACKGROUND

A progressive decrease in exclusive breastfeeding (BF) is observed in Latin America and the Caribbean compared with global results. The possibility of being breastfed and continuing BF for > 6 months is lower in low birth weight than in healthy-weight infants.

AIM

To identify factors associated with BF maintenance and promotion, with particular attention to low- and middle-income countries, by studying geographic, socioeconomic, and individual or neonatal health factors.

METHODS

A scoping review was conducted in 2018 using the conceptual model of social determinants of health published by the Commission on Equity and Health Inequalities in the United States. The extracted data with common characteristics were synthesized and categorized into two main themes: (1) Sociodemographic factors and proximal determinants involved in the initiation and maintenance of BF in low-birth-weight term infants in Latin America; and (2) individual characteristics related to the self-efficacy capacity for BF maintenance and adherence in low-birth-weight term infants.

RESULTS

This study identified maternal age, educational level, maternal economic capacity, social stratum, exposure to BF substitutes, access to BF information, and quality of health services as mediators for maintaining BF.

CONCLUSION
Individual self-efficacy factors that enable BF adherence in at-risk populations should be analyzed for better health outcomes.

Key Words: Breastfeeding; Low birth weight; Latin America; Self-efficacy; Social determinants of health

Core Tip: Analyzing sociodemographic and individual conditions for maintaining breastfeeding (BF) is fundamental for meeting the second sustainable developmental goal. However, analysis of the feeding behavior in low-birth-weight term newborns in Latin America is limited. Few studies have assessed the mediating factors for BF maintenance, paving the way for the challenges faced by at-risk populations, mainly in developing countries. Evidence-based interventions should be based on an understanding of the social and individual factors affecting feeding practices for at-risk populations.

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INTRODUCTION

The United Nations Children's Fund and the World Health Organization estimated that one in seven live births will be underweight by 2020, which is equivalent to 19.8 million babies worldwide. The prevalence of all low-birth-weight infants with stunting and wasting in early childhood is approximately 70% in South Asia and sub-Saharan Africa[1]. The variation has been minimal in Latin America, maintaining a prevalence between 12% and 9.6% over the last decade[1]. No region has experienced significant changes in the prevalence since 2012, preventing the achievement of the low-birth-weight target set by the World Health Assembly for 2030[1]. In this context, low birth weight is considered a public health problem associated with the newborn's well-being because of the high risk of acquiring diseases or disabilities that affect physical and cognitive development and as a predictor of morbidity and mortality[2].

In this sense, access to breastfeeding (BF) is essential and indicates better child health outcomes. However, the likelihood of being breastfed and continuing BF for > 6 months in low-birth-weight infants is lower than that in healthy-weight infants. Underweight children without adequate nutrition have an increased risk of fetal and neonatal death in the first years of life, physical and cognitive growth retardation, and increased chronic diseases later in the perinatal period, childhood, and adulthood[3].

In this regard, the literature has shown the benefits of BF in newborns and infants, and sociodemographic determinants associated with its maintenance are of particular relevance, mainly in low- and middle-income regions[4]. The individual characteristics of the mother and newborn, associated with cultural feeding practices, as well as social and health system determinants, are some factors that influence BF practices[5].

Smoking, schooling, obstetric conditions, newborn complications that require separation from the dyad, and BF education have been identified as moderating individual characteristics factors of feeding practices of the mothers associated with the initiation and continuation of BF[6]. Moreover, conditions specific to the BF woman, such as self-efficacy and her family nucleus, especially the emotional and mental situation, can contribute to the abandonment of BF [6]. Geographical, socioeconomic, and individual factors and health complications are among the factors associated with late or impossible BF initiation in low-birth-weight infants during the first hour postpartum[7,8].

The trend in improving BF duration in Latin America and the Caribbean depends not only on the policies implemented by each government but also on the particularities of population subgroups[9]. However, studies related to BF and nutrition in low-birth-weight term infants have generally been limited, mainly due to the difficulty in generating reference parameters to observe nutritional behaviors and their impact on the neuro-physical development of the child; therefore, efforts have been directed to preterm infants and those with adequate weight for gestational age, for whom follow-up scales have been constructed[10,11]

Global studies have identified the significant variability of feeding practices in low-birth-weight populations[9], reporting the prevalence of BF and its association with socioeconomic conditions of the environment. However, the findings are more limited to Latin America, a region characterized by vast social inequalities, mainly to materializing social policies affecting the health and educational system and generally satisfying basic needs[12].

In this context, aspects related to health equity are considered as determinants. The absence of social, economic, and demographic guarantees can influence the initiation and adherence to BF in low-birth-weight infants[9]; some cultural and social factors can interfere with the promotion and support of BF to ensure adherence. Consequently, sociodemographic determinants and individual conditions associated with BF should be analyzed in low-birth-weight term infants in Latin American countries from a health inequity perspective.

MATERIALS AND METHODS

A scoping review was performed based on five phases proposed by Arksey and Malley[13] and reports according to the Preferred Reporting Items for Systematic Reviews for Systematic Reviews and Meta-Analyses statement[14].

For the present review, the 2018 conceptual model of social determinants of health published by the Commission on Equity and Health Inequalities in the United States was adopted. The social position was considered a central component and an explanatory construct that allows determining the representations of inequality, including income, education, occupation, gender, ethnic belonging, and other dimensions, to determine the health distribution and well-being in the population mediated by the so-called proximate or intermediary determinants, which include material circumstances, social cohesion, human behavior, genetic inheritance, and health system organization[15].

The concept of self-efficacy was determined according to Bandura (1987), who defined it as judgments of each individual about their abilities and use to organize and execute actions with the highest possible performance, contributing to the achievement of human accomplishments and increased motivation[16].

Phase 1: Identification of research questions

This review addresses the following research questions: (1) What sociodemographic factors are involved in initiating and maintaining BF in low-birth-weight term infants in Latin America; (2) What proximal health determinants are involved in the inequality of BF maintenance and adherence in low-birth-weight term infants; and (3) What individual characteristics are related to self-efficacy for BF maintenance and adherence in low-birth-weight term infants?

Phase 2: Identification of relevant studies

The search strategy included articles published in Medline, Embase, OvidSP, CINAHL, and the Latin American and Caribbean Health Sciences Database using the Medical Subject Headings MeSH and DeCS terms reference list. The combinations of search terms using Boolean operators "AND" and "OR" were as follows: Social determinants of health AND self-efficacy AND breastfeeding AND infant, and low birth weight (Supplementary material). Additional information was obtained by manually searching the reference lists of relevant articles. Full-text articles published up to 2022 using qualitative and quantitative methodologies were considered. The search strategy was limited to English and Spanish studies. Commentaries, editorials, opinion articles, and book chapters were excluded.

Phase 3: Selection of studies

In this phase, the following aspects were contemplated: (1) Construction of search formulas elaborated by an experienced research team member; (2) Identification of the search strategy by database exploring the best scientific evidence; and (3) Analysis of titles and abstracts to select relevant studies. Subsequently, three researchers assessed the titles and abstracts of the identified publications and independently performed data extraction. Discrepancies were discussed and resolved by consensus.

Phase 4: Data analysis

The organization and thematic analysis of the scientific evidence was carried out in the Excel program with data extraction such as bibliographic source, study purpose, country of origin, study type, design, sociodemographic characteristics, cultural characteristics, type of BF, and individual aspects of the mother in terms of self-efficacy and knowledge gaps (Table 1). During the process, three reviewers compared the authors' contributions and sociodemographic characteristics of individual conditions responsible for initiating and sustaining BF in low-birth-weight term infants.

Phase 5: Collate, summarize, and communicate the results

The extracted data with common characteristics were synthesized and categorized into two main themes: (1) Sociodemographic factors and proximal determinants involved in the initiation and maintenance of BF in low-birth-weight term infants in Latin America; and (2) Individual characteristics related to the capacity for self-efficacy for BF maintenance and adherence in low-birth-weight term infants (Tables 2 and 3).

RESULTS

Search flow and study characteristics

The search strategy identified 1483 articles; 1263 studies were excluded. Sixty full-text articles were reviewed, and 47 articles were excluded. Eleven studies were finally included after applying the study criteria for synthesizing the results (Figure 1). One clinical trial was identified in the 11 selected studies. Most participants were recruited through convenience sampling, and 46% used comparison groups. Table 1 shows the primary characteristics of the included studies.

Sociodemographic factors involved in the initiation and maintenance of BF with low-birth-weight term infants in Latin America

Seven observational studies have reported sociodemographic factors and proximal determinants associated with BF adherence and maintenance in low-birth-weight term infants. Studies have focused on identifying the prevalence of BF, feeding patterns, and associated factors for its maintenance. Most BF reported in the study population ranged from 34.7%

Table 1 Main characteristics of the included studies

Ref.	Location	Study design	Type of Sampling	Sample size LWB	Control group	Measurements	Analysis
Lizarazo *et al*[2], 2023	Colombia	Observational	Convenience	25	No	Investigator-designed survey. Medical records	Descriptive analysis
Ortelan *et al*[18], 2020	Brazil	Observational	Probabilistic	2370	No	Questionnaire on sociodemographic characteristics of mothers and breast milk consumption. BF prevalence survey	Poisson regression
Agudelo *et al*[23], 2021	Colombia	Clinical trial	Probabilistic	297	Yes	Infant BF assessment tool	Cox proportional hazards analysis. Cox regression models
Montoya *et al*[24], 2020	Colombia	Observational	Convenience	52	Yes	Investigator-designed survey. Medical records	Descriptive analysis
Charpak and Montealegre-Pomar[25], 2023	Colombia	Observational	Convenience	57.154	Yes	Griffiths test. INFANIB test	Bivariate analysis
Sequeiros *et al*[26], 2023	Peru	Observational	Convenience	489	No	Demographic and family health survey. Household questionnaire. Individual woman questionnaire. Health questionnaire	Bivariate and multivariate analysis
Ortiz Romaní and Loayza Alarico [20], 2023	Peru	Observational	Convenience	531	No	National database	Binary logistic regression
Wormald *et al*[19], 2021	Chile	Observational	Convenience	118	No	State trait anxiety inventory. Beck depression inventory; BDI-I. BF self-efficacy scale for mothers with hospitalized preterm infants	Multinomial logistic regression
Javela Rugeles *et al* [21], 2019	Colombia	Observational	Convenience	90	No	Medical records	Descriptive analysis
Mangialavori *et al* [22], 2022	Argentina	Observational	Probabilistic	1044	No	Investigator-designed survey. Medical records	Descriptive analysis
Ortelan *et al*[17], 2019	Brazil	Observational	Probabilistic	2112	Yes	Medical records	Multilevel Poisson regression models

LBW: Low birth weight; INFANIB: Infant neurological international battery; BDI-I: Beck depression inventory-I; BF: Breastfeeding.

to 58.5% at 6 months. The primary mediators of maintaining BF were educational level, access to health services, and social status[2,17-22]. Agudelo *et al*[23] conducted a randomized clinical trial on the effect of the time of initiation of skin-to-skin contact at birth, immediately compared to early, on the BF duration in term newborns, analyzing the percentage of infants exclusively breastfed at 3 months and the period in months of exclusive BF. The results showed that skin-to-skin contact, regardless of the initiation time, improved the percentage of exclusively breastfed infants in at-risk populations[23] (Table 2).

Individual characteristics related to self-efficacy for BF maintenance and adherence in low-birth-weight term infants in Latin America

Individual characteristics associated with BF maintenance in the study population were mainly related to maternal age and education, perception of BF success, type of birth, pathologies related to the newborn or mother, and previous BF experience. Some barriers to BF adherence were associated with the use of breast milk substitutes, advanced ages, separation of the mother–child dyad, and compromised emotional states of the mother. Facilitators for achieving self-efficacy levels were family and social support, maternal education and experience, and adequate follow-up of the mother's and newborn's health status by health services[2,17,19-26] (Table 3).

DISCUSSION

Low birth weight is a public health problem associated with a series of determinants that condition a child's health status in the short and long term, representing a challenge for the health system. This review identified the social and individual determinants in mothers who modify BF practices for its maintenance and adherence in an underexplored at-risk population.

Table 2 Sociodemographic characteristics and proximal determinants associated with breastfeeding outcomes in low-birth-weight term infants in Latin America

Ref.	BF results	Mother's socio-demographic characteristics			Associated proximate determinants
		Age	Education	Social stratum	
Lizarazo *et al*[2], 2023	Information on prenatal BF: 67%. No information on BF: 32.3%. 1-4 prenatal checkups: 43.5%. More than 4 controls: 13.7%. Time to initiation of BF at birth: < 1 h: 33.9%. 1-12 h: 33.1%. > 12 h: 33%. Previous history of BF. BF up to 6 months: 58.5%. BF between 3 and 6 months: 18.5%. No previous BF: 7.1%	Average 28 ± 7.3 years	High School: 38.7%. Technical education: 19.4%. Professional: 31.5%	Low stratum: 31.5%. Very low stratum: 40.3%	Work-related causes: 10.5%. Study: 0.8%. Partially absent mother: 0.8%
Ortelan *et al*[18], 2020	BF prevalence: 54.5%	Age in years (%). < 20: 18.1%. 20-35: 66.9%. > 35: 15%	High School: 47.1%. Professional: 12.5%	No report	Working outside the home (PR = 1.28; 95%CI 1.11-1.48). Residence in municipalities with a prevalence of child undernutrition below 10% (PR = 1.66; 95%CI 1.23-2.24). Mothers with 12 years of schooling or more (PR = 1.35; 95%CI 1.16-1.58)
Agudelo *et al*[23], 2021	Average duration of exclusive BF: 5 months. BF up to 3 months: 78%. No BF up to 3 months: 19.5%. BF up to 6 months: 25%. No BF up to 6 months: 71%	Median age (IQR). Intervention group: 23 years (21-29). Control group: 24 years (20-25)	Elementary education: 11%. High school: 60%. Technical education: 13%. Professional: 16%	Low stratum: 64.3%. Very low stratum:33.6%	Working outside the home
Sequeiros *et al* [26], 2023	Interruption of exclusive BF: 26%. Initiation of BF at birth: Immediately: 70.1%. > 1 h: 29.8%	Age in years of mothers who discontinued BF. < 18: 31.7%. 18-25: 27.7%. 26-35: 25.7%. 36-45: 25.0%	Elementary education: 20.5%. High school: 26.7%. Professional: 31.2%	Low stratum: 22%. Middle stratum: 33%. High stratum: 36%	Higher educational level (PRa: 1.55; 95%CI: 1.06-2.27). Rich *vs* poor family wealth index (RPa: 1.13; 95%CI: 1.03-1.25). Residing in the jungle (RPa: 0.77; 95%CI: 0.71-0.84). Native indigenous language (PRa: 0.82; 95%CI: 0.75-0.91). BF training (PRa: 0.88; 95%CI: 0.82-0.94). Infant with health insurance (PRa: 0.91; 95%CI: 0.84-0.97)
Ortiz Romaní and Loayza Alarico [20], 2023	Prevalence of early initiation of BF: 49.6%.	Age in years (%). 12-14: 0.09%. 15-19: 6.11%. 20-49: 93.80%	High School: 47.2%	Low stratum: 47%. Middle stratum: 21.3%. High stratum: 31.5%	Factors interfering with early initiation of BF: Living in rural area (ORa: 2.37) and jungle (ORa: 1.72). High wealth index. Access to health services and prenatal care
Javela Rugeles *et al*[21], 2019	Children with BF for one year maintain anthropometric measurements below -2 SD.	Age in years (%). < 20: 17%. > 35: 18%	High school: 64%. Elementary education: 18%. Technical education: 18%	Very low stratum: 57%. Low stratum: 36%. High stratum: 8%	Low social stratum
Mangialavori *et al* [22], 2022	Prevalence of BF: 34.7% (95%CI: 31.6-37.9). BF before the first hour of birth: 40.1% (95%CI: 36.9-43.4)	No report	Elementary education: 9.3%. High school: 91.3%	No report	Mother's educational level
Ortelan *et al*[17], 2019	Prevalence of BF: 43.9%	Age in years (%). < 20: 21.3%. 20-35: 65.3%. > 35: 13.4%	High School: 47.6%	No report	Factors favoring BF practices: Age between 20-35 years (PR = 1.35; 95%CI: 1.09-1.69). Work at home. Birth in BF-friendly hospital services. Increased availability of human milk banks per 10000 inhabitants

BF: Breastfeeding; PR: Prevalence radius; IQR: Interquartile range; OR: Odds ratio.

The study revealed that certain social factors hinder exclusive BF within the first 6 months of life. These factors contribute to the low BF rates in Latin America. Demographic factors such as advanced age, mainly in adolescence, low family income, ethnicity, marital status, support, and orientation of health services showed a direct relationship with feeding outcomes in the study population. Various studies have shown how social factors, such as marital status, impact

Table 3 Individual characteristics related to self-efficacy for breastfeeding maintenance and adherence in low-birth-weight term infants in Latin America

Ref.	Reason for BF desertion/difficulties	Barriers	Enablers
Lizarazo *et al*[2], 2023	Perception of low milk production. Newborn's feeling of not satiety. Newborn rejection. Maternal decision	Mother's mood as an influence on BF practice. Work commitments	Family support for housework
Ortelan *et al*[18], 2020	Age, education, multiparity	Inadequate supplementary feeding	High educational level
Agudelo *et al*[23], 2021	Supported to stimulate BF in the first hour of life	Interference with newborn routines; availability of time for skin-to-skin contact at birth; obesity; smoking	Educational support. Immediate skin-to-skin contact in the maternity ward
Montoya *et al*[24], 2020	Newborn hospitalization for low birth weight. Maternal hospitalization. BF technique. No previous experience in BF	Feeding with milk substitutes suggested by health personnel	Mother's willingness to breastfeed. Support from family and health personnel. Mother's previous BF experience
Charpak and Montealegre-Pomar[25], 2023	Respiratory pathology of the newborn	Pathologies of the newborn	Monitoring and follow-up of the health of low-birth-weight newborns and maternal care in mother Kangaroo programs.
Sequeiros *et al*[26], 2023	Lack of knowledge of BF during pregnancy	Mothers with higher education. Infant only child. Age < 18 years. Birth by caesarean section	Early BF training during pregnancy. Early initiation of BF
Ortiz Romaní and Loayza Alarico [20], 2023	Cesarean delivery. First gestation. Pre-milk feeding of the newborn	Lack of BF skills. Limitations for skin-to-skin contact in the first hour of life	Develop skills and abilities in relation to the promotion of BF. Management of the mother's own symptoms that are contemplated in the different prenatal services and delivery room
Wormald *et al*[19], 2021	Manifestation of emotional symptoms	Exposure to triggers for depression or anxiety	Self-efficacy
Javela Rugeles *et al* [21], 2019	Newborn comorbidities	Extreme ages. No support during the first month of the newborn's life	Family support
Mangialavori *et al* [22], 2022	Cesarean delivery	Limitations to BF in the first hour of life. Separation of mother-infant dyad > 4 h	Educational level

BF: Breastfeeding.

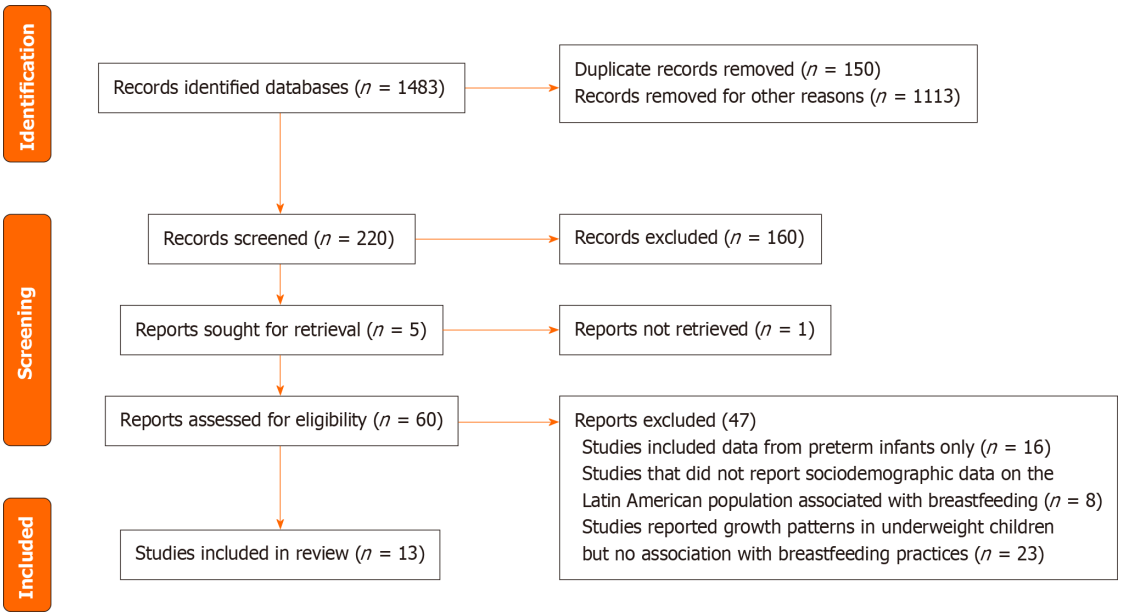

Figure 1 The preferred reporting items for systematic reviews and meta-analyses flow diagram.

BF effectiveness. These factors are related to family stability and economic situations for child rearing and protection[27].

In this context, the educational level is an important factor. Studies report a greater tendency for early discontinuation of exclusive BF during the first hour up to 6 months of life in mothers with low educational levels with lower rates of BF in low-birth-weight infants compared with full-term infants with adequate weight for gestational age[28]. However, a pattern of BF abandonment is also observed in pregnant women with higher educational levels. BF policies focused on vulnerable populations and work activities specific to this educational level may explain this phenomenon; therefore, the needs of the people should be recognized in occupational terms and according to the economic growth of the regions[29].

Consequently, access to quality health services is essential. Our results showed positive effects in mothers who received education on the importance and benefits of BF during follow-up, maternal perinatal care, and newborn hospitalization. Intervention strategies based on population needs and geographic diversity by analyzing the social structure's multiple components can significantly promote BF adherence and maintenance in the study population[30]. However, these intervention processes should be accompanied by the joint construction of skills to develop self-efficacy to minimize the risk of abandonment of good feeding practices in the infant population[31]. Additionally, conditions of the newborn and mother related to the manifestation of pathologies should be considered to strengthen the response capacity and BF technique during the healthcare process to ensure adherence to hospital discharge[27,32].

In this sense, family and health personnel support are essential for the mother to make the right decisions regarding BF. The early diagnosis of risk factors associated with individual characteristics can become a protective factor that contributes to the management of deficient emotional states and, by extension, positively stimulates confidence and security skills to continue BF[33]. In addition, involving parents in the orientation process for BF techniques and encouraging active participation helps foster positive outcomes for the couple. BF self-efficacy in low-birth-weight infants is considered an emotional factor that influences milk production and prolongs BF exclusivity and maintenance, enabling empowerment in the BF process to overcome obstacles and difficulties for comprehensive care[33]. Implementing health interventions on the overall care of low-birth-weight newborns at home from a skilled approach allows interaction in health management with the child. Therefore, mothers' self-efficacies should be assessed to detect the risk of BF abandonment and facilitate a safe transition based on the population's needs[34].

CONCLUSION

Diagnosing the proximal determinants that mediate BF adherence and maintenance using a differential approach and a self-efficacy skills development perspective is essential for the comprehensive care of low-birth-weight term infants in developing countries.

ARTICLE HIGHLIGHTS

Research background

Proximal determinants define the maintenance of breastfeeding (BF) in infants with low birth weights in the Latin American population.

Research motivation

Equity in health is an essential issue to address to achieve sustainable development goals regarding the food security of the population at risk.

Research objectives

To identify proximal determinants associated with BF maintenance in low birth weight infants at term. Little literature describes how proximal determinants affect BF maintenance in populations at nutritional risk. Determining the epigenetic conditions involved in infant feeding practices is essential to develop good health practices.

Research methods

A scoping review was performed according to the five phases proposed and reporting according to the preferred reporting items for systematic reviews for systematic reviews and meta-analyses statement.

Research results

Proximal determinants related to social position are involved in the maintenance of BF in population at nutritional risk. Despite the fact that BF is considered the best food for the population at nutritional risk, the prevalence at a global level does not allow achieving sustainable development objectives. Individual factors and self-management skills should be promoted to reinforce infant feeding practices.

Research conclusions

The analysis of social inequalities is fundamental to reduce the gaps in the provision of health services. A comprehensive approach with a differential emphasis based on individual and collective response capacity is a priority for the formulation of public health policies.

Research perspectives

To analyze individual and collective differences based on the epidemiological behavior of possible nutritional affectations in the population at risk. Develop public policies based on evidence-based medicine and on the needs perceived by the population.

FOOTNOTES

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LETTER TO THE EDITOR

Pressure pain sensitivity: A new stress measure in children and adolescents with type 1 diabetes?

Annemarie Cecilie Grauslund, Emilie Bundgaard Lindkvist, Steffen Ullitz Thorsen, Søren Ballegaard, Jens Faber, Jannet Svensson, Anna Korsgaard Berg

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Abstract

Type 1 diabetes (T1D) is associated with general- and diabetes-specific stress which has multiple adverse effects. Hence measuring stress is of great importance. An algometer measuring pressure pain sensitivity (PPS) has been shown to correlate to certain stress measures in adults. However, it has never been investigated in children and adolescents. The aim of our study was to examine associations between PPS and glycated hemoglobin (HbA1c), salivary cortisol and two questionnaires as well as to identify whether the algometer can be used as a clinical tool among children and adolescents with T1D. Eighty-three participants aged 6-18 years and diagnosed with T1D were included in this study with data from two study visits. Salivary cortisol, PPS and questionnaires were collected, measured, and answered on site. HbA1c was collected from medical files. We found correlations between PPS and HbA1c (rho = 0.35, P = 0.046), cortisol (rho = -0.25, P = 0.02) and Perceived Stress Scale (rho = -0.44, P = 0.02) in different subgroups based on age. Males scored higher in PPS than females (P < 0.001). We found PPS to be correlated to HbA1c but otherwise inconsistent in results. High PPS values indicated either measurement difficulties or hypersensibility towards pain.

Key Words: Stress; Children and adolescents; Type 1 diabetes; Autonomic dysfunction

Core Tip: The aim of present study was to examine whether pressure pain sensitivity (PPS) in children and adolescents associates with other stress measures and determine if it can be used as a clinical tool in this population. Our study revealed some unexpected discrepancies examining PPS in a pediatric population with type 1 diabetes, highlighting the need for more research to validate if PPS is a clinically useful measure in children.

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TO THE EDITOR

Type 1 diabetes (T1D) is associated to general- and diabetes-specific stress, which is linked to high glycated hemoglobin (HbA1c)[1], increased morbidity and mortality, and decreased quality of life[2]. In adults, Ballegaard *et al*[3,4] found pressure pain sensitivity (PPS) measured with an algometer to be correlated with established stress measures, thereby introducing an objective, non-invasive method of measuring stress. The aim of this study was to examine how PPS in children and adolescents associates with other stress measures and whether it can be used as a clinical tool in this population.

Data were collected as part of a prospective study of dermatological complications to diabetes devices. The present study included individuals with T1D between the ages of 6-18 years, and two study visits for each participant were selected based on available data. Exclusion criterium was participant or caregiver not being able to speak or read Danish.

PPS was measured using the algometer with two to three consecutive measurements on the index finger and tibia for method introduction before placement on the sternum. Increasing pressure was put on the skin for three seconds and participants were asked to say "stop" just before or *as* the pressure turned into pain or discomfort. The measurement was also stopped when a noxious withdrawal reflex (NWR) was observed, or if there was an activation of an alarm at maximum pressure (= 30 on PPS scale). PPS-score ranges from 30-100 with values ≥ 60 being the cut-off point for high level of stress in adults, based on receiver operating characteristic curves[4,5]. Salivary cortisol was analyzed with radioimmunoassay and HbA1c collected from medical files. Perceived Stress Scale (PSS) and World Health Organization-5 Well-Being Index (WHO-5), two questionnaires regarding stress and well-being, were completed during visits. PSS was answered by participants from age 10 years and WHO-5 from age 6 years. Examinations were conducted between April 1, 2020 and April 9, 2021. The study was approved by the Danish Data Protection Agency (P-2020-2) and the Regional Committee in Health Research Ethics (H-18059790) and followed Danish legislation regarding consent. Statistical analyses were made using the statistical software package R, version 4.2.2. Spearman's rank correlation was used for correlation analyses. Sex differences were analyzed using Mann-Whitney *U* test. The study population was analyzed as a whole and divided in two age groups (6-12 years, 13-18 years). A P value of < 0.05 was considered statistically significant.

This study comprised 83 participants, 51% male, mean (± SD) age was 12.6 (± 2.9) years and median (Q1-Q3) T1D duration was 0.8 years (0.01; 3.4). Forty-one percent were diagnosed with T1D within three months prior to their first study visit. Tables 1 and 2 show correlation analyses at the first visit (Table 1) and in between visits (Table 2) for the whole population as well as when stratified into age groups. Unexpectedly, negative correlations were found between PPS and cortisol in the total population (rho = -0.25, P = 0.02), in the 13 to 18-year-olds (rho = -0.35, P = 0.045), and between PPS and PSS in the 6 to 12-year-olds (rho = -0.44, P = 0.02). A positive correlation between PPS and HbA1c was present in the 13 to 18-year-olds (rho = 0.35, P = 0.046) and this finding persisted when comparing differences in PPS and HbA1c between the two visits (rho = 0.45, P = 0.048). Males scored higher than females in PPS in the total population (median difference = 17.5, P < 0.001), this being driven by the younger age group (P < 0.001) since no sex difference was present among 13 to 18-year-olds. No sex differences were found among the other variables. The PPS measurements were strongly and internally correlated when measured on the index finger, the tibia, and the sternum (all r > 0.5, all P < 0.001).

To summarize, we found a positive correlation between PPS and HbA1c in the old age group and unexpectedly negative correlations at the first visit between PPS and cortisol and PPS and PSS, the latter being present in the young age group. The negative and missing correlations contrast the findings of Ballegaard *et al*[3] who in adults found significant correlations between PPS and physiological markers of stress (heart rate, blood pressure, pressure rate product), regulation of glucose metabolism in adults with type 2 diabetes[5-7], survival in persons with ischemic heart disease[8] and questionnaires regarding mental and physical health[4]. Interestingly, we found that the younger males scored higher than the younger females but no differences among the older participants. Conversely Ballegaard *et al*[3] found the opposite correlation in adults which is more in line with the general assumption that females score higher in stress than males[9]. When using the algometer, a sex specific scale is activated. Hence our opposing findings may be explained by an irrelevance of different scales for sex in younger children. Despite the set-up with measuring on finger and tibia first

Table 1 Pressure pain sensitivity and correlations to stress measures during the first study visit

	Age: 6-12 yr; (M = 24, F = 25)		Age: 13-18 yr; (M = 18, F = 16)		Total population; (M = 42, F = 41)	
	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)
Pressure pain sensitivity[1]	85 (68; 99), 0		76 (66; 91), 0		81 (66; 96), 0	
Perceived stress scale[2]	12 (8; 16), 23	-0.44 (0.02)[3]	16 (10; 18), 9	0.16 (0.45)	15 (9; 18), 32	-0.18 (0.20)
WHO-5	72 (64; 84), 7	0.29 (0.06)	62 (46; 76), 4	-0.21 (0.26)	68 (59; 80), 11	0.14 (0.23)
Salivary cortisol (nmol/L)	6.8 (5.8; 8.5), 0	-0.13 (0.38)	9.4 (5.6; 15.3), 0	-0.35 (0.045)[3]	7.4 (5.7; 10.4), 0	-0.25 (0.02)[3]
HbA1c (mmol/mol)	63 (53; 8), 0	-0.27 (0.06)	67 (59; 72), 1	0.35 (0.046)[3]	66 (53; 80), 1	-0.07 (0.51)

[1]Pressure pain sensitivity score is an average of two to three measurements at the sternum. Third measurement was performed if a difference > 10 was present between the two first measurements. Distribution of cause of termination: First measurement: 18 with noxious withdrawal reflex, 65 said "stop"; second measurement: 15 with NWR, 66 said "stop", 1 alarm; third measurement: 4 with NWR, 2 said "stop".
[2]Answered by children above age 10 yr.
[3]Indicates a significant correlation (Spearman; $P < 0.05$).
M: Male; F: Female; Q1; Q3: First and third quartile; HbA1c: Glycated hemoglobin; WHO-5: World Health Organization-5 Well-Being Index.

Table 2 Within-variable differences between the two study visits and the correlations between changes in Pressure pain sensitivity and changes in Perceived stress scale, World Health Organization-5 Well-Being Index, salivary cortisol and glycated hemoglobin respectively

	Age: 6-12 yr; (M = 24, F = 25)		Age: 13-18 yr; (M = 18, F = 16)		Total population; (M = 42, F = 41)	
	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)
Pressure pain sensitivity[1]	4.5 (0; 13), 0		3 (-2.9; 8.4), 0		3.5 (-0.8; 11.2), 0	
Perceived stress scale[2]	-2 (-7; 0), 24	-0.08 (0.70)	1.5 (-2.3; 4.3), 10	0.06 (0.77)	-1 (-5; 3), 34	-0.04 (0.80)
WHO-5	4 (-8; 12), 8	-0.08 (0.63)	0 (-12; 8), 5	0.34 (0.068)	0 (-8; 11), 13	0.10 (0.43)
Salivary cortisol (nmol/L)	-0.07 (-0.38; 1.3)	-0.14 (0.33)	-0.2 (-3.1; 5.4), 0	0.25 (0.16)	-0.07 (-3.5; 0.75), 0	0.02 (0.87)
HbA1c (mmol/mol)[3]	0 (-5.5; 2.5), 4	0.05 (0.82)	0 (-5; 2.3), 2	0.45 (0.048)[4]	0 (-5; 2.5), 6	0.19 (0.22)

[1]Pressure pain sensitivity score is an average of two to three measurements at the sternum. Third measurement was performed if a difference > 10 was present between the two first measurements. Distribution of cause of termination: First measurement: 18 with noxious withdrawal reflex, 65 said "stop"; second measurement: 15 with NWR, 66 said "stop", 1 alarm; third measurement: 4 with NWR, 2 said "stop".
[2]Answered by children above age 10 yr.
[3]Participants newly diagnosed with Type 1 Diabetes (duration < 3 months) were excluded from analyses ($n = 49$ participants remained, $n = 27$ aged 6-12 yr, $n = 22$ aged 13-18 yr).
[4]Indicates a significant correlation (Spearman; $P < 0.05$).
M: Male; F: Female; Q1; Q3: First and third quartile; HbA1c: Glycated hemoglobin; WHO-5: World Health Organization-5 Well-Being Index.

and then sternum, a high percentage of participants said stop right away even at repeated visits. The *a priori* fear of being hurt and/or problems with understanding the instruction may be more prominent in younger children. A possible scenario could also be that participants wished to appear strong and therefore waited too long before saying stop. The population's high PPS levels can be interpreted as either an expression of a psychological response, measurement difficulties or a general centrally induced hypersensibility caused by autonomic imbalance due to T1D[7]. PPS was significantly lower in participants with NWR compared to participants saying "stop" but too few measurements terminated because of NWR were available to enable subgroup analyses. The study was running during the COVID-19 pandemic which might have influenced stress and well-being. Cortisol levels were not adjusted to potentially influencing factors such as exercise and food intake. The study had minimal selection bias since participants enrolled in a study regarding skin problems. Furthermore, the variation in age allowed subgroup analyses.

In conclusion, there was a moderate to strong internal correlation between PPS measured on the three locations, however, the correlations of PPS to other indicators of stress such as cortisol and PSS was unexpectedly negative. PPS-values were generally high compared to adults reflecting either measurement difficulties or hypersensibility towards pain and the use of sex-specific scale was less relevant in the youngest age group. Our study revealed some unexpected

discrepancies examining PPS in a pediatric population with T1D highlighting the need for more research to validate if PPS is a clinically useful measure in children.

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FOOTNOTES

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